THE EFFECTS OF NARCOTICS ON SHOCK-INDUCED ROTATION

by

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A dissertation submitted to the Graduate Faculty in Biomedical Sciences in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The City University of New York

1979

This manuscript has been read and accepted for the Graduate Faculty in the Biomedical Sciences in satisfaction of the dissertation requirement for the degree Doctor of Philosophy.

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DEDICATION

I wish to express gratitude to Judy for love, understanding and perseverance through the last several years, to Amanda for keeping my spirits up, to Stan for his training and guidance and to Joe for his many suggestions and comments.

Abstract

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Rats turn in circles (rotate) at night and in response to various drugs during the day. It is believed that the direction and amount of circling are related to the difference between the dopamine contents of the two neostriata.

Circling has been observed to be induced by noxious and arousing stimulation. The first part of this investigation examined the effects of a painful stimulus, i.e. footshock, on rotational behavior. It was found that footshock induced rotational behavior, but that this circling was unrelated to spontaneous circling. The two types of circling were further differentiated on the basis of their sensitivities to dopaminergic drugs.

Because a painful stimulus could induce circling, it was of interest to examine the effects of narcotic drugs on this behavior. Narcotics, in general, enhanced shock-induced circling. This effect was found to be due to an interaction of the narcotic and shock. It was also found to be opiate-specific: naloxone reversed the narcotic enhancement, but dextrorphan was without effect. This enhancement was unrelated to the analgesic activity of these drugs.

Naloxone was without effect on shock-induced circling. Naloxone, however, did block the increase of shock-induced net that occurred when

rats were given a second shock treatment. These data suggest that shock activates an endogenous opiate system that contributes to the increase in net rotation following the second shock treatment.

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LIST OF ABBREVIATIONS

AMPT:	Alpha-methyl-para-tyrosine
cAMP:	Cyclic adenosine monophosphate
CNS:	Central nervous system
CSD:	Cortical spreading depression
Dom:	Dominance
EEG:	Electroencephalogram
FI:	Fixed Interval
GSR:	Galvanic Skin Response
M:	Molar
ma:	Milliampere
MAOI:	Monoamine oxidase inhibitor
NRGC:	Nucleus reticularis gigantocellularis
NRM:	Nucleus raphe magnus
PAG:	Periaqueductal grey
PCPA:	Para-chloro-phenylalanine
SG:	Substantia gelatinosa
SER:	Somatosensory evoked response
SPA:	Stimulation produced analgesia
Sqk:	Squeak
TQT:	Total quarter turn
VPL:	Ventro posterolateral nucleus of thalamus
XQT:	Extra quarter turn

PAIN

Introduction

Pain is a unique sensory modality. Many neurons and axons respond specifically to pain; some respond solely to pain. These neural elements form the pain system, analogous to the visual system. Suprathreshold stimulation of other sensory modalities, however, will also induce pain. Therefore, pain can not be considered only as a sensory modality.

It has also been pointed out that pain is more than sensation. It is seen as being inseparable from the responses it elicits. Pain, in this view, is behavior and not just sensation.

This review will examine what pain means to neuroscientists of various persuasions. Topics to be discussed include: definitions, anatomy and physiology, responses to pain, experimental methods of inducing pain, and theories.

Attempts at Defining Pain

It seems that many pain scientists have felt compelled to attempt to define pain while admitting that they really can not. Some have insisted that a definition is not possible. "I am so far from being able satisfactorily to define pain...that the attempt could serve no useful purpose." (Lewis 1942). "Pain is, it must be admitted, uncommonly difficult to define." (Beecher 1959). The latter author insisted that all of the typical ways of defining pain, i.e. as the opposite of pleasure, as mediated by certain neurons, as arising from injurious stimuli, are not definitions at all.

One of the problems of defining pain has been that it is a personal sensation, and this sensation is impossible to communicate (Bishop 1959; Gasser 1959; Sternbach 1968). Sternbach (1968) indicated that what an

individual does communicate is behavior, not sensation. Some authors, however, have suggested that this sensation of pain has some universally understood attribute of injury. The sense of injury is the meaning of pain (Nakahama 1975; Mumford & Bowsher 1976). Nakahama's statement is typical: "Pain is a sensation elicited by stimuli which are capable of injuring or destroying tissue cells and this is important for the maintenance of life." Pain's function is to protect and alert the organism.

A specific sensation?

Physiologists often have viewed pain as a specific sensation mediated by specific neural structures and pathways. Thus, it is "reasonable to postulate the existence of cells which respond only to nociceptive input and relay this information centrally." (Dykes 1975). Exactly why it is reasonable is unclear, although much evidence has been gathered (see below) to support this statement. Perl (1971), who has reported upon specific pain neurons in the spinal cord and specific peripheral pain nerve fibres, presented the idea that it is the nociceptive stimulus (Sherrington 1906) which imparts the specificity to the defining quality of pain. Perl noted in this paper that if the noxiousness of the stimulus is the distinguishing quality of pain, then "man and animal must have means for distinguishing noxious from innocuous events." Citing evidence of specific pain fibres and cells and the concomitant "reasonable" correlations with the psychophysics of pain, Perl suggested that it is this sensory quality of noxiousness that defines pain. According to Sherrington (1906) the noxious stimulus is the incipient damage to the organism, and its purpose is protective. Pain reflexes become dominant because of this protective need.

To summarize the definition of pain as presented by many physiologists: pain is a specific sensation which is elicited by noxious stimuli; the

sensation's purpose is adaptive in that it affords the organism protection and escape from damage. Support for the adaptive significance of pain has come from cases of congenital insensitivity to pain (Dearborn 1932; Baxter & Oszewski 1960; Swanson et al. 1965). People who have this syndrome often injure themselves without realizing the extent of their injury.

Pain as behavior

The forgoing definition of pain has been soundly criticized, often by psychologists. They have noted that the simple stimulus response relationship is not adequate to explain the many phenomena associated with pain (DeSousa & Wallace 1977). Weisenberg (1975) agreed that pain has a sensory component but cited several reasons why a purely sensory description of pain is incomplete: 1. certain pain syndromes such as causalgia (a burning pain due to deformation of nerve fibres by bullets) present pain after the tissue has healed; 2. surgical destruction of the specific pain fibres and cells should abolish various pain syndromes, but the usual post-operative course is for the pain to reoccur; and 3. psychiatric illnesses may include pain as a symptom in which no obvious physical damage is discernible.

Weisenberg's three points do not adequately refute the sensory definition. Points one and three may be explained by designating such phenomena as hallucinations, analogous to visual or auditory hallucinations. His second argument may be refuted by the fact that pain information is relayed by more than one pathway in the spinal cord and brainstem (see below).

Weisenberg stated that the sensory aspect is accompanied by an "aversive cognitive-motivational and emotional" component; that is, pain "is a psychological experience affected by behavioral variables." Phenomena such as hypnosis (Barber & Hahn 1962) and the placebo effect (Beecher 1972)

demonstrate that the sensation of pain is governed by behavioral variables. Another example of the degree to which sensation is altered by behavioral state was published by Marchand et al (1959). They observed that certain psychotic patients felt no pain when they had injuries requiring surgery. These injuries were almost always painful to normals. Such examples show that even with tissue damage, pain may not be felt.

Further definitions

Sternbach (1968) attempted to combine many attributes of pain into an inclusive definition, although he stated that one reason for the difficulties has been that there are many kinds of pain. His definition consists of three parts: "pain is an abstract concept which refers to 1. a personal, private sensation of hurt; 2. a harmful stimulus which signals current or impending tissue damage; 3. a pattern of responses which operate to protect the organism." Although there is little question that pain is both private and personal, pain is, nonetheless, something that all men understand intuitively. Humans can communicate the sensation of pain. The third part of Sternbach's definition of pain stated that a noxious stimulus produces a certain set of responses. The question of specificity of pain responses will be examined in the Responses section. As a working definition Sternbach's attempt succeeds in describing the major aspects of pain, i.e. sensation, stimulus, and response. The definition does not describe the "particular quality of physical pain" (Adrian 1959), and it has been this sensation-emotion complex that has made pain so difficult to define.

Defining pain is difficult. As shall be discussed below pain is both specific and non-specific, has elements of sensation and behavior, is anatomically complex and often diffuse. It does hurt, and this is often most important for it produces behaviors directed towards its relief

(Keidel 1972). This may simply explain why pain has been observed to disrupt ongoing behavior (see Lyon 1968).

Anatomy and Physiology

The majority of neurophysiological investigations of pain has used either extracellular single unit recording or recording of evoked potentials. Cells are generally classified on the basis of their selectivity. That is, a cell is considered to be nociceptive if either it responds only to noxious input or if it responds differently to noxious input than it does to other input. Those cells whose maximal firing rates are elicited by noxious stimuli or which are strongly inhibited by noxious stimuli are considered to be involved in the transmission of pain despite a lack of specificity. These latter types of cells probably play an integrative role in the central processing of pain.

Stimulation

Stimulation of certain brain regions evokes pain responses. The usual assumption is that these sites are involved in pain transmission. Stimulation of other areas results in stimulation produced analgesia (SPA). It is assumed that these latter sites are involved in modulating or suppressing pain responses.

When stimulation of a site has no effect on inducing or altering pain responses, the usual assumption is that such a site is not involved in pain transmission. However, this may not necessarily be the case. Gross stimulation may not activate enough of a diffusely distributed cell population to generate the behavior in question.

Lesion studies

If stimulation of a region induces a pain response, it could be expected that a lesion of that site should induce analgesia. Conversely,

if a lesion induces a hyperalgesic response, most investigators have assumed that the site must be involved in modulating or suppressing pain.

These two types of experiments, one at the cellular level and the other at the level of a brain region, can be expected to give results that are not always consistent. This can be attributed to the gross difference between recording from one cell and stimulating a large number of cells. These latter cells can be expected to be heterogeneous in type and function. Additionally, stimulation and lesioning affect axons.

This section will discuss the results of employing these techniques in various sites in the nervous system: peripheral nerves, spinal cord, brainstem, diencephalon, and telencephalon.

Nociceptors and peripheral nerves

A great deal of information has accumulated during this century concerning the physiological characteristics of nociceptive receptors and peripheral nerves. It is ironic that the anatomical basis of pain-specific receptors still depends on a process of elimination.

By consensus, free nerve endings in the skin have been considered to be the cutaneous nociceptors (Taub & Collins 1973; Wilson 1974; Nakahama 1975). Only unencapsulated nerve endings have been found in the cornea and in the tooth pulp. Because pain has been evoked in these structures and only one type of nerve ending is present, the implication has been that naked endings are the nociceptors. Stimulation of the cornea, however, has caused touch or pain sensation depending on the intensity (Nafe 1934; Lele & Weddell 1956). Some evidence has been presented showing that stimulation of tooth pulp evoked other sensations besides pain (Mumford & Bowsher 1976). Again, the question has arisen as to the specificity of these receptors.

Peripheral nerves transmit pain information; this was shown by transection (Zotterman 1933). Ransom (1931) blocked large fibres with pressure or blocked small fibres with cocaine and showed that small fibres, i.e. A-delta and C, carry pain information.

Cutaneous pain consists of two types: pricking or first pain and burning or second pain. Each of these is transmitted by a different fibre type. Zotterman (1972) described A-delta as the fibre type specific for first pain and C as the type specific for second pain. (Bishop & Landau 1958; Collins et al. 1960; Torebjork & Hallin 1973). Some C fibres, however, were found to carry other sensory information. Some fibres responded solely to non-noxious stimuli, and others responded to both painful and non-painful input (polymodal nociceptors) in rats, cats, dogs, and humans (Iriuchijima & Zotterman 1960; Torebjork 1974).

Three types of nociceptive receptors have been described based upon the responses of peripheral nerves to various cutaneous stimuli: high threshold mechanoreceptors, mechanoreceptors, and polymodal receptors. The high threshold mechanoreceptors require a stimulus intensity that is an order of magnitude greater than that of touch or pressure receptors (Iggo 1974). They have been found in cat and monkey and may induce activity in either A-delta or C fibres (Perl 1968; Bessou & Perl 1969; Georgopoulous 1976). The receptive fields were described as usually small or punctiform (Iggo 1974), and their fibres increased their firing rate as the stimulus was intensified (Perl 1968).

The mechanoreceptive nociceptors respond to non-noxious stimulation but increase their rate of responding during noxious mechanical input (Perl 1968). The third nociceptor type is the polymodal nociceptor, which

responds to noxious heat, noxious mechanical stimuli, and chemicals that cause pain or irritation (Bessou & Perl 1969; Beck et al. 1974; Torebjork 1974; Beitel 1975).

Spinal cord

Upon entering the spinal cord, primary afferents invariably bifurcate. Small fibres course laterally, large fibres medially (see Kerr 1975b). These axons synapse in the cord in quite complex arrays, but most fibres either synapse with marginal cells (Rexed lamina I) or terminate in the substantia gelatinosa (SG) (see Kerr 1975b). In general, the search for neurons responding to noxious input has been approached by recording cell responses to either stimulation of the skin or electrical stimulation of cutaneous A-delta and C fibres.

Many cells in the dorsal horn respond to noxious stimulation. There are several types of these cells, and they are classified on the basis of their response profiles. Some cells in dorsal horn responded to both mechanical stimulation and noxious heating of the skin (Price & Wagman 1970). Others responded to noxious mechanical stimulation, noxious heat, and noxious chemicals only. Some cells responded to several noxious stimuli and non-noxious stimuli; these are called the wide-dynamic range cells (Wagman & Price 1969; Christensen & Perl 1970; Willis et al. 1974; Handwerker et al. 1975; Price & Browe 1975; Price & Mayer 1975; Cervero et al. 1976). Some dorsal horn units responded only to noxious mechanical stimuli or to graded mechanical stimuli including noxious input (Pomeranz et al. 1968; Christensen & Perl 1970; Willis et al. 1974; Kamazawa et al. 1975; Price & Browe 1975; Cervero et al. 1976). Receptive fields of cells responding to painful and non-painful input were often found to extend over an entire limb, but receptive fields of specific mechano-nociceptors were usually small.

Nociceptive cells occurred primarily in laminae I and V in the cat and monkey. Some investigators found specific high threshold mechanoreceptors occurring preferentially in lamina I (Christensen & Perl 1970; Kamazawa et al. 1975), but others have found only polymodal nociceptors in this lamina (Price & Mayer 1975).

Spinal tracts

As pain information ascends through the neuraxis, this information is distributed diffusely. Several spinal tracts carry pain information: anterolateral tract (Bowsher 1957; Mayer et al. 1975), dorsolateral tract (LaLonde & Poirer 1959), dorsal columns (Petit 1972), and spinocervical tract (Abrahams 1974). The anterolateral columns comprise several pathways: spinothalamic, spinotectal, spinoreticular, and spinocerebellar (Noordenbos & Wall 1976).

The lateral spinothalamic tract projecting to the ventropostero-lateral nucleus (VPL) of the thalamus has classically been considered to carry pain information (Carpenter 1976). Although this tract is thought to be "young" phylogenetically, i.e. the neospinothalamic tract (Bowsher 1957), there is evidence that rodents do have direct spinothalamic tract fibres terminating in the VPL (Mehler 1957; Lund & Webster 1967). The paleospinothalamic tract has been shown to transmit pain information to the intralaminar nuclei (Poggio & Mountcastle 1960; Whitlock & Perl 1961). The spinoreticular tract has been shown to project to the nucleus reticularis gigantocellularis (NRGC) of the medulla (Rossi & Brodal 1957). This nucleus also was found to receive collaterals from the spinothalamic tract (Mehler et al. 1960). The NRGC will be discussed below.

The variety of tracts carrying pain information has been offered as the explanation for the unfortunate recurrence of intractable pain after surgery

in a majority of cases (White & Sweet 1969). Recently, a patient whose spinal cord was severed except for one anterolateral tract not only was able to feel pain on the more severely affected side but was also able to localize pressure to some extent (Noodenbos & Wall 1976). This clinical case has brought into question the classical view of the distribution of sensory modalities in the spinal tracts.

Nociceptive information in the brain is processed at many sites; the number of tracts transmitting information complicates studies attempting to localize central nervous system (CNS) sites receiving pain input. Several anatomically defined sites in the brain possess a high density of units responding to painful input. These include the NRGC, the raphe nuclei, the midbrain periaqueductal grey (PAG), and several thalamic loci. Lesions placed in such areas have produced deficits in behavioral and/or physiological responses to painful stimuli.

Nucleus reticularis gigantocellularis (NRGC)

The NRGC has extensive connections: it receives input from the anterolateral tract (Fields et al. 1975) and sends axons to cord motoneurons (Wolstencroft 1964). It has reciprocal connections with the midbrain (Mancia et al. 1974) and also projects to the centrum medianum (Bowsher 1966; Bowsher et al. 1968).

Two types of cells were found to respond to noxious input: some respond solely to nociceptive stimuli while others respond to either noxious or non-noxious input (Burton 1968; Casey 1969; Benjamin 1970). Neurons responding only to nociceptive information were found in the caudal part of the nucleus; these cells had large receptive fields (Pearl & Anderson 1976). Casey et al. (1974) found that peripheral stimulation of

A-delta and C fibres excited these cells, some of which responded with after-discharges of up to 2 seconds (Goldman et al. 1972). Intradermal or intra-arterial injections of bradykinin were reported to excite a majority of NRGC cells (Besson et al. 1974). Bilateral anterolateral cordotomy completely prevented responses of NRGC cells to heat, pinch, and heavy pressure (Casey 1969).

The NRGC and neighboring caudal reticular formation of the brainstem are thought to be involved in alerting the organism to pain (Bowsher 1976), responding to diffuse pain, or responding affectively to pain (Pearl & Anderson 1976). Stimulation of the NRGC in cats and rats elicited escape behavior in animals trained to escape from cutaneous nerve stimulation (Keene & Casey 1970; Casey 1971).

Medullary and pontine raphe nuclei

The raphe nuclei are a group of serotoninergic cell clusters in the midline of the lower brainstem (Dahlstrom & Fuxe 1964). I will discuss the mesencephalic raphe nuclei in the midbrain section (below).

The one neurophysiological study of the nucleus raphe magnus (NRM) showed that some cells responded maximally to noxious stimulation (Anderson et al. (1977).

The NRM was found to be a site of stimulus produced analgesia (SPA). That is, electrical stimulation of the nucleus blocked behavioral responses to noxious stimulation (Oliveras et al. 1975). Cats were tested for responses to noxious stimuli, which consisted of a pinch to the tail and limbs and electrical stimulation of tooth pulp. These cats were awake and freely moving. Analgesia was found to occur only during the stimulation of the NRM.

Evidence for the mechanism of this SPA was reported by Beall et al. (1976) and by Fields et al. (1977). Cells in laminae I and V that had been excited by cutaneous noxious stimulation were inhibited by SPA. However, after dorsolateral funiculus lesions, SPA was reduced although not completely abolished. Presumably, the blockade was not complete due to descending bilateral input.

The NRM will be discussed further in the section on sites of narcotic-induced analgesia.

Midbrain

The midbrain, in all species investigated including man, is important in the generation and/or modulation of pain responses. Midbrain sites, to be discussed in detail below, that have been intensively investigated include periaqueductal grey (PAG), dorsal raphe, and lateral tegmental mesencephalon. There have also been studies published implicating the red nucleus (Nakahama et al. 1969; Nishioka & Nakahama 1973) and the substantia nigra (Segal & Sandberg 1977) in pain transmission. There have been few neurophysiological studies of midbrain cell responses to noxious input. However, stimulation and lesion studies have been extensive.

In 1955, Delgado found that stimulation in the PAG and in the mesencephalic medial lemniscus and spinothalamic tracts of the cat induced snarling. Others also found apparent pain responses induced by electrical stimulation. Hissing, dilated pupils, piloerection, and arching of the back without attack were evoked by stimulation of the caudal PAG (Skultety 1963). Similar results were obtained by Spiegel et al. (1954), and by Nakao et al. (1968) who also evoked locomotion at sites throughout the PAG.

Nashold et al. (1969) stimulated various sites in the midbrain of humans. Responses evoked by stimulating the PAG included diffuse pain, strong emotions (such as fear), piloerection, and increased pulse and respiration. Upon stimulation in the midbrain lateral spinothalamic tracts sharp pain, EEG afterdischarge, sweating, piloerection, and other emotional responses resulted.

In contrast, stimulation of other midbrain sites elicited analgesia (SPA) in man (Adams 1976) and blocked responses to various noxious stimuli in several other species: pinching with forceps or hemostat (Mayer et al. 1971; Liebeskind et al. 1973; Mayer & Liebeskind 1974; Oliveras et al. 1974; Soper 1976); pinprick (Balagura & Ralph 1973); electric shock, including the flinch jump test (Mayer et al. 1971; Mayer & Liebeskind 1974); heat, including tail flick (Mayer & Liebeskind 1974; Giesler & Liebeskind 1976; Soper 1976); writhing due to 1 molar saline (Giesler & Liebeskind 1976); and jaw opening reflex in response to electric stimulation of tooth pulp but not in response to tapping of the face (Oliveras et al. 1974).

SPA does not attenuate responses to all sensory modalities. Reynolds (1969) performed laparotomy on rats during SPA. Although non-responsive to noxious stimuli, these rats struggled upon hearing a loud noise. Mayer et al. (1971) reported that during SPA rats were in fact hyperresponsive to touch and to objects moved about in front of them.

Electrode placements that elicited SPA were mostly in the ventral posterior PAG or within the dorsal raphe in the cat (Liebeskind et al. 1973; Oliveras et al. 1974). Placements in the rat midbrain resulting in SPA were more widely distributed (Mayer et al. 1971). The analgesia resulting from SPA was usually found over wide areas of the body (Mayer et al.

1971; Balagura & Ralph 1973).

The mechanism of SPA has been investigated anatomically and neurochemically. Several reports implicated a descending system activated by the PAG which inhibited dorsal horn cells (Liebeskind et al. 1973; Oliveras et al. 1974) that increased their firing rates during cutaneous noxious stimuli. SPA also blocked firing of rat NRGC units responding to either electric shock or pinch of the tail (Morrow & Casey 1976).

Serotonin has been suggested to mediate dorsal raphe SPA. SPA elicited by stimulation in the dorsal raphe was blocked by LSD (Guilbaud et al. 1973) and para-chloro-phenylalanine (PCPA) (Akil & Mayer 1972). Simultaneous treatment with PCPA and 5-hydroxytryptophan reversed the block of SPA induced by PCPA (Akil & Liebeskind 1975). The latter authors also noted that dopaminergic blocking agents suppressed SPA while dopamine agonists enhanced it.

Analgesia was often induced by lesions in the midbrain although some workers reported no effect. Those studies in which analgesia resulted from lesions are consistent with data indicating that stimulation of the midbrain induces pain responses.

Lesions in the ventrolateral PAG but not in the dorsal PAG of rats induced deficits in avoidance and escape in some rats while other rats had deficits in either avoidance or escape (Halperin 1968). In another study, rats no longer bar pressed to escape noxious noise after total but not dorsal PAG lesions (Lyon 1964). Lesions in auditory pathways also had no effect on this escape behavior suggesting that interference with sensory input does not induce such changes. Therefore, the effect of total PAG lesions is to interfere with the ability to respond.

Liebman et al. (1970) proposed that behavioral changes induced by PAG lesions in rats were caused by decreased fear. This group reported that such lesions induced open field hyperreactivity, increased step-through avoidance, prevented suppression of responses in a food reward-foot shock conflict test, and induced rats to jump off a 24-inch high perch. The authors noted that lesioned animals when placed on the high perch did not pass feces. Control animals did. Taking defecatory behavior as an index of emotionality, the authors suggested that the lesioned rats were less fearful. The other behavioral changes they observed were seen as consistent with this hypothesis.

Kelly and Glusman (1968) found that PAG lesions in cat did not induce analgesia as measured by the shock titration test. Melzack et al. (1958), however, found that lesions of the medial PAG of the cat did induce analgesia. The lesion resulted in an impairment of escape from a heated compartment. Escape from pin pricks was also depressed, but this change was transient.

A lesion placed in the dorsal raphe increased aggressive behavior elicited by foot shock (Jacobs & Cohen 1976). This study suggests that a lesion in this nucleus results in hyperalgesia, which is consistent with the stimulation studies indicating that this is a site for SPA.

Neurosurgeons have lesioned the midbrain for cases of intractable pain. Wycis & Spiegel (1962) reported that 10 to 20 percent of patients with such lesions received complete and lasting relief, but others who did get relief found that the pain returned. Lesions in the lateral central grey were reported to relieve pain and calm the anxiety resulting from it (Nashold et al. 1974).

Trigeminal system

Pain information from the face is conveyed to the trigeminal nuclear complex, particularly the caudal portion of the spinal nucleus (Mosso & Kruger 1972; Kitahata et al. 1973; Kruger & Mosso 1973). Neurons that responded specifically to nociceptive stimulation (Kitahata et al. 1974) and others that responded maximally to noxious stimuli but also responded to non-noxious input were found in deep regions of this nucleus (Nord & Ross 1973; Dubner et al. 1976). Destruction of the descending spinal trigeminal tract abolished pain sensation of the face (Raney et al. 1950).

Thalamus

The spinothalamic tract was found to terminate in many thalamic nuclei, some of which have been implicated in receiving pain input. These nuclei include: the external portion of the ventrobasal complex or VPL (Poggio & Mountcastle 1960; Perl & Whitlock 1961; Whitlock & Perl 1961); centrum medianum (Bowsher 1957; Poggio & Mountcastle 1960); and the magnocellular part of the medial geniculate and neighboring areas (Poggio & Mountcastle 1960) which are collectively known as the posterior thalamic zone. The centrum medianum-parafascicular complex receives input from the NRGC (Bowsher et al. 1968); this connection is considered to be part of the paleospinothalamic tract.

Perl and Whitlock (1961) found that some cells in the ventral basal complex of the cat responded to noxious stimuli (heat or pinch) only. These units have small contralateral receptive fields. This nucleus may be a site of pain sensation and discrimination although the evidence appears far from conclusive (Price & Dubner 1977).

Evidence for pain input to the centrum medianum-parafascicular complex came from studies in man (Ishijima et al. 1975), and monkey (Perl & Whitlock

1961). Large bilateral receptive fields were also found in posterior thalamic neurons responding to nociceptive input (Poggio & Mountcastle 1960).

Destruction of the centrum medianum in man abolished the sensation of diffuse pain (Hecaen et al. 1949). It is tempting to view the thalamus as receiving two pain inputs: a specific localized input to the ventrobasal complex subserving pricking pain, and a non-specific input via the reticular formation and the paleospinothalamic tract to the posterior thalamic zone and the centrum medianum-parafascicular complex subserving diffuse pain or alerting and response integration. Unfortunately, ablation of the centrum medianum-parafascicular complex did not prevent the return of thalamic pain (Bowsher 1974). Bowsher suggested that pain sensation is due to a widespread excitation of the thalamus. A focal lesion would only eliminate a small fraction of this excitation.

Hypothalamus

Cells in the supraoptic nucleus of the hypothalamus altered their bursting pattern during repeated cutaneous pinprick (Hayward & Jennings 1973). It has been suggested that these units induce vasopressin release, observed to occur during pain (Verney 1947; Kelsall 1949). Lesions in the medial forebrain bundle, which connects the hypothalamus and the midbrain tegmentum, induced lowered response thresholds to hot-plate paw lick and flinch-jump. These lesions also elicited increased stabilimeter response to pain and startle response to noise (Yunger & Harvey 1973).

Basal ganglia, septum

Few studies have investigated the role of basal ganglia in pain transmission. Relief of pain by chronic stimulation has been reported

(Ervin et al. 1966). Lineberry and Vierck (1975) found that unilateral caudate stimulation induced a decrease in the force with which a monkey pressed a button in response to pain. Pain threshold and latency to respond were not affected. The septal area probably mediates many behaviors. Stimulation of this area resulted in lowered escape latencies in rats (Gardner & Malmo 1969) and increased footshock thresholds (Breglio et al. 1970). Septal lesions lowered flinch-jump thresholds, but this effect was not seen until 40 days after the surgery (Stewart et al. 1977). Septal stimulation for the relief of intractable pain in man was successful in one case but without effect in others (Gol 1967).

Cortex

Although the somatosensory cortex receives certain sensory information it appears that pain is not transmitted to this site. Price and Dubner (1977) found it "surprising" that only a few cells responding to noxious input have been discovered there. Surgical procedures for intractable pain that have had some limited success include ablation of the somatosensory cortex. These lesions, however, also involved the second somatosensory area or SII (Lende et al. 1971). In cats, some neurons in SII were observed to respond to polymodal nociceptive input (Carreras & Andersson 1963). Other cells responded to both mechanical and noxious stimuli, the receptive field of each sensory input being different. The authors pointed out that the characteristics of these cells were very similar to posterior thalamic cells.

Several areas of the cortex i.e. the orbital and striate cortices, were found to receive nociceptive input. The orbital cortex in the cat has cells which responded to a variety of noxious cutaneous stimuli.

Korn et al. (1966) reported that the cell responses were abolished if the contralateral VPL of the thalamus had been destroyed. Lesions in the orbital cortex were found to depress passive avoidance behavior (Cornwell 1966). In one study with cats (Murata et al. 1965), 50 percent of cells sampled in the striate cortex responded to pin prick bilaterally. Many of these units showed convergence of nociceptive, visual, and auditory inputs.

Prefrontal lobotomy, perhaps the most notorious of neurosurgical procedures, has given relief to intractable pain patients (Freeman & Watts 1946). This procedure has also been found to have the admirable side-effect of eliminating narcotic addiction (White & Sweet 1969). Various alternatives to bilateral lobotomy have been tried. Unilateral prefrontal lobotomy has given partial or total relief in some patients while lowering the pain threshold (King et al. 1950). Cingulumotomy has been suggested as a means of treating patients with intractable pain who have grossly exaggerated emotional responses to the pain. Many of the patients were no longer concerned with the pain although it was still present after the operation (Foltz & White 1962). Block of the sulcal prefrontal cortex lowered the jump threshold to foot shock without affecting flinch threshold in rats (Cooper 1976).

Summary

Neurons that respond solely to noxious stimuli are found in laminae I and V of the spinal cord dorsal horn, NRGC, and VPL. Because VPL cells have small receptive fields, they can be considered analogous to other VPL cells receiving somatosensory input. NRGC cells have large receptive fields; it is quite conceivable that these units are involved in arousing the organism to the existence of pain.

Responses induced by pain seem to be mediated by NRGC, PAG, and raphe nuclei. In what way these nuclei are organized to either produce or modulate responses is unknown.

Methods

There are four general methods of inducing experimental pain classified as to the type of stimulus employed: chemical, electrical, mechanical and thermal. These are usually used to screen compounds for analgesic activity. Most of the tests require an escape behavior. When the subject responds by flicking its tail or squeaking, the test ends. Thus, most tests record either a latency to respond or a stimulus intensity at which response occurs.

The most common chemical screening method is the phenylquinone writhing test (Hendershort & Forsaith 1959). Some drugs that are clinically inactive, however, give positive results in this test.

Electrical methods have been purported to be simple, almost never damaging, and straightforward (Notermans 1966). However there has not been any consensus as to which electrical parameter, i.e. current, power, or voltage, should serve as the independent variable in testing (for e.g. Hill et al. 1952a). Two of the most common electrical methods that use animals are the flinch jump technique (Evan 1961; 1962) and the shock titration schedules (Weiss & Laties 1958; 1959; 1964). Mechanical methods have been criticized as being non-specific because contact with the skin must also excite touch and pressure receptors (Notermans 1966).

The two most common thermal methods employing rodents are the tail flick (D'Amour & Smith 1941), which has spawned many varieties, and the

hot plate test (Eddy et al. 1950; Eddy & Leimbach 1953).

Experimental versus clinical pain

Beecher (1956c; 1959) suggested that (human) experimental pain is not a good model for clinical pain because of the large variations seen in measuring experimental pain. Beecher's explanation for the irreproducibility of experimental pain threshold is that the reactive component of pain, the "unconscious psychic processing", can not be duplicated in a laboratory. His suggestion is supported by findings that many psychological factors can alter human pain thresholds (Hardy et al. 1943). These factors include: distraction, autosuggestion, placebo effect (Beecher 1955; 1956a), significance of injury (Beecher 1956b), hypnosis (Sears 1932), and anxiety (Malmo & Shagass 1949; Hill et al. 1952b; Kornetsky 1959).

Beecher (1959) described the reaction component as "the subject's concept of the sensation...its significance...its importance and degree of seriousness." He said that this component does not entail such behaviors as flight, withdrawal, or galvanic skin response. Such effects he considered to be the consequences of pain.

Sternbach (1968) stated that the difference between clinical and experimental pain is a limitation of which the experimental subject is aware: no injury will be sustained. Pathologic pain, however, is a threat, and a potentially serious one. Whereas the experimental subject will walk away from the experiment unscathed, the patient with pain has no such exit. The consequences for the patient may be unknown. Thus, Beecher and Sternbach both suggest that the reason experimental pain is often a poor model for clinical pain is because the former has no real psychological impact.

An animal in a pain experiment may not be able to distinguish experimental pain from pathologic pain as humans can. Beecher (1959) suggested that "pain is pain to an animal...and all pain is serious and significant." Beecher (1959) as well as other workers (Bishop 1946; Pfeiffer et al. 1948) stated that what is being measured in an animal experiment is the reactive threshold (which may or may not be purely reflexive) and not the sensation threshold, which is indeterminable in animals.

Pain Responses and their Specificity

The endpoint of an analgesic test is some behavior that is more-or-less clearly described and measurable. For a response to be used as a pain index, it requires some motivational quality, such as aversion, withdrawal, or attack. Some responses have no such obvious motivational component, the tail flick being an example. Tail flick, in fact, was shown to be a purely spinal reflex, as it was unaltered in amplitude although slightly increased in force after spinalization (Irwin et al. 1951). This is not to say that an intact animal has no reactive component to its tail being heated. The way pain is being measured depends only on the latency to reflexly move the tail. This test then does not consider affective responses to pain. Furthermore, the animal is restrained when this procedure is employed, and thus its only available escape is tail flick.

Factors affecting pain responses

There are many pain responses. The response depends upon intensity and severity, duration, relationship to injury, anxiety, apprehension, cognitive modes, perceptual modes, personality characteristics, upbringing, race, sex, age, national origin, and probably a host of environmental factors (see Sternbach 1968; Weisenberg 1977). These factors can have

potent effects on the pain experience, as the following examples demonstrate.

Melzack and Scott (1957) raised dogs in isolation and found that they lacked normal avoidance of a flame. Varying shock duration altered the escape probability of cats (Kelly & Glusman 1976). The probability of a cat making an escape increased when the trial time was doubled from 6 to 12 seconds. However, for either shock duration the latency to escape was nearly the same and almost always less than 4 seconds.

Another example is the phenomenon of counterconditioning, in which an aversive stimulus is paired with a positive reinforcer. Pavlov (1927) found that a dog's responses to electric shock were much different if shock were immediately followed by food presentation. The dog's usual responses were extinguished because the shock had become a conditioned stimulus (or a discriminative stimulus) for food. Various workers have confirmed and extended Pavlov's observations (Williams & Barry 1966; Murray & Nevin 1967; Pearce & Dickinson 1975). From these counterconditioning studies and from the duration experiment (Kelly & Clusman 1976), it can be seen that pain responsivity in animals is under considerable behavioral control. This suggestion parallels Beecher's (1959) idea that the psychic processing component of pain is of great importance.

Classification of responses

Beecher (1959) divided pain reaction into three categories: somatic, autonomic, and emotional. Examples of somatic motor responses include increased motor tone, wince of the outer canthus of the eye, reflex withdrawal of a limb or digit, vocalization, motions of rejection, flight, and escape. Autonomic reflexes include galvanic skin response (GSR), tachycardia, blood pressure rise, renal function depression, alarm, sweating,

pupil dilation, lacrymation, peristalsis acceleration, and nausea. The major emotional responses include anxiety, fear, rage, and terror. To these categories can be added Sternbach's (1968) group of physiologic responses: adaptation and rebound (describing and summarizing Beecher's autonomic category), and stress, which releases ACTH and corticosteroids, among other substances.

Sternbach (1968) believed that some responses are specific to pain although he readily admitted that no experiments have been performed in such a way as to unequivocally demonstrate such specificity. He said that the pattern of physiological responses, i.e. gastrointestinal motility inhibition, respiratory increase, muscle hypermotility and increased tension, and cardiovascular changes, is the same or very similar to the response pattern elicited by any activating stimulus.

The literature supports this latter contention. There is no indication that any response, with perhaps one or two exceptions (see below), is specific to pain. Cannon (1920) described the similarity of responses to pain, hunger, and intense emotion: hyperglycemia, increased serum epinephrine, blood clotting time shortened, raised blood pressure, and increased respiration. With the techniques then available the reactions to the various emotions and sensations were indistinguishable.

A stressor induces a set of responses that also have been found to be non-specific; that is, one type of stressor induces the same responses as any other stressor. Stressor is used here in the way that Selye (1946) described it. It means that a stimulus has some noxious, aversive, or unusual quality although not necessarily painful. Selye maintained that stress is the physiological response of the organism to stressors. In his

review Selye listed examples of stressors: shock, exercise, infection, exposure to cold, burns, drugs, toxins, and x-rays. Some of these can also be considered to be painful. The stress response to these various agents has been called the general adaptation syndrome by Selye. The syndrome consists of three phases: the alarm reaction, the stage of resistance, and the stage of exhaustion. It must be noted that Cannon's fight-or-flight epinephrine-mediated responses are the result of rather intense, temporally short stimuli. Selye's scheme seems to include rather long-lasting stimuli.

The major responses occurring during the alarm reaction are: tachycardia, muscular hypotonus, hypothermia, edema, metabolic changes, hypoglycemia, lowered coagulation time, epinephrine release, lowered pH, and leucocytosis. Both Canon and Selye found epinephrine increased. However, Canon found blood glucose increased, while Selye found it decreased. This difference in direction of change of some responses may be due to the duration of the agent instigating the responses. The release of ACTH and the ensuing rise in plasma and urinary 17-hydroxycorticosteroids resulted from various stressors, particularly those stimuli that are unusual, uncertain, anticipatory, altering previous behaviors, or requiring intense concentration (Mason 1968).

Research that has dealt with stress and/or pain responses (in the literature this distinction is often unclear or even unstated) has considered two questions in particular: the specificity of a response during various stressors, and the lability of the responses, i.e. does the response in question physiologically correlate with either the subjective report of pain in man or assumed painful behavioral response in animals. The

following discussion will include: amplification of Cannon's (1920) findings that various emotional states have similar physiologic response profiles; demonstrate that these response patterns are often specific to individuals and vary greatly from individual to individual; review the literature examining physiological response specificity of affective behavior.

Responses observed during pain

One of the earlier studies that examined responses was that of Malmo and Shagass (1949). These investigators simultaneously recorded electroencephalograms (EEG), finger movement, neck muscle potentials, respiratory rate, heart rate, and GSR during delivery of various intensities of focused radiant heat. The subjects consisted of "normal" hospital staff, schizophrenics, anxiety patients, and other psychiatric patients. The subjects signalled when a heat stimulus was about to become painful. In general, the findings showed that schizophrenics and anxiety patients have increased responses relative to the other groups over the range of heat intensities applied. The responses that showed distinct increases with increasing heat intensity were finger movements, neck muscle potentials, and respiratory irregularity. GSR decreased approximately equally for all four groups while heart rate was decreased slightly.

Engel (1959) examined the effects of cold pressor pain (subjects immersed a foot in ice water maintained at a temperature of 3 to 4 degrees centigrade), and hunger on blood pressure, GSR, temperature, heart rate, respiratory rate, stomach motility, finger pulse volume, and salivary flow. Pain selectively increased blood pressure and heart rate while decreasing finger pulse volume. Hunger significantly decreased blood pressure and had effects on other measures unaffected by cold pressor pain. Neither

GSR nor respiration was altered by pain. These results contradict the findings of the previous study (Malmo & Shagass 1949) although different techniques for inducing pain were employed.

The response profile to pain has been investigated during hypnotic and "waking-imagined" analgesia (Barber & Hahn 1962). Responses measured were frontalis muscle action potentials, respiratory irregularities, heart rate, and GSR. Subjects were also asked to rate the sensation of pain. The first three measures increased during a cold pressor test of the hand while the GSR decreased. Both imagined and hypnotically suggested analgesia (as rated by subjects) totally blocked the enhancement of muscle potentials and reduced the occurrence of respiratory irregularities. Although stating that they sensed no pain, these subjects showed no alteration by suggestion of increased heart rate and lowered skin resistance. Thus, pain responses may or may not occur simultaneously with the sensation of pain. Some responses can be seen to be more behaviorally labile than others. The finding that cold pressor pain decreased skin resistance contradicts Engel's (1959) result that cold pressor pain is without effect on this response.

Engel (1959) found that blood pressure increased during pain but not during hunger. Blood pressure increases during pain were also found by Malmo and Shagass (1952) and Schecter (1957). Hilgard (1969), however, published results suggesting that blood pressure is not specific to pain. He found that pain induced by both ischemia and cold pressor did in fact increase blood pressure. What was surprising was that hypnotic analgesia blocked the blood pressure response during ischemia but had no effect upon its rise resulting from cold pressor pain. Again, it can be seen that

the responses to pain are dependent on the type of pain and the behavioral state of the subject.

Similarly, hypnosis in animals was shown to block pain responsivity (Carli et al. 1976). Formalin injection in rabbits produced increased electromyogram tonicity, thumping, running, and electrocorticogram desynchronization. Hypnosis, induced by maintaining the rabbit on its back until it has ceased to struggle, blocked these changes.

The somatosensory evoked response (SER) has been found to have a pain specific component. Stowell (1977) found that judgements of pain due to electrical stimulation were related to the amplitudes of a positive wave in the SER. Another candidate for pain response specificity is esophageal pressure in humans. Electric shock was found to increase this pressure, while fear decreased it (Parker et al. 1963).

Endocrine responses to stress and pain are extensive (see reviews by Dewhurst et al. 1968 and Mason 1971). Avoidance behavior increased urinary 17-hydroxycorticosteroids (Mason et al. 1961). Patients with chronic pain were found to have greater serum cortisol than controls (Lascelles et al. 1974). In the latter study patients with chronic pain had higher serum cortisol than psychiatric patients who suffered from psychogenic pain. The thyroid was shown to be depressed by stressful manipulations, some of which can be considered to be painful (Paschkis et al. 1950; Hamolsky et al. 1951; Brown-Grant et al. 1954; Mason et al. 1961). The study of Mason and colleagues (1961) employed avoidance and found that the urinary levels of several hormones were altered. Mason (1971) showed, however, that, at least for 17-hydroxycorticosteroids, not all stressful situations have produced increases.

The problem of defining stress is similar to that of defining pain. The difference between pain and stress may be that pain is often a more localized phenomenon. Stress involves gross systemic alterations, such as occur in neuroendocrine and cardiovascular systems. Pain may also activate these as a non-specific stressor, but it may have other specific effects on the nervous system. Many of the responses to pain, then, are non-specific, and other stressors elicit them.

Patterns of response specificity

Individuals have patterns of responses to stressful stimuli, somewhat independent of the kind of stress. In one study, children were tested for blood pressure, heart rate, heart rate variability, and palmar conductance during a cold pressor test (Lacey & Van Lehn 1952). When physiological responses returned to baseline, subjects were tested again. Generally, each individual's physiological response pattern was very similar in the two tests. Thus, this study indicated that it may not be possible to predict from individual to individual what response pain will evoke, but in a given individual it may be possible to predict which responses will increase and which will decrease. If a given person's blood pressure increased in the first test, the chances are good that pressure will again rise during the second test.

In further studies, Lacey et al. (1953) subjected people to four stressful situations and measured palmar conductance, heart rate, and variability of heart rate. The results supported the doctrine of individual response specificity. If a given individual's heart rate increased and palmar conductance decreased during one stress, these effects would most likely occur during the other three stressors. These results were confirmed and

extended by Engel and Bickford (1961). They found that hypertensives were that subgroup of people who physiologically overreact to stressful stimuli by increasing their blood pressure. Hypertensives were also found to have a greater pattern of response reproducibility than nonhypertensives in a variety of tests. Thus, not only can responses be individually specific, there also can be a range of relative stereotypy of the pattern.

"Stress" induced analgesia

Another response to pain and stress is analgesia. Cold water swim, electric foot shock, and rotation induced analgesia in rats (Bodnar et al. 1977; Hayes et al. 1977). Lateral shaking and ether exposure did not induce analgesia (Hayes et al. 1977). Analgesia was assessed by tail flick, hot plate, pressure (Hayes et al. 1977), and flinch jump (Bodnar et al. 1977). Electric shock and cold water swim were also reported to cause deficits in learning escape-avoidance responses (Overmeir & Seligman 1967; Weiss & Glazer 1975). In humans pain has inhibited the sensation of a second pain delivered to another part of the body (Duncker 1937).

Summary

During stress a variety of changes have been seen to occur. These have been characterized as somatic, autonomic, and behavioral. Response profiles vary, to some extent, from person to person. There have been no reports of individual response specificity in the animal literature. This paucity of data suggests an area for future investigation. Such individual to individual variability would explain the large variances seen in some analgesic tests and the discrepancies in results among different laboratories.

As of this writing it seems that pain has access to, or operates through a series of behavioral outputs that are not specifically linked to pain. In this way pain can be considered a stressor. Because stressors usually have an aversive quality, it makes sense that they should excite defensive and/or attack behaviors non-specifically. Pain is not specific, certainly if it is viewed in terms of most of the responses it evokes.

Pain does involve specific elements of the nervous system. The SER has so far proven to be specific to pain. As of now, most responses routinely used in testing pain are not specific to pain and can be considered responses to stress. Man's verbalization of pain is the only response that does fulfill a specificity criterion.

Pain Theories

Pain has been described as almost impossible to define, confusing in its anatomy, lacking specificity, and yet to be one of the most important of medical symptoms. There is no lack of theories attempting to explain it. To establish a working hypothesis is no small task for pain phenomenology is vast.

A pain theory has to explain the need for two peripheral pain fibre types, neither of which is solely employed for transmitting pain. Furthermore, there are central nervous system cells that are both nociceptive only and wide-range receptive, as if there were two kinds of pain, that is, pain itself and pain derived from supramaximal stimulation of sensory modalities. The mechanisms of processing in the brain are not well understood.

There are many pain syndromes that are not easily explainable. Phantom limb pain and causalgia are syndromes that are very difficult to understand in terms of specificity theory. Other intriguing and poorly understood phenomena include referred pain and central pains. Any theory of pain must be able to explain the mechanisms of drug-induced analgesia, placebo effect, and acupuncture.

Specificity theory

Melzack (1973) has indicated that Muller and von Frey were responsible for developing the cornerstones of specificity theory. This theory probably has had the greatest impact on thinking about pain in this century, and it is only recently that it has been seriously challenged (see Wall 1976). Based upon Muller's concept of specific nerve energies, von Frey designated four cutaneous modalities: pain, cold, warmth, and touch. Each modality had specific receptors, nerve fibres, and brain nuclei. By a process of elimination, the naked axon terminals were chosen as the pain receptors.

A typical example of specificity theory is that of Mountcastle (1974).

Mountcastle believes that there are pain-specific aspects of the nervous system. The central circuitry is very complex and is very difficult to unravel. This difficulty is, according to him, the only reason other theories have been put forth. Mountcastle's description of pain mechanism rests upon the findings that certain A-delta and C fibres carry pain specifically, some dorsal horn cells are specifically nociresponsive, and ascending spinal tracts carry pain information. He suggested that A-delta input to the central nervous system subserves sensory input while C input evokes a range of aversive responses. The author accepted the fact that much processing occurs within the substantia gelatinosa (SG) although he

rejected the gate control theory (see below). Referred pain was explained as the convergence of cutaneous and visceral input, but its mechanism is unknown. It is not surprising that Mountcastle made no mention of phantom limb pain. In his view pain is the activation of specific nerves. An amputated limb no longer has nervous input to the CNS.

Perl (1971), another supporter of specificity, responded to criticism of this theory. He suggested that although several phenomena have been unexplained it does not follow that evidence of specificity, particularly in the periphery and in the cord, should be disregarded. It is generally agreed that there are elements in the nervous system that do carry pain specific information.

There are many criticisms of specificity theory (see, for example, Weddell 1955; Melzack 1973). Melzack and Wall (1965) stated that the greatest fallacy of specificity has been its assumption that once pain receptors have been stimulated, pain is felt. Beecher (1956b) has shown that this is not so: severely wounded soldiers often said that they felt no pain.

Pattern theory

Simply put: "There are no specific fibres and no specific endings..." (Sinclair 1955). The determinant of sensation, described as a cerebral and not a peripheral function, is "the pattern of non-specific impulses in the fibres of peripheral nerves," (Bishop 1946). According to Bishop (1946), adaptation, after-discharge, intensity, localization, and summation are those parameters mediating modality, i.e. touch, pain, etc.

Hebb (1949) also presented a pattern theory. He suggested that decreased peripheral intensity, seen in many pain syndromes and in pain

arising from damage, causes the sensation of pain. As evidence for this suggestion Hebb cited phantom limb pain and pain threshold increases seen in thalamic pain.

Hebb was referring to the observations that during a painful event, many fibres turn off. A painful stimulus was found to cause enhanced firing of polymodal and high threshold mechanoreceptors accompanied by decreased low-threshold receptor firing (see Perl 1976). The sensation of pain does not arise if only small fibres are activated without changes in the large fibre firing rates.

Gate control theory

One pain theory has provoked much controversy (Wall 1976) and stimulated much research: the gate control theory (Melzack & Wall 1965; 1970; Melzack & Casey 1968; Melzack 1973; Wall 1976). The authors concluded that neither pattern theory nor specificity theory adequately account for all characteristics of pain and some pain syndromes (Melzack 1973; Wall 1976).

Specificity has not explained referred pain, which is exacerbated by light pressure (Wall 1976). Melzack (1973) stated that pain perception and intensity can not have a one-to-one relationship as specificity implies, especially when the impact of various behavioral factors are considered (Melzack & Casey 1968). Specificity theory has not detailed the mechanisms of various central pains. Often, pain in such syndromes is induced by non-noxious stimuli and spreads beyond the area stimulated (Melzack 1973). Melzack and Casey (1968) stated that specificity theory seems to separate pain into sensation and response. Specificity theorists, they suggested, only deal with sensation while they ignore response.

The gate control theory has tried to explain pain as that sensation evoked by a certain spinal output that exceeds a critical level. The heart of the concept is the proposal that there is a gating mechanism, most

likely in the SG (Melzack & Wall 1970) that modulates afferent input. Small fibres (Ad and C) are thought to excite transmission cells, or T-cells, probably situated in lamina V of the cord, while the large fibres are believed to presynaptically inhibit these small fibres in the SG or post-synaptically inhibit T-cells. One reason that presynaptic inhibition was first suggested is that axo-axonic synapses were observed to occur quite frequently in the SG (see Kerr 1975b).

When activity in the T-cells has reached some critical level, information is conveyed to the brain as pain. The authors recognized that there are descending inputs that act upon these gates. Melzack & Wall (1970) suggested that the dorsal column-lemniscal system activates a central trigger, which identifies the input. The trigger promotes certain brain outputs, which may include descending controls.

After the T-cells have fired, impulses ascend in the neospinothalamic tract, which was suggested to carry sensory and discriminative aspects of pain, and in the paleospinothalamic and spinoreticular tracts, which were thought to activate the reticular formation and limbic system. The latter two systems were thought to subserve the affective and motivational aspects of pain (Melzack & Casey 1968).

The gate control theory can be viewed as an attempt to explain the differences between sensory and pattern theories. The authors agreed that there are specific nociceptive fibres and cells (Melzack 1973). However, they have found spinal cord cells that receive convergent input from various fibre sizes and types (Wall 1960; Wall & Cronly-Dillon 1960; Pomeranz et al. 1968). These cells also vary their firing patterns depending on the intensity and modality of peripheral input (Wall 1960). The

implication, then, is that the pattern of input to the central nervous system indicates the type of sensation perceived. Stimulation of another modality, i.e. vibration, was shown to inhibit pain sensitivity (Melzack et al. 1963). However, at high intensities of vibration, the sensation of pain was enhanced. This latter result suggests that the sensation of pain is determined by the total peripheral input. The interaction of large and small fibres was reported by Hillman and Wall (1969). They recorded from lamina V cells and found that large fibre activity caused a burst followed by an inhibition. Small fibre stimulation induced a prolonged excitation and facilitation of succeeding stimuli (the windup effect). The latter result suggested a form of central summation.

This theory certainly has its advantages. It has eliminated some of the apparent contradictions between specificity and pattern theories. In particular, it has explained clinical data, such as phantom limb pain and central pain syndromes. Such pains arise upon the destruction of inhibitory input mediated by large fibres. Fibre destruction and pain both occur in phantom limb and tabes dorsalis (Noordenbos 1968), a degenerative disease of the spinal cord (Melzack 1973). The analgesia induced by counter-irritation in such procedures as dorsal column stimulation, acupuncture, and rubbing of a wound was explained as preferential excitation of large fibres which causes the gate to close. Their explanation of referred pain, however, is not clear (Melzack and Wall 1970; Melzack 1973). They suggested convergence of visceral and cutaneous inputs and/or transmission in the Tract of Lissauer, which was shown to connect spinal cord segments.

Testing the gate control theory

Experimental testing of their theory has yielded inconclusive results. Some of the earlier criticism was aimed at the suggestion of a pre-synaptic

interaction of large and small fibres. Several workers found that stimulating C fibres produced primary afferent depolarization of myelinated fibres, suggesting inhibition of the gate (Franz & Iggo 1968; Zimmerman 1968; Janig & Zimmerman 1971). The theory had predicted activation.

Other researchers, however, observed primary afferent hyperpolarization, which was the predicted activation of the gate (Mendell & Wall 1964; Dawson et al. 1970; Hodge 1972; Mendell 1972).

The pathology in Frederich's Ataxia includes a selective loss of large diameter fibres, but pain has not been a typical symptom (Dyck et al. 1976). Gate control would predict that pain would result from such a fibre loss. The latter group also noted that in some syndromes in which pain is one symptom selective decreases of A-delta and C fibres occur. Thus, interactions in the spinal cord must be more complex than the gate control theory suggests.

Kerr (1975a) has proposed a similar theory based upon interactions of large and small diameter afferent input to marginal (lamina I) neurons. The marginal neuron, in this theory, is regarded as the cell that responds to nociceptive input from small fibres. Large diameter input activates substantia gelatinosa cells which in turn inhibit the marginal cells. Thus, the interaction of small and large fibres is suggested to be via post-synaptic effects.

Other theories

There are two current chemical theories. Lim and Guzman (1968) have suggested that pain is the chemosensation of the body. They have noted that many chemically unrelated substances cause pain. Lindahl has suggested that pH is the prime determinant of pain. In one paper Lindahl (1974) noted that as a site of injury becomes more acidic it concomitantly becomes

painful. He cited such examples: bicarbonate ameliorates pain of gastric ulcer, injection of alkaline into painful acidic septic abscesses relieves pain, and the pH of painless tuberculosis abscesses is neutral. Both theories seem to regard the nervous system as irrelevant. In fact, their theories may be regarded as specificity in a new guise: activate the peripheral chemoreceptor and pain results. Both theories are unusual in their focus, but their gross disregard of much information suggests that they are untenable.

Summary

In summarizing the pain section, several points are notable:

1) Pain has a diffuse distribution: that is, many tracts in the cord transmit pain information, and many cells in the neuraxis are responsive to pain;

2) Nonetheless, few sites are seen as being specific to pain;

3) The sensation of pain is difficult if not impossible to separate from the responses it elicits; and

4) Pain responses are generally non-specific.

NARCOTICS AND ANALGESIA

Narcotic-induced analgesia has been extensively researched, but the mechanisms whereby narcotics alter pain sensation and/or responses have remained elusive. Questions that have received a great deal of attention are: which aspects of behavior do narcotics affect. What are the sites of drug action in the nervous system? Which neurochemical systems are involved and now are they affected?

Behavioral Effects

Beecher (1956c; 1959), as noted above, has argued that experimental pain in humans has little relationship to clinical pain because of the importance of the reaction component. He has also suggested that the human sensation threshold, the parameter measured most often in experimental studies, is not what is being affected by narcotics. Hardy et al. (1940) found that narcotic drug was effective in suppressing experimental pain if it had been administered prior to the pain. However, if the drug had been administered after the pain commenced, it was ineffective, Yet, patients given narcotic invariably have clinically significant pain preceding administration of the drug. Beecher reported on clinical cases of efficacious narcotic therapy in which pain thresholds were unaffected or even lowered. It follows, then, that narcotics are affecting the reaction component of pain.

Beecher in 1959 said, however, that "threshold changes in animals have been more dependable (in determining analgesic efficacy and potency) than corresponding effects in man." The difference is that animals can not differentiate their surroundings in terms of pain. Beecher assumed that animals are neither aware of the experimental nature of their pain nor "realize" that the pain is often self-limited by their responses. As mentioned previously, Kelly and Glusman (1976) found that cats were certainly aware of pain duration because they produced more escapes when pain was maintained for a longer period of time.

Beecher (1959) has pointed out that the ability of narcotic agonists to raise thresholds in several of the common (laboratory) tests using animals is predictive of clinical efficacy. It follows, then, that narcotics

either act upon sensation thresholds in animals which they do not seem to do in humans, or the sensation threshold in animals is much less independent of the reaction component than it is in humans.

Morphine has often been observed to either decrease the number of responses made to avoid or escape aversive stimuli (Maffii 1959; Cook & Catania 1964; Reynoldson & Bentley 1974) or to increase the frequency or amplitude of shocks received (Weiss & Laties 1964). In such studies morphine can be considered to be an analgesic. There is some doubt, however, if analgesic activity is in fact what is being measured. For example, rate of avoidance is stimulated by a low dose of morphine (Holtzman & Jewett 1971). The drug, if analgesic, would be expected to suppress avoidance. The dose response curve of morphine in the acquisition of avoidance is biphasic (Ageel et al. 1976). Conflicting reports have been published on the effects of narcotics on conditioned emotional suppression. Lauener (1963) found morphine to be ineffective in reversing shock-induced suppression of responding for water. Hill et al. (1954) showed that morphine will reverse this suppression.

McKearney (1968; 1969) and Byrd (1969) found that with appropriate training both monkeys and cats bar-pressed on a fixed-interval (FI) schedule for presentation of electric shock. The initial training consisted of shock avoidance in which the subject responded to postpone shock. The second phase of training consisted of the avoidance paradigm of the first phase coupled with either non-contingent shock or an FI schedule of shock presentation. The third phase consisted of shock upon the first response emitted by the subject after a certain time (an FI schedule). Responding in the third phase was found to have the same pattern of responding seen for food under an FI schedule (McKearney 1974).

When monkeys responding under such an FI schedule for shock received 0.3 mg/kg of morphine, rates of responding were increased (McKearney 1974). In a related study, monkeys whose responses simultaneously produced an increase in shock current and food presentation were given morphine. The drug had no effect on response rates except at high doses (Smith & McKearney 1977). Both of these studies showed that morphine is not necessarily an analgesic because in neither case was the amount of shock accepted by the subjects increased by the drug. In the McKearney (1974) study, the monkeys responded at a greater rate for shock delivery when given morphine.

These behavioral studies suggest that the effect of a narcotic drug depends to a great extent upon its interaction with the behavior being measured. That is, as was suggested above, morphine is not an analgesic in itself. Operationally it can be considered to be an analgesic in most situations because it increases the relative toleration of noxious stimuli. However, when a previously noxious stimulus is no longer aversive (that is, it becomes a positive reinforcer (McKearney 1974)), morphine increases the rate of responding. It follows, then, that morphine is not an analgesic in a situation in which the stimulus is not aversive (although it is to the observer).

Anatomical Sites

Several techniques have been employed to examine the CNS for possible sites of narcotic-induced analgesia. Induction of analgesia after local injection is determined with appropriate tests. After either systemic or local injection of narcotic, the effects of the drug on noxious-stimuli induced firing of neurons in a site are determined. The specificity of

the narcotic-induced changes are determined by the administration of naloxone. If naloxone reverses the morphine effect, it is assumed that the effect is opiate specific.

Action on nerve fibres

There are several studies of morphine's effects on nerves, but the data are in conflict. Jurna and Grossmann (1977) employed both in vivo and in vitro nerve preparations. They found that systemic administration of 2 mg/kg of morphine induced greater activity in A-beta fibres while it induced a depression of activity in A-delta and C fibres of cat sural nerve in situ. Naloxone reversed the morphine effects. In vitro studies, using morphine concentrations of 5×10^{-5} M (molar), 1×10^{-4} M, and 5×10^{-4} M, indicated that morphine's effects on such parameters as resting membrane potential, after hyperpolarization, refractory period, and amplitude of the compound action potential varied with the type of nerve examined. Thus, the drug had no effect on any of these parameters in guinea pig phrenic nerve. Morphine induced an increase in the amplitude of the after hyperpolarization in the cat sural nerve, and a decrease in this latter amplitude in the rabbit vagus nerve.

Kosterlitz and Wallis (1964) found that 3 mg/kg of morphine had no effect on firing rate of cat hypogastric nerve and nerve to the medial muscle of the cat nictitating membrane in situ. Morphine at a concentration of about 3.5×10^{-3} M had no effect on nerve parameters of either rabbit vagus nerve or cat hypogastric nerve in vitro.

Spinal cord

Narcotics have profound effects upon the spinal cord. Not only does morphine and other agonists depress spinally mediated reflexes, but these

drugs do so selectively. That is, narcotics depress nociceptive reflexes such as the crossed extensor without affecting stretch reflexes (Wikler 1944; Wikler & Frank 1948; Houde et al. 1951; Martin et al. 1964) in preparations in which the spinal cord had been severed from the brain. In other studies, however, morphine was found to depress monosynaptic reflexes (Krivoy et al. 1973; Goldfarb & Hu 1976).

Evidence for a spinal site of action of narcotic analgesia has come from the work of Yaksh and Rudy (1976; 1977). Injections of narcotic in the spinal subarachnoid space raised thresholds in four analgesic tests. The block of nociceptive responses was not mimicked by the local anaesthetic dibucaine.

Dorsal horn

As discussed previously, certain cells in the spinal cord respond selectively to noxious input: laminae I and V cells in the dorsal horn. Systematic administration of morphine depressed both spontaneous and noxious-stimuli induced activity in laminae I and V but not in laminae IV and VI (Kitahata et al. 1974; LeBars et al. 1975; Zieglgansberger & Bayerl 1976) and suppressed spontaneous activity in lamina VII (Toyooka et al. 1976). The selective depression of only those cells responding to noxious input suggests that these dorsal horn loci are sites in which morphine induces analgesia.

However, direct application of morphine to lamina V cells, by microiontophoresis, has not always resulted in depression of activity induced by noxious stimulation. Whereas several groups found suppression when morphine was microiontophoretically applied to lamina V (Calvillo et al. 1974; Dostrovsky & Pomeranz 1976), one group found morphine did not affect

lamina V activity (Duggan et al. 1976). They (Duggan et al. 1976) did find that microiontophoresis of morphine in the SG depressed lamina V activity, an effect reversed by naloxone. The discrepancy between these results is not easily explained, but the study by Duggan suggests that morphine may be influencing lamina V cells transynaptically.

Whereas Duggan et al. (1976) found their effects in spinal cats subjected to heat another group found that morphine had no effect on bradykinin-induced activity in dorsal horn (Piercey & Hollister 1977). Piercey and Hollister suggested that the reason they failed to show a morphine effect was due to the spinalization. That is, morphine-induced analgesia is mediated by descending input to the dorsal horn and not by direct effects of the drug upon dorsal horn cells.

The contention that morphine-induced analgesia is mediated at supraspinal levels is supported by experiments in which lesions were placed in the descending dorsolateral tracts. Such lesions suppressed morphine-induced analgesia (Price et al. 1976; Basbaum et al. 1977). Opposite results were also reported. LeBars et al. (1975) found morphine depressed dorsal horn firing induced by bradykinin in decerebrate cats only after spinalization was performed. Similarly, Jurna and Grossmann (1976) found morphine's potency in decreasing ventrolateral tract firing rate induced by stimulation of A-delta and C fibres was enhanced by spinalization.

These opposite results may be explained as a dose effect. Lamina V activity induced by bradykinin was suppressed by morphine in both spinal and intact rabbits. The spinal preparations required higher doses (Takagi et al. 1976).

Direct and indirect (via descending tracts) spinal actions of morphine can be seen to contribute to its induction of analgesia.

Ventral horn

Narcotic agonists have effects on ventral horn neurons although what role these effects have in induction of analgesia is not clear. Morphine, levorphanol, dextrorphan, and naloxone all had no effect on either the resting membrane potential or the conductance of alpha-motoneurons (Kuschinsky et al. 1977). Kuschinsky et al. (1977) showed that morphine enhanced motoneuron discharge. This effect of morphine was abolished by spinalization. Iontophoresis of morphine induced increased firing in Renshaw cells (Davies & Duggan 1974; Davies 1976; Davies & Dray 1976). Naloxone reversed the morphine effect (Davies 1976).

Lower brainstem

Injection of narcotic into the fourth ventricle has induced analgesia (Teschemacher et al. 1973; Dey & Feldberg 1975). These findings indicate that the site(s) of action was most likely to be in the lower brainstem. Sites which have been extensively investigated include: NRGC, raphe nuclei, and PAG.

NRGC

Stimulation-induced firing of NRGC cells was depressed by systemic administration of morphine (Sun & Gatipon 1976). The depression was reversed by naloxone. Microinjection of morphine in the NRGC also induced analgesia (Takagi et al. 1977). This group also found that microinjection of morphine in either the NRM or PAG induced analgesia. However, they found that a lower dose of morphine was required for induction of analgesia in NRGC. They suggested that this dose effect differentiates these sites as to their relative importance in the induction of analgesia. Micro-iontophoresis of morphine in the NRGC produced both excitation and inhibition

of cells although naloxone reversed only the inhibitory effect (Bradley & Bramwell 1977). In what way these effects of morphine influence the sensation of and response to pain has not been elucidated.

Raphe nuclei

Because both the dorsal raphe and nucleus raphe magnus (NRM) were found to be sites of SPA (see above), these nuclei as well as other raphe nuclei have been investigated as possible sites of action of morphine-induced analgesia. The assumption for these studies is that morphine-induced analgesia and SPA have common mechanisms.

Axons of cells in the NRM descend in the dorsolateral funiculus. Activation of these axons induced inhibition of dorsal horn cells responsive to nociceptive input in rats (Basbaum et al. 1976). The NRM is a site of SPA in cats (Oliveras et al. 1975; 1977). The SPA induced in the NRM was blocked both by dorsolateral funiculus lesions (Basbaum et al. 1977) and naloxone (Oliveras et al. 1975). The latter blockade suggests opiate mediation of SPA.

Morphine, systemically administered, excited cells in the NRM (Anderson et al. 1977). Lesions of the nucleus (Proudfit & Anderson 1975) and of the dorsolateral funiculus (Basbaum et al. 1976) blocked analgesia induced by morphine, although Basbaum et al. (1976) found that 20 or 25 mg/kg of morphine administered intraperitoneally to rats reversed the effects of the lesion.

These results suggest that morphine activates cells in the NRM, although if this is a direct action is not known. This activation induces inhibition of cells in the dorsal horn. These effects demonstrate that analgesia induced by morphine is due in part to a descending effect mediated by the NRM. Because larger doses of morphine induced analgesia after

destruction of the NRM other sites are either involved independently in morphine action, or the NRM is one link in a multiply-connected chain mediating analgesia. Morphine, in either case, has multiple sites of action (see the discussion of the spinal cord above).

The mesencephalic raphe nuclei have quite extensive output, particularly ascending axons. In the cat (Bobillier et al. 1976) and rat (Conrad et al. 1974) these nuclei send axons to sites in the telencephalon, diencephalon, and pontine reticular formation. The dorsal raphe in the cat receives many afferents including ascending fibres from caudal raphe nuclei (Sakai et al. 1977). Because these connections were found to be so extensive and diffuse, conflicting results derived from lesion studies are not surprising.

Microinjection of morphine into the dorsal raphe of rats produced analgesia as measured by hot plate (Sharpe et al. 1974) or tail flick (Malick & Goldstein 1976). Stimulation of the dorsal raphe of rats was found to add to a subanalgesic dose of morphine to induce analgesia as measured by tail shock or hot plate (Samanin & Valzelli 1971). These studies taken together suggest that morphine acts within the dorsal raphe. However, both systemic (including 12 mg/kg) and microiontophoretic administration of morphine to rats had no effect on spontaneous firing rates in the dorsal raphe (Korf et al. 1974; Haigler 1976). Haigler (1976) found that less than 10 percent of dorsal raphe cells he sampled changed their firing rates in response to noxious stimulation (pressure applied to the foot). These studies, then, are quite confusing because although microinjection of morphine induced analgesia, no effect of morphine on

cell firing was found. Furthermore, stimulation of the dorsal raphe added to morphine analgesia. These results may be explained at least in part by analgesic test differences, thereby suggesting that the dorsal raphe mediates only certain forms of response to, or certain modalities of pain.

Lesion studies are just as confusing. Lesions of the median raphe were reported to antagonize morphine-induced analgesia in rats (Samanin et al. 1970; Adler et al. 1975; Chance et al. 1978). These lesions, however, were observed by other groups to have no effect on morphine-induced analgesia in rats (Blasig et al. 1973; Lorens & Yunger 1974). Dorsal raphe lesions were reported to block morphine-induced analgesia (Sasa et al. 1977), or to have no effect (Adler et al. 1975). Two laboratories reported that simultaneous lesions of the dorsal and median raphe decreased morphine-induced analgesia in rats (Garau et al. 1975; Yaksh et al. 1977). Buxbaum et al. (1973) found that a simultaneous lesion of the dorsal and median raphe was without effect on morphine. York and Maynert (1978) also induced simultaneous lesions of these two nuclei in rats. They observed that the lesion had no effect on morphine-induced analgesia when the tail flick test was employed but did antagonize morphine when the squeal test (electrical stimulation of the trigeminal nerve) was used.

Finally, Yaksh et al.(1977) found that simultaneous lesions of the dorsal and median raphe, or simultaneous lesions of the dorsal, median, and ventral raphe, antagonized morphine-induced analgesia. However, they found that this antagonism was surmountable by increasing the morphine dose.

PAG

Microinjection of narcotic into the PAG produced analgesia in monkeys (Pert & Yaksh 1974; 1975), mice (Criswell 1976), and rats (Bennett et al.

1975; Yaksh et al. 1976a; Lewis & Gebhart 1977). Naloxone blocked analgesia induced by microinjection of morphine in the PAG, suggesting an opiate specific effect (Pert & Walter 1976). Jacquet and Lajtha (1975) reported cross-tolerance between systemic and PAG-administered morphine. Systemic morphine blocked evoked activity in the central grey, and this effect was also antagonized by naloxone (Palmer & Klemm 1977).

Several studies have suggested that analgesia induced by morphine microinjected in the PAG is mediated by descending output. This descending output probably synapses in the raphe nuclei, as it does in the cat (Hamilton 1973). Lesions of the dorsolateral funiculus abolished analgesia that was induced by microinjection of morphine in the PAG (Murfin et al. 1976). Microinjection of morphine in the PAG blocked dorsal horn responses to noxious stimuli (Bennett & Mayer 1976). These two studies suggest that the PAG activates descending inhibition, via the raphe nuclei, of dorsal horn cells specifically responsive to nociceptive information.

As the PAG is a site of SPA, some workers have suggested that PAG SPA and narcotic-induced analgesia have a common mechanism. Thus, rats made tolerant to morphine were subsequently tolerant to SPA although rats tolerant to SPA were not tolerant to 4 mg/kg of morphine (Mayer & Hayes 1975). Mayer and Murfin (1976) found cross-tolerance between SPA and morphine microinjection in the PAG no matter which treatment was given first. If opiate receptors and endogenous opiate-like substances (see below) mediate SPA, then SPA should be antagonized, as is morphine-induced analgesia, by naloxone. However, results of such tests are conflicting. Yaksh et al. (1976c) and Pert and Walter (1975) found that naloxone, administered to rats, did not reverse PAG SPA. Akil et al. (1976) using

rats and Adams (1976) in studying humans found that naloxone did reverse SPA. The studies using rats found opposing results. This difference can not be explained because species, analgesic test, and dose of naloxone were the same in the Akil et al. (1976) and Yaksh et al. (1976c) studies.

Substantia nigra

Price and Fibiger (1975) bilaterally lesioned the substantia nigra of rats by injections of 6-hydroxydopamine. They found that this treatment prevented analgesia induced by 2 mg/kg of morphine. They did not, however, determine if this prevention was surmountable by higher doses of morphine.

Grossmann et al. (1973) also bilaterally lesioned the substantia nigra of rats with an injection of 6-hydroxydopamine. They found that the lesion itself enhanced tail flick latencies. Grossman et al. (1973) found that the lesioned rats when given 2 mg/kg of morphine had tail flick latencies that were the same as non-drug treated sham-operated controls. This finding can be considered to demonstrate morphine-induced hyperalgesia.

Thalamus

Although several thalamic loci have been implicated in pain pathways, there are few studies of morphine's effects on these sites. Most posterior thalamic units (80 percent) responding to electric stimulation of tooth pulp were inhibited by 20 mg/kg of morphine while 36 percent of VPL cells were inhibited (Shigenaga & Inoki 1976a). Morphine also depressed potentials evoked in the parafascicular-centrum medianum complex by sciatic stimulation in rats (Gildenberg et al. 1976). However, iontophoresis of either morphine or naloxone reduced stimulation-induced firing of medial

thalamic cells of cats, suggesting a non-specific effect. Furthermore, intravenous morphine had no effect on those cells (Duggan & Hall 1977). Large lesions in the medial thalamus of rats potentiated morphine analgesia (Yeung et al. 1975; Yaksh et al. 1977). Because the studies of medial thalamus used different species, they are only suggestive of further work.

Amygdala and basal ganglia

Several structures in the telencephalon and diencephalon have high concentrations of opiate receptors (see below): the amygdala and basal ganglia. Nonetheless, such sites are not necessarily sites of morphine-induced analgesia. It may be that these receptors mediate other functions. Morphine, given systemically increased firing of some cells in the baso-lateral amygdala of cats, an effect partially antagonized by naloxone (Chou & Wang 1977). Rodgers (1977) found increased jump thresholds upon microinjection of morphine in the corticomedial amygdala of rats. Yaksh et al. (1976a) found no effect in this part of the amygdala although the dose used was lower than that used by Rodgers.

The basal ganglia are also loci which contain high concentrations of opiate receptors (see below). Microinjection of morphine into the caudate and globus pallidus did not induce analgesia although injections in the nucleus accumbens did (Dill & Costa 1977). Lesions of the caudate have had varied effects on morphine-induced analgesia (Nakamura et al. 1973; Yeung et al. 1975). This may have been due to the different lesion techniques employed. Morphine suppressed 30 percent of cells in this nucleus, and naloxone reversed this deactivation (Lee et al. 1977).

Thus there is no overwhelming evidence that morphine induction of analgesia is necessarily related to a site having a high concentration of

opiate receptors.

Cortex

Since the effects of noxious stimulation on many telencephalic structures are unknown, it is difficult to evaluate the contribution of cortical effects of narcotic to induction of analgesia. Microiontophoresis of morphine on somatosensory cortex cells induced depression at low ejection currents but induced excitation at high currents. The depressive effect was reversed by naloxone (Satoh et al. 1976). Both ipsilateral and contralateral evoked potentials in SII and contralateral potentials in SI induced by tooth pulp stimulation of rats were suppressed by morphine. One component in the ipsilateral evoked potential was augmented by morphine (Shigenaga & Inoki 1976b). The physiological significance of the alteration induced by morphine of evoked potentials has not been determined.

Summary

The literature dealing with sites of narcotic-induced analgesia presents a crazyquilt of data. There is quite good evidence implicating some sites: dorsal horn of the spinal cord, NRM, NRGC, and PAG. Some other sites have been implicated, but the data is often conflicting: mesencephalic raphe nuclei and medial thalamus. Other sites have been investigated, and the resulting data are quite inconsistent.

Neurochemical Mechanisms

Introduction

There are two types of experiments on the neurochemistry of narcotic-induced analgesia. The first entails the administration of drugs that have known effects on purported neurotransmitter systems in the CNS. That

is, both agonists and antagonists of acetylcholine, dopamine, norepinephrine, serotonin, as well as other substances, are screened for induction of analgesia and for interaction with morphine-induced analgesia. The second type of experiment is the determination of narcotic effects on the neurochemistry of these purported transmitter systems. Levels, turnover, synthesis, and metabolism are determined after administration of narcotic. The assumption underlying these experiments is that if morphine induces some change in a neurochemical system at an analgesic dose, then there is a possibility that this system is mediating narcotic-induced analgesia.

Most studies that have indicated neurochemical changes have used doses of morphine in excess of usual analgesic doses. Minimum effective analgesic doses of morphine in rats are usually in the range of 2.5 to 5 mg/kg in a variety of procedures (Woolfe & MacDonald 1944; Winter & Flataker 1950; Evans 1961; Weiss & Laties 1961; Sewell & Spencer 1976). The dose at which 50 percent of mice reach analgesic criterion was 3.63 mg/kg for tail flick (Bloom et al. 1976) and 2.52 mg/kg in the hot plate (Eddy & Leimbach 1953). Because these studies often did not find neurochemical changes at low doses of morphine, it must be concluded that most of these changes are not specific to analgesia induced by narcotic.

This section will review the neurochemical literature, and will discuss opiate-like and other central peptides.

Altering levels of brain amines

Drugs such as reserpine, tetrabenazine, 6-hydroxydopamine (6HDA), and alphamethyl-para-tyrosine (AMPT) decrease amine levels in the brain. Monoamine oxidase inhibitors (MAOIs) increase brain amine levels. Morphine-induced analgesia is determined after pretreatment with one of these drugs.

Because each drug alters the levels of more than one amine, inconsistent results are not unexpected.

The effects of reserpine pretreatment on subsequent morphine-induced analgesia depend upon pretreatment time and analgesic test. In general, reserpine antagonized morphine-induced analgesia in mice (Schneider 1954; Sigg et al. 1958; Rudzik & Mennear 1965; Dewey et al. 1970; Fennessy & Lee 1970; Pleuvry & Tobias 1971). In one test reserpine had no effect on pain thresholds in mice (Dewey et al. 1970) and in others, reserpine potentiated morphine-induced analgesia (Garcia Leme & Roche e Silva 1954; Sparkes & Spencer 1971).

Tetrabenazine, like reserpine depletes the brain of dopamine, norepinephrine and serotonin (Dewey et al. 1970; Akil & Liebeskind 1975). Pretreatment with this drug antagonized morphine-induced analgesia in mice (Takagi et al. 1964; Takagi & Nakama 1968; Dewey et al. 1970).

Data from 6HDA studies are also quite inconsistent. Injections sites, pretreatment time, and analgesic test vary from study to study. Additionally, although the drug is usually thought to decrease brain levels of only dopamine and norepinephrine (Samanin & Bernasconi 1972; Blasig et al. 1973; York & Maynert 1978), there are reports at variance with these findings (Nakamura et al. 1973b; Navarro 1976). The pretreatment often induced changes in baseline responses to the analgesic test (Blasig et al. 1973; Navarro 1976; York & Maynert 1978). Morphine-induced analgesia was antagonized by 6HDA pretreatment (Ayhan 1972; Nakamura et al. 1973a; Navarro 1976), potentiated (Samanin & Bernasconi 1972; Nakamura et al. 1973b), or unaffected (York & Maynert 1978).

AMPT, which reduces brain norepinephrine and dopamine in rats

(Sorenson 1975) and mice (Porter et al. 1966), antagonized (Gorlitz & Frey 1972; Reinnold et al. 1973), enhanced (Major & Pleuvry 1971; Pleuvry & Tobias 1971), or had no effect (Dewey et al. 1970; Fennessy & Lee 1970) on morphine-induced analgesia in rats and mice.

Dewey et al. (1970) found that upon administration of the MAOI tranylcypromine to mice, morphine-induced analgesia was increased. However, they found that another MAOI, pargyline (50 mg/kg) had no effect. Iwamoto et al. (1976b) showed that 75 mg/kg of pargyline did enhance morphine-induced analgesia in mice. Another MAOI, iproniazid, enhanced morphine-induced analgesia in mice only if it were preceded by administration of AMPT (Major & Pleuvry 1971).

Norepinephrine

Norepinephrine did not induce analgesia after intraventricular injection in the rat (Sparkes & Spencer 1971; Sewell & Spencer 1976). Norepinephrine, 0.5 mg/kg, as well as other agonists, induced analgesia in mice upon systemic administration (Heller et al. 1968; Major & Pleuvry 1971). Intraventricularly injected norepinephrine antagonized morphine-induced analgesia (Sparkes & Spencer 1971; Sewell & Spencer 1976), but systemically administered agonists had no effect on morphine-induced analgesia (Major & Pleuvry 1971). Amphetamine either enhanced or had no effect on morphine-induced analgesia depending on the dose of amphetamine and analgesic test employed. In the mouse tail flick test, 25 mg/kg of amphetamine but not 6.25 mg/kg enhanced morphine-induced analgesia.

Alpha-blockade produced by systemic administration of either phentolamine or phenoxybenzamine potentiated (Elliott et al. 1976; Spiehler &

Randall 1978) or did not alter (Fennessy & Lee 1970; Van derWende & Spoerlein 1973; Takemori et al. 1975; Tulunay et al. 1976) morphine-induced analgesia. The difference in results can not be explained by difference in drug, dose, pretreatment time, or analgesic test. Phenoxybenzamine potentiated analgesia induced by 5 mg/kg of morphine (Dahlstrom et al. 1975).

Systemic administration of some beta blockers, i.e. propranolol and pronethalol, but not others induced analgesia in mice (Shah et al. 1974). In general beta blockers, injected systemically, were reported to have no effect on morphine-induced analgesia in mice (Fennessy & Lee 1970; Cowan & MacFarlane 1975; Takemori et al. 1975; Tulunay et al. 1976) and in rats (Cowan & MacFarlane 1975). For data indicating a blocking effect, see Heller et al. (1968) and Shah et al. (1974).

Narcotic agonists were shown to affect norepinephrine levels in the brain. However, the dose required to demonstrate an effect on these levels was much greater than a usual analgesic dose. Simon et al. (1975) gave doses of from 5 to 20 mg/kg of morphine to rats but found no alteration of norepinephrine levels in amygdala, cortex, hypothalamus, mid-brain, septum, and striatum. Five mg/kg of morphine is quite potent in inducing analgesia in most paradigms. Those studies that did find narcotic-induced effects on norepinephrine levels used high doses (Holtzman 1974; Johnson et al. 1974). These doses can be expected to induce non-specific effects. In fact, both 10 mg/kg of naloxone and 60 mg/kg of morphine decreased mid-brain norepinephrine (Holtzman 1974). Because the antagonist and agonist have induced the same effect, this effect must be non-specific. Because

analgesia induced by morphine is reversed by naloxone, it follows that level of norepinephrine is not a factor in narcotic-induced analgesia.

Additional determinations of narcotic effects on norepinephrine biochemistry also used large doses. Various narcotics were found to increase norepinephrine synthesis in mouse brain (Bloom et al. 1976). Sugrue (1973) found that 20 mg/kg of morphine had no effect on turnover in the hypothalamus. Decreasing norepinephrine levels by blocking dopamine beta-hydroxylase either depressed morphine-induced analgesia in mice (Major & Pleuvry 1971) and rats (Reinhold et al. 1973) or potentiated it (Watanabe et al. 1969).

Dopamine

Systemic administration of dopaminergic agonists to rats induced analgesia in only one type of pain test. The foot pressure threshold was increased by administration of 300 mg/kg of l-dopa (Sparkes & Spencer 1971) and by 10 mg/kg of apomorphine (Dunai-Kovacs & Szekely 1977). In other pain tests, apomorphine was inactive (Dunai-Kovacs & Szekely 1977). Intraventricular administration of dopa in rats resulted in induction of analgesia in the foot pressure test (Sparkes & Spencer 1971) but not in a vocalization test (Reinhold et al. 1973).

Injection of dopamine into the rat cortico-medial amygdala produced hyperalgesia (Rodgers 1977). Injection of dopamine in the rat caudate-putamen elevated response thresholds (Rodgers 1977). Systemic administration of dopaminergic agonists to mice usually induced hyperalgesia (Major & Pleuvry 1971; Tulunay & Takemori 1974; Tulunay et al. 1975).

Dopaminergic agonists antagonized morphine-induced analgesia when given to mice (Major & Pleuvry 1971; Tulunay & Takemori 1974; Tulunay et al. 1976; Van derWende & Spoerlein 1972; 1973) and to rats (Sparkes & Spencer

1971). However, morphine-induced analgesia in rats was potentiated in 5 analgesic tests after systemic administration (Dunai-Kovacs & Szekely 1977), or was unaffected upon intraventricular administration (Reinhold et al. 1973).

Dopaminergic antagonists usually were without effect on nociception (Eidelberg & Erspamer 1975; Tulunay et al. 1975). Additionally, these drugs potentiated morphine analgesia in a variety of pain tests (Van derWende & Spoerlein 1973; Tulunay & Takemori 1974; Dahlstrom et al. 1975; Eidelberg & Erspamer 1975; Tulunay et al. 1976).

Although morphine has been reported to increase (Gauchy et al. 1973; Simon et al. 1975; Bloom et al. 1976), decrease (Johnson et al. 1974), or have no effect (Sasame et al. 1972; Kuschinsky 1973; Sugrue 1973; Puri & Lal 1974) on rat striatal dopamine levels, the consensus has been that the drug increases striatal dopamine turnover (Sasame et al. 1972; Sugrue 1973; Puri & Lal 1974; Johnson et al. 1974; Costa et al. 1975; Lal et al. 1976). In general these effects required large doses. Presumably, lower doses had no effect. Doses of about 7 to 14 mg/kg administered to rats enhanced striatal turnover (Carenzi et al. 1975); these doses are more within the range of analgesic doses. Morphine also was found to increase dopamine synthesis and metabolism in the rodent brain, and these results support the contention of enhanced turnover.

Morphine induced increased dopamine synthesis in rat striatum (Clouet & Ratner 1970; Gauchy et al. 1973; Carenzi et al. 1975). Increased levels of homovanillic acid, a metabolite of dopamine, were found after morphine administration to rats (Kuschinsky & Hornykiewicz 1972; 1974; Ahtee &

Kaajaninen 1973; Lal et al. 1976; Westerink & Korf 1976) and to mice (Fukui & Takagi 1972; Kuschinsky & Hornykiewicz 1974).

Additionally, morphine had no effect on the ability of rat striatal slices to take up dopamine, but morphine did block potassium-stimulated release of dopamine by these slices (Celsen & Kuschinsky 1974).

Cyclic AMP

One group of dopamine receptors is believed to be closely associated with a dopamine-sensitive adenylate cyclase, which generates cyclic adenosine monophosphate (cAMP) upon its activation (see Clouet & Iwatsubo 1976). Some workers found morphine increased striatal cAMP (Bonnet 1975; Clouet et al. 1975; Puri et al. 1976; Von Voigtlander & Losey 1977), but others found cAMP levels to be unaffected (Singhal et al. 1973; Carenzi et al. 1975). Havemann and Kuschinsky (1978) found morphine lowered striatal cAMP in vitro.

Dopamine-sensitive adenyl cyclase

Morphine was reported to have no effect on rat or mouse adenyl cyclase activity in vitro (Carenzi et al. 1975; Clouet et al. 1975; Naito & Kuriyama 1973). Lal et al. (1976) and Puri et al. (1975) found morphine enhanced adenyl cyclase activity in vitro.

In vivo administration of morphine enhanced adenyl cyclase activity (Clouet et al. 1975; Puri et al. 1975). Morphine had no effect on activation of rat striatal dopamine-sensitive adenyl cyclase by dopamine (Carenzi et al. 1975; Iwatsubo & Clouet 1975; Puri et al. 1976). Wilkening et al. (1976) prepared homogenates of Macaca mulatta amygdala which contained dopamine-sensitive adenyl cyclase. The activation of this enzyme

by sodium fluoride or dopamine was blocked by morphine.

The doses of morphine required to induce changes in cAMP levels and adenyl cyclase activity were usually much larger than the doses required to induce analgesia. As large doses were also required, in general, to induce changes in dopamine levels, turnover, and metabolism, the evidence for a link between morphine-induced analgesia and dopaminergic neurotransmission is lacking.

Serotonin

Serotonin is of interest to the study of analgesia because the raphe nuclei are serotoninergic, and, as mentioned above, some laboratories found that lesions of these nuclei attenuated morphine-induced analgesia. Depletion of serotonin with para-chloro-phenylalanine (PCPA) decreased morphine-induced analgesia in both mice and rats (Tenen 1968; Fennessy & Lee 1970; Major & Pleuvry 1971; Pleuvry & Tobias 1971; Gorlitz & Frey 1972; Vogt 1974; Takemori et al. 1975; Tulunay et al. 1976). Some workers, however, found that PCPA pretreatment did not alter morphine's effect (Altenburg & Kuschinsky 1971; Muruyama et al. 1971; Buxbaum et al. 1973; Reinhold et al. 1973).

Systemic administration of serotonin or one of its precursors, either 5-hydroxytryptophan or tryptophan, to mice and rats enhanced (Major & Pleuvry 1971; Pleuvry & Tobias 1971; Takemori et al. 1975; Tulunay et al. 1976); had no effect (Reinhold et al. 1973); or decreased (Ho et al. 1975) morphine-induced analgesia. Serotonin, administered intraventricularly to

mice, enhanced morphine-induced analgesia (Sparkes & Spencer 1971; Sewell & Spencer 1976). Methysergide 5 mg/kg, which blocks serotonin receptors, was without effect on morphine-elicited analgesia (Fennessy & Lee 1970). Fluoxetine, which blocks the reuptake of serotonin (Wong et al. 1974) enhanced analgesia induced by morphine but not analgesia induced by methadone and meperidine (Sugrue & McIndewar 1976).

There are many studies that examined the effects of morphine on serotonin levels and metabolism in the brain. Large doses of narcotic were usually necessary to induce a measurable effect. Nonetheless, the data were often inconsistent.

Brain levels of serotonin were unaltered by morphine (Shen et al. 1970; Gorlitz & Frey 1972; Goodlet & Sugrue 1974; Simon et al. 1975). Turnover was usually increased by morphine in both rat and mouse brains (Haubrich & Blake 1973; Yarbrough et al. 1972; 1973; 1974; Goodlet & Sugrue 1974; Perez-Cruet et al. 1975; Sawa & Oak 1976). Way's group, however, found that morphine had no effect on serotonin turnover in mouse brain (Way et al. 1968; Loh et al. 1969; Shen et al. 1970). Most studies indicated that morphine caused increased levels of 5-hydroxy-indoleacetic acid, the chief metabolite of serotonin, in brains of rats and mice (Haubrich & Blake 1973; Yarbrough et al. 1973; Goodlet & Sugrue 1974; Perez-Cruet et al. 1975; Sawa & Oka 1976).

Almost all of the aforementioned changes induced by morphine required the administration of at least 10 mg/kg of morphine. Sawa & Oka (1976),

however, found that 2.5 mg/kg of morphine produced higher levels of 5-hydroxyindoleacetic acid. Their study was incomplete because the metabolite was only determined 1 hour after the injection of morphine. To establish a causal link between morphine-induced analgesia and serotonin metabolism requires that a comparison of the time courses of both analgesia induced by narcotic and changes in serotonin metabolism be determined.

Two other narcotic agonists were investigated for their effects on serotonin turnover. Methadone had no effect on turnover in rats (Sasame et al. 1972; Goodlet & Sugrue 1974) but induced an increase in turnover in mice (Bowers & Kleber 1971). Goodlet and Sugrue reported that meperidine did not affect turnover in the rat. These results suggest two possibilities. First, narcotic-induced analgesia is not mediated by alterations in serotonin metabolism, at least in rats. It is possible, however, that this alteration of serotonin is causally related to induction of analgesia but only by certain drugs. That is, there are several ways in which a narcotic drug can induce analgesia.

Acetylcholine

Some workers reported that the muscarinic agonists oxotremorine pilocarpine, and arecoline, and the anticholinesterase agent physostigmine induced analgesia. Oxotremorine induced analgesia in a variety of tests in the mouse (Harris et al. 1969; Howes et al. 1969; Metys et al. 1969; Pleuvry & Tobias 1971) and in the rat (Metys et al. 1969). The doses used, 0.01 to 0.2 mg/kg, did not cause peripheral cholinergic effects (Metys et al. 1969). Pilocarpine, 100 mg/kg, increased jump thresholds in rats tested in the flinch jump paradigm (Kaakola & Ahtee 1977). Arecoline, systemically administered to the rat and the mouse (Metys et al.

1969), induced analgesia in several tests. Neither of the latter drugs had any effect on monkeys in the shock titration paradigm (Pert 1975).

Physostigmine also induced analgesia in mice as measured by several tests (Harris et al. 1969; Howes et al. 1969; Pleuvry & Tobias 1969). These studies employed doses, 0.1 to 0.5 mg/kg, which did not cause tremors or other side effects (Pleuvry & Tobias 1971).

Neostigmine, which is also an anticholinesterase, is a quaternary compound. It does not cross the blood-brain barrier. Upon systemic administration it had no effects on the reaction time of mice in the hot plate test, even at a dose, 0.4 mg/kg, that induced salivation and diarrhea (Pleuvry & Tobias 1971). It had no effect on shock titration behavior of monkeys (Pert 1975). When neostigmine was administered intraventricularly to mice, it did induce analgesia (Pedigo et al. 1975). These findings suggest that the analgesia induced by cholinergic agonists in mice depends upon a central, not a peripheral, action.

Although Pert (1975) found no effects of cholinergic agonists on shock titration behavior of monkeys, he did find that the muscarinic antagonist scopolamine, at doses of 0.05 to 0.25 mg/kg, increased the threshold. Kaakola and Ahtee (1977) found that scopolamine had no effect on jump thresholds of rats. Pert's findings suggest that the neurochemistry of pain in the monkey is different from that in the mouse.

There are two approaches to determine if analgesia induced by cholinergic agonists is pharmacologically similar to that induced by morphine. The first entails examining if analgesia induced by cholinergic agonists is mediated by opiate receptors. If it is so mediated, then naloxone

should reverse the effect. On this question, the findings suggest that naloxone's efficacy depends upon the test paradigm, at least in mice. In the tail flick, analgesia induced by physostigmine (Howes et al. 1969) and oxotremorine (Harris et al. 1969) was reversed by naloxone. In the hot plate, however, naloxone did not reverse analgesia induced by either oxotremorine or physostigmine (Pleuvry & Tobias 1971). Support for opiate mediation of analgesia induced by physostigmine in the mouse tail flick comes from the finding that physostigmine lowered the ED_{50} of morphine.

A second approach entails attempts to reverse morphine-induced analgesics by administering cholinergic antagonists. In mice, 10 mg/kg of atropine increased the ED_{50} of morphine when tested in the tail flick (Takemori et al. 1975). In rats atropine had no effect on morphine-induced analgesia measured in two tests (Dahlstrom et al. 1975; Kaakola & Ahtee 1977).

When morphine was injected systemically into rodents, brain acetylcholine was increased (Richter & Goldstein 1970; Domino & Wilson 1973), an effect mimicked by levorphanol but not by dextrorphan (Richter & Goldstein 1970). Enhanced levels of acetylcholine in the hippocampus of rats and mice resulted from intraperitoneal injection of morphine (Green et al. 1976). However, very large doses were required to produce effects in both species. Morphine was also found by Green et al. (1976) to increase acetylcholine levels in the striatum of rats and mice but not in the cortex or hypothalamus. Naloxone and nalorphine did not affect brain acetylcholine (Domino & Wilson 1973). Morphine was reported to block acetylcholine release in cat brain (Beleslin & Polak 1965).

Turnover of acetylcholine varies with species, strain, and the brain sites examined. Morphine decreased cortical turnover in rats (Cheney et al. 1975; Costa et al. 1975). Limbic and hippocampal turnover of acetylcholine decreased or was unaffected by morphine depending on the mouse strain (Racagni et al. 1977). Costa et al. (1975) found that systemic morphine decreased acetylcholine turnover in the nucleus accumbens and parietal cortex but had no effect in the caudate of rats.

Gaba

Gaba has also been implicated by several studies. Increased brain levels of gaba resulted from amino-oxyacetic acid pretreatment, which antagonizes gaba-transaminase (Yoneda et al. 1976). This pretreatment prolonged morphine analgesia but did not enhance it (Yoneda et al. 1976). Ho et al. (1976), however, showed that this enzyme antagonist blocked morphine analgesia. Blockade of gaba receptors with bicuculline shortened the duration of action of morphine (Yoneda et al. 1976). Morphine did not alter brain gaba levels (Maynert et al. 1962).

Glutamate

One group has presented data suggesting a pain specific role for glutamate (Sherman & Gebhart 1975; 1976). In this study mice were subjected to restraint stress for 60 seconds or pain of 15 seconds on an aluminum plate maintained at 60 degrees centigrade. Glutamate and aspartate levels were determined in PAG, hypothalamus, cortex, and midbrain reticular formation. Stress increased aspartate in all four areas without affecting glutamate levels. Pain induced glutamate depletion in the PAG but not in the other sites. Morphine, administered prior to the pain, reversed the glutamate depletion; in fact, it increased it in the PAG, an

effect blocked by naloxone. Morphine had no effect on the altered aspartate levels due to restraint stress. No data were presented for 60 seconds on a hot plate or 15 seconds of restraint. It is possible that the different neurochemical effects of the two treatments resulted from the different times of exposure and not because the hot plate is specifically painful and restraint is specifically stressful. Other substances found in the CNS have been implicated in narcotic analgesia: cAMP (Ho et al. 1973), cyclic guanosine monophosphate (Biggio et al. 1977; O'Callaghan et al. 1978), and prostaglandins (Ehrenpreis et al. 1976; Bekemeier et al. 1977). Cations have been investigated by Way's group. Lanthanum and cerium were shown to induce analgesia in mice and rats; the lanthanum effect was antagonized by calcium and by naloxone (Harris et al. 1976). Calcium was reduced in the rat brain by morphine while the drug had no effect on sodium, potassium, or magnesium levels (Cardenas & Ross 1975). The calcium depletion was reversed by naloxone. Morphine-induced analgesia was inhibited by ventricular administration of calcium, magnesium, and manganese (Harris et al. 1975; Caruso & Takemori 1978). Ethylenebis (oxyethylenenitrilo) tetraacetate which chelates calcium enhanced morphine-induced analgesia (Harris et al. 1975).

CNS peptides

The role of central peptides in behavior has been under extensive investigation. Several CNS peptides are apparently agonists of morphine. In addition, ACTH was found to interact with morphine-induced analgesia.

ACTH and morphine

As noted previously, pain is rather difficult to distinguish from stress on any physiological, biochemical, or behavioral parameter, with

a few exceptions. One of the salient characteristics of the so-called stress response is enhanced release of ACTH. In one of Selye's earliest investigations (1936), he found that drugs, including morphine, are stressors. This result was confirmed: morphine caused enhanced release of ACTH and increased serum corticosterone (George & Way 1955; Nikodijevic & Maickel 1967; Kokka et al. 1973; Kokka & George 1974). The minimally effective dose varied from study to study (from 3.75 to 20 mg/kg in rats). Pentobarbital blocked this stimulant effect, and when pentobarbital and morphine preceded various stressors, the ACTH response was blocked (pentobarbital alone does not block ACTH release). (Briggs & Munson 1955; Ohler & Sevy 1956). The blockade was reversed by nalorphine (Burdette et al. 1961). Thus, when the stimulant effect of morphine was blocked, morphine depressed the release of ACTH. ACTH and several of its N-terminal peptide fragments blocked morphine analgesia (Gispen et al. 1975; 1976). That morphine inhibits pain responses but itself causes at least one feature of the stress response seems to suggest that its effects on pain and stress are separable.

Opiate receptors

The discovery of endogenous opiate-like substances followed the demonstration of stereospecific opiate receptors in vitro (Pert & Snyder 1973b; Simon et al. 1973) and in vivo (Pert & Snyder 1975). Opiate receptors are not homogeneously distributed in the CNS. In the spinal cord these receptors were found to be most prevalent in laminae I, II, and IV (LaMotte et al. 1976; Atweh & Kuhar 1977a). In the brain those areas that have high binding densities in monkey included PAG, anterior amygdala, medial thalamus, head of the caudate, and much of the hypothalamus (Kuhar et al. 1973). In the rat brain dense areas included locus coeruleus, zona

compacta of the substantia nigra, midbrain reticular formation, PAG, dorsal interpeduncular nucleus, basolateral amygdala, lateral medial habenular nucleus, medial thalamus, and parts of the striatum (Pert et al. 1976a). Somewhat different results in rats were reported by Atweh and Kuhar (1977b; 1977c). They found that the densest areas of opiate receptors were parts of the vagal nuclei, superior colliculus, median raphe, ventral lateral geniculate, medial thalamus, amygdala, parts of the striatum, and interstitial nucleus of the stria terminalis. They did not find a dense receptor population in PAG.

Endogenous opiates

The existence of opiate receptors led to the search for their natural ligands. It was suggested that opiate receptors do not sit about in the brain waiting for the organism to ingest some opium. Several peptides were found to be pharmacologically similar to morphine. Two pentapeptides, leucine-enkephalin and methionine-enkephalin, were sequenced in 1975 by Hughes et al. This group found that these substances blocked electrically induced contractions of the mouse vas deferens, and this blockade was reversible by treatment with naloxone. In binding studies, these two peptides were about as potent as morphine (Simantov & Snyder 1976), and their binding was decreased by sodium, suggesting agonist activity (Pasternak et al. 1975).

A second group of peptides, the endorphins, was found by Goldstein's group to have opiate-like activity (Teschemacher et al. 1975; Cox et al. 1975; 1976). These substances have about 30 amino acids. Because of their amino acid sequences it was suggested that they are fragments of beta-lipotropin. These endorphins were found to inhibit electrically stimulated

contraction of the guinea pig ileum, an action reversed by naloxone (Guillemin et al. 1977a).

Enkephalins are distributed unevenly in the brain. In the rat methionine-enkephalin showed greatest concentrations in caudate-putamen and very high concentrations in PAG, interpeduncular nucleus, dorsal raphe, hypothalamus, interstitial nucleus of the stria terminalis, and amygdala (Hong et al. 1977). In the spinal cord methionine-enkephalin was most prevalent in lamina II (Watson et al. 1977). Leucine-enkephalin was not as prevalent as methionine-enkephalin in rat brain, although the former's highest concentrations occurred in striatum and hypothalamus (Yang et al. 1977). In the bovine brain the relative concentrations of the two pentapeptides were different from those in the rat (Simantov et al. 1977).

These substances were found to mimic narcotics in several tests. They have substituted for morphine during opiate abstinence (Lampert et al. 1976; Schulz & Herz 1976; Bhargava 1977), have themselves produced naloxone-induced withdrawal (Wei & Loh 1976), and have been self-administered (Belluzzi et al. 1976b). When administered microiontophoretically, enkephalins inhibited cells in cortex (Frederickson & Norris 1976; Zieglgansberger et al. 1976), locus coeruleus (Young et al. 1977), caudate (Frederickson & Norris 1976), PAG (Frederickson & Norris 1976), and NRGC (Gent & Wolstencroft 1976). They also induced heightened cyclic guanosine monophosphate levels in striatal slices (Minneman & Iversen 1976), and inhibited adenyl cyclase in hybrid glioma cultures (Klee & Nirenberg 1976; Goldstein et al. 1977).

Role of endogenous opiates

The basic question suggested by the finding of opiate-like substances occurring endogenously is: are they involved in endogenous mechanisms of pain and/or analgesia. Extracts of natural enkephalins produced enhanced tail flick latencies when injected into PAG (Pert et al. 1977b). Intraventricular administration of enkephalins to rats and mice induced analgesia (Belluzzi et al. 1976a; Buscher et al. 1976). Several synthetic analogues of the peptides that were found to be resistant to enzymatic destruction also induced analgesia (Pert et al. 1976b; 1977a; Roemer et al. 1977). Beta-lipotropin, administered intraventricularly, induced analgesia, and this activity was antagonized by naloxone (Ronai et al. 1976). Beta-endorphin also induced analgesia, both upon ventricular and intravenous administration (Feldberg & Smyth 1977).

There has been one study showing that footshock enhanced both endogenous opioid peptide concentrations and tail flick latencies (Madden et al. 1977). This study was not confirmed, however, by Fratta et al. (1977). Plasma levels of beta-endorphin were increased by breaking a leg of rats and by administering foot shock (Guillemin et al. 1977b).

There seems to be good evidence that the endogenous opiate-like substances are narcotic agonists and do induce analgesia. If they are released by neurons, endogenous peptides may modulate pain responses or be responsible for blocking responses, as morphine does. However, complete or near complete prevention by endogenous substances would not be adaptive. It has been suggested that pain serves to alert and protect an organism. Therefore, modulation and not depression of pain responsiveness would seem to be much more useful.

Naloxone

A related issue is the problem of the pharmacology of naloxone. The drug is considered to be a "pure" antagonist, blocking morphine effects. It was previously thought that it had no activity when administered alone, but with the discovery of enkephalins and endorphins, this lack of effect caused considerable theoretical problems. Goldstein et al. (1976) and El-Sobky et al. (1976) found no alterations of pain responsiveness after administration of naloxone. It was expected that naloxone should induce hyperalgesia, which it has done in some other tests (Jacob et al. 1974; Grevert & Goldstein 1977). It follows that naloxone's effects on pain depend on the test situation. Why it should possess test specificity is unclear especially if morphine does not show a similar specificity in inducing analgesia. It may be that various painful and stress-induced states are subserved by different loci and different neurochemical systems. Even the opiate receptors were suggested to be heterogeneous, and the enkephalins were suggested to have differential binding affinities (Gilbert & Martin 1976; Martin et al. 1976; Lord et al. 1977; Terenius 1977).

Summary

The most promising areas of neurochemical research that will help elucidate mechanisms of narcotic-induced analgesia are endogenous opiates and other central peptides. The opiate-like peptides were shown to induce analgesia. What the relationship of this pharmacological effect is to the sensation of and responses to pain remains to be seen.

None of the purported neurotransmitters, acetylcholine, dopamine, norepinephrine, and serotonin, seem, in general, to be the transmitter system subserving pain transmission or response. There are several reasons

that the data in this field are so inconsistent. First, large doses of narcotic were often required to induce neurochemical changes. These doses probably induced changes that were unrelated to the induction of analgesia. Two other factors were the type of test and the species used. These factors suggest that the neurochemistry of pain transmission differs among species.

ASSYMETRY

Introduction

It has been said several times that functional brain asymmetry occurs only in man (Dimond 1972; Levy 1977). Functional asymmetry means that certain behaviors are under the control of one hemisphere, or that one hemisphere is dominant in controlling that behavior. An example of asymmetry is language. Laterality is the non-symmetric use of body parts that are apparently symmetric in structure. Handedness is an example of laterality.

Language in right-handed persons is generally regarded as a left-hemisphere function (Hecaen & Ajuriaguerra 1964; Dimond 1972; Levy 1974). However, studies with commissurotomy patients indicated that the ability to comprehend language is not entirely limited to the left hemisphere, although the left is far superior to the right (Gazzaniga 1970). The right hemisphere was found not to have the capabilities to speak or write (Gazzaniga 1970).

The most obvious example of laterality in humans is handedness. Most people are right-handed. The laterality of usage, although suggesting cerebral asymmetry, does not necessarily mean that it does exist. Hecaen

and Ajuriaguerra (1964) suggested that hand preference is a result of culture and social training and that the relationship of brain asymmetry and functional laterality is not clear. Dimond (1972) found that in reviewing the literature not all test paradigms demonstrated differences in the abilities of the two hands.

In all vertebrates the brain on gross inspection appears bilaterally symmetrical. Witelson (1977), however, has reviewed evidence that primates and humans do have anatomic asymmetries. Even so, the processing of output does not necessarily occur equally in both hemispheres. It was suggested that man functions in two cognitive modes, each of which is contained in its own hemisphere (see Galin & Ornstein 1975; Galin 1977; Puccetti 1977). On the other hand, some authors think that hemispheric differences are a matter of degree and not absolute (Harnad & Doty 1977).

Laterality of Stress and Pain Response

There is evidence that sensory systems in humans are lateralized, such as the visual system (see Gur & Gur 1974; 1977) and auditory system (Broadbent 1954; Kimura 1961; Berlin 1977). Little attention has been given to the somatosensory system.

Examples of somatosensory asymmetry

Semmes et al. (1960) found that the left hand has: a lower threshold for pressure sensitivity, a tendency to have a greater acuity in localization, and no difference in two-point discrimination, relative to the right hand. Interestingly, this study found that somatosensory defects arising from cortical lesions do not confirm classical neurological ideas. Defects in the right hand were correlated with lesions of the left somatosensory

cortex, but left hand defects were not localized to the right somatosensory cortex. Furthermore, ipsilateral hand defects occurred much more often from left hemisphere somatosensory lesions than from right somatosensory lesions. Their results suggested that the non-dominant hand is more "diffusely represented" in the brain although the dominant somatosensory cortex has greater ipsilateral activity. It follows that the brain is asymmetric, and this asymmetry "explains" the laterality of hands. The question may be raised as to the purpose of the lower sensory threshold in the left hand. Is this a compensation for the diffuse input to the brain?

Pain sensitivity and tolerance (the range of values commencing with threshold and terminating at intolerable) were found to differ left versus right in hands and feet. The left hand and left foot were more sensitive (that is, to have a lower threshold) and less tolerant of pain than the respective right limb in a variety of tests (Wolff et al. 1965; Haslam 1970; Murray & Safferstone 1970; Murray & Hagan 1973). This laterality of pain sensitivity and tolerance was independent of handedness (and presumably footedness) of the subjects (Murray & Hagan 1973). No difference in sensitivity was found between left and right teeth (Newton & Mumford 1972). In a related study, Kameyama (1977) examined patients suffering from central pain induced by unilateral thalamic lesions. He found that right thalamic lesions induced central pain much more often than left lesions. Kameyama suggested that these findings indicated an asymmetry in pain pathways. It is interesting to note that both pain and pressure sensitivity are lower on the left side of the body.

Several studies of patients that had right hemispherectomies indicated that pain sensation still remained on the left side of the body

(Walker 1943; Mensh et al. 1952). The pain felt on the left side of the body was often described as more unpleasant and more diffuse than on the intact side (Dandy 1933; Bell & Karnosh 1949; Gardner et al. 1955). Walker (1943) suggested that ipsilateral innervation accounts for the remaining pain sensitivity. The Gardner study noted that these hemispherectomy patients often evinced extinction upon simultaneous stimulation. That is, pin prick sensation on the paretic side distal to the elbow and knee was eliminated by a simultaneous pin prick in the same locus on the intact side. This phenomenon of extinction was also found in cases of hemi-inattention (see below).

Lateralized changes in pain sensitivity were noted in other clinical situations as well. Conversion reactions, giving rise to lateralized sensory changes, occurred more frequently on the left side of the body. Agnew and Mersky (1976) and Edmonds (1947) observed that when lateralized pain occurs in psychiatric patients, it is more often on the left side. Conversion reactions, be they pain or loss of sensation, have also been shown to be lateralized to the left side (Galin et al. 1977; Stern 1977). The occurrence of left-sided sensory change was independent of handedness (Stern 1977).

Selective activation

Stress was observed to selectively activate the right hemisphere (Tucker et al. 1977). This study used lateral eye movements in response to "stressful" questions. The subject was told that the answers to such questions indicated his or her intelligence or stability. The assumption was that these questions were stressful, and this may not have been true for all persons.

Activation of the right hemisphere by stress was found by Schwartz et al. (1975) using similar techniques. Questions were designed to evoke both positive and negative emotions (both of these may be considered to be stressors, using Selye's formulation). Dimond et al. (1976) showed that the right hemisphere judges input to be more unpleasant than does the left side. This result supports work of Gainotti (1972) who found that lesions of the left hemisphere were correlated with catastrophic emotional reactions, such as anxiety and aggression, while right hemisphere lesions often produced indifference and denial. Harman and Ray (1977) utilizing the EEG found instead that the dominant hemisphere reacted much more than the right to both positive and negative emotional input. The discrepancy between the last two studies may be explained by the different methods employed.

Hemi-inattention syndrome

Lateralized sensory changes occur in a particularly interesting syndrome, the hemi-inattention or neglect syndrome (see Friedland & Weinstein 1977). This syndrome is associated with a constellation of symptoms including disregard of one side of the body, non-response to sensory input on the affected side, hemianaesthesia or hemiparesis, extinction upon simultaneous stimulation, anosognosia, and disorientation for time and place (but not necessarily sensory defects: patients can respond with and use limbs on the affected side). (Critchley 1949; Denny-Brown et al. 1952; Weinstein & Kahn 1955; Battersby et al. 1956; Kinsbourne 1970; Heilman & Watson 1977b).

Several mechanisms have been suggested to account for these effects. Battersby et al. (1956) suggested that the syndrome arises from a combined sensory and mental defect. They noted that patients with homonymous

hemianopia and somatosensory defects do not present the hemi-inattention syndrome. Critchley (1949) disputed any interpretation based on sensory defects, stating that either repeating or intensifying the stimuli presented to the inattentive side would induce responses. He suggested that this syndrome was due to the inability of a brain-damaged patient to respond to too many stimuli. This would explain extinction upon double simultaneous stimulation wherein the patient responds to only one of two stimuli. Inattention is a decrement in the ability of attentional response to stimuli.

Denny-Brown (Denny-Brown et al. 1952; Denny-Brown and Banker 1954) explained the syndrome on the basis of the high incidence of unilateral parietal lesions occurring concomitantly with the syndrome. He proposed a hypothesis based on this brain locus, in which spatial summation of sensory input is thought to occur. Kinsbourne (1970; 1974) has viewed the syndrome as arising from the lateralizing bias of each hemisphere. Injury to one hemisphere uncovers the lateral response of the intact hemisphere. Thus, such a patient is inattentive to one side because he or she can only orient to the intact side. Kinsbourne (1974) suggested that in intact brains the corpus callosum inhibits these lateralized orienting biases of the two hemispheres. He presented evidence for the lateralized bias of the hemispheres in intact persons (1977). If one or the other hemisphere was "activated" by having subjects swing their eyes, head, and shoulder to one side or the other, performance on a reaction test depended on the direction of movement of the upper trunk.

Heilman and Watson viewed the syndrome as a defect in attention and arousal (Watson et al. 1974; Heilman & Watson 1977a; 1977b; Heilman et al. 1978). They based their hypothesis on the proposal of a cortico-limbic-reticular loop that mediates arousal. Because neglect has been experimentally

induced in animals by lesioning brain loci other than the inferior parietal lobule (the site of Denny-Brown's morphosynthesis or summation) and other than the primary sensory areas, the syndrome, they felt, would be better explained by an arousal hypothesis. Those loci in which lesions induced neglect in man and animals are reticular formation (Reeves & Hagamen 1971; Watson et al. 1974), midbrain loci including specific sensory tracts (Sprague et al. 1961), intralaminar nuclei of the thalamus (Watson & Heilman 1978), lateral hypothalamus (Marshall 1975), olfactory tubercle (Hagamen et al. 1977), cingulate gyrus (Watson et al. 1973), frontal lobe (Kennard & Ectors 1938; Welch & Stuteville 1958; Heilman & Valenstein 1972), and inferior parietal lobule (Heilman et al. 1970). Most of these loci are believed to be involved in the cortico-limbic-reticular loop. Heilman and Wilson (1977b) cited literature indicating that the inferior parietal lobule projects to the frontal lobe, and the frontal lobe projects to the cingulate gyrus (Pandya & Kuypers 1969). The midbrain reticular formation was found to have connections with the cingulate gyrus (Nauta 1964), the frontal lobe (Astruc 1971), and the hypothalamus and medial thalamus (Scheibel & Scheibel 1967).

Animals that received lesions in one of these sites evinced strikingly similar characteristics to those seen in human neglect: multimodal unilateral neglect, circling, allesthesia, and indifference to handling on the lesioned side (Watson et al. 1974). Welch and Stuteville (1958) noticed that their animals maintained the affected side of their bodies directed toward the observer and also circled more during arousal. Similarly, Sprague et al. (1961) observed that their subjects presented the affected

side to an attacking animal.

In a recent paper Heilman et al. (1978) proposed that a lesion in this loop produces hypoarousal (as measured by GSR) on both sides. Presumably this is because the reticular formation bilaterally arouses the cortex (Moruzzi & Magoun 1949). Although they did not demonstrate laterality of arousal in this study, they noted that in one study (Howes & Boller 1975), right hemisphere lesions induced slower reaction times than left hemisphere lesions. This result suggested that there is an asymmetry in arousal.

Animal Models of Asymmetry

The question of brain asymmetry and lateralized function is being pursued in infra human species. There have been four main methods of investigating the question of animal asymmetry and laterality: unilateral neglect syndrome in animals (discussed above); handedness; inactivation of one hemisphere by cortical spreading depression (CSD); and circling behavior, particularly in rodents.

Handedness

Handedness in rhesus monkeys was found to be inconsistent from task to task, and the strength of the preference was poor until after training (Warren 1977). Hamilton (1977) suggested that hand preference in rhesus monkeys has no relationship to cerebral asymmetry. Others also found no evidence of hand preference in monkeys (Beck & Barton 1972; Deuel 1975).

Although monkeys do not seem to possess hand preference, the issue of cerebral asymmetry in monkeys is not settled (Stamm et al. 1977). These authors suggested that monkeys may have lateralized orienting biases. Monkeys were trained on a delayed response task. Certain subjects were

trained with alternate hands. That is, one arm was free to respond, while the other arm was restrained. During the training sessions, recordings of bilateral prefrontal surface potentials were made. It was found that potential shifts were greater in the right prefrontal cortex than in the left.

Animals lower on the phylogenetic tree than primates were found to have paw preferences, including cats (Webster 1977) and bush possums (Megirian et al. 1977). One of the earliest reports on handedness in rats was by Tsai and Maurer (1930): "Now we find that even such a low animal as the white rat exhibits hand preference." They found that more rats are right-handed than left-handed than ambidextrous in reaching for food. Martin and Webster (1974) found more left-handed rats than right-handed. Paw preference was found to be stable and consistent (Peterson 1934; Peterson & Devine 1963). Handedness can be reversed by forcing the animal to use the non-preferred paw (Peterson 1951) or by lesioning the frontal cortex contralateral to the prefered paw, particularly in the pyramidal cell layer (Peterson & Barnett 1961; Peterson & Devine 1963). Lesioning the frontal cortex of rat pups had a significant effect in inducing paw preference ipsilateral to the lesion (Webster & Shoup 1975).

Mice also have a paw preference that is stable and correlated with grip strength (Collins 1968; 1970;1977). When placed in an environment that makes it difficult to use the preferred paw, some mice (about 10 percent) continue to utilize the preferred paw (Collins 1975).

CSD

CSD in rats has been extensively studied by Bures and Buresova (for early work see Bures 1959; Bures & Buresova 1960), particularly in

experimental examination of memory. They found that if one hemisphere is given CSD, the other will learn an active avoidance paradigm as well as an intact brain does although it will require more trials (Bures & Buresova 1960). If retested by giving CSD to the opposite hemisphere and leaving the originally depressed hemisphere untreated, the animal required just as many trials to criterion as on the first test. Passive avoidance, however, has been shown to transfer to a CSD-treated hemisphere (Bures et al. 1964). The authors suggested that passive avoidance induces subcortical memory traces. In a related procedure each hemisphere was given a different task to learn while the other received CSD (Buresova & Bures 1965; Buresova et al. 1966). The subjects were required to effect responses consisting of a combination of both learned behaviors (without CSD), which they did. When two antagonistic memories were so stored and the animals retested with both hemispheres untreated, these subjects showed regressive behavior, suggesting an unsolvable conflict (Hatta 1974).

Schneider (1966) suggested that the failure to demonstrate transfer of memory from an intact hemisphere to one that had gotten CSD is interpretable as generalization decrement. Rats given training during unilateral CSD for 2 days and retested with bilateral CSD, showed fewer trials to criterion on the third day than animals trained for two days with both hemispheres intact and tested on day three with bilateral CSD. CSD, then, can be viewed as a discriminative stimulus for behavior.

Inherent in these studies is the belief that the hemispheres of the rat brain are identical in their abilities to respond and learn. Steele-Russell and Plotkin (1969) have argued against this assumption. They noted

one intact hemisphere required as many trials on the average to criterion as the other hemisphere. When the correlations of left and right hemispheres were examined, however, the correlation coefficient was -0.04 for six animals. Some rats showed fewer trials upon the retest with the opposite hemisphere while others were found to require more trials. It follows that learning in the two halves of the brain of a given rat is not identical.

Circling behavior

Circling is that behavior in which an animal pivots or ambulates in one direction 360 degrees. A preferential direction over time (that is, more circles to the left as opposed to the right or vice versa) is one example of motor laterality. The question is what is the relationship of lateralized circling to brain asymmetry.

Lateralized circling has been produced by lesioning various brain loci. Lesions of the mesencephalic reticular formation produced circling in monkeys (Watson et al. 1974), cats (Greeley et al. 1974), and rats (Costall et al. 1974). The latter group found that apomorphine and amphetamine were without effect on this circling, but Marsden and Guldberg (1973) found that amphetamine induced contralateral circling (that is, opposite in direction to the side of the lesion). Lesions of the raphe nuclei also induced spontaneous circling. Asymmetric lesions of the median raphe but not the dorsal raphe resulted in contralateral circling that was enhanced by both apomorphine and amphetamine (Costall et al. 1976b). Marsden and Guldberg (1973) found that combined lesions of these two raphe nuclei resulted in spontaneous circling that disappeared about one week after the operation.

Lesions placed unilaterally in the locus coeruleus of the rat also resulted in contralateral circling which was intensified by apomorphine and

amphetamine (Pycock et al. 1975; Donaldson 1976). Large unilateral ablations of the tectum and posterior isocortex of rats also resulted in transient ipsilateral circling (Kirvel & Greenfield 1974). Two loci in the rat that were unilaterally lesioned and found to induce contralateral circling upon the administration of amphetamine were the medial hypothalamus (Marshall 1975) and the claustrum (Fleisher & Glick 1975).

There has been disagreement about the mesolimbic dopamine system. Costall et al. (1976a) and Kelly (1975) found that unilateral lesions of the nucleus accumbens induced neither spontaneous nor amphetamine-induced circling. Yehuda and Wurtman (1975) found that unilateral lesions of the olfactory tubercle in the rat induced ipsilateral circling upon administration of amphetamine. Costall et al. (1976a) did not confirm this.

Unilateral lesions of the frontal cortex induced spontaneous circling in monkeys (Kennard & Ectors 1938; Welch & Stuteville 1958) and in rats (Glick and Greenstein 1973).

The nigrostriatal dopamine system has probably been studied the most. Unilateral electrolytic lesions of the nigrostriatal bundle or corpus striatum of rats produced slight circling ipsilateral to the side of the lesions (Anden et al. 1966). Unilateral lesions of the substantia nigra also produced ipsilateral circling in rats (Crow 1971). Unilateral lesions of the caudate using 6-hydroxydopamine, which reduced forebrain dopamine by about 80 percent without altering other biogenic amines, induced ipsilateral circling in mice (VonVoigtlander & Moore 1973). The spontaneous rotation induced by caudate lesions in rats disappeared several days after the lesion, although disturbing the rats re-induced its occurrence (Ungerstedt 1971a).

Unilateral electrical stimulation of the substantia nigra (Arbuthnott & Crow 1971) or the nigrostriatal bundle (Arbuthnott & Ungerstedt 1975) induced contralateral (away from the side stimulated) circling. It follows from the lesion and stimulation studies that the nigrostriatal system is a central site involved in circling.

Drugs, particularly those interacting with dopaminergic neurotransmission, have profound effects on rodents that have received unilateral nigrostriatal lesions and have already ceased spontaneous circling (see below).

Studies of unilateral microinjection of dopamine into the caudate of intact rats indicated that such treatment induced contralateral circling (Ungerstedt et al. 1969; Costall & Naylor 1974). Costall & Naylor (1974) found that several dopamine agonists, such as amphetamine, apomorphine, and amantadine, also induced contralateral rotation upon unilateral intracaudate injection into intact rats. Furthermore, circling in rats produced by unilateral electrical stimulation of the nigrostriatal bundle was suppressed by administration of haloperidol, pimozide and fluphenazine, as well as tetrabenazine (Costall & Naylor 1974).

In unilaterally nigrostriatal lesioned rodents dopaminergic drugs also have induced circling. Amphetamine has induced ipsilateral circling in rodents with unilateral electrolytic lesions of the substantia nigra (Marsden & Guldberg 1973) or the nigrostriatal bundle (Ungerstedt 1971a). Rats that received unilateral microinjection of 6-hydroxydopamine in the substantia nigra (Ungerstedt & Arbuthnott 1970; Ungerstedt 1971a) and the caudate (VonVoigtlander & Moore 1973) also circled ipsilaterally upon administration of amphetamine.

When animals with unilateral lesions in the nigrostriatal system were given apomorphine or l-dopa, the ensuing direction of circling depended upon the location of the lesion. Administration of apomorphine to animals with unilateral caudate lesions caused ipsilateral circling (Jerussi & Glick 1975). Apomorphine given to rats with unilateral nigral or nigrostriatal bundle lesions induced contralateral turning if the drug was administered at least several days after the lesion had been made (Ungerstedt 1971b).

The difference in amphetamine and apomorphine direction may reside in their different sites of action. Amphetamine-induced circling in unilaterally lesioned rats was blocked by haloperidol and spiroperidol (Ungerstedt 1971a). The circling induced by amphetamine in rats with unilateral lesions was also blocked by AMPT but not by bis-(1-methyl-4-homopiperazinyl-thiocarbonyl)-disulphide (FLA-63); the former drug inhibits tyrosine hydroxylase, FLA-63 inhibits dopamine-beta-hydroxylase (Christie & Crow 1971; Marsden & Guldberg 1973; VonVoigtlander & Moore 1973). However, AMPT had no effect on turning induced by apomorphine (Marsden & Guldberg 1973; VonVoigtlander & Moore 1973). FLA-63 reduced cortical norepinephrine by about 80 percent without altering dopamine levels (Marsden & Guldberg (1973). These results suggested that: 1. dopamine, not norepinephrine, is the catecholamine mediating circling; 2. amphetamine acts by releasing dopamine, and 3. apomorphine acts by directly stimulating post-synaptic dopamine receptors.

Furthermore, lesions of the nigrostriatal bundle or the nigra induced supersensitivity of the post-synaptic receptors in the denervated striatum

(Ungerstedt 1971b). This was the explanation given for the ability of apomorphine to induce contralateral circling in unilateral bundle or unilateral nigral lesioned rats. The circling was not inducible by apomorphine during the first few days after the lesions (Ungerstedt 1971b).

Glick's group has expanded these findings. They found that amphetamine (Jerussi & Glick 1974) and apomorphine (Jerussi & Glick 1975) induced lateralized circling in naive, non-lesioned rats. These two studies suggest that there are asymmetries of the nigrostriatal system both pre- and post-synaptically. An asymmetry of dopamine levels in the striata of rats was reported by Glick et al. (1974), and this paper indicated that this asymmetry was enhanced by amphetamine. The direction of rotation induced by amphetamine was positively correlated with the contralateral striatal dopamine asymmetry (Glick et al. 1974). Additionally, striatal dopamine-stimulated adenyl cyclase activity was found to be higher in the striatum opposite to the preferred direction of rotation (Jerussi et al. 1977). Adenyl cyclase has been suggested to be either linked to or part of the post-synaptic dopamine receptor (Kebabian et al. 1972; Satoh et al. 1976). In intact rats amphetamine-induced lateralized circling was blocked by AMPT, but apomorphine-induced circling was not (Jerussi & Glick 1976).

Glick and Cox (1978) found that amphetamine-induced circling was correlated with spontaneous circling occurring during the 12 hours of the night when these rats were most active. The latter paper suggested that circling is part of or an exaggeration of the rodent's normal behavior and arises from, at least in part, asymmetries in the dopaminergic nigrostriatal system.

Glick's group also investigated the significance of circling, proposing that it is related to side preference. Zimmerberg et al. (1974) found that dopamine levels were greater in the striatum contralateral to the direction rats chose in a T-maze. This direction was the same as the preferred circling direction induced by amphetamine in 78 percent of the rats (significantly greater than random). Another set of findings has suggested that side preference strength is correlated with the ability to obtain reinforcement (Glick & Jerussi 1974; 1975) and the ability to learn passive avoidance (although there was found an inverse correlation of strength of side preference and learning of active avoidance). (Glick et al. 1977c).

Several of the studies mentioned above have noted, often anecdotally, that circling is enhanced when the animal is aroused or given aversive stimuli, even after spontaneous rotation has ceased to occur (Welch & Stuteville 1958; Ungerstedt 1971a; Costall et al. 1976a; Glick et al. 1977c). Stress was found to induce circling in vols (Fentress 1977) and in cats (Giammanco 1976).

Narcotic drugs were found to induce circling behavior in naive, non-lesioned rats when given systemically (Morihisa & Glick 1977), and when given by unilateral intranigral microinjection (Iwamoto & Way 1977), or by injection into the mesencephalic reticular formation (Jacquet et al. 1976). Morphine was found to induce ipsilateral circling in unilateral nigral-lesioned rats (Cowan et al. 1975; Iwamoto et al. 1976a; 1976c). Morphine blocked amphetamine and apomorphine rotation in unilateral nigral lesioned animals (Blundell et al. 1976), but haloperidol blocked morphine

circling when injected into one substantia nigra of the rat (Iwamoto & Way 1977). In the study of systemic morphine given to intact animals, 5 mg/kg of the narcotic induced asymmetry of the striatal dopamine content. The dopamine content of the ipsilateral striatum was inversely correlated with the net rotation.

THE PRESENT INVESTIGATION

Several investigators have noticed that so-called stressful procedures intensified circling behavior. Nonetheless, no systematic examination of the effects of stress, or pain, on circling has been performed. Foot shock was chosen as the stimulus for examining circling induced by an aversive procedure.

This investigation consisted of two parts. The first examined the effects of several different shock intensities on circling and other pain responses. The shock-induced circling was compared to normal circling. Secondly, two classes of drugs were examined for their effects on shock-induced circling. Narcotics were studied because they have been observed to induce circling and because they have been observed to suppress responses induced by aversive stimuli. Thus, the effect of narcotics on shock-induced circling could not have been predicted. Dopaminergic drugs were studied to determine if their effects on shock-induced circling were similar to their effects on normal circling.

METHODS

Subjects

The subjects in this investigation were female Sprague-Dawley rats, weighing 200 to 300 grams. They were caged in pairs and allowed ab libitum access to food and water.

Apparatus

The shock chamber consisted of a lucite cylinder, 12 inches in both height and diameter, mounted upon a grid floor. This chamber is called the shock rotometer. A recording device (Greenstein & Glick 1974) was mounted on the removable cover of the cylinder. Each rat was harnessed when it was placed in the shock rotometer. Wire connected the harness to the sensing device.

Two other rotometers were also used: a diurnal rotometer and a spherical rotometer. The only difference between the shock rotometer and the diurnal was that the floor of the diurnal chamber was mesh. Animals were maintained individually for up to 8 days in the diurnal rotometers. The spherical rotometer consisted of two hemispheres that fit together to form a sphere. The recording device was mounted on the upper hemisphere. The rat was harnessed, placed in the lower hemisphere, the harness was attached by wire to the recording device, and the two hemispheres were fitted together (for details see Greenstein & Glick 1974).

The shock apparatus was a SGS-003 Shock Generator (BRS Foringer). This device supplies constant peak current scrambled DC shock.

Drugs

All drugs were injected intraperitoneally. The doses are given as milligrams per kilogram (mg/kg) of the salts.

Narcotic agonist drugs used were: morphine sulfate, levorphanol tartrate, meperidine hydrochloride, methadone hydrochloride, and propoxyphene hydrochloride. Partial narcotic agonists were: d-cyclazocine and d-pentazocine (both solubilized with several drops of 0.1 N HCl), and

nalorphine hydrochloride. The antagonist drug naloxone hydrochloride and the inactive enantiomer of levorphanol, dextrorphan tartrate, were also tested. Other drugs used were: alpha-methyl-para-tyrosine (AMPT), d-amphetamine sulfate, apomorphine hydrochloride, haloperidol, scopolamine hydrobromide, and sodium salicylate. All drugs were dissolved in saline, except apomorphine, haloperidol, and sodium salicylate, which were dissolved in distilled water.

Behaviors Measured

The rotation sensor responds to 90 degree shifts in position. Such a shift is designated a quarter turn. A counter maintains a running total of quarter turns to the left and quarter turns to the right. The behavior designated total quarter turns (TQT) is simply the sum of quarter turns to the right and to the left during the test period.

A full turn is 4 consecutive quarter turns in the same direction. The counter also keeps a running total of full turns to the left and to the right. The behavior designated net rotations, or net, is the difference between full turns in the preferred direction and full turns in the other direction. Percent dominance, or dominance, is turns in the preferred direction multiplied by 100 and divided by the sum of right and left full turns. The preferred direction was also recorded.

Rotational behavior was assessed by these three indices: direction, net, and percent dominance. Net was found to be positively correlated with contralateral striatal dopamine levels and inversely correlated with ipsilateral striatal dopamine levels in rats treated with 20 mg/kg of amphetamine (Glick et al. 1974). Net, then, is associated with a neurochemical asymmetry in the rodent striatum (also see Glick et al. 1977c).

Net, percent dominance, and direction, were consistent when rats were tested twice. These rats received either amphetamine 1 mg/kg 1 week apart or apomorphine 10 mg/kg 1 week apart (Jerussi & Glick 1976). These two measures are therefore reproducible. In addition, the direction of rotation of drug-naive rats maintained in diurnal rotometers for 7 days was consistent from day to day. Net and dominance, however, apparently are not the same. Glick and Cox (1978) found that net followed a diurnal pattern. Dominance, however, was constant over time, independent of the activity of the rats.

In addition to net, dominance, and direction, two other aspects of circling behavior were recorded: total quarter turns (TQT) and extra quarter turns (XQT). The latter is calculated by the following formula:

XQT=TQT - 4 (Full Turns Left + Full Turns Right).

Two other behaviors measured were squeaks and jumps. A squeak is a vocalization by the subject. A jump is defined as that behavior wherein all four paws leave the grid simultaneously. These two behaviors were counted to determine if there is some relationship between these measures of pain responsiveness and rotational behavior induced by foot shock.

Procedures

Each subject was tested individually and received only one shock current even if tested twice.

Acute shock studies

In the acute shock tests, each rat received a saline injection. Thirty minutes after the injection the rat was harnessed and placed in the shock rotometer. An initial 5 minutes of no shock was given to allow the rat to habituate to the apparatus. This habituation time was allowed

in all experiments. Following this was 5 minutes of intermittent shock.

Current was chosen as the independent variable. Masterson and Campbell (1972) tested several shock sources. They found that constant current sources produced the least variable results when rats were given a forced-choice discrimination.

Currents used were 0, 1, 1.5, 2, and 4 milliamperes (ma). Higher currents were not tested because they were thought to be too aversive. It was also thought that at some higher current the rats would freeze.

Separate groups of animals were tested at each of, but only one, shock current. Each shock lasted for 0.1 second and was separated from the subsequent shock by 10 seconds. These parameters were determined in a pilot study and were then maintained for all experiments.

During the shock period the counters recorded quarter turns to the right, quarter turns to the left, full turns to the right, and full turns to the left. Squeaking and jumping were counted by the experimenter.

Acute drug studies

In the acute drug studies, the procedure was essentially the same as in the shock studies. The current for almost all the drug studies was 2 ma. Morphine was also tested at 1.5 and 4 ma. In all drug studies, 5 minutes of habituation preceded 5 minutes of intermittent shock.

In general, drugs were injected intraperitoneally 30 minutes before the test. Exceptions were naloxone which was injected 10 minutes before, and AMPT, which was injected 120 minutes before the test.

The dose of AMPT was 150 mg/kg. This dose was shown to inhibit amphetamine-induced rotation in rats that were given AMPT 120 minutes prior to the injection of amphetamine (Jerussi & Glick 1976). This

experiment was performed to determine if shock-induced rotation is similar to amphetamine-induced rotation.

Similarly, 1 mg/kg of haloperidol blocked rotation induced by amphetamine (Jerussi & Glick 1976). Haloperidol was thereby tested to determine if it would antagonize shock-induced rotation.

The dopaminergic agonists amphetamine and apomorphine and the muscarinic antagonist scopolamine were administered 30 minutes prior to the test because these three drugs were shown to induce net rotation in non-shocked rats (Jerussi & Glick 1976). If shock-induced rotation were mediated by a mechanism similar to that of one (or more) of these three drugs, it would be expected that rotation induced by some dose would add to the rotation induced by shock.

Because shock was found to induce net rotation, morphine was given to determine if this effect was either blocked by, enhanced by, or unaffected by this drug. Morphine was shown to enhance net rotation in non-shocked rats (Morihisa & Glick 1977). Nonetheless, shock-induced rotation (see Results) apparently is induced by aversive stimuli. Morphine is usually considered to suppress behaviors induced by aversive stimuli (see Introduction).

The specificity of the morphine effect was tested in three ways. First, several other narcotic agonists and partial agonists were tested. Second, dextrorphan, the inactive enantionmer of levorphanol, was tested. Third, the ability of the "pure" narcotic antagonist naloxone to reverse the effects of morphine was determined.

An additional group of rats was tested in the spherical rotometers. These rats were placed individually in a rotometer for 15 minutes, injected

with 5 mg/kg of morphine, and then allowed to remain in the rotometers for 1 hour. Net and dominance were calculated for the 60 minutes following the injection of morphine. The correlation of net and dominance was determined and compared to the correlation of net and dominance of those rats receiving shock and 5 mg/kg of morphine.

Diurnal studies

Rats were monitored in the diurnal rotometers for 24 hours to determine net, dominance, and preferred direction of non-shock rotation. One group was removed, placed in the shock rotometers as in the acute studies, and given 5 minutes of footshock. They were then returned to the diurnal rotometers for 7 days. Net, dominance, and direction were determined every 24 hours. These 3 measures of asymmetry for the 24 hours pre-shock and post-shock were compared to the respective values occurring during shock.

The second group received no shock and was monitored for an additional 7 days in the diurnal rotometers. This experiment was performed to determine if changes occur in either net, dominance, or direction during an 8 day period.

Repeated tests

Because the morphine net rotation dose response curve determined at 2 ma was found to be bimodal, experiments were performed to determine if the directions of the peak doses, i.e. 5 and 80 mg/kg, were opposite or the same (in the same rats). The amphetamine net dose response curve, determined without shock for rats, was also found to be bimodal. These rats were found to rotate in one direction at a low dose and in the opposite direction at a high dose (Jerussi & Glick 1976). Tests were done by giving 5 mg/kg of morphine to rats and shocking at 2 ma in the usual manner. The rats were retested with 80 mg/kg and 2 ma 1 week leter.

The converse experiment, i.e. 80 mg/kg of morphine followed by 5 mg/kg one week later, was not done because of the expected complicating factor of tolerance. Results of these experiments required that additional repeated tests be performed. These included (in each experiment the two tests were separated by one week): 2 ma and saline twice, 2 ma and 5 mg/kg of morphine twice, 2 ma and saline followed by 2 ma and morphine 5 mg/kg, 2 ma and saline followed by 2 ma and morphine 80 mg/kg, and 2 ma and saline followed by 2 ma and naloxone 5 mg/kg.

Additional studies examined the effects of shock pretreatment upon subsequent (one week later) morphine--shock interactions. The current for both of these shock periods was also 2 ma.

Analysis

Statistical analyses of the data were performed with one way analysis of variance, Duncan's Multiple Range Test, t-tests, and chi square analysis. Data expressed in percentages were transformed to arc sine when the statistical tests were employed. Data were analyzed using the PROPHET system time-sharing computer of the National Institute of Health (Raub 1974).

RESULTS AND DISCUSSION

Shock Studies

The effects of shock on the behaviors studied are presented in Table 1.

Net rotations

Net rotation increased with current. The number of net rotations that occurred at 2 and 4 ma was significantly greater than that occurring at 0 ma. Net induced by 4 ma was also greater than the net induced by 2 or 1.5 ma.

Dominance

Because most rats made no full turns at 0 ma (mean total full turns was 0.4 ± 0.4), dominance could not be determined. It can be estimated, however, from the dominance of rats maintained in diurnal rotometers (see Table 3 below; also see Glick & Cox 1978). The 24 rats tested in diurnal rotometers had a mean dominance of about 67 percent. It is assumed that the 24-hour determination of dominance reflects the baseline dominance (0 ma) because in rats tested in diurnal rotometers dominance was consistent from day to day.

At 2 and 4 ma dominance was 66 and 69 percent, respectively, neither of which was significantly different from the value determined in rats tested in diurnal rotometers. However, the values at 1 and 1.5 ma are much higher. This suggests that dominance is altered by 1 and 1.5 ma. The average number of total full turns that rats made during either 1 or 1.5 ma was about 4. Because there were so few total turns, the data suggesting enhanced dominance must be viewed cautiously. For example, a rat that made 2 total turns and 2 net turns had a dominance of 100%. If it were to have made 1 of its 2 turns in the opposite direction, its dominance would have been 50 percent, thus a reversal in direction for only 1 turn

Table 1

Effects of shock current on behaviors. Values are means ± standard deviations (S.D.)

Current (ma)	n	Net	Dom. (%)	TQT	XQT	Sqk	Jump
0	10	0.2±0.4	-	3.8± 5.4	2.2± 2.4	0	0
1	7	2.7±2.6	89.7±11.6	26.6±22.8	5.9± 8.3	6.5± 7.9	0
1.5	6	2.3±1.9	84.3±20.6	29.8±16.8[b]	12.5± 7.1	8.3±12.6	0.3± 0.5
2	12	2.6±2.2[c]	65.6±12.9[d]	59.0±16.2[c]	19.9±12.0[b]	25.1± 6.6[c,f]	11.6± 7.8[c,f]
4	8	5.3±4.1[c,e]	68.8±12.7[d]	136.6±26.7[c,d,e]	80.6±37.0[c,d,e]	58.5±12.6[c,d,e]	19.8±15.4[c,d,e]
F[a]		3.91	5.17	27.76	64.86	48.16	9.05
p-value		<.003	<.004	<.0001	<.0001	<.0001	<.001

[a]Analysis of variance.

[b]Significantly different from 0 ma group at p <.05 (Duncan's test).

[c]Significantly different from 0 ma group at p <.01 (Duncan's test).

[d]Significantly different from 1 ma group at p <.05 (Duncan's test).

[e]Significantly different from 2 ma group at p <.01 (Duncan's test).

[f]Means computed from data of 8 rats.

encompasses the full range of possible values of dominance. Therefore, with small numbers of total turns, the dominance data are subject to large error. At higher currents, the total turns were large enough that a change of 1 turn would maximally alter the dominance by about 11 percent (mean total turns at 2 ma was about 9 and at 4 ma was 14).

XQT and TQT

Because XQT were found to be related to locomotor activity and inversely correlated with net rotations in amphetamine-treated mice that did not receive shock (Greenstein & Glick 1974), XQT were calculated from TQT in the present study. TQT were increased relative to 0 ma at currents of 1.5, 2, and 4 ma. XQT were enhanced at 2 and 4 ma.

The relationship of net, dominance, TQT, and XQT was investigated in 50 rats that received 2 ma foot shock (see Table 2). Net and dominance were positively correlated. (These two measures were also correlated for the 8 rats that received 4 ma ($r = 0.85$, $p < .01$)). Dominance was negatively correlated with TQT and XQT. TQT were positively correlated with XQT. Whereas Greenstein and Glick (1974) noted an inverse correlation between net and XQT in mice that received amphetamine no such correlation was observed herein.

Dominance versus net

In those reports indicating that stressful and arousing stimuli induced circling, no attempt was made to measure the circling or separate out the two indices, net and dominance. Therefore it is important to ask: what is the difference, if any, between them. There is one paper that suggests that the two measures reflect different functions (Glick & Cox 1978).

Table 2

Correlation coefficients of 50 rats which received 2 ma footshock.

	Net	Dom.	TQT	XQT	Sqk	Jump
Net	-	.72[d]	.24	-.18	-.16	-.16
Dom.	.72[d]	-	-.47[c]	-.41[c]	-.32[a]	-.38[b]
TQT	.24	-.47[c]	-	.78[d]	.19	.50[b]
XQT	-.18	-.41[c]	.78[d]	-	.13	.54[c]
Sqk	-.16	-.32[a]	.19	.13	-	.20
Jump	-.16	-.38[b]	.50[b]	.54[c]	.20	-

[a]Significant at $p < .05$.

[b]Significant at $p < .01$.

[c]Significant at $p < .001$.

[d]Significant at $p < .0001$.

In that paper, the authors maintained rats in diurnal rotometers. They reported that net increased at night when the rats were more active, but dominance did not change. These data suggest a possible model. There is an underlying asymmetry which can be viewed as a gate and is expressed as dominance. Net represents the activity going through the gate and is dependent upon or related to arousal.

The data in the present study are analogous to the description of this model, for currents of 2 and 4 ma. With an increase in shock intensity, rats averaged about twice as many net rotations and were twice as active, assuming TQT indicates the relative amount of activity. Dominance did not change. Thus, in both spontaneous and shock-induced circling, when rats moved more, they exhibited increased net but unchanged dominance.

Pain indices

Squeaks and jumps were also counted (see Table 1). Both were significantly increased at 2 and 4 ma relative to 0 ma.

Correlations between net and these two behaviors were calculated at 2 ma (Table 2). No correlations were found between either net and squeaks, net and jumps, or squeaks and jumps. Thus, no obvious relationship was noted between either measure of pain response and net rotations. Percent dominance, however, was negatively correlated with squeaks and jumps (Table 2). However, when rats were tested twice with 2 ma 1 week apart. dominance increased (see below and Table 14) during the second test. Jumps and squeaks were unchanged. The correlation of pain indices and dominance present in the first test did not occur in the second test. Because of the inconsistency of these 2 correlations, it is unlikely that

there is a relationship between dominance and pain responses.

Diurnal Studies

Relationship of shock-induced circling to non-shock circling

Rats were tested in diurnal rotometers for the 24 hours immediately preceding the shock test. They were then retested in the diurnal rotometers. Net rotation during shock was not significantly correlated with net for either the 24 hours prior to ($r = 0.07$, $p > .1$) or the 24 hours following ($r = 0.09$, $p > .1$) the shock test. The results for dominance were quite similar. The correlation coefficients for shock dominance versus that in pre- and post- 24 hour diurnal tests were 0.01 ($p > .1$) and 0.04 ($p > .1$), respectively. These correlations did not take into consideration the directions during, before, or after shock, but correlations were performed that included the relative directions of net and dominance. These correlations were all non significant.

The preferred direction of rotation during the 24 hours following shock was the same as the preferred direction for the 24 hours prior to shock ($X^2 = 5.33$, $p < .025$). The direction of rotation during shock was independent of the direction prior to shock ($X^2 = 0.4$, $p > .1$).

Net was increased by shock, when comparing 4 ma to 2 ma. Net induced by both 2 and 4 ma was greater than spontaneous (0 ma) net. Thus, shock-induced net and spontaneous net are unrelated and are mediated by different mechanisms. Furthermore, although dominance at 0, 2, and 4 ma all have the same value, the dominance recorded at 0 ma is not mediated by the same mechanisms that mediate non-shock, or spontaneous dominance.

Post shock diurnal testing was continued for an additional 6 days. The daily 24 hour-total mean scores are presented in Table 3.

Table 3

Daily net and dominance (means ± S.D.s) of rats maintained in diurnal rotometers.

Rats that received shock.

	(pre-shock)							
Day	1	2	3	4	5	6	7	8
Net	27.3±26.3	53.5±70.2	34.2±34.2	32.8±31.2	44.1±53.5	45.6±45.9	37.6±50.4	45.1±62.1
Dom. (%)	64.6± 9.6	66.6±13.8	65.8±11.1	68.7±12.2	68.3±12.3	68.2±10.1	69.2±14.9	67.9±16.2

Rats that did not receive shock.

Day	1	2	3	4	5	6	7	8
Net	27.4±22.2	32.2±26.1	32.1±25.4	29.7±26.8	27.3±24.7	28.1±20.0	26.2±26.3	27.4±24.0
Dom. (%)	67.1±10.0	66.3±13.2	68.2± 8.8	67.8±10.9	68.1±13.4	67.4±10.9	65.9±12.0	66.4±11.3

Analysis of variance for the effects of time after shock was not significant for net ($F = 0.25$, $p > .1$) or for dominance ($F = 0.37$, $p > .1$). The statistics on these measures were done without regard to the direction of circling.

However, 8 of the 12 rats reversed their daily direction of circling at least once during the 7 days (see below). No significant analyses of variances were found when all data were expressed in terms of the dominant direction prior to shock. In these instances, the range of possible dominance values is from 0 to 100 percent, and net may be either positive or negative.

Rats that were not shocked and were maintained in diurnal rotometers for 8 days showed no change in circling behavior (Table 3). Only 1 of these 12 rats changed its preferred direction on any day following the first day. This rat made only 3 net rotations, the fewest of any of these 12, during the first 24 hours. It is not surprising that its direction varied from day to day because it was almost without directional preference.

Eight rats that received shock did reverse their directional preference, and the frequency of reversal was significantly different from this frequency in the non-shocked rats ($\chi^2 = 5.34$, $p < .0005$). Reversal of direction occurred on any day except the first day following shock. No consistent pattern was observed.

Shock disrupted subsequent directional preference but altered neither dominance nor net for the group. Changes in net and dominance, however, were observed in some of the shocked rats, but no consistent effect in the group was seen.

Shock and subsequent directional preference

There is additional evidence suggesting that foot shock alters subsequent rotational behavior relative to circling prior to shock. As mentioned above, shocked rats made more reversals of their daily preferred direction. This finding will now be amplified.

Thirty-six rats were tested for 24 hours in diurnal rotometers, 12 of which were subsequently shocked. When the distribution of net rotations for this 24-hour period was tested (w-test) for normality ($n = 36$), it was found non-normal even at the 50 percent level. If the distribution was arbitrarily divided into two distributions, the cut-off being 15 net rotations for the first distribution, each of these distributions was found to be normal at the 1 percent level. These two were designated low rotators and high rotators. Each high rotator that was shocked ($n = 6$) switched its preferred direction relative to that prior to shock by day 7. This number of reversals is significantly greater than expected if the relationship of the directions were random ($\chi^2 = 6.0$, $p < .01$). Two of the six low rotators that were shocked switched their preferred direction by day 7.

The change in net for the switching in the two groups was determined by subtracting net on day 8 from net on day 1, with the proviso that if direction changed this was taken into account. Thus, net could have positive or negative values. When this was done the change in net of the high rotators was significantly greater than that of the low rotators ($t = 2.3$, $p < .05$).

Therefore, shock seems to reverse the preferred direction of those rats designated as high rotators. Low rotators, apparently because their

directional preferences are not great, may or may not have switched direction. The data suggest that shock has a greater effect on the high rotators. A larger sample would be necessary to explore this possibility further.

Summary

The first set of experiments suggested that foot shock induces circling behavior. The second set of experiments indicated that shock-induced rotation is not related to the spontaneous rotation measured in diurnal rotometers.

Dopaminergic Drugs

There is good evidence that spontaneous rotation is mediated by nigrostriatal dopaminergic asymmetry (see Glick et al. 1977c; Glick & Cox 1978). Amphetamine induces rotation in rats by enhancing dopaminergic asymmetry (Glick et al. 1974; Jerussi & Glick 1976).

Shock-induced rotation is not primarily mediated by dopaminergic systems (see below). This hypothesis is consistent with the lack of correlation between shock-induced circling and spontaneous circling.

Agonists

Neither amphetamine (Table 4) nor apomorphine (Table 5) had any significant effect on shock-induced net rotation. Inspection of the data shows that apomorphine induced very variable effects on shock-induced net. The mean net rotations induced by 2.5, 5, and 10 mg/kg of apomorphine were, respectively, 10.7, 7.0 and, 11.17. The variance of each of these means was quite large and, therefore, the analysis of variance did not yield a significant dose effect. Nonetheless, several rats at each dose made in excess of 20 net rotations, but others made 0 net.

Table 4

Effects of amphetamine on shock (2 ma)-induced behaviors. Values are means±S.D.s.

Dose (mg/kg)	n	Net	Dom. (%)	TQT	XQT	Sqk	Jump
0	(12)	2.6±2.2	65.6±12.9	59.0±16.2	19.9±12.0	25.1± 6.6[b]	11.6± 7.8[b]
0.25	(9)	2.2±2.4	80.8±20.1[b,c]	30.6±29.2[c]	11.9±10.0	7.9± 8.7	2.4± 4.7
0.5	(10)	4.3±3.8	83.6±16.0[c]	60.2±36.6	27.8±25.3	15.1±12.0	8.4±13.4
1	(9)	3.2±3.3	69.0±16.4[b]	98.3±63.9	60.6±45.0[c]	23.8±31.5	13.8±11.4
2.5	(9)	5.4±5.1	71.4±14.7	76.5±32.8	31.7±22.2	17.9±11.8	19.3±25.4
5	(6)	4.5±1.9	68.6± 7.9	108.3±42.5[c]	54.3±18.9[c]	3.7± 4.3	24.0±11.6
F[a]		1.29	2.69	4.28	5.18	2.18	2.28
p-value		>.1	<.03	<.002	<.001	<.07	<.06

[a]Computed from one-way analysis of variance.

[b]Means computed from data of 8 rats.

[c]Significantly different from 0 mg/kg controls at p<.05 (Duncan's test).

Amphetamine, at doses of 0.25 and 0.5 mg/kg, and apomorphine, at 10 mg/kg, increased shock-induced dominance. There is a difference between the dose dominance curves of the two drugs. Amphetamine induced increased dominance only at low doses. However, 1 mg/kg, in the present study did not induce enhanced dominance (see Table 4, dominance is 69.0 percent). Jerussi (1974) found that 1 mg/kg of amphetamine induced dominance of 88.7% in rats maintained in spherical rotometers; Glick et al. (1977b) reported that 1 mg/kg of amphetamine induced dominance of 85.1% in rats maintained in rotometers having a mesh floor. It can be assumed that these latter studies found that this dose of amphetamine enhanced dominance relative to saline controls. No comparable effect of 1 mg/kg of amphetamine was observed in the present study.

Apomorphine, in the present study, enhanced shock-induced dominance only at the highest dose. This dose induced dominance of 87.2 percent in rats maintained in spherical rotometers for 1 hour (Jerussi 1974).

Amphetamine had biphasic effects on shock-induced TQT. TQT were significantly greater at 5 mg/kg but significantly less at 0.25 mg/kg than that of saline-treated controls. Apomorphine increased shock-induced TQT at 2.5 mg/kg but not at higher doses. Amphetamine increased shock-induced XQT at 1 and 5 mg/kg. Apomorphine had no significant dose effect on shock-induced XQT.

Amphetamine had no significant effects on squeaks or jumps (Table 4). At doses of 1.25 and 5 mg/kg of apomorphine squeaks were significantly decreased relative to controls. Apomorphine had no significant effect on jumping (Table 5).

Table 5

Effects of apomorphine on shock (2 ma)-induced behaviors. Values are means ± S.D.s.

Dose (mg/kg)	n	Net	Dom. (%)	TQT	XQT	Sqk	Jump
0	12	2.6± 2.2	65.6±12.9	59.0±16.2	19.9±12.0	25.1± 6.6[b]	11.6± 7.8[b]
1.25	6	5.3± 5.0	79.6±21.8	47.2±38.9	15.2±11.8	8.3± 8.1	2.8± 5.6
2.5	7	10.7±15.6	82.5±52.3	119.0±58.9[c]	29.9±17.6	16.7±10.6	21.3±30.4
5	6	7.0± 7.2	86.2±46.2	73.3±39.2	29.3±19.1	9.3± 8.2[d]	18.5±28.1
10	6	11.2±10.1	96.4±30.5[d]	98.7±59.0	31.8±33.0	19.7±14.8	12.2±11.4
F[a]		1.50	2.97	3.19	0.95	3.44	0.85
p-value		>.1	<.03	<.03	>.1	<.02	>.1

[a]Computed by one-way analysis of variance.

[b]Means computed from data of 8 rats.

[c]Significantly different from controls (0 mg/kg) at p <.05 (Duncan's test).

[d]Significantly different from controls (0 mg/kg) at p <.01 (Duncan's test).

AMPT

The mean shock-induced net (± S.D.) for rats (n = 6) pretreated with 150 mg/kg AMPT was 4.3 ± 1.5. This value was not significantly different from the net of saline-treated rats ($t = 1.7$, $p > .1$). This pretreatment increased mean shock-induced dominance ($t = 4.3$, $p < .01$), which was 95.0 ± 34.5. AMPT also induced a decrease in shock-induced TQT (mean ± S.D. = 31.0 ± 9.2; $t = 3.05$, $p < .008$) and shock-induced XQT (mean ± S.D. = 8.3 ± 5.0; $t = 2.89$, $p < .01$) relative to saline-treated controls. The drug decreased the number of squeaks (mean ± S.D. = 10.1 ± 1.3; $t = 3.86$, $p < .002$) and the number of jumps (mean ± S.D. = 0 ± 0; $t = 3.62$, $p < .004$).

Haloperidol

Haloperidol (Table 6) was without significant effect upon shock-induced net. A dose of 1 mg/kg of haloperidol blocked amphetamine-induced rotation when measured in a spherical rotometer (Jerussi & Glick 1976). Although a comparison of the shock-induced net rotations in the presence of saline and in the presence of 1 mg/kg of haloperidol showed a significant difference ($t = 4.68$, $p < .0005$), the analysis of variance indicates that this can only be attributed to chance. All other doses had no significant effect on net (Duncan's test). Therefore, as the analysis of variance indicates, no dose effect is discernible.

Although analysis of variance indicates a significant dose effect on shock-induced dominance (Table 6), there are several factors that suggest otherwise. The doses at which dominance was increased were those at which rats made few or no total turns. Because of the small number of rats that rotated and the few rotations made, the data indicating an increase in dominance induced by haloperidol are not convincing.

Table 6

Effects of haloperidol on shock (2 ma)-induced behaviors. Values are means ± S.D.s.

Dose (mg/kg)	n	Net	Dom. (%)[b]	TQT	XQT	Sqk	Jump
0	12	2.6±2.2	65.6±12.9	59.0±16.2	19.9±12.0	25.1± 6.6[c]	11.6±7.8[c]
0.0625	6	2.2±2.3	78.4±18.8	29.0±18.1	9.0± 5.4	21.8± 5.8	4.0±4.2
0.125	14	2.6±2.1	75.4±18.8	54.7±32.8	28.1±22.9	19.6± 8.2	4.3±4.4
0.25	6	1.7±1.8	94.4± 7.9[d]	14.0± 8.9[d]	6.0± 3.6[d]	17.7±12.1	1.0±1.4[e]
0.5	4	4.5±2.7	90.8± 9.2[d]	41.8±20.1	19.8±12.1	31.5± 6.9	0.8±0.8[e]
1.0	6	1.0±0.8	93.8±10.8[d]	11.7±13.8[d]	6.3± 8.4[e]	12.5± 8.5[d]	2.8±4.6[d]
F[a]		1.43	3.38	4.48	3.01	2.85	4.48
p-value		>.1	<.025	<.005	<.005	<.05	<.005

[a]Computed from one-way analysis of variance.

[b]Animals that made 0 total full turns were not included in determinations of dominance. Thus, the n at each dose was 0.0625 (n=5), 0.125 (12), 0.25 (3), 0.5 (4), 1.0 (4).

[c]Computed from 8 rats.

[d]Significantly different from controls (0 mg/kg) at $p < .05$ (Duncan's test).

[e]Significantly different from controls (0 mg/kg) at $p < .01$ (Duncan's test).

Haloperidol induced decreases in shock-induced TQT and XQT (Table 6). Its effect on each was inconsistent. The doses that decreased TQT and XQT were 0.25 and 1 mg/kg.

At 1 mg/kg of haloperidol squeaking was significantly less than that of saline-treated controls. The drug's effect on jumping was more pronounced; at every dose tested significantly fewer jumps occurred than did in controls.

Scopolamine

At doses of 1 and 5 mg/kg of scopolamine (Table 7) shock-induced net was significantly increased relative to that of controls. Jerussi & Glick (1976) reported that significant rotation was elicited by 1, 10, 100, and 200 mg/kg of scopolamine administered to rats tested in spherical rotometers. Thus, 10 mg/kg of scopolamine has a significant effect on spontaneous rotation but does not have a significant effect on shock-induced rotation.

Scopolamine had no significant dose effect on shock-induced percent dominance (Table 7). Although no scopolamine dose-dominance curve has been published, Jerussi (1974) reported dominance induced by 1 mg/kg in rats was 71.5 percent. This latter figure is apparently not significantly different from dominance observed in untreated rats maintained in diurnal rotometers (Glick & Cox 1978).

At 0.5, 1, and 5 mg/kg of scopolamine shock-induced TQT were significantly greater than that of saline-treated controls (Table 7). Scopolamine had no significant dose effect on shock-induced XQT (Table 7). The drug also had no significant dose effect on squeaking (Table 7). At a dose of 5 mg/kg, jumping was significantly increased relative to that of saline-treated controls.

Table 7

Effects of scopolamine on shock (2 ma)-induced behaviors. Values are means ± S.D.s.

Dose mg/kg	n	Net	Dom. (%)	TQT	XQT	Sqk	Jump
0	12	2.6± 2.2	65.6±12.9	59.0±16.2	19.9±12.0	25.1± 6.6[b]	11.6± 7.8[b]
0.5	6	7.5± 4.8	74.0±15.2	85.7±18.1[d]	23.6±14.0	26.2± 9.83	14.5±14.9
1.	6	11.2±11.5[d]	76.3±18.8	91.2±28.6[d]	19.8±23.1	30.2± 7.0	7.8±13.8
5	6	10.6± 6.3[d]	80.0±16.1	136.0±36.7[d]	38.0±23.4	24.6± 7.4	42.0±41.6[c]
10	5	4.3± 1.9	72.4±12.8	39.5±20.1	8.8± 9.7	15.2±17.4	0.3± 0.8
F[a]		3.23	1.33	14.81	2.26	1.73	3.68
p-value		<.025	>.1	<.0001	<.09	>.1	<.02

[a]Computed from one-way analysis of variance.

[b]Means computed from data of 8 rats.

[c]Significantly different from controls (0 mg/kg) at $p < .05$ (Duncan's test).

[d]Significantly different from controls (0 mg/kg) at $p < .01$ (Duncan's test).

Effects of dopaminergic agonists during 5 minutes of no shock

As reported above, neither amphetamine nor apomorphine increased shock-induced rotation. This may be due to the fact that the 5-minute test is not sensitive enough to indicate a shock-amphetamine or shock-apomorphine interaction.

Since it is not known how much net will be induced by either drug in 5 minutes without shock, rats were treated with either 1 mg/kg of amphetamine or 10 mg/kg apomorphine and placed in shock rotometers 30 minutes later. No shock was given to these groups. Determinations of net were made during the second 5 minutes.

Amphetamine, 1 mg/kg, induced significantly greater net rotations than that of saline-treated controls during this second 5 minutes ($t = 2.51$, $n = 6$, $p < .02$). Apomorphine, 10 mg/kg, also induced a significantly greater number of net rotations than that of controls ($t = 2.48$, $n = 6$, $p < .02$). Mean (± S.D.) net rotations for the amphetamine-treated rats was 1.7 ± 1.6 and for the apomorphine-treated rats was 2.3 ± 2.4.

If net induced by shock and net induced by amphetamine are distinct, separate effects, it is conceivable that the two effects are additive. The total net (4.3) resulting from adding (2.6) net induced by shock to net induced by amphetamine (1.7) would not be significantly different from shock alone.

This lack of significance indicates that the 5-minute test is not sensitive enough to show an amphetamine-shock interaction if such an interaction is additive. Apomorphine's interaction with shock will also be discussed below.

Discussion

Jerussi and Glick (1976) suggested that arousing stimuli, such as noxious stimulation and pharmacological stimulation, induce lateralized rotational behavior in rodents. Their explanation consisted of several points. First, circling induced by dopaminergic agonists is mediated by functional asymmetries in the nigrostriatal system. Second, there is some indication that the striatum is associated with arousal (Kirkby 1973). Third, it is possible that the orienting reflex has a lower threshold on one side of the brain than the other, presupposing a relationship of orienting to the striatum. Fourth, activation of the nigrostriatal system with dopaminergic agonists or noxious stimuli should activate this asymmetrical system and thereby induce lateralized circling. One assumption in this reasoning is that arousal resulting either from administration of dopaminergic agonists or from noxious stimulation is similar in terms of the effect each produces on circling.

The present study suggests otherwise. Several findings discussed above indicate that shock-induced rotation is not mediated by dopaminergic systems.

First, the antagonist haloperidol did not block shock-induced net. If shock were increasing dopaminergic asymmetry in the nigrostriatal system as amphetamine does (Glick et al. 1974), shock-induced rotation should be blocked by haloperidol. Similarly, AMPT blocked amphetamine-induced net rotation (Jerussi & Glick 1976). In the present study, AMPT was ineffective in blocking shock-induced net. Moreover, AMPT reduced shock-induced TQT. Even though the AMPT-treated rats moved less than saline-treated controls during the shock test, the AMPT group made as many net rotations.

Second, the interactions of agonists and shock-induced rotation were not what would be expected if the two types of rotation be similarly mediated.

If shock-induced rotation and either amphetamine-induced or apomorphine-induced rotation are similar in mechanism, the interactions of shock and either drug could reasonably be predicted. Because net at 4 ma is greater than net at 2 ma, administration of amphetamine or apomorphine in the presence of 2 ma can be expected to increase net relative to that induced by 2 ma alone. In other words, shock and drug are equal to greater shock or greater drug. For amphetamine, no dose affected shock-induced net, but this is an equivocal finding as noted above (see "Effects of dopaminergic agonists during 5 minutes of no shock" above).

For apomorphine, large variability in shock-induced net rotations was observed at doses of 2.5, 5, and 10 mg/kg. If apomorphine and 2 ma were additive in inducing net no large variations would have been seen. One possible explanation for these data is that apomorphine's effect on net rotation is independent of shock-induced rotation. The relative dominance and directional bias of each "gate" is independent. This is consistent with the lack of correlations between shock-induced circling and circling measured in diurnal rotometers. This would result in variable effects. If the shock and the apomorphine gates were similarly biased, the two would induce increases in net. If the two gates were oppositely biased, a rat would be expected to make few net turns.

Low doses of amphetamine enhanced shock-induced dominance. Assuming that these doses are lower than those required to enhance spontaneous

dominance, it appears that shock of 2 ma shifts the amphetamine-dominance curve to the left. This shift suggests that amphetamine and shock are agonists. However, since shock apparently does not affect the circling mediated by the nigrostriatal system, it follows that amphetamine interacts with the shock-gate.

Apomorphine enhanced shock-induced dominance at a dose which also increased spontaneous dominance. This dose was also the highest tested. It is assumed that the apomorphine-dose dominance curves are similar for both spontaneous and shock-induced circling. Presumably, the apomorphine effect on spontaneous dominance is independent of the shock effect. That is, apomorphine in the presence of footshock has no effect on dominance until a large dose is administered. One explanation for this effect is that at 10 mg/kg the drug's effect on spontaneous rotation becomes the predominant effect. This is consistent with the data that shows that 10 mg/kg of apomorphine induced the greatest mean net during shock.

AMPT also enhanced shock-induced dominance. There is an interesting parallel between AMPT and amphetamine. At the lowest dose of amphetamine tested, i.e. 0.25 mg/kg, shock-induced TQT were reduced but shock-induced dominance was increased. AMPT produced the same two effects. An explanation for this seeming contradiction is that animals shocked with 2 ma dominance is inversely correlated with TQT. The effect of either 0.25 mg/kg amphetamine or AMPT on shock-induced dominance may result from the decrease in TQT and not be a direct action on the shock gate.

Summary

The data discussed so far can be summarized thus:

1). Shock increases net but apparently does not affect dominance.

2). Shock-induced circling, as measured by preferred direction, net, and dominance, is not related to normal circling.

3). Haloperidol and AMPT do not prevent shock-induced circling.

4). The interaction of amphetamine and shock on circling is complex. Shock can be considered to be an agonist of amphetamine in terms of their interaction on dominance; the amphetamine dose-dominance curve is shifted to the left by 2 ma foot shock. If shock and amphetamine are agonists, AMPT should not have increased shock-induced dominance.

5). Apomorphine seems to activate the nigrostriatal system during shock. The interaction of apomorphine and shock induces great variability in net. The dose-dominance curve probably is very similar to that of apomorphine without shock.

Therefore, shock activates some system that is asymmetric, but it is clearly not the nigrostriatal dopaminergic system.

Furthermore, although circling is induced by shock, as is squeaking and jumping, no relationship among these three shock-induced behaviors was apparent.

Narcotics

The present investigation has indicated that shock elicits increases in net rotations, TQT, and XQT. These behaviors can therefore be considered as responses to intermittent painful stimuli. A narcotic can reasonably be expected to decrease the occurrences of each of these. Therefore, the effects of narcotics on shock-induced rotational behavior, as well as on squeaks and jumps, were determined. Because 5 mg/kg of morphine significantly increased spontaneous net rotations in rats (Morihisa & Glick 1977), it is not possible to predict the results of the

Table 8

Effects of morphine on shock (1.5 ma)-induced behaviors. Values are means ± S.D.s.

Dose (mg/kg)	n	Net	Dom. (%)	TQT	XQT	Sqk	Jump
0	6	2.3±1.9	84.3±20.6	29.8±16.8	12.5±7.1	8.3±12.6	0.3±0.5
2.5	6	2.3±2.4	74.5±40.8	42.5±15.6	10.5±4.9	15.2± 9.7	7.7±7.7
5	6	2.5±2.3	89.1±42.6	28.2±24.2	8.8±5.6	1.8± 4.5	3.0±6.9
7.5	6	5.2±3.6	86.2±31.5	34.2±14.1	5.5±2.7	1.0± 1.6[b]	0.5±0.8
10	6	2.7±2.2	89.6±41.7	28.0±15.3	10.7±9.2	1.5± 1.6[b]	0 ±0
40	6	5.3±2.7	99.8±12.0	24.5±13.6	1.8±1.6[c]	0 ± 0[c]	0 ±0
80	6	4.8±3.8	85.3±36.2	26.2±13.8	4.2±4.1	3.5± 5.4	3.0±7.4
F[a]		1.61	1.56	0.82	3.02	4.67	1.89
p-value		>.1	>.1	>.1	<.02	<.001	>.1

[a]Computed from one-way analysis of variance.

[b]Significantly different from controls (0 mg/kg) at $p < .05$ (Duncan's test).

[c]Significantly different from controls (0 mg/kg) at $p < .01$ (Duncan's test).

interaction of morphine and shock-induced rotation. The morphine effect on non-shock circling was thought to be due to increased striatal dopamine asymmetry (Morihisa & Glick 1977).

The design of the experiments was to establish which changes in shock-induced behaviors can be characterized as opiate specific. This was approached by testing several agonists, several partial agonists, and a pure antagonist naloxone. These studies were followed by testing dextrorphan, the inactive enantiomer of the narcotic agonist levorphanol. Finally, if certain effects are opiate-specific, these should be antagonized by naloxone.

Morphine--shock current interactions

The effects of morphine on shock-induced behaviors were determined at 3 currents: 1.5 ma (Table 8), 2 ma (Table 9), and 4 ma (Table 10).

The effect of morphine on net rotations induced by 2 ma appeared bimodal. Net was increased at 5 and 7.5 mg/kg and at 80 mg/kg but was not significantly different from control (saline) at 10, 20, and 40 mg/kg. When tested at 4 ma shock, however, only the 40 and 80 mg/kg doses increased net rotation. No dose of morphine significantly altered net rotation in rats tested with 1.5 ma.

It is possible that the increase in shock-induced rotation induced by morphine is an additive effect because 5 mg/kg of morphine induced significant net rotation when measured in spherical rotometers (Morihisa & Glick 1977). To test this possibility rats were injected with 5 mg/kg of morphine and placed in the shock rotometers. During the second 5 minutes, rotations were recorded without shock.

Table 9

Effects of morphine on shock (2 ma)-induced behaviors. Values are means ± S.D.s.

Dose mg/kg	n	Net	Dom. (%)	TQT	XQT	Sqk	Jump
0	12	2.6±2.2	65.6±12.9	59.0±16.2	19.9±12.0	25.1± 6.6[b]	11.6± 7.8[b]
1	14	4.5±4.4	73.0±15.4	62.4±41.0	25.5±37.6	22.1± 7.8	5.1± 4.8[d]
2.5	13	2.2±2.8	65.7±15.8	42.0±26.1	17.2±17.4	16.0±10.2[d]	3.8± 5.3[d]
3.75	6	2.7±2.3	64.0± 9.6	58.3±16.1	19.7±21.6	18.2±11.7	8.2±11.6
5	12	7.9±4.6[e]	90.8±16.9[e]	45.6±23.2	6.6± 5.8	7.6± 9.0[b,e]	2.1± 3.5[b,e]
7.5	10	6.1±4.9[d]	86.9±14.8[e]	43.5±19.9	11.1±11.1	7.0± 9.1[b,e]	6.3±13.7[b]
10	16	1.8±2.9	71.6±18.4[b]	19.7±28.8[e]	7.9±17.2	0.6± 1.2[e]	0.4± 1.2[e]
20	16	1.9±2.1	90.7±15.7[c,e]	14.4±13.7[e]	3.6± 4.5[d]	3.3± 7.9[e]	0.8± 2.1[e]
40	6	6.5±4.1	93.3±16.3[e]	35.0±15.6	3.7± 1.9[d]	0.3± 0.8[e]	1.0± 0.2[e]
80	6	8.3±6.6[e]	96.1±10.0[e]	38.2±22.0	3.5± 4.8[d]	0.3± 0.8[e]	1.0± 0.2[e]
120	6	6.6±2.9	100.0± 0[e]	28.8±10.2	2.2± 2.3[d]	0.3± 0.8[e]	0± 0[e]
F[a]		4.90	8.10	5.06	2.35	14.17	3.47
p-value		<.0001	<.0001	<.0001	<.01	<.0001	<.001

[a] Computed from one-way analysis of variance.

[b] Means computed from data of 8 rats.

[c] Mean computed from data of 10 rats.

[d] Significantly different from control (0 mg/kg) at $p < .05$ (Duncan's test).

[e] Significantly different from control (0 mg/kg) at $p < .01$ (Duncan's test).

Net rotations of rats receiving morphine and shock were significantly higher than that of rats receiving morphine only ($t = 5.72$, $p < .001$). The mean net (± S.D.) of the rats that received morphine only was 0.3 ± 0.4. This value was no different ($t = 0.5$, $p > .1$) from saline-treated rats tested at 0 ma in the second 5 minutes (Table 1). Therefore, in a period of 5 minutes, the interaction of footshock (2 ma) and morphine induced greater net rotation in rats than that of either morphine alone or footshock alone, or than that of footshock of 2 ma alone added to morphine alone.

Percent dominance was clearly altered by morphine in the 2 ma group. As with net, the dose response curve is bimodal. Dominance was increased at all doses tested equal to or greater than 5 mg/kg, except for 10 mg/kg. Although the shape of the curve and magnitude of the changes in the 4 ma group appeared similar to those of the 2 ma group, the variance was large and the analysis of variance was not statistically significant. There was no significant effect of morphine at any dose tested on dominance in the 1.5 ma rats. It should be noted, however, that baseline dominance (saline-treated animals) was 84.3 percent. This was significantly higher than 2 and 4 ma (see Table 1). As was suggested above this value may not be a good estimate of dominance for rats shocked with 1.5 ma.

Morphine decreased TQT in the 4 ma rats at all doses tested. In the 2 ma group TQT were only decreased by doses of 10 and 20 mg/kg. No dose of morphine tested had any significant effect on TQT in the 1.5 ma group.

XQT were also decreased by all doses of morphine in the 4 ma group. High doses, i.e. 20, 40, 80, and 120 mg/kg, significantly decreased XQT in the 2 ma group. XQT were decreased by 40 mg/kg of morphine in the 1.5 ma rats.

Table 10

Effects of morphine on shock (4 ma)-induced behaviors. Values are means ± S.D.s.

Dose (mg/kg)	n	Net	Dom. (%)	TQT	XQT	Sqk	Jump
0	8	5.3±4.1	68.8±12.7	136.6±26.7	80.6±37.0	58.5±12.6	19.8±15.4
2.5	6	3.7±3.4	85.2±43.5	52.2±25.0[c]	24.2±15.9[b]	42.8±27.3	29.8±28.4
5	6	7.0±4.6	90.0±38.9	72.3± 9.1[c]	28.3±14.6[b]	16.2± 9.5[c]	12.8±14.0
7.5	6	6.7±4.7	80.8±34.3	66.8±29.0[c]	21.5±21.3[b]	27.2±49.6[b]	24.2±21.0
10	6	7.5±5.1	83.0±33.4	59.8±15.5[c]	9.8±14.4[b]	9.7± 2.3[c]	8.7±20.7
20	6	9.8±6.7	89.1±39.9	66.7±27.1[c]	11.3±16.9[b]	5.2± 5.3[c]	21.0±33.4
40	6	13.7±8.5[b]	96.1±42.6	80.7±17.8[c]	10.0±14.2[b]	5.2± 9.9[c]	9.3±12.7
80	6	13.5±4.9[b]	96.5±38.9	74.0±23.5[c]	2.5± 2.5[c]	0± 0[c]	1.8± 1.8
120	6	9.2±4.3	91.7±32.4	56.2±19.1[c]	7.5±11.4[b]	10.2±24.9[c]	1.7± 4.1
F[a]		2.63	1.40	9.38	10.76	4.02	1.51
p-value		<.02	>.1	<.0001	<.0001	<.001	>.1

[a]Computed from one-way analysis of variance.

[b]Significantly different from controls (0 mg/kg) at $p < .05$ (Duncan's test).

[c]Significantly different from controls (0 mg/kg) at $p < .01$ (Duncan's test).

Pain indices, i.e. squeaking and jumping, were also modified differentially in the 3 experimental groups.

Squeaks were decreased by all doses equal to or greater than 2.5 mg/kg in the 2 ma rats. Squeaks were decreased by all doses equal to or greater than 5 mg/kg in the 4 ma rats. In the 1.5 ma group, doses of 7.5, 10, and 40 mg/kg reduced the incidence of squeaking. Although no dose of morphine significantly decreased jumping in the 1.5 and 4 mg groups, most doses (1, 2.5, 5, 10, 20, 40, 80, and 120 mg/kg) did reduce the number of jumps in the 2 ma rats.

Interrelationship of morphine effects

Correlations were determined for 31 rats treated with 5 mg/kg of morphine and shocked with 2 ma (Table 11). This was done in order to investigate the possibility that morphine's effect on shock-induced circling was related to its effect on shock-induced pain responses. Percent dominance was negatively correlated with squeaks and jumps; these negative correlations were also found for rats that only received shock (Table 2). Net and dominance, however, were not correlated (Table 11). These rats were treated with 5 mg/kg of morphine, a dose that significantly increased net and dominance (Table 9). When the correlation coefficient of net and dominance for these 31 rats was compared to the correlation coefficient of the 50 rats that received only 2 ma footshock, a significant difference was found ($c = 2.46$, $p < .02$). Only one other correlation coefficient was significantly different in the shock - 5 mg/kg morphine group. Whereas squeaks and jumps were not correlated in the footshock group, they were positively correlated in the footshock-morphine group ($c = 2.08$, $p < .04$).

Table 11

Correlation coefficients of 31 rats that were shocked with 2 ma and received 5 mg/kg of morphine.

	Net	Dom.	TQT	XQT	Sqk	Jump
Net	-	.21	.39[a]	.00	-.21	-.02
Dom.	.21	-	-.51[b]	-.61[c]	-.35[a]	-.50[b]
TQT	.39[a]	-.51[b]	-	.85[d]	.45[a]	.73[d]
XQT	.00	-.61[c]	.85[d]	-	.59[c]	.82[d]
Sqk	-.21	-.35[a]	.45[a]	.59[c]	-	.61[c]
Jump	-.02	-.50[b]	.73[d]	.82[d]	.61[c]	-

[a]Significant at $p < .05$.

[b]Significant at $p < .01$.

[c]Significant at $p < .001$.

[d]Significant at $p < .0001$.

Because of the lack of correlation of net and dominance in shocked rats treated with 5 mg/kg of morphine, the correlation between net and dominance was also determined for rats treated with 80 mg/kg of morphine. For 11 of those rats given 2 ma footshock, no correlation between net and dominance was found ($r = 0.01$, $p > .1$). This correlation coefficient was also significantly different from that of the 50 rats (Table 2) that were given 2 ma footshock only ($c = 2.27$, $p < .03$).

It is conceivable that the lack of correlation is due to some change induced by morphine independent of footshock. Therefore, 18 rats given 5 mg/kg of morphine were placed in spherical rotometers for 1 hour. Net and dominance were calculated and were found to be significantly correlated ($r = 0.58$, $p < .01$). Because net and dominance were positively correlated in the presence of either footshock or 5 mg/kg of morphine but not in the presence of both, the interaction of footshock and morphine induced the change that eliminates this correlation.

The results of these experiments show that morphine increases two measures of shock-induced lateralized circling: net and dominance. The lack of correlation between the two measures suggests that each is affected by the interaction of morphine and shock differently. Comparison of the net- and dominance-dose responses curves in either the 2 ma or 4 ma rats supports this contention.

For rats shocked with 2 ma the dose response curves of net and dominance are bimodal. However, whereas net is increased at only 5, 7.5, and 80 mg/kg, dominance is increased at all doses from 5 mg/kg to 80 mg/kg except 10 mg/kg. At the low doses (5 and 7.5 mg/kg) at which net and dominance were increased, TQT and XQT were unchanged. Thus, at these doses

morphine is altering neither the amount of movement nor the total number of turns the rats are making. It follows that at these doses morphine alters the gate; that is, dominance is increased. Because the amount of movement is unchanged, net is increased as a result of the increased dominance.

At higher doses, for rats shocked with 2 ma, dominance was increased, except at 10 mg/kg. At 10 and 20 mg/kg, TQT were decreased. Perhaps net is not significantly increased at these doses because the rats move much less than they do at 5 and 7.5 mg/kg. At 40, 80, and 120 mg/kg, net rotations were significantly increased relative to that of 10 and 20 mg/kg ($p < .05$ for all 6 comparisons, Duncan's Multiple Range Test). TQT were no longer decreased compared to that of saline at these high doses, i.e. 40, 80, and 120 mg/kg. Thus, at high doses where movement is no longer suppressed relative to saline-treated controls, net is enhanced. There seems to be a relationship between movement and net rotations. This relationship is consistent with the model proposed in "Shock Studies" above.

Rats treated with high doses of morphine, particularly 80 and 120 mg/kg, were observed to be quite cataleptic. When placed in the shock apparatus they usually lay on their sides. However, during the footshock period, these animals circled. It should be noted that not only was dominance quite high for rats treated with 40, 80, and 120 mg/kg but they additionally made very few XQT. Having high dominance and few XQT, these animals, when they moved, showed very distinct lateral bias, circling almost invariably in 1 direction.

Bimodality of morphine dose response curves

Morphine's shock-induced net-dose response curve is bimodal. The (non-shock) net dose curve of amphetamine is also bimodal. Direction induced by 1 mg/kg of amphetamine tends to be in the opposite direction to that induced by 20 mg/kg (Jerussi & Glick 1976). Because of the possibility that the preferred direction induced by the high dose (80 mg/kg) of morphine was opposite to that induced by the low dose (5 mg/kg), rats were shocked twice with 2 ma 1 week apart. For the first shock test, the rats were given 5 mg/kg of morphine. For the second, the rats received 80 mg/kg. The preferred directions during the first test were usually opposite to the preferred directions during the second test (Table 12). In table 13 comparisons of the effects of the two doses of morphine on shock-induced behavior are shown. No significant changes were found except for the reversal of direction.

It was necessary to determine whether this reversal of direction was a dose phenomenon or due to just two shock treatments. This was investigated by determining the consistency of the effects of two shock treatments and the consistency of shock interactions with morphine. Table 12 shows that 2 ma induced a consistent direction when tested twice. Two treatments of 5 mg/kg of morphine and 2 ma also induced consistent directional preference. However, if rats were shocked during the first test and retested with shock and given either 5 or 80 mg/kg, the preferred direction during the second test was random relative to that of the first (Table 12).

Several other findings came out of these studies of repeated tests. Rats shocked with 2 ma twice showed significant increases in net and dominance during the second test. TQT and XQT, as well as squeaks and

Table 12

Consistency of preferred direction of rats that were tested twice; 1 week separated the two tests. Rats were shocked with 2 ma during each test.

Test 1 Drug & dose (mg/kg)	Test 2 Drug & dose (mg/kg)	Ratio[a]	χ^2	p-value
saline	saline	11/12	8.33	<.01
saline	morphine 5	5/8	0.50	>.1
saline	morphine 80	2/7	1.28	>.1
morphine 5	morphine 5	9/10	8.00	<.005
morphine 5	morphine 80	2/11	4.46	<.04
saline	naloxone 5	13/14	10.28	<.0005

[a]Number of rats that maintained their preferred direction in both tests is expressed as a fraction of the total number of rats tested.

Table 13

Determination of effects of 2 shock (2 ma) tests separated by 1 week (Tests 1 and 2). In the first test, rats (n=11) received 5 mg/kg of morphine; in the second, 80 mg/kg of morphine.

Test	Morphine Dose (mg/kg)	Net	Dom. (%)	TQT	XQT	Sqk	Jump
1	5	3.1±3.2	86.8±20.0	24.3±18.6	5.3±6.6	5.1±8.1	1.3±4.3
2	80	4.6±3.2	90.3±16.9	31.7±17.2	6.4±5.0	1.1±2.9	0.3±0.5
t[a]		0.95	0.16	0.84	0.46	1.54	0.85
p-value		>.1	>.1	>.1	>.1	>.1	>.1

[a]Paired t-test.

Table 14

Determination of effects of 2 shock (2 ma) tests separated by 1 week (Tests 1 and 2). In both tests rats (n=11) received saline.

Test	Net	Dom. (%)	TQT	XQT	Sqk	Jump
1	2.7±2.1	66.0±11.0	59.3±20.7	23.9±18.8	23.0±11.0	11.9± 8.6
2	7.1±4.6	85.0±17.0	77.2±52.1	34.2±46.0	27.8± 6.2	12.8±24.7
t[a]	4.12	4.41	1.55	0.92	1.83	0.13
p-value	<.0014	<.001	>.1	>.1	>.1	>.1

[a]Paired t-test

Table 15

Determination of effects of 2 shock (2 ma) tests separated by 1 week (Tests 1 and 2). In the first test rats (n=8) received saline; in the second, rats received 5 mg/kg of morphine.

Test	Drug & dose (mg/kg)	Net	Dom. (%)	TQT	XQT	Sqk	Jump
1	saline	2.6±2.2	68.0±14.1	53.2±30.6	16.9±10.3	25.6± 8.8	12.3±11.0
2	morphine 5	4.3±4.1	82.2±18.0	38.4±19.4	13.2±11.9	27.3±20.5	4.2± 8.1
t[a]		1.61	2.48	2.13	0.89	0.34	2.82
p-value		>.1	<.03	<.06	>.1	>.1	<.02

[a]Paired t-test.

Table 16

Determination of effects of 2 shock (2 ma) tests separated by 1 week (Tests 1 and 2). In the first test, rats (n=7) received saline; in the second, rats were given 80 mg/kg of morphine.

Test	Drug & Dose (mg/kg)	Net	Dom. (%)	TQT	XQT	Sqk	Jump
1	saline	3.4±4.1	69.0±17.4	40.9±12.0	12.2±8.4	16.0±6.5	6.0±8.2
2	morphine 80	8.6±3.1	96.9± 6.0	38.9±11.6	2.6±2.8	1.5±3.1	0.4±0.5
t[a]		3.72	4.24	0.37	3.44	7.92	2.29
p-value		<.004	<.002	>.1	<.0064	<.001	<.045

[a]Paired t-test.

Table 17

Determination of effects of 2 shock (2 ma) tests separated by 1 week (Tests 1 and 2). In both tests, rats (n=10) received 5 mg/kg of morphine.

Test	Drug & dose (mg/kg)	Net	Dom. (%)	TQT	XQT	Sqk	Jump
1	morphine 5	7.6±4.6	88.2±20.0	52.3±33.0	10.8±13.7	3.4±4.5	2.9±3.5
2	morphine 5	5.2±4.5	84.4±17.1	41.8±32.8	7.3±10.6	7.4±6.9	2.3±6.1
t[a]		3.24	1.49	1.15	0.76	1.70	0.46
p-value		<.009	>.1	>.1	>.1	>.1	>.1

[a]Paired t-test.

jumps, were unchanged (Table 14). It follows that a second shock experience alters the gate and the activity going through it without increasing the rat's movement.

The data for rats shocked with 2 ma and subsequently shocked with 2 ma and given 5 mg/kg of morphine are shown in Table 15. Net rotations were not significantly increased during the second test, but dominance was. This can be viewed in two ways: shock pretreatment antagonizes morphine's increase of shock-induced net rotation, or morphine antagonizes the second shock treatment's induction of significantly increased net.

When 80 mg/kg of morphine and 2 ma shock were administered 1 week after 2 ma, net rotations were significantly enhanced (Table 16). Thus, although the increase in net rotation was blocked by 5 mg/kg, it was not blocked by 80 mg/kg. The dose effect difference prompted a determination of morphine dose response curves for rats pretreated with shock (see below). If rats were given 2 ma footshock and 5 mg/kg morphine twice, net rotations were significantly decreased in the second test (Table 17).

Effects of shock pretreatment on morphine-shock interactions

Because shock pretreatment induced some changes in the subsequent interaction of morphine and shock, dose responses curves in the presence of 2 ma footshock were determined 1 week after testing with 2 ma only (Table 18).

Shock pretreatment can be considered to antagonize morphine. That is, higher doses were required to significantly alter squeaking, jumping, and TQT than those doses required without shock pretreatment (compare Tables 18 and 9). In fact, TQT, XQT, squeaking, and jumping were not altered by 2 shock treatments (Table 14). Although the baselines remained

Table 18

Effects of shock (2 ma) pretreatment on subsequent shock (2 ma)-morphine interactions. Values are means ± S.D.s of the second test, determined 1 week after shock pretreatment.

Dose (mg/kg)	n	Net	Dom. (%)	TQT	XQT	Sqk	Jump
0	10	8.2±4.6	87.2±15.2	74.3±52.8	28.7±44.4	28.7± 3.8	15.0±29.7
1	5	4.6±2.6	73.9± 4.5	73.8±28.6	36.2±36.7	40.4±34.0	19.8±16.0
2.5	11	5.7±5.2	89.7±12.0	72.5±35.2	37.5±43.0	25.3± 8.7	19.4±23.4
5	10	4.4±2.5	87.1±15.8	42.7±19.7	14.3±12.7	38.2±29.6	4.3± 9.1
7.5	6	9.2±7.2	84.4±14.8	90.4±48.9	40.8±52.6	22.0±16.8	30.8±45.2
10	9	10.2±3.2	96.6± 5.1[b]	51.7±20.6	8.6± 9.4	11.3± 8.8	0.4± 1.0[b]
20	9	8.8±4.8	90.0±11.1	47.8±18.1	8.2± 7.8	3.2± 6.3[b]	3.6± 7.9
80	5	8.2±2.5	97.1± 5.7[b]	36.0± 6.9[b]	1.8± 1.3	1.8± 4.0[b]	0.2± 0.5[b]
120	6	8.8±3.7	96.4± 5.5[b]	41.3±14.7[b]	3.3± 3.2	1.2± 2.4[b]	0.3± 0.5[b]
F[a]		0.42	2.14	2.39	1.57	5.03	2.21
p-value		>.1	<.05	<.02	>.1	<.001	<.04

[a]Computed from one-way analysis of variance.

[b]Significantly different from control (0 mg/kg) at $p < .05$ (Duncan's test).

the same for these behaviors, the potency of morphine in decreasing them was clearly reduced. Morphine's efficacy as an analgesic and as a drug that reduces shock-induced movement is not only determined by the interaction of dose and shock intensity but also by previous experience.

Net induced by shock was no longer altered by morphine. Rats shocked twice averaged 8 net (Table 18). A possible explanation for the antagonism of morphine's enhancing property is that shock pretreatment induces a maximal increase in the gate. This hypothesis is consistent with the observed increase in dominance induced by a second shock treatment (Tables 14 and 18). All doses of morphine except 1 mg/kg in this shock pretreatment group increased shock-induced dominance. The difference from baseline was, at most 14 percent (at 80 mg/kg). The greatest difference of dominance in the acute shock-morphine group was about 34 percent (see Table 9, 120 mg/kg). Therefore, morphine maintained an ability to alter the shock gate but its effect was smaller. It was more potent if potency means the lowest dose required to induce the effect. Shock-induced net was not significantly altered because of this ceiling effect.

Methadone

Methadone (Table 19) at doses of 2.5 and 5 mg/kg increased shock-induced net. The drug also increased shock-induced dominance at doses of 2.5, 5, and 7.5 mg/kg. Shock-induced TQT were reduced by 7.5 mg/kg. Shock-induced XQT were decreased by 5, 7.5, and 10 mg/kg.

Methadone also was analgesic. It induced a significant reduction in the number of squeaks at all doses tested. It also decreased jumping at all doses except 2.5 mg/kg.

Table 19

Effects of methadone on shock (2 ma)-induced behaviors. Values are means ± S.D.s.

Dose (mg/kg)	n	Net	Dom. (%)	TQT	XQT	Sqk	Jump
0	12	2.6±2.2	65.6±12.9	59.0±16.2	19.9±12.0	25.1±6.6[b]	11.6±7.8[b]
1.25	6	4.3±2.3	81.0±11.7	50.3±25.5	14.3±10.3	14.8±8.3[d]	3.4±3.6[c]
2.5	6	8.8±7.3[c]	85.5±20.7[c]	61.3±26.7	16.7± 8.9	5.3±5.1[d]	6.3±8.7
5	6	10.0±7.8[d]	83.8±20.1[c]	56.3±25.6	3.0± 2.4[d]	2.2±3.9[d]	0.5±1.2[d]
7.5	6	5.2±3.3	95.8±10.2[d]	27.7±16.3[c]	4.3± 3.1[d]	0± 0[d]	2.2±5.3[d]
10	6	2.7±2.2	78.8±23.6	35.5±24.1	7.5± 6.9[c]	0.2±0.4[d]	0.8±1.2[d]
F[a]		3.37	14.03	2.47	3.20	28.20	3.96
p-value		<.01	<.007	<.05	<.02	<.0001	<.006

[a]Computed from one-way analysis of variance.

[b]Means computed from data of 8 rats.

[c]Significantly different from controls (0 mg/kg) at $p < .05$ (Duncan's test).

[d]Significantly different from controls (0 mg/kg) at $p < .01$ (Duncan's test).

Table 20

Effects of meperidine on shock (2 ma)-induced behaviors. Values are means ± S.D.s.

Dose (mg/kg)	n	Net	Dom. (%)	TQT	XQT	Sqk	Jump
0	12	2.6±2.2	65.6±12.9	59.0±16.2	19.9±12.0	25.1± 6.6[b]	11.6± 7.8[b]
5	6	3.2±1.6	77.4±18.7	62.0±36.8	32.0±25.7	21.7±11.2	12.3±11.7
10	7	6.1±3.9	79.7±14.7	65.4±30.6	19.1±17.3	9.9± 8.8[d]	8.3±11.6
25	6	9.7±4.9[c]	97.8± 5.3[d]	47.5±23.5	6.2± 7.0[c]	8.2± 7.5[d]	1.6± 1.4[c]
50	6	5.7±4.3	88.7±20.3[d]	35.3±21.3	6.0± 7.3[c]	5.0± 7.4[d]	2.8± 2.1[c]
F[a]		5.00	4.99	1.47	3.23	7.71	2.67
p-value		<.003	<.003	>.1	<.02	<.001	<.05

[a]Computed from one-way analysis of variance.

[b]Means computed from data of 8 rats.

[c]Significantly different from controls (0 mg/kg) at $p < .05$ (Duncan's test).

[d]Significantly different from controls (0 mg/kg) at $p < .01$ (Duncan's test).

Meperidine

Meperidine (Table 20) induced significant increases in shock-induced net at 25 mg/kg. At 25 and 50 mg/kg this drug increased shock-induced percent dominance. Although shock-induced TQT were not affected by meperidine, shock-induced XQT were depressed by 25 and 50 mg/kg.

Meperidine reduced squeaking at 10, 25, and 50 mg/kg. At 25 and 50 mg/kg it suppressed jumping.

Levorphanol

The effects of levorphanol on shock-induced behaviors are shown in Table 21. At a dose of 1.5 mg/kg levorphanol increased shock-induced net. A dose of either 1 or 1.5 mg/kg increased shock-induced dominance. Both shock-induced TQT and XQT were unaltered by any dose tested.

Squeaks and jumps were both reduced by the same doses: 1.5, 2, and 4 mg/kg.

Propoxyphene

Propoxyphene increased shock-induced net rotations at a dose of 5 mg/kg, but it was without effect on shock-induced dominance (Table 22). The drug decreased shock-induced TQT at 25 and 12.5 mg/kg but not at 5 and 7.5 mg/kg. It had no significant effect on shock-induced XQT.

Although propoxyphene had no significant effect on jumping, it decreased squeaking at all doses tested.

Pentazocine

The effects of pentazocine on shock-induced behaviors are shown in Table 23. It increased shock-induced net at 15 mg/kg. At doses of 15 and 20 mg/kg pentazocine elicited significant increases in shock-induced dominance. Shock-induced TQT and XQT were unaffected by the drug.

Table 21

Effects of levorphanol on shock (2 ma)-induced behaviors. Values are means ± S.D.s.

Dose (mg/kg)	n	Net	Dom. (%)	TQT	XQT	Sqk	Jump
0	12	2.6±2.2	65.6±12.9	59.0±16.2	19.9±12.0	25.1±16.6[b]	11.6±7.8[b]
1	6	4.7±2.6	88.3±15.1[c]	44.5±15.5	19.2±16.4	7.2± 5.5[d]	7.5±9.3
1.5	6	6.0±2.4[c]	84.8±14.0[c]	50.7±15.3	14.7±10.0	1.0± 0.9[d]	2.0±3.3[d]
2	6	4.0±2.8	82.6±20.8	38.7±20.3	8.0± 5.0	2.7± 1.8[d]	1.3±2.8[d]
4	6	2.3±2.3	77.7±23.2	34.8±27.8	10.8±13.3	3.8± 5.5[d]	0.8±2.0[d]
F[a]		2.73	2.67	1.95	1.38	31.42	4.53
p-value		<.04	<.05	>.1	>.1	<.0001	<.005

[a]Computed from one-way analysis of variance.

[b]Means computed from data of 8 rats.

[c]Significantly different from controls (0 mg/kg) at $p < .05$ (Duncan's test).

[d]Significantly different from controls (0 mg/kg) at $p < .01$ (Duncan's test).

Table 22

Effects of propoxyphene on shock (2 ma)-induced behaviors. Values are means ± S.D.s.

Dose (mg/kg)	n	Net	Dom. (%)	TQT	XQT	Sqk	Jump
0	12	2.6±2.2	65.6±12.9	59.0±16.2	19.9±12.0	25.1± 6.6[b]	11.6± 7.8[b]
2.5	6	1.6±1.8	74.5±38.9	37.3±20.8[c]	8.0± 4.9	15.3±10.4[c]	1.3± 2.4
5	6	8.2±7.3[d]	82.5±36.2	63.7±19.5	11.8± 8.4	15.5± 7.0[c]	11.5±13.8
7.5	6	5.8±3.5	87.7±41.7	48.5± 9.6	14.5±16.5	11.5± 8.1[d]	11.4± 1.4
12.5	5	2.4±2.3	84.7±49.7	27.4±12.4[d]	5.7± 5.0	6.6± 5.4[d]	1.3± 2.2
F[a]		3.47	1.22	5.08	2.33	5.24	2.21
p-value		<.02	>.1	<.003	<.08	<.003	<.09

[a]Computed from one-way analysis of variance.

[b]Means computed from data of 8 rats.

[c]Significantly different from controls (0 mg/kg) at $p < .05$ (Duncan's test).

[d]Significantly different from controls (0 mg/kg) at $p < .01$ (Duncan's test).

Table 23

Effects of pentazocine on shock (2 ma)-induced behaviors. Values are means ± S.D.s.

Dose (mg/kg)	n	Net	Dom. (%)	TQT	XQT	Sqk	Jump
0	12	2.6±2.2	65.6±12.9	59.0±16.2	19.9±12.0	25.1±6.6[b]	11.6± 7.8[b]
10	6	4.3±4.6	76.9±18.8	39.2±20.9	5.8± 2.6	7.7±8.9[d]	1.0± 2.0
15	6	8.7±6.1[d]	94.8± 8.7[d]	52.3±37.0	13.7±23.4	1.3±2.8[d]	9.2±18.7
20	6	6.0±3.9	82.2±16.7[c]	52.3±21.4	11.0± 8.5	3.3±5.8[d]	1.3± 1.5
F[a]		3.28	5.29	0.46	1.62	20.79	1.98
p-value		<.03	<.005	>.1	>.1	<.0001	>.1

[a]Computed from one-way analysis of variance.

[b]Means computed from data of 8 rats.

[c]Significantly different from controls (0 mg/kg) at $p < .05$ (Duncan's test).

[d]Significantly different from controls (0 mg/kg) at $p < .01$ (Duncan's test).

Table 24

Effects of cyclazocine on shock (2 ma)-induced behaviors. Values are means ± S.D.s.

Dose (mg/kg)	n	Net	Dom. (%)	TQT	XQT	Sqk	Jump
0	12	2.6±2.2	65.6±12.9	59.0±16.2	19.9±12.0	25.1±6.6[b]	11.6± 7.8[b]
0.625	4	4.0±2.9	69.0± 9.6	86.8±36.4[c]	44.7±25.2[c]	19.8±9.8	21.3±14.5
1	6	4.5±3.0	77.8±18.1	47.3±11.4	13.2± 9.0	16.2±2.6[c]	8.0±13.5
1.25	6	4.8±2.7	91.0±14.8[d]	40.8±21.0	14.8±13.6	13.3±9.9[d]	4.3± 4.6
2	6	2.3±2.3	79.2±22.4	38.8±22.5	25.5±19.5	4.8±4.8[d]	11.3±14.4
F[a]		1.38	3.70	4.14	3.18	7.67	1.49
p-value		>.1	<.01	<.008	<.01	<.001	>.1

[a]Computed from one-way analysis of variance.

[b]Means computed from data of 8 rats.

[c]Significantly different from controls (0 mg/kg) at $p < .05$ (Duncan's test).

[d]Significantly different from controls (0 mg/kg) at $p < .01$ (Duncan's test).

Pentazocine decreased squeaking at all doses tested, but the drug was without effect on jumping.

Cyclazocine

Cyclazocine (Table 24) was without effect on shock-induced net, but it increased shock-induced dominance at 1.25 mg/kg. Shock-induced TQT and XQT were increased relative to controls by a dose of 0.625 mg/kg.

Cyclazocine reduced squeaks at doses of 1, 1.25, and 2 mg/kg, but it had no significant effect on jumping.

Nalorphine

Nalorphine increased shock-induced net at doses of 25 and 50 mg/kg, but it was without significant effect on shock-induced dominance (Table 25). Shock-induced TQT and XQT were increased at 100 mg/kg.

Nalorphine had no significant effect on squeaking. At 100 mg/kg nalorphine increased jumping.

Dextrorphan

The dose chosen for the test was 1.5 mg/kg. This dose is the same as the dose at which levorphanol induced an increase of shock-induced net. The rationale for this is that dextrorphan is the inactive enantiomer of levorphanol.

At this dose relative to saline-treated rats dextrorphan did not alter shock-induced net ($t = 0.93$, $p > .1$), dominance ($t = 1.76$, $p > .1$), TQT ($t = 1.11$, $p > .1$), XQT ($t = 0.68$, $p > .1$), squeaks ($t = 1.62$, $p > .1$), or jumps ($t = 0.23$, $p > .1$).

Naloxone

Naloxone, at all doses tested, had no significant effect on any of the shock-induced behaviors (Table 26).

Table 25

Effects of nalorphine on shock (2 ma)-induced behaviors. Values are means ± S.D.s.

Dose (mg/kg)	n	Net	Dom. (%)	TQT	XQT	Sqk	Jump
0	12	2.6±2.2	65.6±12.9	59.0±16.2	19.9±12.0	25.1± 6.6[b]	11.6± 7.8[b]
5	6	4.3±3.7	82.5±34.3	46.3±20.0	16.7±20.3	17.3± 7.7	5.2±12.2
12.5	6	6.0±5.7	85.2±43.5	46.5±17.9	9.2± 5.6	15.3±11.2	3.8± 4.0
25	6	7.3±5.2[c]	77.1±14.0	73.7±24.6	25.0±16.6	25.0±17.4	16.5±15.8
50	6	7.5±2.8[c]	82.5±16.9	78.3±48.8	31.0±50.8	28.3±51.2	17.3±31.1
100	6	6.7±4.2	77.1±21.8	110.0±38.2[d]	68.0±24.9[c]	33.7±36.6	47.8±34.0[d]
150	6	2.7±2.7	68.2±20.8	53.3± 23.9	25.3±19.5	20.3± 6.3	23.8±15.3
F[a]		2.34	1.47	3.96	2.65	0.40	3.49
p-value		<.05	>.1	<.003	<.03	>.1	<.003

[a]Computed from one-way analysis of variance.

[b]Means computed from data of 8 rats.

[c]Significantly different from controls (0 mg/kg) at $p < .05$ (Duncan's test).

[d]Significantly different from controls (0 mg/kg) at $p < .01$ (Duncan's test).

Table 26

Effects of naloxone on shock (2 ma)-induced behaviors. Values are means ± S.D.s.

Dose (mg/kg)	n	Net	Dom. (%)	TQT	XQT	Sqk	Jump
0	12	2.6±2.2	65.6±12.9	59.0±16.2	19.9±12.0	25.1± 6.6	11.6± 7.8
0.5	6	2.0±1.8	81.9±46.2	54.0±25.8	30.0±20.3	21.5±11.1	26.3±25.7
2.5	6	3.5±3.1	79.0±36.2	44.7±32.9	16.0±13.9	15.8± 6.7	9.0±14.8
5	6	2.6±2.1	74.5±39.9	59.4±56.3	26.6±45.0	26.6± 3.7	9.4±19.4
10	6	2.8±2.9	84.7±43.5	31.3±14.8	9.3± 8.9	29.5±22.5	3.0± 3.9
25	6	3.5±3.0	90.7±48.8	28.7± 9.9	8.0± 5.3	23.7± 7.4	1.7± 2.6
F[a]		0.33	0.99	1.57	1.24	1.02	2.26
p-value		>.1	>.1	>.1	>.1	>.1	<.07

[a]Computed from one-way analysis of variance.

[b]Means computed from data of 8 rats.

Morphine-naloxone interactions

Morphine dose response curves for the shock-induced behaviors were determined in the presence of 0.5 mg/kg of naloxone (Table 27). Morphine induced significant shock-induced net rotation at doses of 40 and 80 mg/kg. Within the morphine dose range studied this curve was unimodal, but without naloxone treatment the net morphine dose curve was bimodal (Table 9). It is not apparent, in comparing these two dose response curves, if naloxone shifted the morphine dose response curve to the right or only blocked the low dose, i.e. 5 and 7.5 mg/kg, effects of morphine. That is, is the induction of increased net seen at 40 and 80 mg/kg, the low dose effect shifted to the right by naloxone or is this the high dose effect of morphine? If the latter be true, then the high dose effect is not antagonizable by naloxone and is presumably not opiate specific.

The high dose effect was found to also be naloxone responsive. Six rats were given 1 mg/kg of naloxone (twice the naloxone dose used in the previous determination) and 80 mg/kg or morphine. Net rotations were significantly reduced by this naloxone treatment ($t = 2.88$, $p < .02$).

Shock-induced dominance was increased at 80 mg/kg of morphine in the presence of 0.5 mg/kg of naloxone. If naloxone were only antagonizing the first peak shown in Table 9, it would be expected that there would be more doses at which dominance is increased in the presence of naloxone, i.e. 20, 40, 80, and 120 mg/kg. On the other hand, if the high dose effect is blockable by naloxone, then the increase in dominance in the presence of 0.5 mg/kg naloxone seen at 80 mg/kg should also be seen at 120 mg/kg. That is, in Table 9 7.5 mg/kg of morphine (1½ times 5 mg/kg) also increased

Table 27

Effects of morphine and 0.5 mg/kg of naloxone on shock (2 ma)-induced behaviors. Values are means ± S.D.s.

Dose of morphine (mg/kg)	n	Net	Dom. (%)	TQT	XQT	Sqk	Jump
0	12	2.6±2.2	65.6±12.9	59.0±16.2	19.9±12.0	25.1± 6.6[b]	11.6± 7.8[b]
2.5	6	2.8±2.9	70.6±17.7	34.2± 8.2	9.5± 6.7	15.8±12.9	6.7± 6.4
5	6	3.3±1.2	79.5±11.5	30.8±10.9[c]	7.5± 4.3	8.0± 7.9	4.5± 5.2
7.5	6	1.2±1.7	61.0±14.9	35.2±20.8	12.5± 7.7	10.8±11.5	8.2±10.5
10	4	2.8±1.7	71.3±11.7	37.8± 8.2	10.8± 5.9	14.0± 5.3	9.0± 7.8
20	6	1.3±1.4	71.8±22.5	29.3±12.9[c]	10.7± 8.5	41.7±82.6	7.0± 7.8
40	6	9.0±6.4[d]	77.1±20.4	33.7±23.6	14.5±23.4	18.2± 5.4	17.5±20.4
80	6	13.2±5.9[d]	92.9±16.0[d]	85.2±38.8	10.6±16.1	16.3±10.7	13.7±18.7
120	5	5.2±5.5	83.7±19.3	71.4±17.7	24.2±24.5	37.0±75.6	14.4±24.7
F[a]		7.06	2.51	4.15	0.73	0.51	0.61
p-value		<.0001	<.02	<.006	>.1	>.1	>.1

[a]Computed from one-way analysis of variance.

[b]Means computed from data of 8 rats.

[c]Significantly different from controls (0 mg/kg) at $p < .05$ (Duncan's test).

[d]Significantly different from controls (0 mg/kg) at $p < .01$ (Duncan's test).

dominance. Thus, 120 mg/kg (1½ times 80) should induce enhanced dominance in the presence of 0.5 mg/kg naloxone.

Shock-induced TQT were decreased by 5 and 20 mg/kg of morphine, in the presence of 0.5 mg/kg of naloxone (Table 27). Shock-induced XQT were unaffected by morphine.

Naloxone, at 0.5 mg/kg, reversed the analgesia induced by morphine. That is, neither squeaking nor jumping was significantly affected by morphine at all doses tested.

Sodium salicylate

Sodium salicylate, in the dose range tested, was without effect on any of the shock-induced behaviors (Table 28).

Discussion--specificity of morphine effects

Three sets of experiments were performed to determine if intermittent foot shock-induced behaviors are affected by morphine, and if the morphine effects are mediated by opiate receptors. The first series examined the interaction of morphine and 3 different shock currents. Here, the interaction of morphine with 2 ma will be discussed; the 4 ma - morphine interactions will be discussed below.

Morphine increased foot-shock (2 ma) induced net at 5, 7.5, and 80 mg/kg. The lowest effective dose at which morphine increased both shock-induced net and dominance was 5 mg/kg (see Tables 9 and 29). At this dose neither shock-induced TQT nor XQT were affected by morphine. Therefore, the alteration in shock-induced lateralized movement is not associated with a decrease in movement. Morphine suppressed squeaking at 2.5 mg/kg and decreased jumping at 1 mg/kg (Tables 9 and 29). Thus, analgesia induced by morphine was seen to occur at doses lower than those at which

Table 28

Effects of sodium salicylate on shock (2 ma)-induced behaviors. Values are means ± S.D.s.

Dose (mg/kg)	n	Net	Dom. (%)	TQT	XQT	Sqk	Jump
0	12	2.6±2.2	65.6±12.9	59.0±16.2	19.9±12.0	25.1± 6.6[b]	11.6± 7.8[b]
25	6	3.7±5.7	76.0±22.4	47.2±35.9	12.5± 8.6	16.3±10.4	2.0± 2.5
50	6	2.0±1.7	68.2±22.0	39.8±18.8	19.2± 9.4	24.8±11.8	10.8±10.9
100	5	5.2±1.2	66.8±20.0	64.8±17.4	24.8±11.3	38.8±32.9	17.2±11.4
150	5	2.6±1.5	67.2±48.1	55.2±20.5	20.4±11.7	31.0± 9.0	12.2± 5.8
F[a]		0.83	1.08	0.99	0.92	1.52	2.51
p-value		>.1	>.1	>.1	>.1	>.1	<.07

[a]Computed from one-way analysis of variance.

[b]Means computed from data of 8 rats.

rotational behavior was altered.

The second series of experiments involved determining the interaction of various opiates with 2 ma foot shock. All the opiates tested, with the exception of cyclazocine and naloxone increased shock-induced net rotation. In Table 29, a comparison of the minimum dose of each at which net rotation was increased shows the relative potencies of these drugs: levorphanol > methadone > morphine = propoxyphene > pentazocine > meperidine = nalorphine. The relative potencies of the opiates (Table 29) when comparing the minimum dose at which dominance was increased are: levorphanol > cyclazocine > methadone > morphine > pentazocine > meperidine. With the exceptions of the surprising potency of propoxyphene in enhancing shock-induced net and the relatively weak activity of nalorphine, the relative potencies of the other drugs are in good agreement with both experimental and clinical data.

In terms of clinical induction of analgesia, methadone had either the same potency as morphine (Denton & Beecher 1949) or was slightly more potent than morphine (Taber 1974). Cyclazocine was more potent than methadone (Taber 1974). In agreement with the present findings are clinical studies that showed that meperidine was 1/5 to 1/10 as potent as morphine (Lasagna & Beecher 1954a) but slightly less potent than pentazocine (Taber 1974).

In rodent studies these relative activities were also maintained, particularly in those tests in which cyclazocine, pentazocine, and nalorphine are effective. The 3 latter drugs were ineffective in the rat tail pressure test (Collier & Schneider 1973) and in the hot plate and tail

Table 29

Minimum dose (mg/kg) of opiate drugs at which significant alteration of 6 behaviors occurred.

Drug	Net[a]	Dom.[a]	TQT[b]	XQT[b]	Sqk[b]	Jump[b]
Morphine	5	5	10	20	2.5	1
Levorphanol	1.5	1	-	-	1	1.5
Methadone	2.5	2.5	7.5	5	1.25	1.25
Meperidine	25	25	-	25	10	25
Propoxyphene	5	-	2.5	-	2.5	-
Pentazocine	15	15	-	-	10	-
Cyclazocine	-	1.25	0.625[a]	0.625[a]	1	-
Nalorphine	25	-	100[a]	100[a]	-	100[a]

- No dose was effective.

[a]Dose at which shock-induced behavior was increased.

[b]Dose at which shock-induced behavior was decreased.

flick tests (Taber 1974). In the writhing test in rats cyclazocine was more potent than morphine which was more potent than pentazocine (Blumberg et al. 1965; Collier & Schneider 1973).

Propoxyphene is a weak analgesic when given to humans (Lasagna 1964). It was also much less potent than methadone in the rat tail-burn test (Pohland & Sullivan 1953).

Nalorphine has been found to have the same potency as that of morphine clinically (Lasagna & Beecher 1954b; Taber 1974). In the rat flinch jump test (Evans 1961) and in the rat writhing test (Blumberg et al. 1965) morphine and nalorphine had the same potency.

There are other laboratory assays for narcotic activity. These generally are in agreement with the analgesia data. For example, the dose at which the opiates inhibited by 50 percent the contraction of the guinea pig ileum induced by coaxial stimulation is called the ID_{50}. Comparing ID_{50}s for various opiates yielded the following potency scheme: cyclazocine > levorphanol > nalorphine > morphine > pentazocine (Kosterlitz et al. 1973). Another assay, the decrease in rat serum testosterone, yielded a similar potency scheme, except that methadone is slightly less effective than morphine: levorphanol > morphine > methadone > pentazocine (Cicero 1977).

It follows from these analgesia and other assays, that there is an overall concensus concerning the relative potencies of these drugs, allowing for some variation from test to test. Additionally, it must be remembered that some opiates are inactive in certain tests.

The most specific assay is the determination of binding of a drug to opiate receptors in rat brain homogenates. Pert and Snyder (1973a)

determined the ED_{50}s of opiates for displacing ^{3}H-naloxone from binding to these receptors: levorphanol > nalorphine > morphine > cyclazocine > naloxone > methadone > pentazocine > meperidine = propoxyphene. The results of this binding assay are in good agreement with the analgesia studies mentioned above except for naloxone and cyclazocine. Naloxone has no ability to induce analgesia. Cyclazocine was usually found to be more potent than morphine. However, other factors have to be considered because binding studies are done with brain homogenates. Analgesia screens are done by systemic injection. Thus, absorption, distribution, lipid solubility, and metabolism are some factors that may alter the potency of these drugs when comparing induction of analgesia to their binding affinities. This is not a sufficient explanation, however, because having a high binding affinity does not necessarily indicate that a drug will induce analgesia. Naloxone, having almost the same binding affinity as morphine, does not induce analgesia.

As noted above the effects of propoxyphene and nalorphine on shock-induced net and dominance were not comparable to their potencies in other tests and in the binding assay. In the present study propoxyphene also was as potent as morphine in suppressing squeaking. Nalorphine had an even more bizarre effect in the present work. It increased jumping at a dose of 100 mg/kg. This is the first time, to the writer's knowledge, that nalorphine has been observed to induce hyperalgesia. It is possible that the data in the present study are at odds with that of other studies because of technique. Almost all other studies employ threshold testing. The present study used repeated footshock. The demands put on the subject by a threshold test as opposed to continuous shock are much less.

With the exception of cyclazocine, all the opiates mimic morphine's low dose effect on shock-induced net. With the exceptions of nalorphine and propoxyphene, all the opiates increased shock-induced dominance.

No overall relationship between the effect of an opiate on net or dominance and the effect on shock-induced TQT or XQT was seen (Table 29). That is, shock-induced net was increased at a dose at which shock-induced TQT and XQT were unaffected by morphine, levorphanol, methadone, pentazocine, and nalorphine. However, propoxyphene increased shock-induced net at a dose twice that which reduced shock-induced TQT. Cyclazocine increased shock-induced TQT and XQT at a dose lower than that at which it increased shock-induced net.

The agonists, then, alter shock-induced net and shock-induced dominance, but there are some exceptions. Nonetheless, the hypothesis of specificity is supported by two other findings. Dextrorphan was inactive. This is predictable for an opiate-specific effect because it is the inactive enantiomer of the narcotic drug levorphanol. The nonnarcotic sodium salicylate does have analgesic activity in the flinch-jump test (Evans 1961). In the present study, it altered neither pain indices nor circling behavior.

The third set of experiments demonstrated that the effects induced by morphine were blocked by naloxone.

These latter findings suggest that morphine's effects are opiate specific. Data from the agonist drugs support this contention as does the inactivity of both dextrorphan and sodium salicylate.

Repeated shock in the presence of naloxone

Table 14 shows that a second treatment with 2 ma footshock increased shock-induced net and dominance. Morphine, when given in the presence of the first footshock experience, also increased net and dominance. It is possible that shock pretreatment induced increased net and dominance by a mechanism similar to that of morphine. The data in Table 30 are from an experiment to determine if there is such a similarity.

Five mg/kg of naloxone prevented the increase in net induced by a second shock experience. This dose, however, had no effect on the increase in shock-induced dominance. These findings are consistent with the suggestion that net and dominance are different (see above). Not only does each measure represent a different function, each is now differentiated pharmacologically.

Comparison of Table 30 and Table 14 shows that 5 mg/kg of naloxone also induced hyperalgesia during the second shock treatment, but this effect was only seen for squeaks not jumps.

Jacob et al. (1974) observed that a subcutaneous dose of 1 mg/kg naloxone decreased jump latencies in both rats and mice in a hot plate test, at 55°C., but did not alter the latency of paw-lick. When the temperature of the hot plate was lowered to 50°C., thereby increasing the baseline latency, naloxone did have a significant effect in lowering the paw-lick latency. This study showed that several variables must be considered when evaluating the hyperalgesic effect of naloxone. Several groups confirmed Jacob et al.'s findings in mice (Pomeranz & Chiu 1976; Frederickson et al. 1977; Grevert & Goldstein 1977).

Table 30

Determination of effects of 2 shock (2 ma) tests separated by 1 week (Tests 1 and 2). In the first test rats (n=14) received saline; in the second, rats received 5 mg/kg of naloxone.

Test	Drug & Dose (mg/kg)	Net	Dom. (%)	TQT	XQT	Sqk	Jump
1	saline	3.0±2.6	71.0±12.7	38.9±20.8	12.4± 9.2	25.1±20.2	9.9±12.6
2	naloxone 5	4.7±3.5	90.3±13.3	40.4±20.9	17.5±15.2	42.3±36.6	17.8±33.2
t[a]		1.71	4.45	0.36	1.36	3.18	1.06
p-value		>.1	<.001	>.1	>.1	<.007	>.1

[a]Paired t-test.

Naloxone's ability to induce hyperalgesia in rats seems to be dependent upon the test paradigm and the responses measured. Several studies employing electric shock found that naloxone was without effect. Naloxone, 12.5 to 100 mg/kg, did not alter avoidance or escape threshold from footshock (Goldstein et al. 1976). Naloxone at 1 or 10 mg/kg did not alter vocalization threshold elicited by tailshock (Crowley et al. 1976). Flinch jump thresholds were unaffected by naloxone, 1 to 20 mg/kg (Bodnar et al. 1978). Naloxone, 2 mg/kg, however, was reported to increase startle amplitude and the incidence of vocalization induced by intermittent footshock (Bass et al. 1978).

In other paradigms in which rats were tested, naloxone also had variable effects on pain. The incidence of acetic acid-induced writhes was doubled by 4 mg/kg naloxone (Kokka & Fairhurst 1977). At a dose of 10 mg/kg, naloxone had no effect on observer pain ratings of rats responding to subdermally injected formalin (North 1978). Naloxone, 2 mg/kg, decreased rat tail flick latency but had no effect upon escape threshold in response to calibrated tail pinch (Bernston & Walker 1977).

Although baselines were unaltered during a second test in the present experiment, pretreatment prior to the second test induced enhanced squeaking but not jumping in the presence of naloxone. As has been noted above, dose of naloxone, type of and intensity of painful stimulus, species, and the responses being measured are variables that in part determine the hyperalgesic activity of naloxone. To this list must now be added prior experience with the painful stimulus.

GENERAL DISCUSSION

The orienting response, as measured by the electrical properties of the skin (Wyatt & Tursky 1969; Varni et al. 1971), pain sensitivity (Wolff et al. 1965; Haslam 1970; Murray & Safferstone 1970; Murray & Hagan 1973), and pain tolerance (Murray & Safferstone 1970; Murray & Hagan 1973) are lateralized in humans. This lateralization is independent of handedness (Wyatt & Tursky 1969; Murray & Safferstone 1970; Murray & Hagan 1973). In fact, the left hand usually had the lower pain threshold and less pain tolerance (Wolff et al. 1965; Haslam 1970; Murray & Safferstone 1970). Interestingly, Kameyama (1976) found that thalamic pain occurred more frequently after right thalamic pathology than after left. Although the data are far from convincing, the author felt that this evidence suggested an asymmetry in the pain system.

The right hemisphere in humans is generally considered to be dominant in the processing of spatial information (Hecaen & de Ajuriaguerra 1964; Joynt & Goldstein 1975). In fact, the left hand of right-handed people was more accurate in judging the direction of tactile stimulation (Benton et al. 1978). Either right or left hemisphere lesions resulted in equal impairment of the contralateral hand in judging the direction of tactile stimulation. However, in many of those patients with right hemisphere lesions, the right hand was impaired, but in those with left hemisphere lesions, the left hand was functionally normal. That is, lesions in the right hemisphere, but not in the left, induced bilateral deficits (Carmon & Benton 1969; Fontenot & Benton 1971). These studies suggest that the right hemisphere is dominant for orienting in space in response to stimuli.

It is intriguing that the right hemisphere also appears to be dominant for pain and the orienting response. When a painful stimulus is presented, it is clear that what is needed is some escape or attack behavior. The hemisphere that is involved in orienting should become predominant. This suggestion is supported by the finding that right hemisphere lesions impaired simple reaction time more than left lesions (Howes & Boller 1975). Conceivably, this differential effect of lesion could be due to an asymmetry in arousal.

Semmes et al. (1960) suggested that the input to the right hemisphere is more diffuse than that to the left. Hecaen and de Ajuriaguerra (1964) offered support for this hypothesis (see Introduction). A diffuse input could explain the multitude of responses induced by aversive stimuli.

Heilman et al. (1973) found that humans with the hemi-inattention syndrome, as well as monkeys and cats that received lesions producing the syndrome, showed unilateral diffuse slowing of the EEG. The slowing occurred in the hemisphere contralateral to the affected side of the body, and this hemisphere was more often the right (see Heilman & Watson 1977b). The affected hemisphere also demonstrated focal EEG changes (Heilman et al. 1973). These data suggested to the authors that hemi-inattention resulted from a defect in alerting and arousal. It follows that decreased arousal, as measured by the EEG, is associated more often with right hemisphere lesions. The result of such a lesion that induces hemi-inattention is gross deficits in orienting to stimuli and spatial agnosia (see Joynt & Goldstein 1975). Again, the right hemisphere is apparently the dominant one for processing arousal and orienting.

The above discussion suggested that the brain asymmetry related to arousal and pain is independent of the asymmetry related to handedness.

In the present study, rats were found to circle preferentially in one direction when shocked. This shock-induced circling was unrelated to spontaneous circling. Rats therefore show more than one form of lateralization. This is not to say that spontaneous circling is analogous to handedness in humans. However, both rats and humans evince laterality when given painful stimuli. In humans, the sensation of and tolerance to pain are lateralized, but in rats the direction to which they run is lateralized.

The distribution of circling was not equal in each direction in the present study. Of the 178 rats tested at 2 ma, 104 (58.4 percent) circled to the right (X^2=5.06, $p < .03$). Interestingly, 5 of the 6 high spontaneous rotators rotated to the right during shock independent of their spontaneous direction. The sixth rat showed no directional preference. No comparable preference was seen in the shock-induced directions of low spontaneous rotators. These data suggest that rats have a population difference as to which side of the brain is dominant for processing pain input, and this bias can be considered to be analogous to the right hemisphere bias of humans.

Adaptive Significance

The adaptive significance of shock-induced circling may be envisioned as follows. When the rat is shocked, it circles preferentially in response to symmetric noxious stimulation. The purpose of this preference is to preclude the need for an interhemispheric decision as

to which direction to turn away from the shock. Such a decision would presumably require more time to generate movement from the onset of the stimulus than would a preset choice.

If a rat were to be attacked from its preferred side, the bias in direction could be conceived to be maladaptive: the animal would automatically turn toward its attacker. However, the mean for dominance during shock was about 67 percent. This value conceivably represents an optimum difference which will still allow the nondominant side to become dominant when the stimulus so demands it. That is, a rat with a dominance of 90 to 100 percent would not be able to turn away from its preferred side.

Laterality's adaptive advantage is suggested to be an ability to cope with the environment (Glick et al. 1977a; 1977c). Consistent with this suggestion are the data presented by Glick et al. (1977c). His group found that side preference strength was positively correlated with rate of responding in fixed interval and fixed ratio schedules but negatively correlated with rate of responding in a differential-reinforcement-low-rates schedule. In the latter, reinforcement is usually inversely related to response rate. Therefore, in all 3 schedules greater side preference is related to more effective responding to the demands of the environment.

A further advantage of brain asymmetry could be the availability of areas in the brain for additional functions. That is, anatomical mirror image sites do not have to do the same things. If the control of movement in response to pain were localized, the mirror side could

be utilized for some other function.

Morphine and Shock-induced Rotation

In what manner does morphine enhance shock-induced rotation? Certainly, morphine induced spontaneous rotation when administered systemically (Morihisa & Glick 1977) and intranigrally (Iwamoto & Way 1977) to naive rats. These effects were attributed to dopaminergic actions of the drug.

In the present study, such an action can be ruled out. As the shock-induced circling is not dopaminergic and as the sum of morphine-induced spontaneous circling and shock-induced circling was less than that of the morphine-shock interaction, it appears that this interaction is not dopaminergic.

Microinjection of 5 or 10 micrograms of morphine or heroin into the midbrain reticular formation of rats induced ipsilateral circling. The circling usually required some innocuous stimulus (such as a whisper or a white cloth waved in the subject's visual field) and was unaffected by systemic administration of pimozide or microinjection of dopamine. Neither levorphanol nor methadone, each given at a dose of 40 micrograms, induced circling. Naloxone, microinjected (20 micrograms) or systemically injected (20 mg/kg), potentiated the morphine effect (Jacquet et al. 1976).

In a later study Jacquet et al. (1977) found that the inactive isomer, (+)-morphine, upon microinjection in the mesencephalic reticular formation, also induced ipsilateral circling. This substance was neither active in an opiate receptor binding assay nor in an analgesic assay

(PAG microinjection).

The explanation offered for these findings is that morphine induced circling by activating a non-opiate receptor.

The circling observed in the present study and in that of Jacquet's studies are different. Jacquet et al. (1976) described the circling as occurring in bursts and as usually consisting of pivoting about a rear paw. In the present study, the circling was often pivoting, but just as often it also consisted of running. The stimuli that interacted with morphine were also different. Jacquet's group employed innocuous stimulation, but in the present study noxious stimulation was used.

Furthermore, although each study reported that a dopaminergic blocking agent was ineffective, Jacquet found that naloxone either potentiated or was without effect on circling. In the present study naloxone blocked the increase in shock-induced circling elicited by morphine. Therefore, the mesencephalic reticular formation is not a likely site in which morphine interacts with foot shock-induced rotation.

Shock Pretreatment

Pretreatment with shock altered subsequent morphine-shock and naloxone-shock interactions. Foot shock has been observed to induce various aspects of the stress response in rats (Fortier et al. 1959; Friedman & Uhley 1959; Khan et al. 1964; Bassett & Cairncross 1975). Although the foot shock procedures in these studies usually involved longer periods of shock and longer durations of each shock, the shock used in the present study can also be considered to be stressful because of the induction of behaviors associated with aversive stimuli,

i.e. squeaks and jumps, and of increased activity (TQT), which can be considered to demonstrate enhanced locomotor arousal.

Thus, the pretreatment with shock is suggested to alter subsequent drug effects by means of stress. Consistent with this suggestion is the study reported by DeMontis et al. (1978). This group found that 25 mg/kg of morphine increased striatal dopamine and 3,4-dihydroxy-phenylacetic acid (DOPAC) in rats. Rats that were fasted for 24 hours no longer showed any change in DOPAC in response to morphine. Naloxone, at a dose (2.5 mg/kg) which had no effect on DOPAC in naive animals, reduced striatal DOPAC in 24-hour fasted rats. Fasting, by itself, had no effect on either dopamine or DOPAC. These findings are analogous to those of the present study. Morphine, 5 mg/kg, reduced squeaking in an acute shock test, but it was ineffective if the rats had received footshock previously. Five mg/kg of naloxone was without effect on squeaking in an acute shock test, but increased squeaking in rats pre-tested with footshock. Squeaking was the same in both shock tests. Thus, whereas a stressful procedure by itself does not alter baseline responding, the stress itself did alter the effects of both morphine and naloxone.

Similarly, morphine was observed to have different effects dependent on the state of the animal. In freely moving rats, morphine induced hyperthermia, but it induced hypothermia in restrained rats (Martin et al. 1977). Restraint did not affect the baseline temperature.

Both the DeMontis et al. and Martin et al. studies as well as the present study showed that certain forms of stress altered morphine's effects. At the same time, stress induced a naloxone-like effect.

In the present study, five mg/kg of naloxone was without effect on shock-induced net rotation during the first shock test, but it prevented the rise in net induced by a second shock test. The effects of naloxone during a second test, i.e. increased squeaking and reduced net rotation, were opposite to the effects of morphine, i.e. reduced squeaking and enhanced net rotation, in an acute test. Thus, dependent on the behaviors studied and the conditions employed, naloxone can be seen to have the opposite effects to morphine.

It is conceivable that these two behaviors, squeaking and net rotations, are mediated in part by endogenous opiate receptors. The data suggest that in an acute test, the endogenous opiate component is contributing very little to either behavior. During stress, however, endogenous opiate is activated. Squeaking is maintained at the same baseline in a second shock test, but naloxone increased squeaking in a second test. One explanation for the effect of naloxone is that increased levels of endogenous opiates were induced by an acute footshock test. Thus, naloxone would become active in this situation. The increase in shock-induced net rotation resulting from a previous foot shock test can also be thought of as mediated by endogenous opiates. Naloxone blocked this increase in net. It is interesting to note that the increase in shock-induced dominance seen during a second foot shock test was not blocked by naloxone. Thus, the two measures of asymmetry employed in this study are different in the function each represents and in the possible involvement of endogenous opiates. Presumably, prior foot shock exposure and morphine affect shock-induced net rotation in the same way, but prior foot shock and morphine do not increase dominance by the same mechanism.

SUMMARY

Rats were found to circle in a preferential direction in response to intermittent footshock. Shock-induced circling behavior was unrelated to indices of pain. Although net rotation increased with increasing current, percent dominance did not. These data suggest that the two measures of circling reflect different aspects of asymmetry.

Comparison of shock-induced circling to spontaneous circling showed that these two behaviors are unrelated. It was not possible to block shock-induced rotation with either haloperidol or AMPT, both of which block rotation induced by amphetamine. Amphetamine is believed to increase spontaneous rotation by its ability to increase the intrinsic asymmetry in the rodent neostriata. Rats, then, have more than one form of cerebral asymmetry that is expressed as circling.

Narcotic drugs were found to enhance shock-induced circling. Several agonists and several partial agonists increased circling. This increase was found to be opiate-specific as it was reversed by naloxone. Naloxone had no effect on shock-induced circling, but it did block the increase in net rotation that resulted from a second shock treatment. It was postulated that pretreatment with shock activates an endogenous opiate system that contributes to the increase in net rotation following a second shock treatment.

It would be of interest to determine if rats have lateralized pain sensitivity. Humans do have lateralized pain sensitivity, and this laterality may relate to the specialization of the cerebral hemispheres. It is possible that shock-induced circling is related to an asymmetry of arousal and has a protective advantage for the rat.

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