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NEONATAL MONOSODIUM GLUTAMATE: BEHAVIORAL CHARACTERIZATION OF NOCICEPTIVE AND STRESS RESPONSE ALTERATIONS IN THE RAT

by

DIANA BADILLO DE MARTINEZ

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

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Abstract

NEONATAL MONOSODIUM GLUTAMATE: BEHAVIORAL CHARACTERIZATION OF NOCICEPTIVE AND STRESS RESPONSE ALTERATIONS IN THE RAT

by

Diana Badillo de Martinez

Adviser: Professor Richard Bodnar

Neonatal administration of monosodium glutamate (MSG) produces in rats neurotoxic degeneration of the medial basal hypothalamus (MBH), particularly the arcuate nucleus and median eminence and depletes these structures of neuropeptides and neurotransmitters. This treatment produces multiple neuroendocrine and behavioral disturbances, including attenuations in cold water swim (CWS) and morphine analgesia. The first experiment examined whether MSG-induced alterations in stress analgesia were accompanied by alterations in other stress responses. MSG rats showed attenuated analgesia and hypothermia following CWS, potentiated 2-DG analgesia and reduced 2-DG hyperphagia. Locomotor activity changes failed to account for response differences following either manipulation. Therefore, it appears that MSG treatment alters a number of stress responses and that interpretation of the analgesic alterations in terms of a specific role for the circumventricular system in certain pain-inhibitory systems should be considered in light of the multi-faceted effects of MSG. Since MSG treatment destroys beta-endorphin cells, but increases opiate receptors and reduces morphine analgesia on the jump test, but increases morphine

analgesia on the hot-plate, the second experiment assessed the test-specific effects of MSG upon morphine analgesic and locomotor dose-response curves as well as changes in analgesia, thermoregulation and body weight folowing chronic morphine treatment. Test-specific and gender-specific effects were observed in MSG-treated rats following acute morphine injections. While male MSG animals showed lowered morphine analgesia on the jump test and increased analgesia on the hot-plate test, the MSG females displayed potentiated analgesia on both tests following high morphine dose, but attenuated hot-plate analgesia following a low dose. Moreover, HMSG treatment altered morphine tolerance more on the jump test, than on the hot-plate test. MSG also disrupted other morphine coping behaviors since decreased hyperthermia and increased weight loss accompanied the alterations in analgesia in MSG-treated rats. The third experiment assessed the relationship between early MSG-induced endocrine imbalances and the development of nociceptive thresholds. Nociceptive thresholds, body weight and lengths were measured at various critical ages. MSG-treated rats were shorter, weighed more and after sexual maturity, their nociceptive thresholds were test-specifically altered. Long standing MSG-induced hormonal changes are suggested to influence these basal nociceptive effects.

Acknowledgements

This accomplishment would not have been possible without the patience, support and encouragement given me by my family and Dr. R. Bodnar. In particular, I am extremely grateful to Dana, Melissa and Jose for their willingness to help, and uncomplaining sacrifices. To Pamela Butler, Annette L. Kirchgessner, and Nora Nicotera for their valuable assistance and companionship.

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Introduction

A stressful stimulus is generally defined in terms of the well integrated autonomic and physiological responses it elicits. These include elevations in levels of plasma adrenocorticotrophic hormone (ACTH) and corticosteroids, increased rate and strength of the heart beat, constriction of the spleen to release red blood cells which carry increased oxygen, release of glycogen from the liver, deepened respiration and dilated bronchi, dilated pupils, increased coagulation of blood, and constricted capillary beds in the skin (see reviews: Cannon, 1939; Gray, 1971; Selye,1952). These responses are regulated by the adreno-cortical pituitary system which is in turn modulated by terminals in the median eminence of the medial-basal hypothalamus through the hypothalamo-hypophyseal portal blood system (Hodges, 1970; Muller, Nistico and Scapagnini, 1977). Stressful stimuli are also defined in terms of an organism's perception of its environmental circumstances (Gray, 1971; Schacter and Singer, 1962). One behavioral adjustment following acute exposure to stress is a transient increase in pain thresholds (see review: Bodnar, Kelly, Brutus and Glusman, 1980). Given the integral regulatory role in modulating stress responses of the median eminence and its afferent inputs from the medial basal hypothalamus (MBH), an initial study (Bodnar, Abrams, Zimmerman, Krieger, Nicholson and Kizer, 1980) found that neonatal administration of monosodium glutamate (MSG), which destroys MBH perikarya (Olney, 1969), attenuated analgesia following morphine

and stress. However, this non-invasive procedure also produces a variety of other neuroendocrinological and behavioral imbalances (Kizer, Nemeroff and Youngblood, 1978). Therefore, the purpose of the present proposal will be to analyze whether the attenuated analgesic effects following MSG pretreatment are selectively altering intrinsic pain inhibition or affecting a cohort of responses that are elicited following exposure to stress or opiates. Before proceeding, brief selective reviews will be made of a) the hypothalamo-hypophysial-adrenal system, b) the MBH neural system, c) the MSG syndrome and d) the physiological substrates of stress and morphine analgesia.

A. The Hypothalamo-Hypophysial-Adrenal System: Two systems, the sympatho-medullary and the adreno-cortical, mediate initial physiological and autonomic responses during and following exposure to stress. While the sympathetic nervous system appears to be one mechanism by which epinephrine release is stimulated from the adrenal medulla (Gray, 1971), the adreno-cortical stress reponse is dependent upon the anterior lobe of the pituitary which in turn is modulated by the median eminence of the hypothalamus (see review: Krieger and Liotta, 1979). The hypothalamo-hypophysial portal system constitutes the major connection between the hypothalamus and anterior lobe of the pituitary through which releasing factors are secreted (see review: Harris, 1955) such as corticotropin releasing factor (CRF), growth hormone releasing hormone, thyrotropin releasing hormone (TRH), luteinizing hormone releasing hormone (LHRH), and dopamine (Muller, Nistico and Scapagnini, 1977). Since the median eminence capillary system is in close relation to the highly permeable pericapillary space (Palkovits, 1982), this area is considered to be free of a blood-brain-barrier (BBB) and is thereby susceptible to neurotoxic effects (Mezey and Palkovits, 1982; Weindl, 1973).

Release of CRF (Vale, Spiess, Rivier, & Rivier, 1981) from the median eminence stimulates ACTH release from the anterior lobe of the pituitary (Schally, and Arimura, 1977). ACTH stimulates glucocorticoid release from the adrenal which in turn acts upon anterior pituitary and median eminence receptors to

inhibit further ACTH release (long feedback loop: see Rees, 1977). In addition, a short-loop feedback system appears to originate in the anterior pituitary with receptors localized in the median eminence and other neural structures (Motta, Piva and Martini, 1970). Both long and short feedback mechanisms appear to regulate further CRF release and thus allow fine adjustments in subsequent ACTH secretion. Exposure to stressful situations such as noise, cold water immersion, hypoglycemia, pain, fear or fever appear to override both feedback systems and thereby induce greater than normal ACTH secretion (Rees, 1977). In contrast, long-term administration of natural or synthetic corticosteroids (e.g., cortisol,dexamethasone, prednisalone) can suppress release of both CRF from the hypothalamus and ACTH from the anterior pituitary and result ultimately in adrenal atrophy (Jones and Hillhouse, 1976; Sampson, Winstone and Brooke, 1962). Yet, surgical stress can still induce ACTH release despite its pairing with either dexamethasone or cortisol, suggesting that environmental circumstances can strongly determine stress responses (Estep, Island, Ney and Liddle, 1963).

B. The MBH Neural System: Though the precise source of neuropeptides in the median eminence has not been fully determined, it receives input from so-called parvicellular hypothalamic nuclei (see reviews: Palkovits, 1982; Rose and Ganong, 1980) which represents the final common pathway for neural regulation of the anterior pituitary (Harris, 1955; Mezey

and Palkovits, 1982; Muller et al., 1977; Renaud, 1978). These neurons act to transduce "neural" into "hormonal" information (Muller et al., 1977; Renaud, 1978). Projections from cell bodies in the arcuate nucleus and neighboring basal hypothalamus terminate on portal systems which are on the surface zone of the median eminence (Blackwell and Guillemin, 1973; Moss, 1976; Palkovits, 1982; Renaud, 1978; Vale, Rivier and Brown, 1977). Moreover, these MBH perikarya are the sole source of neural ACTH, and beta-endorphin (Watson, Richard and Barchas, 1978) and project to the paraventricular hypothalamic nucleus (Sawchenko, Swanson and Joseph, 1982), brainstem and locus coeruleus (Watson, Akil, Sullivan and Barchas, 1977; Watson, et al., 1978). In contrast, relatively few MBH neurons project to the median eminence (Holzwarth and McBride, 1976; Renaud, 1976). While such hypothalamic neurons may be influenced by short-loop and long-loop feedback, they are also influenced by neural afferents (Rose and Ganong, 1980). Dopamine in the external and internal layers of the median eminence originates from arcuate cells (Muller et al., 1977). In contrast, norepinephrine originates from medullary cells which ascend through the ventral noradrenergic bundle (Cuello, Weiner and Ganong, 1973; Cuello, Shoemaker and Ganong, 1974; Olson and Fuxe, 1972). Serotonin containing cells in the brain stem raphe nuclei also project to the ventral hypothalamus (Ungerstedt, 1971). While noradrenergic and serotonergic terminal are concentrated in the arcuate nucleus, these amines are not localized in arcuate cells

(Hokfelt, Elde, Fuxe, Johannson, Ljungdahl, Goldstein, Luft, Efendic, Nilsson, Terenius, Ganten, Jeffcoate, Rehfeld, Said, Perez de la Mora, Possani, Tapia, Teran, and Palacios, 1978; Palkovits, Brownstein and Kizer, 1976). Acetylcholine as measured by choline acetyltransferase levels is found in the median eminence, as well as the arcuate, dorsomedial and paraventricular nuclei (Brownstein, Kobayashi, Palkovits and Saavedra, 1975). As surgical isolation of the MBH significantly reduces choline acetyltransferase activity in all of these cell groups but the median eminence, this suggests an extra-hypothalamic source of acetylcholine in the median eminence (Brownstein, Palkovits, Saavedra and Kizer, 1976). Examination of the median eminence and surrounding MBH reveal that these areas contain the highest concentrations of LHRH, TRH, somatostatin, vasopressin, oxytocin, beta-endorphin and ACTH in the brain as well as significant amounts of alpha-melanocyte stimulating hormone, neurotensin, enkephalin, substance P, vasoactive intestinal polypeptide, cholecystokinin, motilin and bombesin (see review: Palkovits, 1982).

C. The MSG Syndrome: The classic approach to assess the influence of hypothalamic structures in the function of the hypothalamo-hypophysial adrenal axis is to place specific lesions and observe subsequent behavioral and physiological changes. However, either electrolytic lesions or central injections of specific neurotoxins into the median eminence or MBH can produce ancillary damage to adjacent and superiorally-placed structures. Neonatal administration of high doses of MSG (0.5-4 g/kg, SC) destroys the perikarya of the arcuate nucleus (80-90%), median eminence (100%), retina and other circumventricular organs in mice (Cohen, 1967; Dawson and Lorden, 1981; Olney, 1969; Takasaki, 1978), rats (Nemeroff, Grant, Bissette, Ervin, Harrell and Prange, 1977; Olney, 1978), guinea pigs (Olney, Ho, Rhee and Gubareff, 1973), hamsters (Lamperti and Blaha, 1976; Tafelski, 1976), chicks (Snapir, Robinzon and Perek, 1971) and rhesus monkeys (Olney and Sharpe, 1969; Olney, Sharpe and Feigin, 1972) Such damage presumably occurs because these structures lack the protection of a well defined blood-brain-barrier neonatally (Olney, 1978; Weindl, 1973). Indeed MSG's neurotoxic effects decrease with age (Olney, 1978), presumably because of either blood-brain-barrier maturation or an increased ability of the liver to metabolize glutamate (Kizer et al., 1978; Olney and Price, 1978; Takasaki, 1978). That such neurotoxic effects are specific in the diencephalon is supported by the observation that neonatal treatment with MSG in mice increased glutamate fourfold in the arcuate nucleus and median eminence without concomitant

changes in other diencephalic areas (Perez and Olney, 1972). MSG neurotoxicity occurs within 3 h after injection and is characterized by swelling of the somas and dendrites of ependymal, glial, arcuate and median eminence cells, intracellular edema, disappearance of the nucleus, clumping, and necrosis (Nemeroff, Lipton and Kizer, 1978; Olney, 1969; Olney, 1978; Takasaki, 1978). Yet, glial cells, axonal projections and blood vessels are not damaged irreversibly, suggesting that neurotoxicity is not attributable to vascular inadequacy (Nemeroff et al., 1978; Olney and Price, 1978; Takasaki, 1978).

While the precise mechanisms subserving MSG neurotoxicity have not been fully characterized, neurotoxic potency appears to parallel the neuroexcitatory potentials of glutamate (Curtis, Phillis and Watkins, 1960; Kizer et al., 1978; Shenozaki and Shibuya, 1976; Watkins, 1978). The changes in membrane physiology is receptor mediated since labelled glutamic acid has been localized by autoradiography on dendrites and soma (Kizer et al., 1978; Olney, 1978). Glutamate induces long lasting cellular depolarization and increases membrane permeability to sodium (Curtis et al., 1960; Curtis, Duggan, Felix, Johnston, Tabecis and Watkins, 1972; Watkins, 1978). Excitatory amino acids increase intracellular sodium in guinea pig brain slices (Bradford and McIlwain, 1966) and depolarize locust (Anwyl and Usheerwood, 1974) and crayfish muscles (Onodera and Takeuchi, 1976) without altering potassium (Watkins, 1978). Thus,

glutamate-induced interference with sodium conductance appears to interrupt maintenance of normal cellular ionic and osmotic gradients, thereby increasing cellular energy expenditures to a point which may lead to cell death (Olney, 1978; Watkins, 1978). Since saline, sodium glutarate, serine or glycine injections fail to produce similar effects, osmotic load itself does not appear to be a factor (Kizer et al., 1978; Olney, 1969; Olney and Ho, 1970; Olney, 1978). Moreover, neurotoxicity depends upon glutamate contact with the outer membrane of a neuron since neither intraneural injections of glutamate into spinal motor neurons nor application of glutamate onto cells lacking glutamate receptors produce similar effects (Olney, 1978).

MSG-induced cell loss within the arcuate nucleus and median eminence appear to produce disruptions in the feedback relationship of the hypothalamo-hypophysial axis resulting in neuroendocrine and behavioral abnormalities (Nemeroff, Konkol, Bissette, Youngblood, Martin, Brazeau, Rone, Prange, Breesee and Kizer, 1977; Nemeroff et al., 1978; Nemeroff, Lamarteniere, Mason, Squibb, Hong, and Bondy, 1981; Olney, 1969). MSG-treated animals exhibit obesity, tail automutilation, sexual dysfunction, hypogonadism and stunted growth as measured by a 10% reduction in linear bone growth (Araujo and Mayer, 1973; Kanarek, Meyers, Meade and Mayer, 1979; Nemeroff et al., 1978c; Olney, 1969; Olney and Price, 1978; Pizzi and Barnhart, 1976; Redding, Schally, Arimura and Wakabayashi, 1971). Since MSG-treated animals weigh

significantly less and are significantly shorter than controls, but their Lee Index, which measures carcass fat accumulation, is significantly higher (Kanarek et al., 1979).

Observed behavioral abnormalities of MSG-treated animals sometimes appears paradoxically related to their physiological deficits. Though obese, MSG-treated animals have been found to be either hypophagic (Araujo and Mayer, 1973; Dawson and Lorden, 1981; Kanarek et al., 1979; Olney, 1969) or normophagic (Nemeroff et al., 1978) and either hypodipsic (Dawson and Lorden, 1981) or hyperdipsic (Kanarek et al., 1979). Hypophagia has been linked with both hypoactivity (Nemeroff et al., 1978; Olney, 1978; Pizzi and Barnhart, 1976) and hyperactivity (Araujo and Mayer, 1973). However, both ingestive and locomotor measures in MSG-treated mice can vary as a function of housing condition (Dawson and Lorden, 1981). Individually housed mice display hypophagia and normal activity, while group-housed mice were both hypophagic and hypoactive. Yet, both groups displayed significant obesity and exhibited inadequate compensatory responses to a high fat diet (Dawson and Lorden, 1981; Kanarek et al., 1979). These conflicting data have been explained in terms of inherent deficits in regulation of energy intake and/or metabolism (Kanarek et al., 1979; Nemeroff et al., 1977b).

MSG-treated animals manifest other endocrinological abnormalities as well. The anterior lobe of the pituitary is reduced by 70-75% in mice and by 36% in rats (Clemens, Roush and

Sharr, 1977; Nemeroff et al., 1977; Olney, 1969). Moreover, decreased levels of growth hormone, follicle stimulating hormone, luteinizing hormone, testosterone and stradiol have been observed (Nagasawa, Yanai and Kikuyama, 1974; Nemeroff et al., 1981; Olney and Price, 1978; Redding et al., 1971). The size, but not the weight of the adrenals is reduced (Dawson and Lorden, 1981; Nemeroff et al., 1978; Olney, 1978) with hypertrophy of adrenal cortex (Olney, 1969). MSG-treated animals also display abnormal estrous cycles, infertility, hypogonadism and thermoregulatory disturbances (Clemens et al., 1977; Nagasawa et al., 1977; Nemeroff et al., 1978; Nemeroff et al., 1979; Redding et al., 1971). MSG-treated animals show concomitant elevations in serum prolactin levels (Clemens et al., 1977; Nemeroff et al., 1977) and decreased dopamine levels in the arcuate nucleus, but not in median eminence fibers (Clemens et al., 1977; Conte-Devolx,Giraud, Castana, Boudouresque, Orlando, Gillioz and Oliver, 1981; Dawson and Lorden, 1981; Nemeroff et al., 1977) as indicated by histofluorescence, radioimmunoassay and immunocytochemical techniques. Depletion of brain levels of choline acetyltransferase (Conte-Devolx et al., 1981; Nemeroff et al., 1978), met-enkephalin (Romagnano, Chafel, Pilcher and Joseph, 1982), ACTH and beta-endorphin (Krieger, Liotta, Nicholsen and Kizer, 1979) are also observed following neonatal MSG treatment. Yet, plasma and pituitary ACTH is unaffected following MSG (Krieger et al., 1979) in normal or ether-stressed rats (Conte-Devox et al., 1981), while plasma beta-endorphin

levels are reduced following stress and adrenalectomy (Conte-Devolx et al., 1981). MSG treatment does not alter neuropeptides and neurotransmitters traversing the arcuate nucleus since normal levels of LHRH, TRH, serotonin, norepinephrine and glutamic acid decarboxylase are observed in MSG animals (Conte-Devolx et al., 1981; Dawson and Lorden, 1981; Kizer et al., 1978; Nemeroff et al., 1978).

D. Stress and Morphine Induced Analgesia: Research investigating the substrates of stimulation-produced analgesia and morphine microinjection analgesia (see reviews: Mayer and Price, 1976; Yaksh and Rudy, 1978), have suggested the existence of an intrinsic opioid pain-inhibitory system since both are attenuated by naloxone (Akil, Mayer and Liebeskind, 1976; Oliveras, Hosobuchi, Redjemi, Guilhaud and Besson, 1977), display synergy (Samanin and Valzelli, 1971), display tolerance and partial cross-tolerance (Mayer and Hayes, 1975). One neural pathway mediating both effects originates in the medullary nucleus raphe alatus, and projects to the dorsal horn of the spinal cord through the dorsolateral funiculus (Bausbaum, Marley, O'Keefe and Clanton, 1977; Fields and Bausbaum, 1978).

Assessment of exogenous stimuli capable of activating this proposed endogenous pain-inhibitory systems led to the observation that acute exposure to either inescapable electric footshock (IFS), centrifugal rotation or hypertonic saline injections increased tail-flick latencies (Akil, Madden, Patrick and Barchas, 1976; Hayes, Bennett, Newlon and and Mayer, 1976; Hayes, Bennett, Newlon and Mayer, 1978; Rosecrans and Chance, 1976). Subsequently, other stressors such as cold water swims (CWS) (Bodnar, Kelly and Glusman, 1978), 2-deoxy-D-glucose (2-DG) injections (Bodnar, Kelly, Brutus, Mansour and Glusman, 1978), immobilization (Amir and Amit, 1978; Bhattachary, Kreshary and Sanyal, 1978), insulin injections (Bodnar, Kelly, Mansour and Glusman, 1979), food deprivation (Bodnar, Kelly, Spiaggia and

Glusman, 1978c) and body pinch (Ornstein and Amir, 1981) also induced analgesia on a variety of reflex and operant pain tests. However, stress is neither a sufficient, nor a necessary condition to induce analgesia since exposure to either ether vapors or horizontal oscillation elevates plasma corticosterone levels without inducing analgesia (Hayes et al., 1978b).

Parametric considerations are important in assessing the substrates of a stressor's analgesic effects. For instance, tail-pinch stress increases writhing and hot-plate thresholds (Levine, Wilcox, Grace and Morley, 1982), but decreases jump thresholds and tail- flick latencies (Simone and Bodnar, 1982). Moreover while immobilization over 2 h produces analgesia (Amir and Amit, 1978), inescapable holding produces a transient hyperalgesia (Vidal and Jacob, 1982). Yet, dissociations can be made between the analgesic and other responses following stress: IFS analgesia is not accompanied by impairments in motor behavior, vocalization, startle responses and righting and corneal reflexes (Hayes et al., 1978b; Lewis, Cannon and Liebeskind, 1980). The substrates mediating 2-DG hyperphagia (Smith and Epstein, 1969; Smith and Root, 1969) and 2-DG analgesia as well as CWS analgesia and CWS hypothermia have also been dissociated from each other (see: Bodnar, Kramer, Simone, Kirchgessner and Scalisi, 1983; Bodnar et al., 1978f, 1980b).

Initial biochemical studies suggested a role for plasma opioids in stress-induced analgesia since prolonged IFS exposure increased plasma beta-endorphin five-fold without altering brain levels of beta-endorphin and met-enkephalin (Fratta, Yang, Hong, and Costa, 1977; Rossier et al., 1977). The role of endogenous opioids in stress-induced analgesia has also been assessed by the ability of opiate antagonists and morphine tolerance to block its effects. CWS analgesia appears to be non-opioid since it is non-significantly attenuated by high doses of naloxone (Bodnar, Kelly, Spiaggia, Ehrenberg, and Glusman, 1978) and fails to develop cross tolerance with morphine analgesia (Bodnar, Kelly, Steiner and Glusman, 1978). 2-DG analgesia possesses opioid properties in terms of its cross-tolerance and synergistic effects with morphine, but appears non-opioid since naloxone fails to reverse its effects (Bodnar et al., 1979b; Spiaggia, Bodnar, Kelly, and Glusman, 1979). Analgesia induced by immobilization (Amir and Amir, 1978), tail pinch (Levine et al., 1982), and body pinch (Ornstein and Amir, 1981) have also been partially blocked by moderate naloxone doses.

Stimulus parameters also appear to critically determine opioid mediation. While brief (3 min) continuous IFS analgesia is not reversed by naloxone (10 mg/kg) nor cross-tolerant with morphine, prolonged (30 min) intermittent (1 sec/5sec) IFS analgesia is reduced by both naloxone and chronic morphine pretreatment (Lewis et al., 1980; Lewis, Sherman and Liebeskind,

1981). Moreover, analgesia induced by eighty, but not twenty, IFS was reversed by naltrexone (Grau, Hyson, Maier, Madden and Barchas, 1981). The area of the body receiving IFS is also critical since IFS delivered to the front paws, but not to the hind paws induces analgesia that is reversible by naloxone and cross tolerant with morphine (Watkins and Mayer, 1982). Swim parameters such as temperature, duration and swim-test interval can differentially activate opioid mechanisms. While baths of 2 and 8 C induced analgesia that was not naloxone reversible, opiate antagonism blocked analgesia induced by a 15 C bath which could not be attributable to thermoregulatory changes. Indeed evidence for individual differences was observed since the magnitude of analgesia was related to the partial effectiveness of naloxone to reverse its effects (Bodnar and Sikorszky, 1983).

The hypothalamo-hypophysial-adrenal axis also appears to modulate certain analgesic responses. Hypophysectomy attenuates analgesic responses induced by prolonged-intermittent IFS (MacLennon, Drugan, Hyson, Maier, madden and Barchas, 1982; Millan, Przewlocki, and Herz, 1980) immobilization (Amir and Amit, 1979), acupuncture (Pomeranz, Chang, and Law, 1977), insulin (Bodnar et al., 1979c), and CWS (Bodnar, Glusman, Brutus, Spiaggia and Kelly, 1979a; Marek, Panocka and Hartman, 1982), with the anterior lobe apparently essential in both CWS and prolonged-intermittent IFS analgesic responses (Glusman, Bodnar, Kelly, Sirio, Stern and Zimmerman, 1979; Lewis et al., 1980;

MacLennon et al., 1982). In contrast, hypophysectomy potentiates analgesia induced by morphine (Bodnar et al., 1979c; Holaday, Law, Tseng, Loh and Li, 1978), 2-DG (Bodnar et al., 1979c) and electroconvulsive shock (Lewis, Cannon, Chudler and Liebeskind, 1981). Adrenalectomy also exerts differential effects upon analgesic processes. While adrenalectomy potentiates CWS (Glusman, Bodnar, Mansour and Kelly, 1980; Marek et al., 1982) and morphine analgesia (Holaday, Law, Loh and Li, 1979; Marek et al., 1982; Bodnar et al., 1979c; Gebhart and Mitchell, 1972) it reduces prolonged intermittent IFS analgesia (Lewis et al., 1982; MacLennan et al., 1982). Attempts have been made to dissociate effects upon the adrenocortical and sympathomedullary systems. Dexamethasone potentiates morphine analgesia (Slater, Lewis, Terman and Liebeskind, 1982), yet reduces prolonged-intermittent IFS (Lewis et al., 1980; MacLennan et al., 1982) and CWS analgesia (Marek et al., 1982; Mousa, Miller and Couri, 1981). In contrast, corticosteroid synthesis inhibition with metyrapone, potentiates CWS analgesia (Mousa et al., 1981). On the other hand, adrenal demedullation reduces prolonged-intermittent IFS analgesia, yet fails to alter the analgesic response to morphine or CWS (Bodnar, Sharpless, Kordower, Potegal and Barr, 1982; Lewis et al., 1982). Enkephalin-like substances released from the adrenal medulla during stress appear to mediate the IFS analgesic response (Lewis et al., 1982).

Rationale

Damage to the MBH also alters analgesic processes in that rats treated neonatally with MSG display reduced analgesic responses to CWS and morphine (Bodnar et al., 1980a) while radio-frequency lesions placed in the arcuate nucleus attenuate brief-continuous IFS analgesia (Millan, Gramsch, Przewlocki, Holt and Herz, 1980a). These findings suggest that the MBH is necessary for the mediation of both opioid and non-opioid analgesic responses. In a large number of previous studies investigating the analgesic responses following stress, it has been generally assumed that any manipulation that increases or decreases this analgesic response is doing so because the manipulation is directly affecting some component of an intrinsic pain- inhibitory syste. Such an assumption would be correct if only the analgesic response to stress and no other response elicited by a given stressor would be altered. However, in most of these studies, only the analgesic response was assessed so critical evaluation of whether a specific response or a number of responses following stress are affected by a given manipulation could not occur. This point is of critical importance because the underlying assumption for making particular manipulations is that they are affecting a hypothesized pain-inhibitory system. As reviewed previously, a number of pain-inhibitory systems have been hypothesized, so this indicates that systematic analysis of given manipulations that affect stress-induced analgesia for

effects on other stress responses is complex, time-consuming and open to a wide range of alternative explanations. In this study, an attempt will be made to determine whether MSG treatment will alter a number of responses following given stressors and following morphine. In this regard, the study must be of necessity data-bound, that is, exploration into MSG effects on certain stress and opiate responses will be examined for the first time. This tactic while providing a great deal of information into the studied parameters of MSG effects, cannot provide the precise mechanisms of action by which MSG exerts its effects upon particular responses. So the first aim of this study is to provide input regarding the relative specificity of alterations in analgesic effects following MSG and not to detail the mechanisms by which such alterations occur.

Therefore, if MSG is reducing CWS analgesia because it is directly altering a specific pain-inhibitory system activated by CWS, it would follow that the deficient CWS analgesic response would not necessarily be accompanied by alterations in CWS hypothermia and/or hypoactivity. In contrast, if the neonatal MSG treatment is interfering with processes in addition to specific pain- inhibitory mechanisms, then CWS analgesic deficits might be accompanied by covarying deficits in this animal's adaptive thermoregulatory and/or locomotor activity responses. Similarly, changes in the dose-response relationship of 2-DG analgesia in the MSG treated rat should not necessarily be

accompanied by 2-DG-induced changes in ingestive and/or locomotor patterns if MSG alterations specifically affect an endogenous pain inhibitory system. Alternatively, if MSG alters processes in addition to specific pain-inhibitory mechanisms, disruptions in analgesic, ingestive and/or locomotor responses might occur. Therefore, this first experiment proposes to examine whether animals exposed neonatally to different levels of MSG display similar or disimilar changes in their analgesic, hypothermic and locomotor responses following a 2 °C, 3.5 min CWS and in their analgesic, hyperphagic and locomotor responses following a dose range of 2-DG.

Additionally, MSG treatment destroys cell bodies that contain either beta-endorphin, enkephalin or ACTH within the arcuate nucleus (Bodnar et al., 1980a; Conte-Devolx et al, 1981; Romagnano et al., 1982). It reduces morphine (10 mg/kg) analgesia as measured by the jump test (Bodnar et al., 1980a), yet increases morphine (1 mg/kg) analgesia as measured by the hot-plate test (Simantov and Amir, 1983). Therefore, the second aim of this study is to explore whether MSG effects upon opiate related responses are test-specific. Depending upon whether MSG treatment affects either opioid pain-inhibitory systems in particular or opioid processes in general, the expected changes in opiate analgesia may or may not be accompanied by alterations in other responses such as locomotor activity. Therefore, the gender- specific effects of various acute morphine doses on two

pain tests and locomotor responses will be assessed in MSG treated rats. This study will also attempt to characterize the development of tolerance manifested by MSG-treated animals following repeated injections of morphine. Indeed, if opioid processes in general are affected then the normal analgesic and hyperthermic responses, as well as the weight loss associated with chronic morphine treatment are expected to be concomitantly affected. However, if pain-inhibition in particular is affected then only a reduction in the analgesic response would be anticipated.

A third aim of this study is to assess the developmental and gender-specific effects of MSG upon sensory nociceptive processes. Since gonadal hormones influence CNS differentiation with regard to adult sexual and other behavioral patterns (Levine and Mullins, 1966; Pfaff and McEwen, 1983), and since MSG induces multiple endocrine imbalances during early development (see review: Kizer et al., 1978), it is possible that the normal organization induced by gonadal and other hormones upon the CNS did not occur. For instance, altered adreno-cortical activity early in life induces increased responsiveness to stress in adulthood (Levine, 1970). Therefore, examination of nociceptive thresholds and locomotor activity during various critical periods (21, 45, 80 days of age) in MSG-treated and control rats would discern whether specific nociceptive sensitivity is altered and if the change is manifested during early or late development.

Weight and body lengths will also be measured at various critical ages.

General Methods

Subjects: Female albino Sprague-Dawley rats were mated, impregnated, and then were housed individually until delivery of the pups. All pups remained with the dam until weaning at 21 days. At 30 days of age, the pups were separated by sex and housed four to a cage. At 45 days of age housing was reduced to two rats per cage. There was ad libitum access to Purina rat chow and water. Animals were maintained on a 12 h light: 12 h dark cycle at ambient temperatures between 22-24°C.

Experimental Treatment: All pups within a given litter were randomly assigned either the high dose regimen of MSG (HMSG), the low dose regimen of MSG (LMSG) or a control (SAL). HMSG animals received a 2 mg/g dose of MSG (Sigma; 200 mg MSG/ml normal saline/g body weight, SC) on the second and fourth post-natal days and a 4 mg/g dose of MSG (400 mg MSG/ml normal saline/ g body weight, SC) on the sixth, eighth and tenth post-natal days. LMSG animals received a 1 mg/g dose of MSG (100 mg MSG/ml normal saline/ g body weight, SC) on the second and fourth post-natal days, and a 2 mg/g dose of MSG (200 mg/ml normal saline/g body weight, SC) on the sixth, eight and tenth post-natal days. SAL animals received normal saline injections at equal volume (0.01 ml/g body weight, SC) on the second, fourth, sixth, eighth and tenth post-natal days.

Flinch-Jump Test: A modification of the procedure developed by Evans (1961) was employed. Electric shocks were delivered by a 60 Hz constant current shock generator (BRS/LVE, Beltsville, 521S) and a grid scrambler (Camden Instruments SG-903) through a 30 cm by 24 cm floor composed of 16 grids. In an ascending method of limits procedure, the flinch threshold was defined in mA as the lowest intensity that elicited a withdrawal of a single paw from the grids. The jump threshold was defined as the lowest of two consecutive intensities that elicited simultaneous withdrawal of both hindpaws from the grids. Each trial began with the animal receiving a 300 msec foot shock at a current intensity of 0.1 mA. Subsequent shocks occurred at 10 sec intervals and were increased in equal 0.05 mA steps until both thresholds were determined. After each trial, the current intensity was reset to 0.1 mA for the next trial until six trials were completed. Mean flinch and jump thresholds were determined for each animal over four days of baseline testing.

Hot Plate Latencies: In a modification of the procedure developed by Johannesson and Woods (1964), each animal was placed on the copper floor of a 28x26.5x26 cm chamber (IITC Hot-Plate Analgesic Meter) with the floor temperature adjusted to 55°C (+ 0.3°C). The thermonociceptive threshold was defined as that latency in sec (Lafayette Digital Timer: Model 54519-A) required to elicit either a paw lick or an escape response. Once a response was elicited, the digital timer was automatically

deactivated and the rat removed from the chamber. If the rat failed to emit an appropriate response within 12 sec, the trial was automatically terminated to prevent tissue damage. A single trial was used for any given experimental session.

Activity Levels: Activity levels of all animals were recorded in a secluded, sound-isolated room which contained two activity monitors (Omicron Omni Tech: Model 41523) separated from each other by a wooden partition. In a typical test session, a rat and the sawdust from its home cage were transferred to a test cage which was placed on top of the activity meter. After a 10 min adaptation period, the rat underwent a given experimental treatment and was returned to the test cage. After a 2 min interval to allow for handling effects, activity levels consisting of horizontal and vertical movements were recorded in four equal 30 min time blocks over 120 min. Food and water were available ad libitum. The sensitivity of the apparatus excluded small grooming and chewing movements as well as such autonomic measures as heart rate and respiration.

Statistical Analysis: Split-plot analyses of variance were performed on all data and appropriate comparisons were used to reveal differences between means. In the cases in which the experimental neonatal MSG regimen caused significant changes in baseline measures, the data were transformed by calculating difference scores to partial out the baseline variance. Analyses of variance were then performed on the transformed data with

appropriate comparisons used to reveal differences between the means. As the primary concern of the activity level study is to assess the relative activity levels among the groups, a split plot analysis of variance will be performed at each sampling time period to avoid confounding the data with temporal relationships.

Histology: Selected animals, paired by age, gender and condition, received an overdose of Nembutal (200 mg/ml normal saline/kg body weight, IP) and were perfused transcardiacally with 0.9% normal saline followed by 10% buffered formalin. The brains were removed, maintained in 10% buffered formalin, blocked, mounted and stained with cresyl violet for visualization of cell bodies. The localization and extent of the necrosis produced by the MSG treatment was then determined.

Experiment I

Cold Water Swim (CWS) Analgesia: Following the determination of baseline flinch-jump thresholds at 80 days of age, each animal in the HMSG, LMSG and SAL groups was exposed to a 3.5 min swim in a 2°C bath with flinch-jump thresholds determined 30 min later. The water was deep enough to force the animal to swim to prevent submersion. During the swim-test interval, each animal was housed individually in a polyethylene cage lined with paper. CWS analgesia was assessed for 31 HMSG rats (14 males, 17 females), 36 LMSG rats (17 males, 19 females) and 27 SAL rats (12 males, 15 females).

CWS Hypothermia: One week later, the core body temperatures of all animals were monitored immediately prior to and then 0, 15, 30, 60 and 120 min following a 3.5 min swim in a 2°C bath. Rectal temperatures were recorded by inserting a probe (Bailey Instruments: Model HPI) which was held in place until a stable reading (0.1°C) was obtained from a digital thermometer (Bailey Instruments: Model BAT-8). All of the above animals except, for one SAL rat that died, were assessed for their hypothermic reactions.

2-deoxy-D-glucose (2-DG) Analgesia: Two weeks following the determination of CWS hypothermia, all animals received each of

five doses of 2-DG (0, 50, 250, 450, 650 mg 2-DG (Sigma)/1.5 ml sterile water/kg body weight, IP) according to an incomplete counterbalanced design. Flinch-jump thresholds were assessed 30 min later with the tester unaware of the injection condition. A minimum of 48 h elapsed between injections.

2-DG Hyperphagia: Three weeks following the 2-DG analgesia paradigm, all animals received each of three doses of 2-DG (0, 650, 1200 mg/1.5 ml sterile water/ kg body weight, IP) according to an incompletely counterbalanced design. Each animal was housed in a wire mesh cage and was allowed ad libitum access to pre-weighed Purina rat chow pellets and water for 2 h prior to and 5 h following each injection. Food intake (+ 0.1 g) was determined at hourly intervals following each injection by weighing the remaining pellets in each animal's cage. Spillage was accounted for and the experimenter was unaware of the injection condition. A minimum of 48 h elapssed between injections.

CWS Activity Levels: Separate groups of rats were treated neonatally with either the HMSG (9 males; 5 females), the LMSG (6 males; 7 females) or the SAL (11 males; 8 females) regimens. At 100 days of age, activity levels of all animals were determined following either a 3.5 min swim in a 2°C bath or handling (no swim). A one week interval separated the conditions which were counterbalanced across animals.

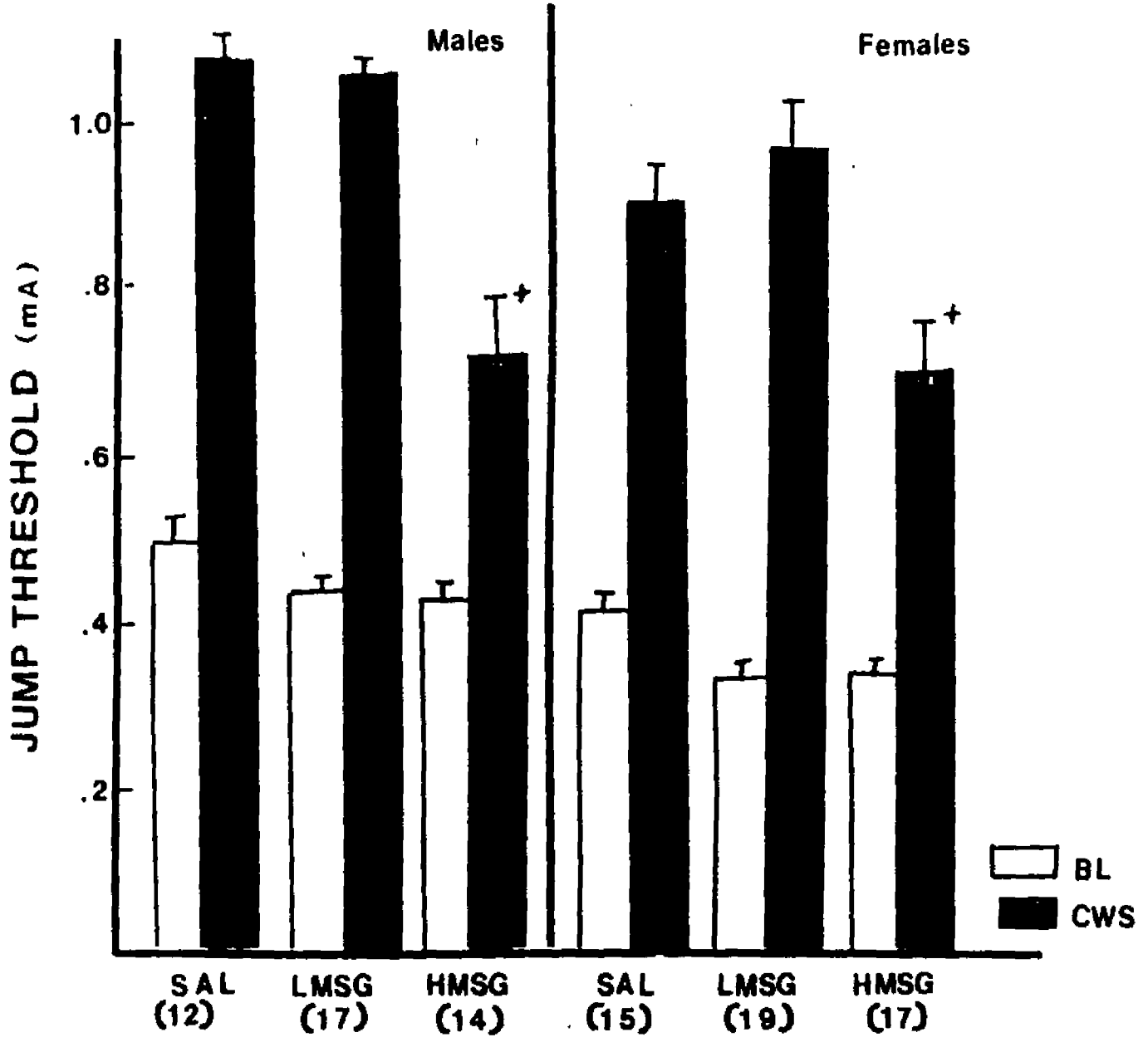
2-DG Activity Levels: Three weeks following the CWS paradigm, the activity levels of all animals were assessed following each of three doses of 2-DG (0, 250, 650 mg 2-DG/1.5 ml sterile water/ kg body weight, IP) according to an incompletely counterbalanced design. A one week interval elapsed between injections, the conditions of which the experimenter was unaware.

Results

CWS Analgesia: Figure 1 summarizes the significant alterations in jump thresholds between baseline and CWS conditions ($F(1,88)= 631.50$, $p< .001$), among the three groups ($F(2,88)= 26.14$, $p< .001$), between males and females ($F(1,88)= 19.27$, $p< .001$), and for the interaction between groups and conditions ($F(2,88)= 21.51$, $p< .001$). While CWS significantly elevated the jump threshold of all groups of both genders above baseline levels, Dunnett comparisons revealed baseline jump thresholds were significantly lower in MSG-treated rats of both sexes relative to the SAL group. Therefore, a difference score was calculated by subtracting the baseline thresholds from the CWS thresholds. Significant differences in the magnitude of CWS analgesia was observed between groups ($F(2,88)= 21.94$, $p< .0001$), but not between males and females ($F(1,88)= .01$). The magnitude of CWS analgesia was markedly smaller in HMSG rats of both genders relative to the SAL group while the magnitude of CWS analgesia in LMSG rats was slightly, though significantly increased.

Significant alterations in flinch thresholds were observed between baseline and CWS conditions ($F(1,88)= 16.65$, $p< .001$), among the three groups ($F(1,88)= 6.33$, $p< .01$), and for the interaction between groups and conditions ($F(2,88)= 9.10$, $p< .001$). While baseline flinch thresholds failed to differ among

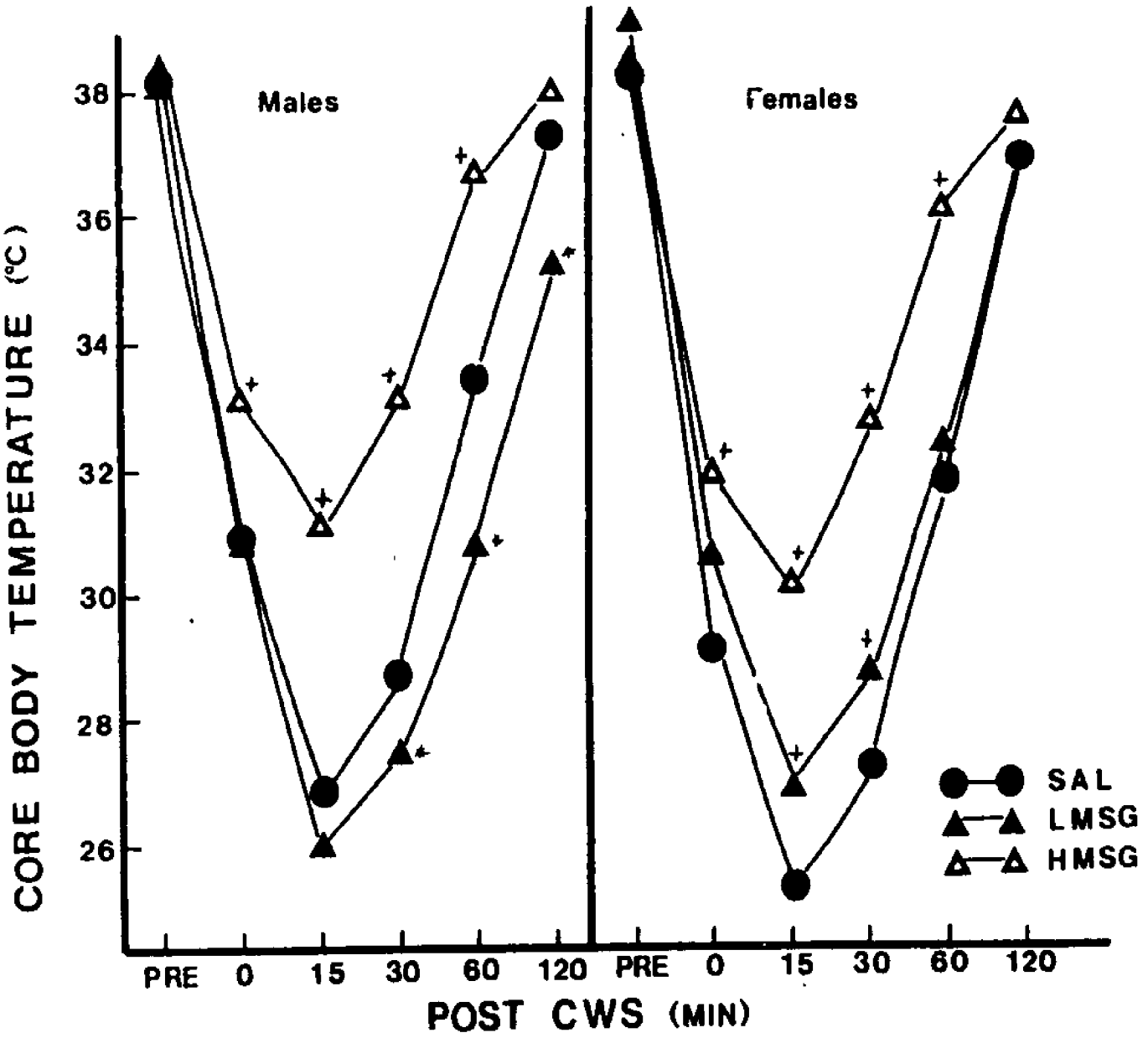
Figure 1. Decrease (+: Dunnett comparisons, $p < .05$) in cold-water swim (CWS) analgesia in rats treated with the high monododium glutamate (HMSG) dose regimen, but not the low (LMSG) dose regimen as compared to saline (SAL) controls. This effect was observed in males and females.


Males
Females
JUMP THRESHOLD (mA)
1.0
.8
.6
.4
.2
+
+
BL
CWS
SAL (12)
LMSG (17)
HMSG (14)
SAL (15)
LMSG (19)
HMSG (17)

groups or between genders, CWS significantly elevated flinch thresholds in all groups. Like the jump threshold data, the magnitude of CWS analgesia was significantly smaller in HMSG rats as compared to the SAL group. In contrast, CWS analgesia elicited by the SAL and LMSG groups failed to differ from each other.

CWS Hypothermia: Figure 2 displays the significant alterations in core body temperatures among groups ($F(2,87)= 30.06$, $p< .001$), across the post-swim time course ($F(5,435)= 546.25$, $p< .001$), as well as for the interactions between groups and gender ($F(2,87)= 3.57$, $p< .05$) and between groups and time ($F(10,435)=16.13$, $p< .001$). While pre-swim core body temperatures of the three groups failed to differ from each other, significant hypothermia was observed for up to 60 min following CWS in the SAL and HMSG groups and for up to 120 min in the LMSG group. The magnitude of CWS hypothermia was significantly smaller in HMSG rats of both sexes relative to the SAL group at 0, 15, 30 and 60 min following the swim. This effect was dose-dependent since the LMSG group displayed smaller differences which varied as a function of gender. While core temperatures of male rats of the LMSG and SAL groups failed to differ from each other 0 and 15 min following CWS, the LMSG males displayed greater hypothermia thereafter. Moreover, while core temperatures of LMSG and SAL females failed to differ from each other 60 and 120 min after CWS, the LMSG female rats were

Figure 2. Significant reduction (+: Dunnett comparison, $p < .05$) in magnitude of CWS-induced hypothermia in HMSG rats of both sexes. While the hypothermic response of LMSG rats spoaradically diverged (* significantly lower, Dunnett comparison, $p < .05$) from that of SAL group, the magnitude of their response differed less from SAL than that of HMSG.


Males
Females
CORE BODY TEMPERATURE (°C)
38
36
34
32
30
28
26
PRE
0
15
30
60
120
POST CWS (MIN)
SAL
LMSG
HMSG

significantly less hypothermic at 0, 15, and 30 min following CWS. Therefore, like CWS analgesia, HMSG rats displayed a marked impairment in their hypothermic response while LMSG rats exhibited smaller effects on this measure.

CWS Activity: Table 1 illustrates the significant decreases in activity levels following CWS as compared to baseline conditions at 30 ($F(1,39)= 75.63$, $p< .001$), 60 ($F= 53.82$, $p< .001$), 90 ($F= 27.24$, $p< .001$) and 120 ($F= 21.12$, $p< .001$) min after treatment. Gender failed to exert any significant effect, therefore the data of both sexes were pooled for purposes of analyses. A difference score done to partial out the initial baseline hypoactivity of the LMSG failed to reveal significant differences among groups following the CWS (30: $F(2,39)= 0.96$; 60: $F= 1.03$; 90: $F= 1.36$; 120 min: $F= .05$). Thus, while MSG treatment altered the analgesic and hypothermic responses following CWS, it failed to systematically change CWS-induced hypoactivity.

2-DG Analgesia: Tables 2 and 3 summarize the significant alterations in jump thresholds across 2-DG doses ($F(5,435)= 90.93$, $p< .001$), among the three groups ($F(2,87)= 15.64$, $p< .001$), between males and females ($F(1,87)=31.97$, $p< .001$), and for the interactions between groups and doses ($F(10,435)=7.11$, $p< .001$) and groups and gender ($F(5,435)= 3.35$, $p< .01$). While jump thresholds of HMSG rats of both sexes displayed significantly

Table 1. Activity Levels of HMSG, LMSG and SAL Rats Following Baseline (BL) and CWS Conditions

Group		Post Manipulation (min) 30		60		90		120	
		BL	CWS	BL	CWS	BL	CWS	BL	CWS
HMSG	$\bar{x}$	1762.0	300.2	2479.0	778.9	3150.4	1540.0	3526.6	2128.8
	SEM	337.8	71.5	474.5	168.7	702.0	285.0	696.0	398.3
LMSG	$\bar{x}$	1372.8*	330.1	1964.3*	889.2	2199.5*	1332.0	2451.3*	1543.4
	SEM	314.9	108.5	390.1	211.7	380.0	32.7	378.3	491.2
SAL	$\bar{x}$	2029.8	228.5	3147.3	487.4	3659.4	1007.4	4049.9	1481.7
	SEM	177.9	48.0	273.0	85.8	345.8	181.3	381.6	252.4

Note: Significantly lower (*) than corresponding SAL values ($p < .05$, Dunnett comparisons).

Table 2. Jump Thresholds (mA) following 2-deoxy-D-glucose in MSG-treated and Control Male Rats.

Group		2-DG Dose (mg/kg) 0	50	250	450	650
HMSG	$\bar{x}$	.39	.39	.60+	.65+	.74+
	SEM	.02	.02	.03	.05	.03
LMSG	$\bar{x}$	.46	.53+	.46	.56+	.60+
	SEM	.03	.05	.02	.03	.03
SAL	$\bar{x}$	.59	.61	.62	.67+	.74
	SEM	.05	.05	.03	.05	.07

+ Significant difference ($p < .05$, Dunnett comparison) from corresponding vehicle condition.

Table 3. Jump Thresholds (mA) following 2-deoxy-D-glucose in MSG-treated and Control Female Rats.

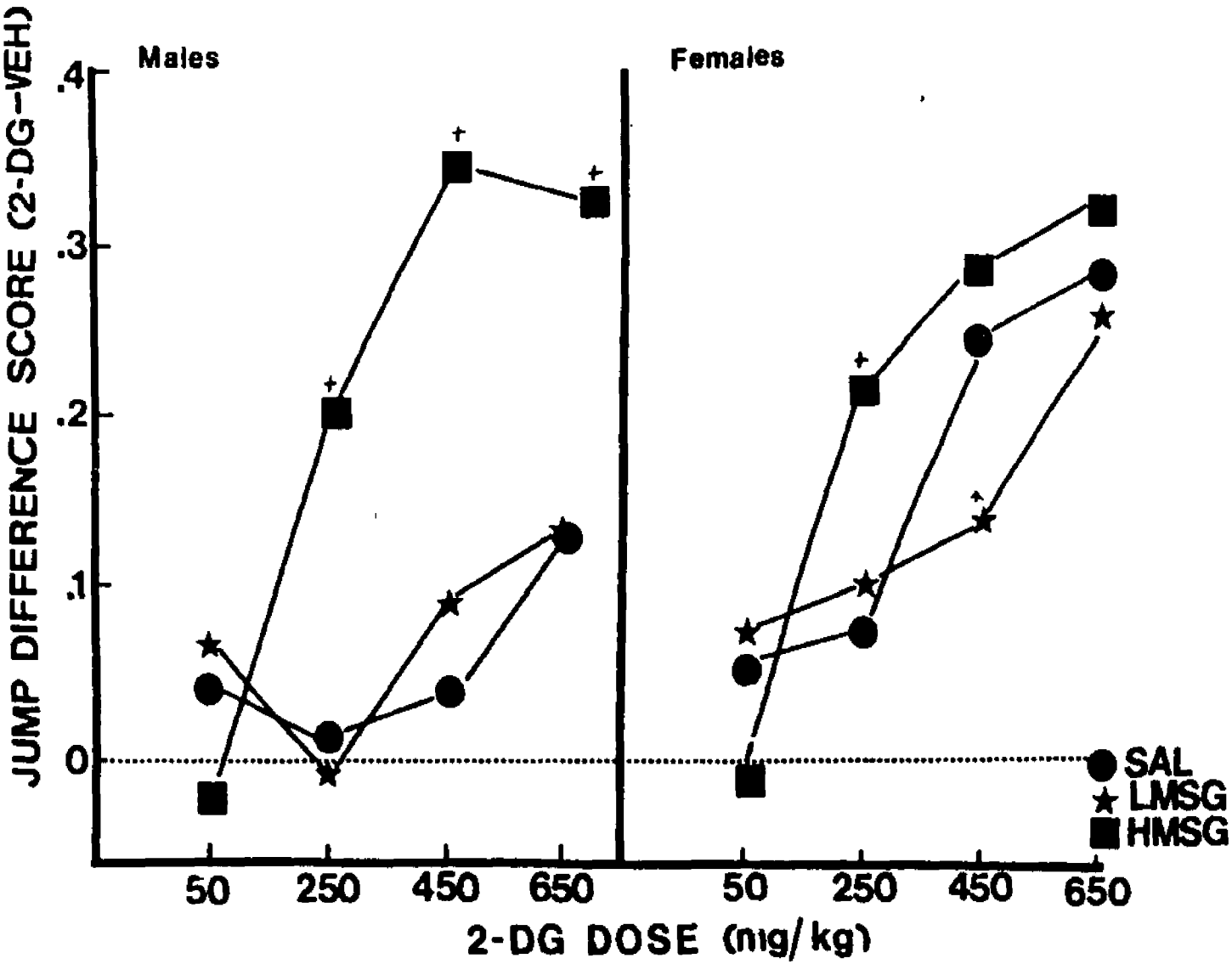
Group		2-DG Dose (mg/kg) 0	50	250	450	650
HMSG	$\bar{x}$	.29	.31	.52+	.58+	.66
	SEM	.02	.02	.03	.03	.03
LMSG	$\bar{x}$	.32	.39	.43+	.46+	.58+
	SEM	.02	.02	.03	.03	.04
SAL	$\bar{x}$	.41	.43	.50+	.67+	.71+
	SEM	.02	.02	.04	.06	.05

+ Significant difference ($p < .05$, Dunnett comparison) from corresponding vehicle condition.

greater jump levels following 2-DG doses of 250, 450 and 650 mg/kg, the analgesic response of the LMSG and SAL groups varied as a function of gender. 2-DG increased jump thresholds of LMSG and SAL females following the 250, 450 and 650 mg/kg doses. In contrast, 2-DG analgesia was observed in LMSG males following the 50, 450 and 650 mg/kg doses and in SAL males following the 450 and 650 mg/kg doses.

Since the jump thresholds of MSG-treated rats were lower than the SAL group following the vehicle injection, analysis of difference scores revealed significant differences in jump thresholds across 2-DG doses ($F(3,240)= 37.31$, $p< .001$), among the three groups ($F(2,80)= 7.52$, $p< .001$), between males and females ($F(1,80)= 5.06$, $p< .05$) and for the interaction between groups and doses ($F(6,240)=7.62$, $p< .001$). Figure 3 indicates that the magnitude of 2-DG analgesia observed in males of the HMSG group was significantly greater than the SAL group following the 250, 450 and 650 mg/kg doses. In contrast, males of the SAL and LMSG groups failed to differ from each other in the magnitude of 2-DG analgesia. Smaller and less consistent effect were observed for females of the three groups in that the magnitude of 2-DG analgesia was significantly greater for HMSG rats following the 250 mg/kg dose and significantly less for LMSG rats following the 450 mg/kg dose.

Figure 3. Potentiation (+: Dunnett comparison, $p < .05$) of 2-deoxy-D-glucose (2-DG) analgesia in HMSG, but not LMSG rats relative to SAL controls. The effect was more marked in male animals.


Males
Females
JUMP DIFFERENCE SCORE (2-DG-VEH)
.4
.3
.2
.1
0
50
250
450
650
2-DG DOSE (mg/kg)
SAL
LMSG
HMSG

Flinch thresholds were significantly altered across 2-DG doses ($F(5,435)= 95.84$, $p< .001$), among the three groups ($F(2,87)= 18.61$), $p< .001$), between males and females ($F(1,87)= 29.67$, $p< .001$) and for the interaction between groups and doses ($F(6,435)= 10.71$, $p< .001$). While flinch thresholds failed to differ among groups following the vehicle injection, 2-DG significantly increased flinch thresholds in HMSG rats of both sexes following doses of 250, 450 and 650 mg/kg and in LMSG rats of both sexes following the 450 and 650 mg/kg doses. While SAL males exhibited significant elevations in flinch thresholds following all doses, SAL females displayed higher thresholds at the 450 and 650 mg/kg doses. A less consistent pattern was observed for 2-DG-induced changes in flinch thresholds than for jump thresholds, effects which were gender specific. The magnitude of 2-DG induced changes in flinch thresholds observed in HMSG males was significantly less than SAL males following the 50 mg/kg dose, yet significantly greater after the 250 and 650 mg/kg doses. In contrast, LMSG males displayed significantly lower flinch thresholds than SAL rats following 2-DG doses of 250, 450 and 650 mg/kg. In turn, flinch thresholds of HMSG females were significantly less than SAL females after the 250 and 650 mg/kg doses, but significantly greater after the 450 mg/kg dose. Female LMSG rats also displayed lower flinch thresholds at 250, 450 and 650 mg/kg. Thus, in contrast to attenuations in CWS analgesia observed in HMSG rats, this treatment potentiated 2-DG analgesia. The effect was more

consistently observed in jump rather than flinch thresholds and was subject to gender differences. Again, MSG dose played a critical role in the strength and direction of effect.

2-DG Hyperphagia: Tables 4, 5 and 6 illustrate the significant changes in food intake across injection conditions ($F(2,142)= 9.88$, $p< .01$), among the three groups ($F(2,71)= 5.45$, $p< .01$), between males and females ($F(1,71)= 21.94$, $p< .001$), across the post injection time course ($F(6, 426)= 130.18$, $p< .001$) and for the interactions between conditions and gender ($F(2,142)= 5.61$, $p< .001$), between times and gender ($F(6,426)= 3.05$, $p< .01$), between conditions and time ($F(12,852)= 2.43$, $p< .01$), and among conditions, group and time ($F(24,852)= 1.56$, $p< .05$). Intake of female rats of the three groups failed to differ significantly from each other following a vehicle injection; LMSG male rats ingested significantly less food than SAL male rats during the last four hourly sampling periods and HMSG males ingested less food than SAL during the last three hourly sampling periods. Relative to vehicle injection, while the 650 mg/kg dose of 2-DG significantly increased food intake in SAL and LMSG males at each of the hourly sampling periods, intake of HMSG males was significantly increased only during the third and fourth post-injection hours. The 1200 mg/kg dose of 2-DG significantly increased intake over the last two hourly sampling periods for SAL males, and over the final three hourly sampling periods for LMSG males. In contrast, HMSG males ate significantly less food

Table 4. Cummulative Food Intake (g) Following Vehicle Dose in MSG-treated and Control Male and Female Rats

Group		Post-Injection (h)				
Male:		1	2	3	4	5
HMSG	$\bar{x}$	1.78	2.87	3.96*	5.21*	6.27*
	SEM	.28	.42	.69	.76	1.01
LMSG	$\bar{x}$	1.56	2.44*	3.94*	5.23*	6.15*
	SEM	.20	.24	.29	.41	.40
SAL	$\bar{x}$	1.88	3.51	5.64	7.19	8.44
	SEM	.36	.68	.82	.73	.84
Female:						
HMSG	$\bar{x}$	1.74	3.12	4.18	5.48	6.39
	SEM	.23	.30	.37	.51	.63
LMSG	$\bar{x}$	1.21*	2.24	3.34	4.27	5.38
	SEM	.14	.24	.33	.40	.50
SAL	$\bar{x}$	1.52	2.77	3.80	5.11	6.18
	SEM	.22	.36	.34	.47	.54

Note: Significantly less (*) than same-sex SAL control group at same hourly period ($p < .05$, Dunnett comparisons).

Table 5. Cummulative Food Intake (g) Following 650 mg/kg 2-deoxy-D-glucose in MSG-treated and Control Male and Female Rats.

Group		Post-Injection (h)				
Males:		1	2	3	4	5
HMSG	$\bar{x}$	1.51	3.23	5.10^{+}	6.92^{+}	7.80
	SEM	.24	.42	.62	.87	.80
LMSG	$\bar{x}$	2.12^{+}	3.93^{+}	5.45^{+}	6.82^{+}	7.66^{+}
	SEM	.35	.53	.69	.94	.92
SAL	$\bar{x}$	3.14^{+}	6.14^{+}	8.56^{+}	10.39^{+}	11.23^{+}
	SEM	1.06	1.36	1.75	1.56	1.58
Females:						
HMSG	$\bar{x}$	.92*	2.03*	3.34	4.39	5.32
	SEM	.24	.25	.37	.43	.49
LMSG	$\bar{x}$	1.08	3.09^{+}	4.84	5.64^{+}	6.36
	SEM	.21	.28	.35	.40	.39
SAL	$\bar{x}$	1.44	3.33	5.01^{+}	6.57^{+}	7.45
	SEM	.28	.51	.55	.54	.52

Note: Significantly greater (+) or less (*) than corresponding values ($p < .05$, Dunnett comparisons).

Table 6. Cummulative Food Intake (g) Following 1200 mg/kg 2-deoxy-D-glucose in MSG-treated and Control Male and Female Rats.

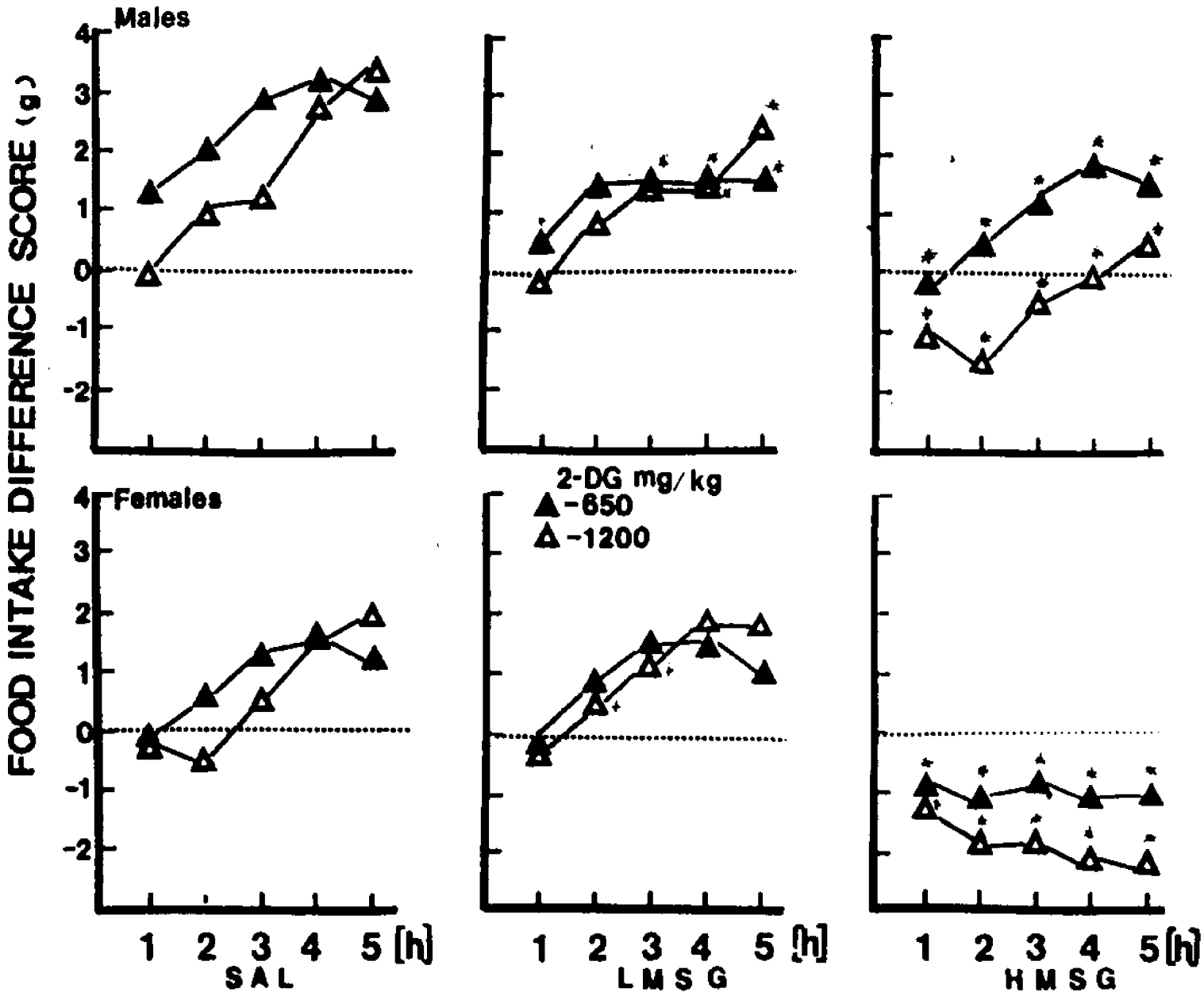
Group		Post-Injection (h)				
Males:		1	2	3	4	5
HMSG	$\bar{x}$	.61*	1.44*	3.48	5.07	6.66
	SEM	.19	.28	.53	.84	1.03
LMSG	$\bar{x}$	1.48	3.23	4.94+	6.72+	8.23+
	SEM	.42	.51	.53	.61	.63
SAL	$\bar{x}$	1.86	4.50	6.88	9.91+	11.46+
	SEM	.49	.90	1.30	1.74	1.62
Females:						
HMSG	$\bar{x}$	.51*	1.23*	2.33*	3.42*	4.25*
	SEM	.12	.18	.27	.38	.40
LMSG	$\bar{x}$	.67*	2.60	4.46+	6.10+	7.17+
	SEM	.19	.34	.50	.60	.60
SAL	$\bar{x}$	1.16	2.27	4.29	6.88+	8.14
	SEM	.36	.25	.68	.76	.75

Note: Significantly greater (+) or less (*) than corresponding values ($p < .05$, Dunnett comparisons).

following the 1200 mg/kg 2-DG dose over the first two sampling periods. 2-DG hyperphagia following the 650 mg/kg dose was observed during the third and fourth sampling periods in SAL females and during the second and fourth sampling periods in LMSG females. By contrast, HMSG females exhibited significant hypophagia during the first and second sampling periods. Following the 1200 mg/kg dose, SAL females displayed significant hyperphagia over the last two sampling periods. While LMSG females displayed an initial hypophagia during the first hour followed by hyperphagia during the last three hours, HMSG females displayed significant hypophagia across all sampling periods.

Since there were significant differences in intake following the vehicle injection among groups, analysis of difference scores revealed significant effects among doses ($F(1,71)= 6.92$, $p< .05$, among the three groups ($F(2,71)= 6.20$, $p< .005$), between males and females ($F(1,71)= 4.76$, $p< .05$), across the post-injection time course ($F(4,284)= 16.79$, $p< .0001$) and for the interaction between doses and times ($F(4,284)= 4.88$, $p< .001$). Figure 4 indicates that the magnitude of 2-DG hyperphagia in HMSG males following both the 650 and the 1200 mg/kg doses was significantly less than SAL males over the full five hourly sampling period. In turn, the magnitude of 2DG hyperphagia in LMSG males was significantly less than SAL males during the first, third, fourth and fifth hours following the 650 mg/kg dose and during the last two sampling periods following the 1200 mg/kg dose. The

Figure 4. Significant decrease (*: Dunnett comparison, $p < .05$) in 2-DG hyperphagia following HMSG and LMSG treatment. While male HMSG rats failed to exhibit 2-DG hyperphagia following the 650 mg/kg 2-DG dose, significant hypophagia was observed in HMSG males following the 1200 mg/kg 2-DG dose and in HMSG females following both 2-DG doses. (+: Significantly greater hyperphagia, Dunnett comparison, $p < .05$).


Males
Females
FOOD INTAKE DIFFERENCE SCORE (g)
4
3
2
1
0
-1
-2
2-DG mg/kg
▲-650
△-1200
1 2 3 4 5 [h]
SAL
LMSG
HMSG

magnitude of 2-DG hyperphagia following the 650 and the 1200 mg/kg doses was significantly higher in SAL females than HMSG females across all sampling periods. In turn, the SAL and LMSG females failed to differ from each other following the 650 dose, but LMSG females were significantly more hyperphagic than SAL females during the second and third sampling period after the 1200 mg/kg dose. Thus, MSG treatment attenuated the hyperphagic response to 2-DG while potentiating the analgesic response to 2-DG.

2-DG Activity: Table 7 illustrates significant effects were observed at 30 ($F(2,78)= 6.84$, $p< .002$), 60 ($F= 9.35$, $p< .001$), 90 ($F= 3.83$, $p< .05$), but not at 120 ($F= .70$) min after injection. Significant differences among groups were observed only at 90 ($F= 3.33$, $p< .05$) and 120 ($F= 3.28$, $p< .05$) min after injection. As gender failed to exert any significant effects, the data of both sexes within each group were pooled for purposes of analysis. While all animals became significantly hypoactive following the 250 and 650 mg/kg dose of 2-DG at 30, 60 and 90 min, the magnitude of the hypoactivity did not differ between the two doses at any of the three intervals. Analysis of difference scores done to partial out significant differences in baseline activity among groups failed to reveal any significant differences in the magnitude of 2-DG hypoactivity elicited by either 2-DG dose among the SAL, HMSG or LMSG groups. Like the hypoactivity induced by CWS, 2-DG-induced hypoactivity failed to

Table 7. Activity Levels of HMSG, LMSG and SAL Rats Following Vehicle and 2-DG Condition

		Post Manipulation (min)			
Dose (mg/kg)		30	60	90	120
Vehicle					
HMSG	$\bar{x}$	1762.0	2679.0	3150.4	3526.6
	SEM	337.8	474.5	702.0	696.0
LMSG	$\bar{x}$	1372.8*	1964.3*	2199.5*	2451.3*
	SEM	314.9	390.1	380.0	378.3
SAL	$\bar{x}$	2029.8	3147.3	3659.4	4049.9
	SEM	177.9	272.9	345.8	381.6
250					
HMSG	$\bar{x}$	1381.3	1756.5	1937.7	2989.5
	SEM	295.6	274.1	251.2	259.0
LMSG	$\bar{x}$	1004.7	1194.2	1737.5	2444.3
	SEM	124.5	157.4	248.6	387.8
SAL	$\bar{x}$	1365.8	1866.4	2637.6	3329.0
	SEM	200.9	200.9	257.3	287.9
650					
HMSG	$\bar{x}$	974.2	1402.1	1793.6	2388.6
	SEM	204.7	256.2	324.6	420.8
LMSG	$\bar{x}$	1352.7	1864.7	2390.6	3202.8
	SEM	257.0	355.3	405.6	484.9
SAL	$\bar{x}$	1305.8	1892.9	2802.0	3734.7
	SEM	182.8	317.0	427.8	532.1

*Significantly lower than corresponding SAL values ($p < .05$, Dunnett comparisons).

be affected by MSG treatment and thus failed to covary with the potentiated 2-DG analgesia and attenuated 2-DG hyperphagia.

Discussion

First, the present results support previous findings that MSG treated animals displayed such characteristics as tail autoamutilation, stunted growth, and increased body fat accumulation despite lower absolute body weight and basal hypophagia (Olney, 1969; Kizer, Nemeroff and Youngblood, 1978; Kanarek et al., 1979; Dawson and Lorden, 1981; Poon and Cameron, 1978). This experiment also demonstrated that MSG decreased baseline nociceptive thresholds on the jump test and altered analgesic responses following two different stressors. The hyperalgesic jump response noted in MSG-treated rats parallels the decrease in tail-flick latencies noted in animals with lesions placed in the arcuate nucleus (Millan et al., 1980). The analgesic and hypothermic, but not the hypoactive responses following CWS were significantly decreased in MSG treated animals. In contrast, MSG treatment potentiated 2-DG analgesia, reduced 2-DG hyperphagia and failed to affect 2-DG hypoactivity.

It appears that the behavioral disruptions associated with neonatal MSG treatment vary as a function of MSG dose. The underlying assumptions of the present study in employing more than one dose was that the LMSG condition would produce uniformly less damage to medial-basal hypothalamic structures than the HMSG condition and thereby induce a smaller effect relative to the HMSG group. Yet, in a number of cases to be detailed subsequently, the LMSG group displayed inexplicable divergences

from the HMSG actions. However, the magnitude of LMSG-induced changes in behavior was invariably less than the larger HMSG disruption. Moreover, since those studies displaying the MSG-induced behavioral, anatomical and biochemical alterations typically used a dose comparable to the HMSG condition of this study (Nemeroff et al., 1981; Dawson and Lorden, 1981; Krieger et al., 1979; Greely et al., 1978; Simantov and Amir, 1983), the major part of the following discussion will therefore attempt to correlate HMSG effects upon behavior with the known HMSG effects upon anatomical and biochemical pathways.

MSG induced alterations also varied as a function of gender. This may be due to the number of multiple sexual dysfunctions exhibited by MSG animals characterized by disruptions in the hypothalamo- hypophyseal-gonadal axis, low levels of gonadal steroids and gonadotropin, hypogonadism (Nemeroff et al., 1981) and subsequent impairments in reproductive capacity (Bakke, Lawrence, Bennet, Robinson, and Bowers, 1978; Olney, 1969; Pizzi, Barnhart and Fanslow, 1977). Most MSG studies have employed male animals (Kanarek et al., 1979; Nemeroff, Bissette, Greeley, Mailman, Martin, Brazeau, and Kizer, 1978; Krieger et al., 1979; Bodnar et al., 1980), however, those investigating both genders reveal that biochemical differences exist between genders. Prolactin levels in MSG-treated males, but not females, are greater than controls (Nemeroff et al., 1976), yet MSG-treated females display significantly greater depletions in dopamine and

norepinephrine (Dawson and Lorden, 1981; Conte-Devolx et al., 1981), higher corticosterone levels and lower ACTH and beta-endorphin levels (Conte-Devolx et al., 1981) than males. MSG-treated females also gain greater proportions of weight relative to controls, than did MSG-treated males (Olney, 1969). In the present study, MSG-treated females displayed a smaller analgesic and an absent hyperphagic response following 2-DG relative to MSG-treated males. Although it is not possible to identify precisely the specific systems in the MBH that determine such gender differences, this study clearly indicates a number of behaviors wherein gender influences the MSG disruption and/or MSG disruptions influence the already present gender differences.

HMSG rats of both sexes displayed significant decreases in CWS analgesia and CWS hypothermia. Given the known MSG neurotoxic effect upon the area of the arcuate nucleus and median eminence, which includes the depletion of previously described neuropeptides and neurotransmitters, this study attempted to assess systematically the analgesic, thermoregulatory and locomotor activity responses in MSG-treated animals folowing CWS. As the MBH modulates a variety of neuroendocrine functions through the hypothalamo-hypophyseal system (Cohen, 1967; Olney, 1969) it might be expected that damage to this area would mimic the effects observed following hypophysectomy if the hypothalamo-hypophyseal system specifically modulates pain-inhibition. It has been previously demonstrated that hypophysectomy (Bodnar et

al., 1979b), and MSG treatment (Bodnar et al., 1980) significantly attenuate CWS analgesia. Further, while complete adrenalectomy potentiates CWS analgesia (Panaocka and Hartmann, 1982), adrenal demedullation has no effect (Bodnar et al., 1982) suggesting adrenocortical modulation of this response. Moreover, since CWS analgesia does not display cross-tolerance with morphine and is only reversed by high doses of naloxone (Bodnar, Kelly, Steiner and Glusman, 1978; Bodnar, Kelly, Spiaggia, Ehrenberg and Glusman, 1978), CWS appears to exert its effects primarily through a non-opioid component of the hypothalamo-hypophyseal axis. That the analgesic response is due to the stressful consequences of the swim rather than to the effects of water temperature or the swim per se is indicated by the findings that concomitant CWS hypothermia does not adapt following repeated CWS as does analgesia (Bodnar et al., 1978), is not attenuated following hypophysectomy (Bodnar et al., 1979), or D-phenelalanine injections (Bodnar et al., 1980). Yet, alternatively other results have shown that the analgesic response following CWS can be reduced either by increasing the water temperature, decreasing the swim duration or increasing the interval between the swim and the nociceptive test (Bodnar and Sikorszky, 1983) and that pretreatment with clonidine, an alpha-noradrenergic receptor stimulant, enhances both the analgesic and hypothermic response following CWS (Bodnar et al., 1983) suggesting that the analgesic response sometimes varies as a function of the hypothermia. The reduced CWS analgesic

response of the MSG animal mirrors a normal animal's response to either a swim at a higher water temperature (Bodnar et al., 1979) or a swim of shorter duration (Bodnar and Sikorszky, 1983). The mechanisms by which MSG-inmduced alterations in CWS hypothermia and analgesia occur cannot be discerned by the present data, only that co-variance between the two stress responses are present. Further, given MSG damage to the circumventricular system and to the MBH particularly, it might be assumed that this structure may be integrally involved in the mediation of both responses. Again, the present experiment was not designed to address this question and therefore any discussion of the nature of the covariance would be speculative, particularly in terms of whether both responses are mediated by the same system. The similar hypoactive response following CWS among the groups suggests that MSG treatment is not producing a generalized alteration in all responses. Therefore, to state that MSG treatment alters an intrinsic pain-inhibitory system activated by CWS would be premature. Alterations in either intrinsic systems or external coping behaviors (e.g. shivering) ahould be examined in future experiments.

When challenged with 2-DG, HMSG rats displayed a potentiated 2-DG analgesia which shifted the 2-DG dose-response curve such that a lower 250 mg/kg dose produced a near-maximal analgesic response. Male HMSG rats displayed less hyperphagia following the 650 mg/kg dose of 2-DG and exhibited no change in intake

following the 1200 mg/kg dose. In contrast, female HMSG rats displayed significant hypophagia following the higher 2-DG dose. These ingestive deficits parallel previous findings that indicate MSG-treated rodents are hypophagic relative to controls when placed on a normal or low-calorie diet and fail to compensate properly to food deprivation or high-fat diet challenges (Dawson and Lorden, 1981; Kanarek et al., 1979). Again, the changes in LMSG rats were smaller and less consistent with 2-DG analgesia minimally affected and the decrease in 2-DG hyperphagia less pronounced. The present study found that the 2-DG responses dissociated from each other with potentiated 2-DG analgesia and reduced 2-DG hyperphagia noted in MSG-treated rats. The best explanation for the present results appears to be that the MSG-treated rat is not processing the stressful properties of the glucoprivic stimulus in a normal manner. Yet, damage to the MBH is not the only instance in which 2-DG analgesia and hyperphagia dissociate. Potentiated 2-DG analgesia and reduced hyperphagia are observed following hypophysectomy (Bodnar, 1979b) dopamine blockade (Bodnar and Nicotera, 1982; Stricker and Zigmmond, 1974) and acute exposure to foot shock (Bodnar, Kramer, Simone, Kirchgessner and Scalisi, 1983). Moreover, 2-DG hyperphagia, but not analgesia, is decreased following naloxone pretreatment (Lowy, Meickel and Yim, 1980; Wayner et al., 1971). Finally, 2-DG analgesia, but not hyperphagia, is decreased following prior repeated exposure to either 2-DG itself, morphine or CWS (Bodnar et al., 1978a, 1983; Spiaggia et al., 1979). Moreover, in no

situation have the hyperphagic and analgesic response varied in the same direction. Similar to CWS, the 2-DG effects can not be attributed to concurrent changes in locomotor activity. Again, the purpose of this study was to examine the effects of MSG treatment upon a variety of 2-DG-induced responses. The nature and/or mechanisms underlying the dissociation between 2-DG analgesia and hyperphagia cannot be precisely identified, but as in the case of MSG-induced effects upon CWS analgesia and hypothermia, must await replacement studies in which depleted or absent transmitters and/or peptides are systematically administered to the MSG-treated rat.

That CWS analgesia and 2-DG analgesia are altered differentially by MSG treatment provides further evidence for the multiplicity of mechanisms in coping responses to stress. The normal adaptive responses mediated through the MBH do not appear to be unidimensional since damage to this structure by neonatal MSG-treatment fails to alter all responses in the same direction and to the same extent. Although 2-DG shares common properties with CWS such as full and reciprocal cross-tolerance (Spiaggia et al., 1979) and naloxone non-reversibility (Bodnar, Kelly and Glusman, 1979) they appear to possess some different physiological substrates since 2-DG analgesia possesses some opioid properties including morphine tolerance and synergy (Spiaggia et al., 1979), and decreased analgesia following lesions placed in the dorsal raphe area of the caudal

periaqueductal grey (Brutus, Kelly, Glusman and Bodnar, 1979). Therefore, the assumption that analgesic response alterations following stress manipulations in MSG-treated rats are due to alterations to components of a specific pain-inhibitory system must be interpreted with caution and qualified by its effects upon other processes that may in turn modulate or interact with pain-inhibitory systems.

Experiment II

Morphine Analgesia and Flinch-Jump Thresholds: Following the determination of baseline flinch-jump thresholds at 90 days of age, all animals received each of four doses of morphine (0, 2.5, 5, and 10 mg morphine/ ml buffered solution/ kg body weight, SC). Thresholds were assessed at 30, 60 and 120 min after each injection. Injection order was determined according to an incompletely counterbalanced design. The experimenter conducting the tests was unaware of the injection conditions. Morphine analgesia was assessed for 17 SAL (6 males; 11 females), 21 LMSG (7 males; 14 females) and 19 HMSG rats (7 males; 12 females).

Morphine Analgesia and Hot-Plate Latencies: Two weeks later, the same morphine doses were administered to determine their effects upon paw-lick or jump-escape latencies 30, 60 and 120 min after injection. As before, injection order was determined according to an incompletely counterbalanced design and the tester was unaware of the experimental condition. A minimum of 48 h elapsed between injections.

Morphine Tolerance: Three weeks later, baseline flinch-jump thresholds and hot-plate latencies were determined on successive days. Baseline levels were determined over three sessions with the second and third sessions following the first after 30 and 90 min intervals. Core body temperatures were also determined after

the second nociceptive test session. Following determinations of both baseline thresholds, each rat received daily 15 mg/ kg dose of morphine (15 mg/ ml buffered solution/ kg body weight, SC) between 0900 and 1100 for 14 consecutive days. To assess the progressive effects of chronic morphine injection on nociception, flinch-jump thresholds were determined on the first, fifth, ninth and thirteenth injection days, while hot-plate latencies were determined on the second, sixth, tenth, and fourteenth injection days. All nociceptive measures were ascertained 30, 60 and 120 min after injection with core body temperatures measured immediately after the second nociceptive test. In addition, each animal's body weight was ascertained immediately before injection on the first, fifth, ninth and fourteenth days. To assess withdrawal effects, three sessions of flinch-jump thresholds and three sessions of hot-plate latencies were carried out on the fifth, and sixth days after the last injection respectively. Body weights were determined immediately prior to the first nociceptive test and core body temperatures were measured after the second nociceptive session.

Morphine Activity Levels: Separate groups of rats were treated neonatally with either the SAL (11 males; 8 females), the LMSG (6 males, 7 females), or the HMSG (8 males, 5 females) regimens. At 100 days of age, activity levels of all animals were assessed following each of three doses of morphine (0, 2.5 and 10 mg morphine/ 1 ml buffered solution/ kg body weight, SC)

according to an incompletely counterbalanced design. A one week interval elapsed between injections and the testers were unaware of the injection conditions.

Results

Morphine Analgesia and Flinch-Jump Thresholds: Tables 8, 9 and 10 display the significant changes in thresholds across morphine doses ($F(3,153)= 126.94$, $p< .001$), between males and females ($F(1,51)= 17.96$, $p< .0001$), among post-injection test times ($F(2,102)= 19.88$, $p< .0001$), as well as for the interactions between groups and times ($F(4,102)= 4.76$, $p< .0015$), and doses and times ($F(6,306)= 7.51$, $p< .0001$). All three groups of male rats exhibited a significant increase in jump thresholds over pre-injection values at 30 min and 60 min following the 2.5 mg morphine dose and at 30, 60 and 120 min following both the 5 and 10 mg/kg doses of morphine. In contrast, jump thresholds of SAL female rats were significantly elevated over pre-injection values at 30, 60 and 120 min following the 5 and 10, but not the 2.5 mg/kg morphine doses. HMSG females exhibited significant analgesia at 30 and 60 min following the 5 mg/kg dose and at 30, 60 and 120 min following the 10 mg/kg dose. LMSG females displayed significant analgesia at each post-injection test following each dose.

Since the jump thresholds of MSG-treated rats were significantly lower than the SAL group following the vehicle injection, analysis of difference score revealed significant differences across morphine doses ($F(2,102)= 104.24$, $p< .0001$), among post-injection test times ($F(2,102)= 19.49$, $p< .0001$), and for the interactions between doses and times ($F(4,204)= 20.63$, $p<$

Table 8. Jump Thresholds (mA) 30 min Following Morphine in MSG-treated and Control Male and Female Rats.

Group		Morphine Dose (mg/kg)			
Males:		0	2.5	5.0	10.0
HMSG	$\bar{x}$	.43*	.53+	.56+	.70+
	SEM	.04	.02	.03	.04
LMSG	$\bar{x}$	.49*	.55+	.64+	.80+
	SEM	.03	.04	.04	.06
SAL	$\bar{x}$	.58	.63+	.69+	.94+
	SEM	.10	.12	.08	.07
Females:					
HMSG	$\bar{x}$	.42	.43	.53+	.70+
	SEM	.03	.03	.02	.03
LMSG	$\bar{x}$	.37*	.49	.52+	.69+
	SEM	.02	.03	.02	.02
SAL	$\bar{x}$	.43	.47	.53+	.69+
	SEM	.04	.03	.03	.03

Note: Significantly greater (+) than corresponding vehicle condition ($p < .05$, Dunnett comparisons).

Significantly less (*) than same-sex SAL control value ($p<.05$, Dunnett comparisons).

Table 9. Jump Thresholds (mA) 60 min Following Morphine in MSG-treated and Control Male and Female Rats.

Group		Morphine Dose (mg/kg)			
Males:		0	2.5	5.0	10.0
HMSG	$\bar{x}$	.45*	.52+	.57+	.82+
	SEM	.02	.03	.02	.06
LMSG	$\bar{x}$	.48	.54+	.62+	.82+
	SEM	.04	.04	.02	.07
SAL	$\bar{x}$	.49	.63+	.69+	.87+
	SEM	.08	.11	.08	.04
Females:					
HMSG	$\bar{x}$	.43	.47	.54+	.73+
	SEM	.02	.03	.02	.03
LMSG	$\bar{x}$	.37*	.48+	.52+	.68+
	SEM	.01	.03	.02	.02
SAL	$\bar{x}$	.44	.47+	.52+	.65+
	SEM	.03	.03	.03	.03

Note: Significantly greater (+) than corresponding vehicle condition ($p < .05$, Dunnett comaparisons).

Significantly less (*) than same-sex SAL control value ($p < .05$, Dunnett comparisons).

Table 10. Jump Thresholds (mA) 120 min Following Morphine in MSG-treated and Control Male and Female Rats.

Group		Morphine Dose (mg/kg)			
Males:		0	2.5	5.0	10.0
HMSG	$\bar{x}$	.48*	.47	.53+	.71+
	SEM	.03	.03	.02	.05
LMSG	$\bar{x}$	.52	.54	.59+	.72+
	SEM	.05	.04	.03	.07
SAL	$\bar{x}$	.55	.58	.69+	.79+
	SEM	.07	.09	.09	.03
Females:					
HMSG	$\bar{x}$	.44	.43	.48	.66+
	SEM	.02	.02	.02	.04
LMSG	$\bar{x}$	.39*	.44+	.45+	.60+
	SEM	.02	.03	.01	.02
SAL	$\bar{x}$	.45	.48	.50+	.63+
	SEM	.04	.04	.02	.03

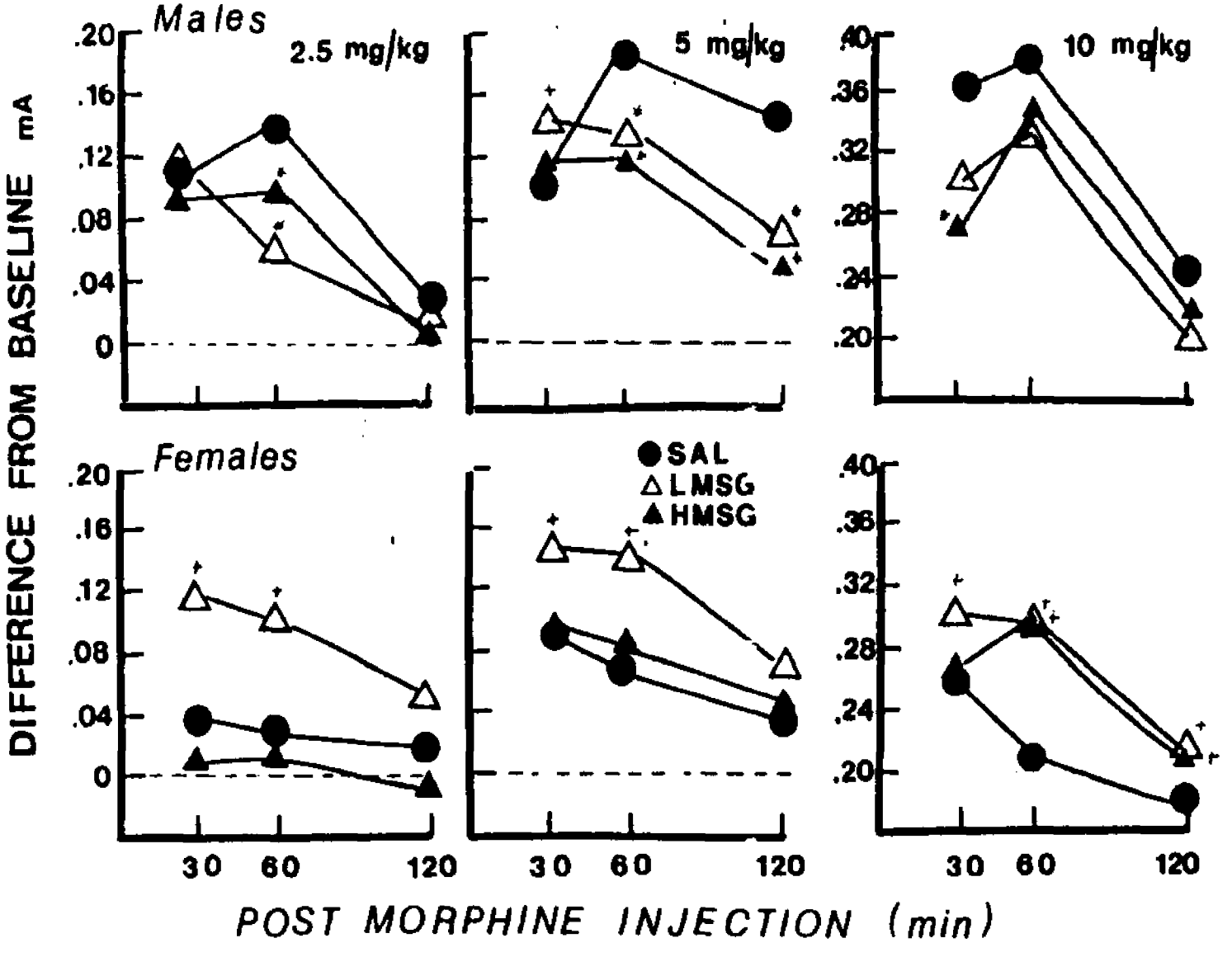
Note: Significantly greater (+) than corresponding vehicle condition ($p < .05$, Dunnett comparisons).

Significantly less (*) than same-sex SAL control value ($p < .05$, Dunnett comparisons).

.05), and among doses, time and gender ($F(4,204)= 2.56$, $p< .05$). Figure 5 shows that the magnitude of morphine analgesia of HMSG was significantly smaller than following SAL males 60 min following the 2.5 mg/kg dose, 60 and 120 min following the 5 mg/kg dose and 30 min following the 10 mg/kg dose of morphine. Alterations in the analgesic response of LMSG males in relation to SAL males was less consistent with significant reductions observed 60 min following the 2.5 mg/kg dose, and at 60 and 120 min following the 5 mg/kg dose and a potentiation observed 30 min following the 5 mg/kg dose. Marked gender differences were observed for this opiate response. In contrast to the diminution in morphine analgesia seen in male HMSG rats, HMSG females displayed significant increases in morphine analgesia 60 and 120 min following the 10 mg/kg dose. Moreover, LMSG females showed significant increases in morphine analgesia relative to SAL females at 30 and 60 min following the 2.5 and 5 mg/kg doses and at 30, 60 and 120 min following the 10 mg/kg dose. Thus, morphine analgesia is reduced by MSG treatment in male rats, yet potentiated by MSG treatment in female rats when the jump threshold is employed as the nociceptive measure.

Flinch thresholds were significantly altered across morphine doses ($F(3,153)= 17.95$, $p< .0001$), and for the interactions between groups and test time ($F(4,102)= 4.35$, $p< .003$), between doses and test times ($F(6,306)= 2.56$, $p< .05$), among groups, doses and test times ($F(12,306)= 2.62$, $p< .005$) and among groups,

Figure 5. Differential alterations (greater (+) or less than (*) SAL, Dunnett comparison, $p < .05$) in morphine analgesia on the jump test was observed after MSG treatment. While HMSG males displayed attenuations in morphine analgesia across doses, female HMSG animals exhibited potentiations in morphine analgesia following the 10 mg/kg dose. LMSG rats displayed a similar pattern.


Males
2.5 mg/kg
5 mg/kg
10 mg/kg
Females
SAL
LMSG
HMSG
DIFFERENCE FROM BASELINE mA
.20
.16
.12
.08
.04
0
.40
.36
.32
.28
.24
.20
30
60
120
POST MORPHINE INJECTION (min)

gender, doses and test times ($F(6,306)= 2.83$, $p< .05$). Flinch thresholds were significantly elevated over vehicle only after the 10 mg/kg morphine dose for HMSG males (60 min) and HMSG females (120 min). Flinch thresholds were significantly increased over vehicle values 30 min following the 2.5 and 5 mg/kg doses and 30 and 60 min following the 10 mg/kg dose in LMSG males and 30 and 60 min following the 2.5 and 10 mg/kg dose in LMSG females. Flinch thresholds were significantly elevated over vehicle values at 120 min following the 2.5 mg/kg dose in SAL males and at 30 and 60 min following the 10 mg/kg dose in SAL males and females.

Since flinch thresholds following vehicle injections were significantly lower in HMSG males, a difference score analysis revealed alterations across morphine doses ($F(2,102)= 14.20$, $p< .0001$), post-injection test times ($F(2,102)= 3.81$, $p< .03$), and for the interaction among doses, times and groups ($F(8,204)= 2.66$, $p< .01$). The magnitude of the flinch response in HMSG males was significantly lower than that of SAL males 60 and 120 min after the 2.5 mg dose and 30 min after the 10 mg/kg dose. Yet, in contrast it was significantly greater 60 and 120 min after the 5 mg/kg dose. LMSG male rats exhibited a greater response than SAL rats 30 min after the 2.5 and 5 mg/kg dose and a smaller response 30 min after the 10 mg/kg dose. In contrast to males, the magnitude of the flinch response of the HMSG females was significantly greater than their SAL counterpart at

60 and 120 min after the 10 mg/kg dose, but lower 120 min after the 2.5 mg/kg dose. In contrast, the magnitude of analgesia in LMSG females was greater than SAL females at 60 min after the 2.5 and 10 mg/kg dose. Again, flinch responses showed less reliable and consistent effects than jump responses.

Morphine Analgesia and Hot-Plate Latencies: Significant alterations in hot plate latencies were observed across morphine doses ($F(3,147)= 28.48$, $p< .0001$), among groups ($F(2,49)= 20.60$, $p< .0001$), across test times ($F(2,98)= 68.30$, $p< .0001$), and for the interactions between groups and gender ($F(2,49)= 3.79$, $p< .05$), doses and groups ($F(6,147)= 5.79$, $p< .0001$), times and groups ($F(4,98)= 2.79$, $p< .03$), doses and times ($F(6,294)= 7.11$, $p< .0001$), and among doses, times and gender ($F(6,294)=3.63$, $p< .005$). As observed in Tables 11, 12 and 13 HMSG males displayed significantly longer latencies than vehicle 30 min following the 5 mg/kg dose and at 30 and 120 min following the 10 mg/kg dose. Latencies of LMSG males were significantly longer than vehicle at 30 and 60 min following the 5 mg/kg dose and 60 min following the 10 mg/kg dose. Latencies of SAL males were significantly longer than vehicle at 30 min following the 2.5 mg/kg dose and 30 and 60 min following the 10 mg/kg dose. Again gender played an important role in this response. Significantly shorter latencies were observed following the 2.5 mg/kg dose for HMSG (120 min) and LMSG (60 min) females, following the 5 mg/kg dose for HMSG (120 min) females and following the 10 mg/kg dose for

Table 11. Hot Plate Latencies (sec) 30 min Following Morphine in MSG-treated and Control Male and Female Rats.

Group		Morphine Dose (mg/kg)			
Males:		0	2.5	5.0	10.0
HMSG	$\bar{x}$	6.47	7.63	8.65 +	9.88 +
	SEM	.88	.92	1.16	1.04
LMSG	$\bar{x}$	4.44	4.52	7.17 +	5.60
	SEM	.48	.46	1.03	.70
SAL	$\bar{x}$	4.00	5.64 +	5.02	7.15 +
	SEM	.53	.61	.40	.91
Females:					
HMSG	$\bar{x}$	5.44	6.57	5.11	10.23 +
	SEM	.84	.65	.81	.86
LMSG	$\bar{x}$	5.42	4.57	5.43	5.42
	SEM	.55	.50	.74	.62
SAL	$\bar{x}$	4.67	5.52	5.05	9.00 +
	SEM	.30	.61	.50	.71

Note: Significantly greater (+) or less (*) than corresponding vehicle condition ($p < .05$, Dunnett comparisons).

Table 12. Hot Plate Latencies (sec) 60 min Following Morphine in MSG-treated and Control Male and Female Rats.

Group		Morphine Dose (mg/kg)			
Males:		0	2.5	5.0	10.0
HMSG	$\bar{x}$	6.17	5.18	7.71	10.89+
	SEM	1.20	.51	.73	1.11
LMSG	$\bar{x}$	4.36	3.78	5.94+	6.82+
	SEM	.44	.45	.87	1.28
SAL	$\bar{x}$	2.93	4.00	3.64	7.19+
	SEM	.14	.60	.28	1.49
Females:					
HMSG	$\bar{x}$	5.30	5.69	6.12	9.92+
	SEM	.54	.82	.75	.85
LMSG	$\bar{x}$	5.19	3.73*	4.42	4.81
	SEM	.54	.45	.52	.68
SAL	$\bar{x}$	4.33	4.55	3.62	7.32+
	SEM	.39	.47	.38	.75

Note: Significantly greater (+) or less (*) than corresponding vehicle condition ($p < .05$, Dunnett comparisons).

Table 13. Hot Plate Latencies (sec) 120 min Following Morphine in MSG-treated and Control Male and Female Rats.

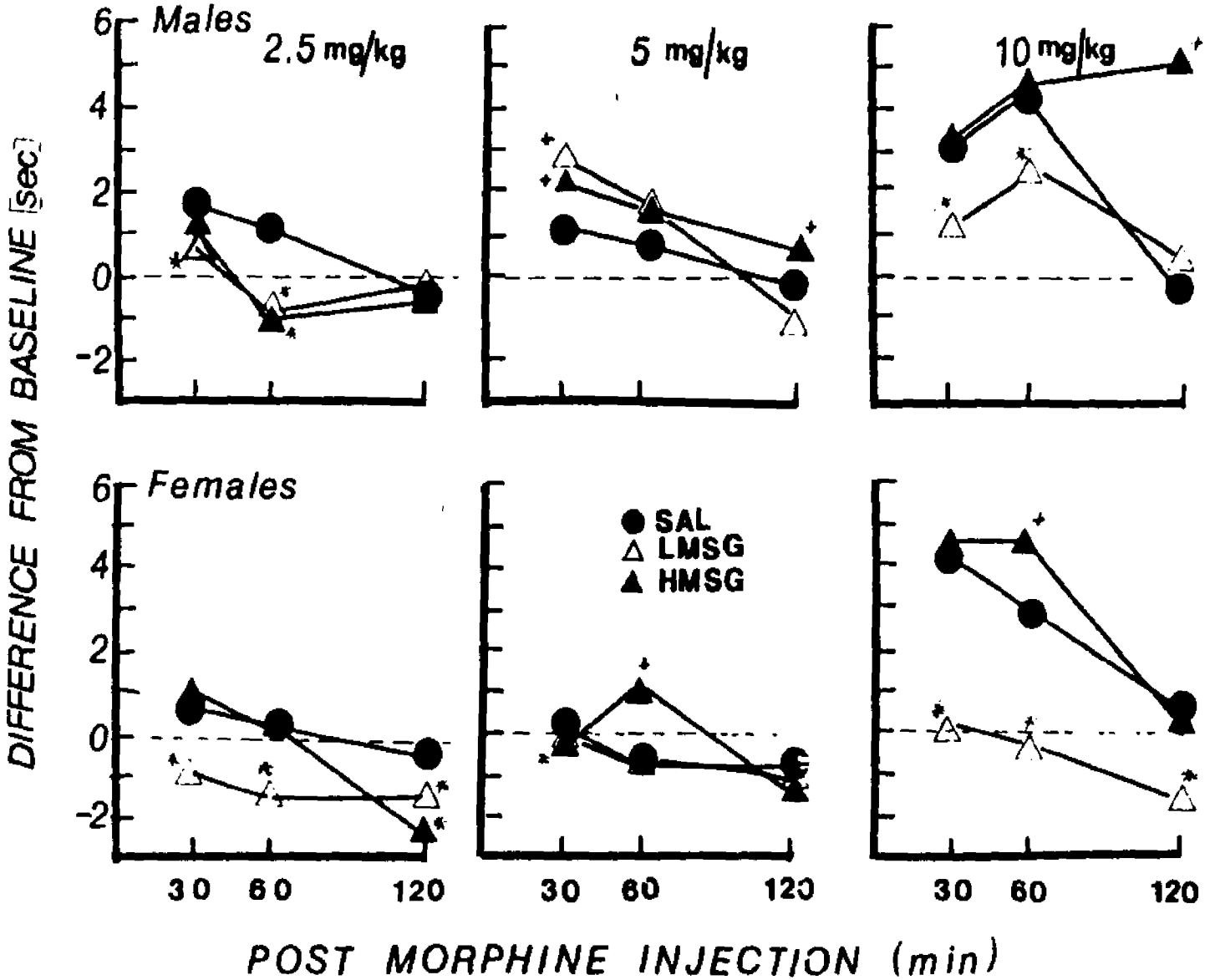
Group		Morphine Dose (mg/kg)			
Males:		0	2.5	5.0	10.0
HMSG	$\bar{x}$	4.92	5.94	5.81	10.05+
	SEM	.72	1.45	.69	1.30
LMSG	$\bar{x}$	4.51	4.25	3.30	4.95
	SEM	.50	1.30	.31	.64
SAL	$\bar{x}$	3.19	2.76	2.80	3.15+
	SEM	.39	.31	.27	.52
Females:					
HMSG	$\bar{x}$	5.82	3.61*	4.02*	5.31
	SEM	.78	.19	.52	.83
LMSG	$\bar{x}$	5.07	3.58*	4.07	3.38*
	SEM	.51	.40	.50	.45
SAL	$\bar{x}$	4.15	3.63	3.42	4.79
	SEM	.56	.47	.36	.47

Note: Significantly greater (+) or less (*) than corresponding vehicle condition ($p < .05$, Dunnett compariosons).

LMSG (120 min) females. Analgesia was noted for SAL females 30 and 60 min following the 10 mg/kg dose.

Since MSG lengthened latencies following vehicle, a difference score revealed significant latency alterations across groups ($F(2,49)= 5.03$, $p< .05$), across genders ($F(1,49)= 5.91$, $p< .05$), across morphine doses ($F(2,98)= 35.38$, $p< .0001$), across post-injection test times ($F(2,98)= 11.64$, $p< .0001$) and for the interaction between doses and groups ($F(4,98)= 6.61$, $p< .001$) doses and times ($F(4,196)= 3.63$, $p< .05$) among doses, times and groups ($F(8,196)= 2.20$, $p< .03$), and among doses, times and groups ($F(4,196)= 4.58$, $p< .002$). As revealed in Figure 6, the magnitude of hot-plate morphine analgesia in HMSG males was significantly attenuated 60 min following the 2.5 dose, but significantly potentiated 30 and 120 min following the 5 mg/kg dose and at 120 min following the 10 mg/kg dose. In contrast, LMSG males displayed significantly less morphine analgesia than SAL males at 30 and 60 min following the 2.5 dose, and at 30 and 60 min following the 10 mg/kg, but potentiated analgesia 30 min following the 5 mg/kg dose. Like HMSG males, HMSG females displayed altered latencies as a function of morphine dose: significant attenuations were observed 120 min following the 2.5 mg/kg dose and 30 min following the 5 mg/kg dose, while significant potentiation occurred 60 min following the 5 and 10 mg/kg doses. Again, like males, LMSG females exhibited significantly shorter latencies than SAL females 30, 60, and 120

Figure 6. Significant potentiation (+: Dunnett comparison, $p < .05$) in morphine analgesia on the hot-plate test was observed in HMSG animals of both sexes. Less consistent results were observed for the LMSG group. (Significantly less (*) Dunnett comparison, $p < .05$).


Males
2.5 mg/kg
5 mg/kg
10 mg/kg
Females
SAL
LMSG
HMSG
6
4
2
0
-2
30
60
120
DIFFERENCE FROM BASELINE [sec]
POST MORPHINE INJECTION (min)

min following the 2.5 and 10 mg/kg morphine doses. In summary, jump thresholds and hot-plate latencies display dose-dependent analgesia following morphine, yet dissociate in terms of alterations in opiate responses in MSG-treated animals.

Morphine Tolerance Flinch-Jump Thresholds: Jump thresholds were significantly altered across morphine injection days ($F(5,215)= 40.30$, $p< .0001$), among groups ($F(2,43)= 17.95$, $p< .0001$), between males and females ($F(1,43)= 24.49$, $p< .0001$), across post-injection test times ($F(2,86= 25.71$, $p< .0001$) and for the interactions between days and groups ($F(10,215)= 3.54$, $p< .001$), days and gender ($F(5,215)= 3.62$, $p< .005$), days and test times ($F(10,430)= 3.87$, $p< .0001$), and among days, test times and groups ($F(20,43)= 1.66$, $p< .05$). Tables 14, 15 and 16 show that jump thresholds of HMSG males were significantly greater than baseline over the 120 min test intervals following the first, fifth and ninth morphine injections, but not following the thirteenth morphine injection or withdrawal. Jump thresholds of LMSG males were significantly greater than baseline over the 120 min test intervals up to the fifth morphine injections but not thereafter. Jump thresholds of SAL males were significantly greater than baseline over the 120 min test intervals following the first and fifth morphine injections, at 60 and 120 min following the ninth injection, but not thereafter. Females show a similar, though not an identical pattern. Morphine analgesia was observed in HMSG females over the 120 min test intervals

Table 14. Thirty Min Jump Thresholds (mA) During and After Days of Morphine Injection (15 mg/kg) in MSG-treated and Control Male and Female Rats

Group		Days					
Males:		PRE	1	5	9	13	Post 5
HMSG	$\bar{x}$	.49*	.70+	.87+	.59+	.49	.47
	SEM	.01	.06	.02	.07	.05	.03
LMSG	$\bar{x}$	.44*	.57+	.60+	.49	.43	.48
	SEM	.05	.04	.04	.06	.03	.03
SAL	$\bar{x}$	.55	.86+	.63+	.60	.55	.60
	SEM	.07	.07	.03	.07	.05	.07
Females:							
HMSG	$\bar{x}$	.40	.50+	.60+	.47+	.47	.38
	SEM	.02	.03	.03	.02	.03	.02
LMSG	$\bar{x}$	.35*	.52+	.44+	.41+	.37	.38
	SEM	.02	.03	.02	.04	.02	.02
SAL	$\bar{x}$	.40	.60+	.53+	.60+	.50+	.46
	SEM	.02	.04	.04	.03	.02	.04

Note: Significantly greater (+) than corresponding vehicle condition ($p < .05$, Dunnett comparisons).

Significantly less (*) than same-sex SAL control value ($p < .05$, Dunnett comparisons).

Table 15. Sixty Min Jump Thresholds (mA) During and After Days of Morphine Injection (15 mg/kg) in MSG-treated and Control Male and Female Rats

Group		Days					
Males:		PRE	1	5	9	13	Post 5
HMSG	x	.44*	.79+	.73+	.66+	.50	.43
	SEM	.02	.05	.02	.01	.02	.03
LMSG	x	.45*	.65+	.58+	.44	.47	.48
	SEM	.04	.04	.04	.07	.03	.03
SAL	x	.57	.91+	.70+	.69+	.59	.52
	SEM	.07	.05	.03	.07	.06	.07
Females:							
HMSG	x	.43	.60+	.55+	.48	.50+	.40
	SEM	.03	.03	.04	.03	.05	.03
LMSG	x	.36*	.60+	.47+	.47+	.36	.37
	SEM	.03	.02	.03	.06	.02	.02
SAL	x	.44	.70+	.54+	.67+	.59+	.44
	SEM	.03	.03	.03	.04	.03	.04

Note: Significantly greater (+) than corresponding vehicle condition ($p < .05$, Dunnett comparisons).

Significantly less (*) than same-sex SAL control value ($p < .05$, Dunnett comparisons).

Table 16. One Hundred Twenty Min Jump Threshold (mA) During and After Days of Morphine Injection (15 mg/kg) in MSG-treated and Control Male and Female Rats

Group		Days					
		PRE	1	5	9	13	Post 5
Males:							
HMSG	$\bar{x}$	.48*	.73+	.83+	.65+	.56	.46
	SEM	.01	.05	.02	.06	.07	.05
LMSG	$\bar{x}$	.49*	.61+	.68+	.47	.46	.53
	SEM	.03	.03	.06	.06	.03	.03
SAL	$\bar{x}$	.63	.93+	.78+	.77+	.62	.56
	SEM	.08	.08	.07	.08	.05	.04
Females:							
HMSG	$\bar{x}$	.46	.63+	.60+	.60+	.50	.45
	SEM	.03	.04	.03	.03	.04	.03
LMSG	$\bar{x}$	.38*	.57+	.53+	.42	.42	.40
	SEM	.02	.04	.04	.04	.02	.02
SAL	$\bar{x}$	.46	.68+	.56+	.75+	.58+	.49
	SEM	.04	.04	.03	.04	.04	.03

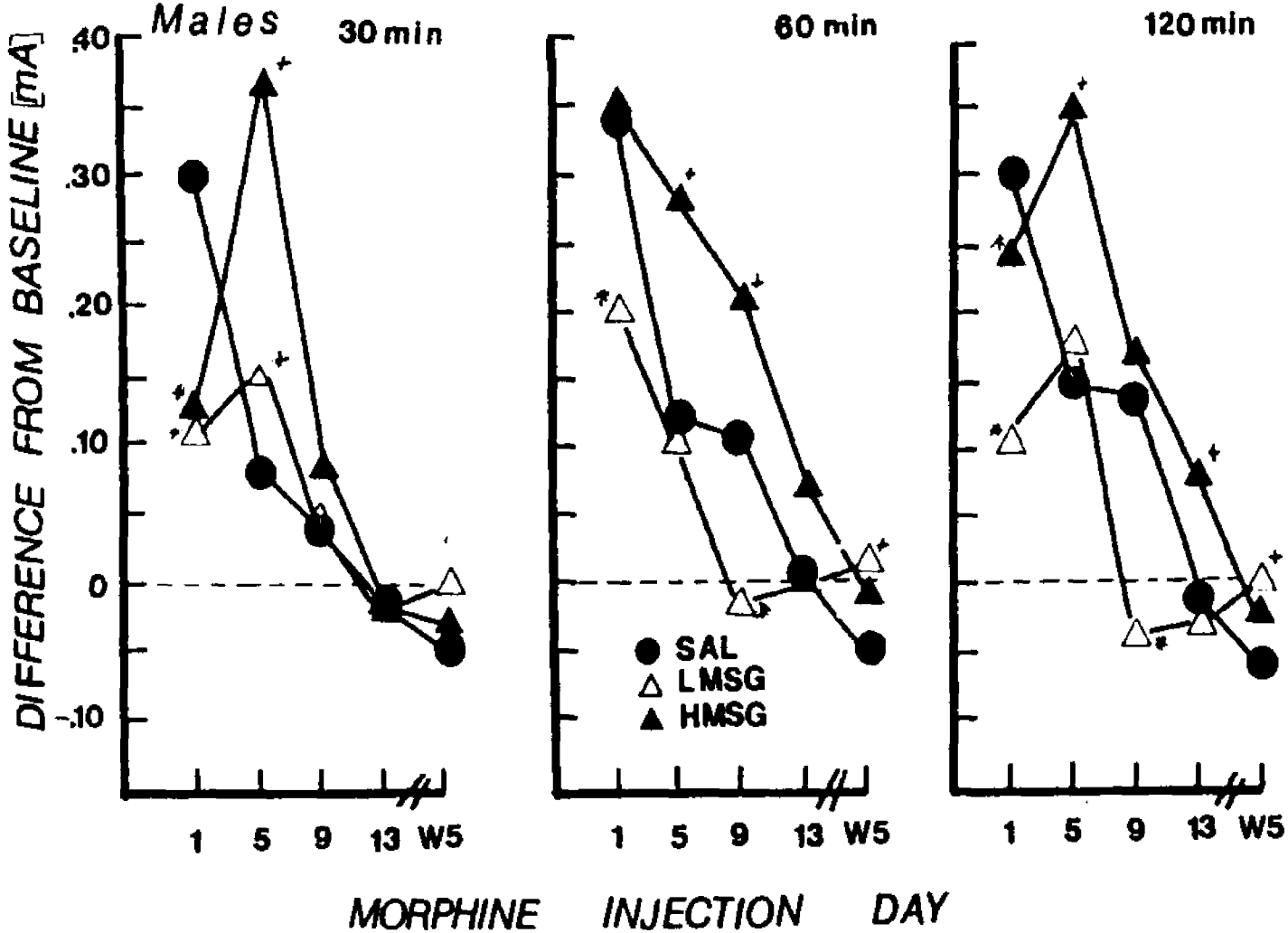
Note: Significantly greater (+) than corresponding vehicle condition ($p < .05$, Dunnett comparisons).

Significantly less (*) than same-sex SAL control value ($p < .05$, Dunnett comparisons).

following the first and fifth injections, at 30 and 120 min following the ninth injection, at 60 min following the thirteenth injection, but not during the fifth day of morphine withdrawal. Morphine analgesia of the LMSG females was observed at 30, 60 and 120 min following the first, fifth and ninth injections, but not thereafter. In contrast, SAL females displayed a significantly greater and prolonged analgesic response 30, 60 and 120 min of day 1, 5, 9 and 13, but failed to differ from baseline on the fifth day of morphine withdrawal.

Since MSG treatment significantly lowered baseline thresholds, a difference score analysis revealed significant effects across injection days ($F(4,172)= 36.11$, $p< .0001$) and for the interactions between days and groups ($F(8,172)= 3.97$, $p< .0005$), days and gender ($F(4,172)= 4.27$, $p< .005$), days and test times ($F(8,344)= 4.98$, $p< .0001$), and among days, test times and groups ($F(16,344)= 2.17$, $p< .01$). Figure 7 shows the magnitude of morphine analgesia on the jump threshold test in HMSG relative to SAL males varied across the injection time course with significant attenuations noted on the first day (30 and 120 min), and significant potentiations on the fifth (30, 60 and 120 min), ninth (60 min), and thirteenth (120 min) days. Withdrawal (30 min) jump thresholds were significantly lower in HMSG rats. In contrast, the magnitude of morphine analgesia as measured by the jump test in LMSG, relative to SAL, males was significantly smaller on the first (30,60 and 120 min), and ninth (60 and 120 min), but greater on the fifth (30 min) days. Further,

Figure 7. Alterations (significantly less (*) or greater (+), Dunnett comparison, $p < .05$). in the development of morphine tolerance on the jump test following MSG treatment. While maximal morphine analgesia in HMSG animals was delayed until day 5, the rate of subsequent analgesic tolerance across the injection sequence is similar among groups.

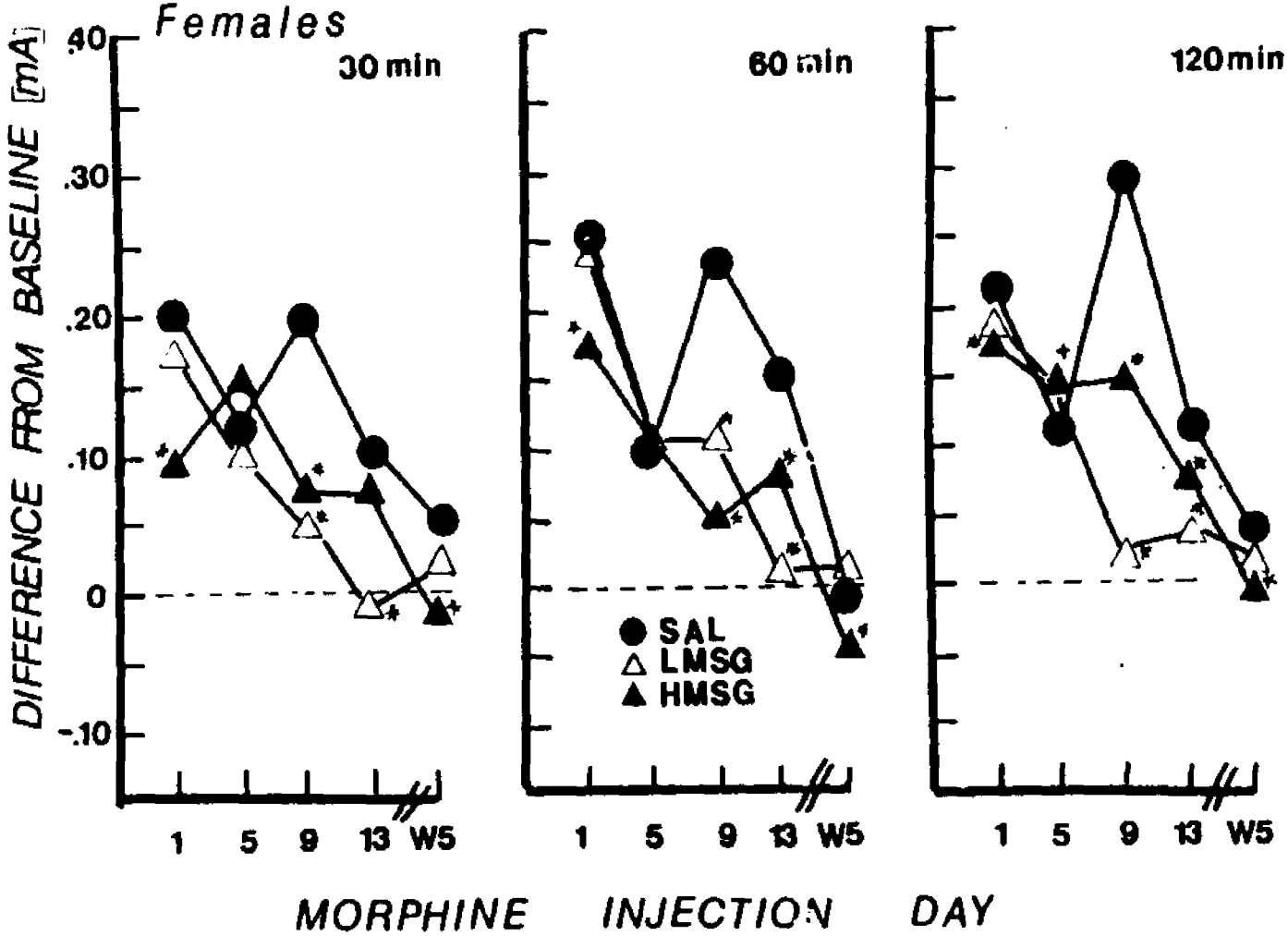

Males
30 min
60 min
120 min
DIFFERENCE FROM BASELINE [mA]
.40
.30
.20
.10
0
-.10
1
5
9
13
W5
SAL
LMSG
HMSG
MORPHINE INJECTION DAY

withdrawal (60 and 120 min) jump thresholds were significantly greater in LMSG males.

Again gender differences were apparent in the results. Figure 8 shows the magnitude in morphine analgesia in HMSG females was significantly lower than SAL females on the first (30, 60 and 120 min), ninth (30, 60 and 120 min) and thirteenth (60 and 120 min) morphine injection days as well as during withdrawal (30, 60 and 120 min), but greater on the fifth (30 min) day. While morphine analgesia of LMSG females failed to differ significantly from SAL females following the first injection, it was significantly greater on the fifth day (120 min), yet significantly less on the ninth and thirteenth days (30, 60 and 120 min). After morphine withdrawal, responses of the two groups failed to differ. Thus, MSG treatment significantly altered the analgesic response to chronic morphine on the jump test with gender altering the direction of results.

Significant flinch threshold alterations were observed across morphine injection days ($F(5,215)= 5.13$, $p< .001$), among groups ($F(2,43)= 10.88$, $p< .0001$), between males and females ($F(1,43)= 14.90$, $p< .001$) across post-injection test times ($F(2,86)= 25.95$, $p< .0001$), and for the interactions between groups and gender ($F(2,43)= 3.36$, $p< .05$), days, and groups ($F(10,215)= 2.40$, $p< .05$) and among days, test times, and groups ($F(10,430)= 4.01$, $p< .0001$). Flinch thresholds were significantly increased only on the fifth injection day (30 and 120 min) for HMSG males and were significantly decreased on the fifth and thirteenth days (30 min)

Figure 8. Unlike MSG-treated males, MSG-treated females displayed a less consistent pattern on the jump test across the morphine injection sequence The magnitude of the initial analgesic response of HMSG females was less than their SAL-treated counterparts.


Females
30 min
60 min
120 min
DIFFERENCE FROM BASELINE [mA]
.40
.30
.20
.10
0
-.10
SAL
LMSG
HMSG
1 5 9 13 W5
1 5 9 13 W5
1 5 9 13 W5
MORPHINE INJECTION DAY

for LMSG males. Flinch thresholds of SAL males were greater than baseline only on the first day (60 min), but were lower than baseline on the first (30 min), fifth (30 and 60 min), ninth (30 and 60 min) and thirteenth (30, 60 and 120 min) injection days as well as during withdrawal (30, 60 and 120 min). Neither LMSG, HMSG nor SAL females displayed alterations in flinch thresholds from baseline. Since MSG treatment significantly lowered baseline flinch thresholds, a difference score analysis revealed significant alterations across injection days ($F(4,172)= 6.04$, $p< .0001$), and for the interactions between days and groups ($F(8,172)= 2.88$, $p< .05$), days and gender ($F(4,172)= 3.15$, $p< .05$), days and test times ($F(8,344)= 3.77$, $p< .0005$), and among days, test times and gender ($F(8,344)= 4.42$, pp< .0001). Flinch thresholds of HMSG males were of significantly greater magnitude than SAL males on the first (30 min), fifth and thirteenth (30 min) days. Flinch thresholds of LMSG males were of significantly lower magnitude only on the fifth (30 min) day. Flinch thresholds of female HMSG and LMSG rats failed to differ from SAL females. Again, flinch thresholds displayed less consistent and less robust effects than jump thresholds.

Morphine Tolerance Hot Plate Latencies: Significant alterations in the hot plate latencies were observed across morphine injection days ($F(5,215)= 50.28$, $p< .0001$), among groups ($F(2,43)= 9.30$, $p< .0005$), across post-injection test times ($F(2,86)= 46.97$, $p< .0001$), and for the interactions between

days and groups ($F(5,215)= 2.30$, $p< .05$), days and test times ($F(10,430)= 3.08$, $p< .001$), and among days, test times and groups ($F(20,430)= 2.42$, $p< .001$). Chronic administration of morphine elicited the expected progressive decline in analgesic responsivity. Tables 17, 18 and 19 show latencies of HMSG males were significantly longer than baseline on the second (30, 60 and 120 min), sixth (30 and 120 min), tenth (30 min) and fourteenth (30 and 60 min) days, but not during withdrawal. Latencies of LMSG males were significantly longer on the second (30, 60 and 120 min) and sixth (30 min) days, yet shorter on the tenth and fourteenth (60 min) injection days as well as during withdrawal (60 min). In turn, SAL males showed significant hot-plate analgesia on the second (30, 60 and 120 min), sixth (30, 60, and 120 min), tenth (30 and 60 min) and fourteenth (30, 60, 120 min) days, but were hyperalgesic during withdrawal (60 min). Female HMSG rats displayed hot-plate analgesia on the second (30, 60 and 120 min), sixth (30 and 60 min), tenth (60 and 120 min) and fourteenth (30 and 60 min) days, and were also hyperalgesic during withdrawal. Like LMSG males, LMSG females showed significant analgesia on the second day (30, 60 and 120 min), followed by significant hyperalgesia on the tenth day (60 min). SAL female rats displayed significant analgesia on the second (30, 60 and 120 min), sixth (30 and 60 min) and tenth (60 min) days, but were hyperalgesic during withdrawal.

Table 17. Thirty Min Hot-Plate Latencies (sec) During and After Days of Morphine Injection (15 mg/kg) in MSG-treated and Control Male and Female Rats.

Group		Days					
		PRE	2	6	10	14	Post 6
Males:							
HMSG	$\bar{x}$	4.10	10.24+	7.12+	8.66+	7.55+	4.61
	SEM	.47	1.03	1.47	1.72	1.14	.56
LMSG	$\bar{x}$	4.45	6.56+	6.34+	3.73	4.02	3.60
	SEM	.82	1.08	.76	.30	.65	.43
SAL	$\bar{x}$	3.45	10.62+	7.51+	5.46+	8.30+	3.31
	SEM	.41	.93	1.00	1.32	1.16	.46
Females:							
HMSG	$\bar{x}$	5.41	9.19+	8.05+	6.19	7.06+	3.03*
	SEM	.30	1.07	1.24	1.01	.91	.47
LMSG	$\bar{x}$	4.55	6.71+	5.69	4.76	3.62	5.63
	SEM	.43	.62	.69	.32	.29	.79
SAL	$\bar{x}$	5.63	10.27+	8.47+	6.51	6.88	3.34*
	SEM	.70	.93	.77	.65	1.30	.15

Note: Significantly greater (+) or less (*) than corresponding vehicle condition ($p < .05$, Dunnett comparisons).

Table 18. Sixty Min Hot-Plate Latencies (sec) During and After DAys of Morphine Injection (15 mg/kg) in MSG-treated and Control Male and Female Rats.

Group		Days					
		PRE	2	6	10	14	Post 6
Males:							
HMSG	$\bar{x}$	3.83	11.12+	5.58	5.53	7.05+	2.98
	SEM	1.02	.88	1.94	1.85	2.09	.03
LMSG	$\bar{x}$	4.96	8.02+	4.78	2.83*	3.53*	3.13*
	SEM	.70	.99	.63	.31	.58	.37
SAL	$\bar{x}$	4.04	10.13+	8.94+	6.31+	6.46+	2.03*
	SEM	.44	1.09	.98	1.62	1.38	.15
Females:							
HMSG	$\bar{x}$	4.43	10.44+	6.58+	5.94+	5.89+	3.14
	SEM	.48	.80	.97	1.14	1.03	.39
LMSG	$\bar{x}$	4.82	7.37+	4.52	3.20*	3.85	4.69
	SEM	.64	.89	.41	.34	.57	.69
SAL	$\bar{x}$	4.12	8.72+	9.40+	7.55+	4.25	3.54
	SEM	.33	.90	.96	1.26	.59	.53

Note: Significantly greater (+) or less (*) than corresponding vehicle condition ($p < .05$, Dunnett comparisons).

Table 19. One Hundred Twenty Min Hot Plate Latencies (sec) During and After Days of Morphine Injection (15 mg/kg) in MSG-treated and Control Male and Female Rats.

Group		Days					
		PRE	2	6	10	14	6 Post
Males:							
HMSG	$\bar{x}$	3.62	10.38+	6.25+	3.78	5.60	2.81
	SEM	.39	1.62	.53	.58	1.19	.22
LMSG	$\bar{x}$	3.51	5.21+	3.43	2.78	2.24	3.03
	SEM	.62	.74	.72	.32	.25	.44
SAL	$\bar{x}$	3.27	9.09+	5.05+	4.41	5.29+	2.43
	SEM	.53	1.29	.65	.85	.55	.24
Females:							
HMSG	$\bar{x}$	4.40	7.66+	3.99	5.71+	4.09	2.54*
	SEM	.27	1.09	.74	1.16	.60	.23
LMSG	$\bar{x}$	3.60	4.94+	4.08	2.55	2.92	4.36
	SEM	.38	.65	.47	.23	.35	.57
SAL	$\bar{x}$	4.49	7.26+	4.77	4.68	3.33	3.87
	SEM	.51	1.31	.56	.56	.44	.46

Note: Significantly greater (+) or less (*) than corresponding vehicle condition ($p < .05$, Dunnett comparisons).

Since MSG treatment lowered baseline latencies, a difference score analysis revealed significant alterations among groups ($F(2,43)= 6.45$, $p< .005$),across injection days ($F(4,172)= 54.37$, $p< .0001$), across post-injection time intervals ($F(2,86)= 5.84$, $p< .005$), and for the interactions between days and groups ($F(8,172)= 6.10$, $p< .0001$), and among days, times and groups ($F(16,344)= 2.17$, $p< .01$). Figure 9 summarizes that the magnitude of the HMSG analgesic response in males was significantly greater than SAL on the second (120 min) and tenth days (30 min), yet attenuated on the sixth day (60 min). As shown in Figure 10 the magnitude of the HMSG analgesic response in females was significantly greater than SAL on the second (60 min), tenth (120 min) and fourteenth (120 min) days, yet attenuated on the second (30 min) and the sixth and tenth (60 min) days. The magnitude of analgesia in LMSG males and females was significantly shorter than the SAL on all injection days. While all three male groups failed to differ from each other during withdrawal, HMSG females were significantly more hyperalgesic, and LMSG females appeared analgesic. Thus, MSG treatment altered hot-plate latencies as a function of MSG dose and stage of morphine tolerance. Moreover, the analgesic response also varied according to the nociceptive measure as MSG treatment decreased analgesia in HMSG females on the flinch-jump, but according to stage of tolerance, biphasically increased hot-plate latencies in HMSG rats.

Figure 9. HMSG males displayed an erratic and less consistent development of tolerance on the hot-plate than on the jump test. Their rate of tolerance was generally similar to that of vehicle. LMSG rats in turn, display a significantly smaller analgesic response throughout the injection sequence.

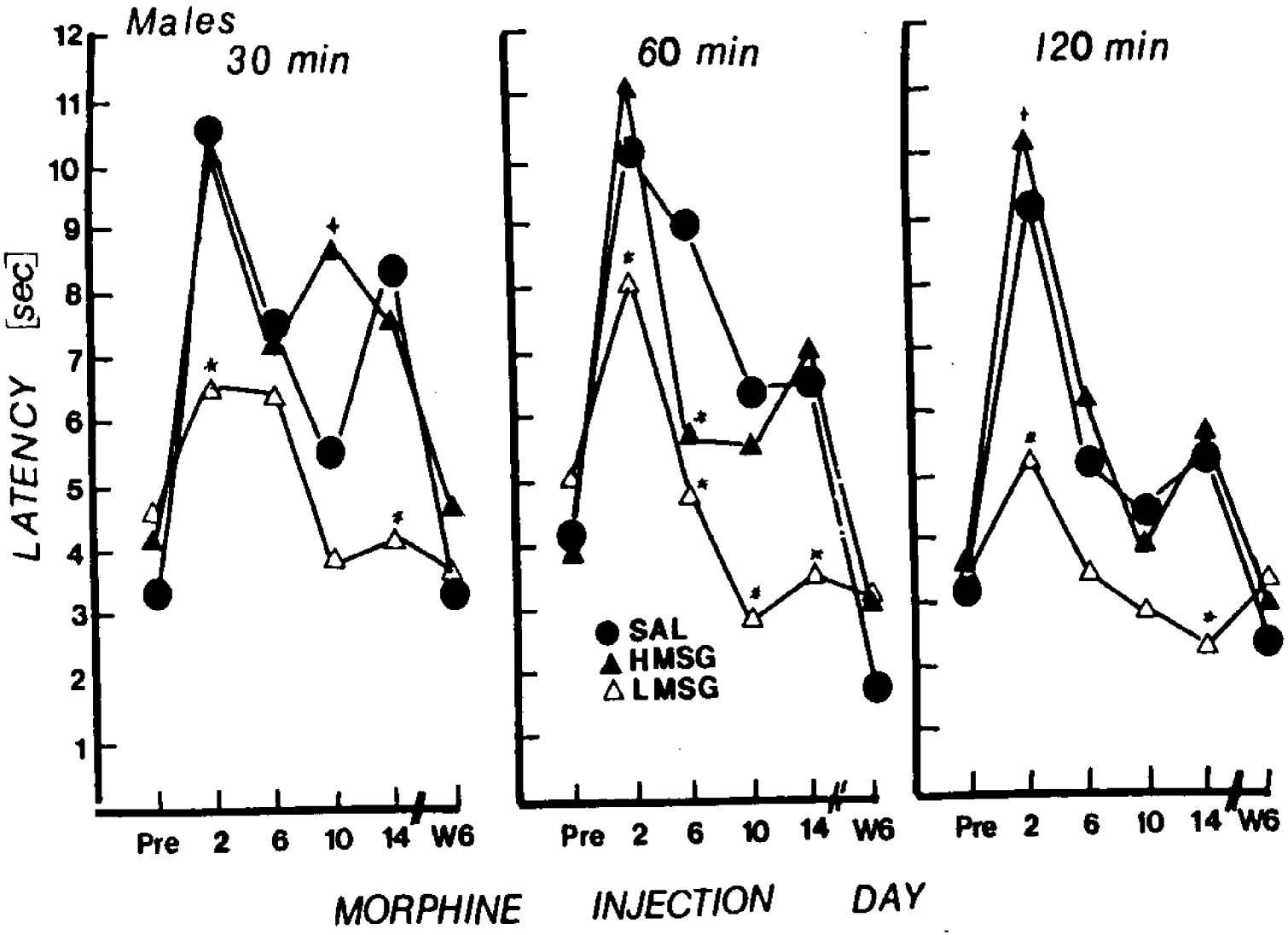
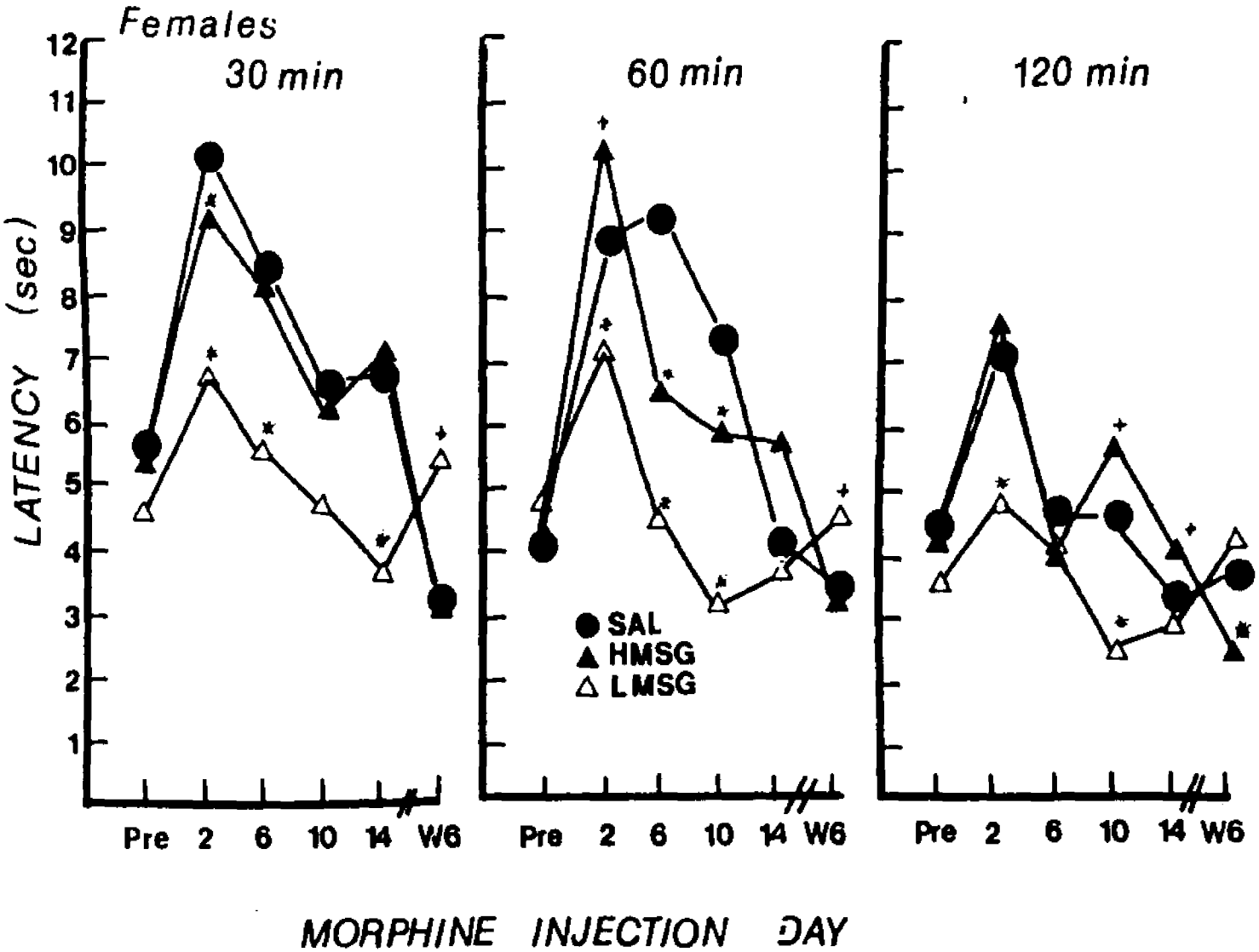

Males
30 min
60 min
120 min
LATENCY [sec]
12
11
10
9
8
7
6
5
4
3
2
1
SAL
HMSG
LMSG
Pre 2 6 10 14 W6
Pre 2 6 10 14 W6
Pre 2 6 10 14 W6
MORPHINE INJECTION DAY

Figure 10. While the analgesic response of HMSG females was greater than the vehicle control on the second day of the injection sequence at 60 min, their rate of decline was faster. As males, LMSG females displayed a smaller analgesic response throughout the injection sequence.


Females
30 min
60 min
120 min
LATENCY (sec)
12
11
10
9
8
7
6
5
4
3
2
1
SAL
HMSG
LMSG
Pre 2 6 10 14 W6
Pre 2 6 10 14 W6
Pre 2 6 10 14 W6
MORPHINE INJECTION DAY

Morphine Hyperthermia: Significant alterations in core body temperatures were observed across morphine injection days ($F(11,473)= 93.49$, $p< .0001$), among groups ($F(2,43)= 5.20$, $p< .01$), between males and females ($F(1,43)= 9.67$, $p< .005$), and for the interactions beteen days and groups ($F(22,473)= 3.55$, $p< .0001$), days and gender ($F(11,473)= 3.16$, $p< .0005$), and among days, groups and gender ($F(22,473)= 2.10$, $p< .001$). Tables 20 and 21 show that while both SAL and LMSG groups of both genders displayed significant hyperthermia throughout the morphine injection sequence, HMSG males displayed significant hyperthermia only on days 5, 6, 9 and 13 and HMSG females were hyperthermic only on days 1, 5, 6, 9, 10, 13 and 14. During withdrawal, male and female HMSG rats as well as LMSG male rats did not differ significantly from their baseline values. In contrast, LMSG female rats as well as SAL males and females displayed significant hypothermia. Since pre-treatment core body temperatures of male HMSG rats were significantly higher than SAL males, a difference score analysis revealed significant differences across morphine injection days ($F(9,387)= 71.78$, $p< .0001$) and for the interactions between days and groups ($F(18,387)= 2.98$, $p< .0001$), days and gender ($F(9,387)= 3.37$, $p< .0005$). The magnitude of hyperthermia in HMSG male rats was significantly lower than SAL males on all but the thirteenth injection day while the magnitude of hypothermia during withdrawal was significantly less than SAL males. In contrast, the magnitude of hyperthermia in LMSG males was significantly

Table 20. Body Core Temperature (C°) During and After Morphine Injection (15 mg/kg) in MSG-treated and Control Male Rats

Group		Days										
		PRE	1	2	5	6	9	10	13	14	Post 5	6
HMSG	$\bar{x}$	38.8	39.1	39.0	39.7+	39.7+	40.1+	39.6	40.4+	39.0	38.4	38.4
	SEM	.3	.1	.2	.4	.3	.3	.5	.3	.8	.1	.1
LMSG	$\bar{x}$	38.0	39.9+	40.4+	40.5+	40.7+	40.8+	40.2+	40.4+	40.6+	37.9	37.5
	SEM	.1	.2	.2	.3	.1	.2	.3	.1	.3	.4	.2
SAL	$\bar{x}$	38.3	39.6+	39.8+	40.3+	39.7+	40.5+	39.9+	40.2+	39.6+	37.4*	37.3*
	SEM	.5	.2	.2	.2	.3	.3	.3	.2	.2	.2	.3

Note: Significantly greater (+) or less (*) than corresponding values ($p < .05$, Dunnett comparisons).

Table 21. Body Core Temperatures (C°) During and After Morphine Injection (15 mg/kg) in MSG-treated and Control Female Rats

Group		Days										
		PRE	1	2	5	6	9	10	13	14	Post 5	6
HMSG	$\bar{x}$	38.9	39.4^{+}	39.2	40.2^{+}	39.8^{+}	40.5^{+}	40.1^{+}	40.4^{+}	40.2^{+}	39.0	38.4
	SEM	.2	.2	.2	.2	.2	.2	.2	.2	.3	.1	.3
LMSG	$\bar{x}$	39.1	40.2^{+}	40.3^{+}	40.5^{+}	40.4^{+}	40.5^{+}	40.5^{+}	40.3^{+}	40.1^{+}	38.5*	38.4*
	SEM	.2	.2	.2	.1	.1	.2	.1	.1	.2	.1	.1
SAL	$\bar{x}$	39.1	40.2^{+}	40.0^{+}	40.0^{+}	40.1^{+}	40.4^{+}	39.7^{+}	40.0^{+}	39.8^{+}	38.9	38.3*
	SEM	.1	.2	.1	.1	.1	.1	.1	.1	.2	.1	.1

Note: Significantly greater (+) or less (*) than corresponding values ($p < .05$, Dunnett comparisons).

greater than SAL males following all morphine injections and during withdrawal. The magnitude of hyperthermia in HMSG females was significantly smaller than SAL females on the first two injection days, yet larger on the fifth, tenth, thirteenth, fourteenth and withdrawal days. Like LMSG males, the hyperthermic response of LMSG females was greater than SAL females on the second, fifth, sixth, tenth and fourteenth days, yet LMSG females were more hypothermic than SAL females during withdrawal. Thus, gender and MSG dose differentially altered the hyperthermic response to morphine.

Morphine Weights: Table 22 summarizes the significant alterations in body weights observed across morphine injection days ($F(4,172)= 49.62$, $p< .0001$), among groups ($F(2,43)= 11.65$, $p< .0001$), between males and females ($F(1,43)= 167.79$, $p< .0001$), and for the interactions between days and groups ($F(8,172)= 4.57$, $p< .0001$), and among days, groups and gender ($F(8,172)= 2.62$, $p< .01$). The body weights of the HMSG, LMSG and SAL males were significantly lower than pre-injection values on the fifth, ninth and thirteenth day of morphine treatment and during withdrawal. While both LMSG and HMSG females displayed significant weight loss on the ninth, and thirteenth injection days as well as withdrawal, SAL females failed to differ from pre-injection weights.

Table 22. Body Weight (g) During and After Morphine (15 mg/kg) Injection in MSG-treated and Control Male and Female Rats.

Group		Days				
		PRE	5	9	13	Post 5
Males:						
HMSG	$\bar{x}$	413.03	393.50*	367.93*	363.80*	370.67*
	SEM	46.89	33.53	30.58	27.86	23.57
LMSG	$\bar{x}$	441.45	417.95*	405.52*	399.72*	381.28*
	SEM	12.17	17.50	15.75	14.74	19.09
SAL	$\bar{x}$	482.73	469.53*	450.88*	444.55*	464.72*
	SEM	11.34	11.97	11.60	12.00	11.69
Females:						
HMSG	$\bar{x}$	287.46	289.19	278.71*	271.61*	279.15*
	SEM	11.28	9.02	10.37	10.26	10.53
LMSG	$\bar{x}$	287.28	281.42	272.96*	268.57*	275.31*
	SEM	10.03	8.31	7.00	5.83	7.50
SAL	$\bar{x}$	311.70	310.55	304.47	309.44	313.33
	SEM	6.37	6.89	6.20	6.35	8.57

Note: Significantly less (*) than corresponding pre-morphine values ($p < .05$, Dunnett comparisons).

Since MSG animals were significantly lighter before the chronic morphine treatment, a difference score analysis showed significant alterations in weight across morphine injection days ($F(3,129)= 26.30$, $p< .0001$), among groups ($F(2,43)= 3.63$, $p< .05$), between genders ($F(1, 43)= 33.37$, $p< .0001$), and for the interactions between days and groups ($F(6,129)= 6.80$, $p< .001$), days and gender ($F(3,129)= 6.79$, $p< .0005$) and among days, groups and gender ($F(6,129)= 6.04$, $p< .0001$). While the weight loss observed in HMSG males after the ninth injection day was of significantly greater magnitude than the SAL males, LMSG males lost more weight on the fifth injection day and during withdrawal. While HMSG females lost significantly more weight than SAL females after the thirteenth injection day, LMSG females lost more than SAL females after the fifth injection day. Thus gender, as well as MSG dose altered the morphine-induced weight loss.

Morphine Activity: Analyses of the sampling time intervals revealed changes in activity among doses at 30 min ($F(2,78)= 17.59$, $p< .001$), 60 ($F= 27.66$, $p< .0001$), 90 ($F(26.36$, $p< .0001$) and 120 ($F= 27.23$, $p< .0001$) min. As no gender effects were obtained at any of the four time intervals, the data of both sexes within a group were pooled for purposes of analysis. A difference score was performed to partial out the initial hypoactivity of the LMSG group and as illustrated in Table 23 no significant difference in activity levels were observed at 30

Table 23. Activity Levels of HMSG, LMSG and SAL Rats Following Vehicle and Morphine Condition

		Post Manipulation (min)			
Dose (mg/kg)		30	60	90	120
Vehicle					
HMSG	$\bar{x}$	1762.0	2479.0	3150.4	3526.6
	SEM	481.1	650.8	930.9	918.3
LMSG	$\bar{x}$	1372.8*	1964.3*	2199.5*	2451.3*
	SEM	452.5	545.6	529.5	524.5
SAL	$\bar{x}$	2029.8	3147.3	3653.6	4049.9
	SEM	262.4	404.4	506.3	569.4
2.5					
HMSG	$\bar{x}$	989.2	1989.5	2997.0	4138.6*
	SEM	302.3	477.9	599.8	757.9
LMSG	$\bar{x}$	1130.9	2468.4	3971.7	5599.6
	SEM	242.8	427.8	620.5	833.4
SAL	$\bar{x}$	1542.5	2869.1	4554.7	6617.0
	SEM	392.8	446.0	690.8	986.0
10.0					
HMSG	$\bar{x}$	670.2	965.6	1224.6	1703.2*
	SEM	216.4	650.8	358.8	535.3
LMSG	$\bar{x}$	510.1	868.7	1488.4	2528.5+
	SEM	165.8	546.6	472.1	714.1
SAL	$\bar{x}$	716.9	1114.0	3653.6	2533.6
	SEM	140.4	247.3	404.2	623.9

Note: Signif' antly less (*) or greater (+) than SAL control values ($p < .05$, Dunnett comparisons).

($F(2,39) = 2.89$, $p < .07$), 60 ($F = 2.73$, $p < .08$), or 90 ($F = 3.01$, $p < .06$) min. At 120 ($F = 4.49$, $p < .05$) min the HMSG were less active than SAL after both morphine doses, while LMSG were more active than SAL after 10 mg/kg morphine dose. Thus, while MSG treatment altered analgesia, thermoregulation and weight regulation following morphine, it did not significantly affect locomotor activity.

Discussion

As in Experiment I, this experiment also confirmed neonatal MSG treatment induced typical characteristics of tail autamutilation, stunted growth and obesity in spite of lower absolute body weight (Dawson and Lorden, 1981; Kanarek et al., 1979; Olney, 1969). Furthermore, this experiment demonstrated that HMSG treatment differentially altered basal nociceptive thresholds in that it increased hot-plate latencies and decreased flinch-jump thresholds. Alterations in morphine analgesic dose-response functions, analgesic tolerance development as well as thermoregulatory and body weight changes during tolerance development (Herz and Blasig, 1979; Martin and Papp) varied as functions of MSG dose, gender, and the analgesic test. In contrast, differences in activity level among groups does not appear to account for these changes.

Again, it was assumed that the use of LMSG and HMSG dose conditions would provide a systematic and proportional index of MBH tissue destruction and that the LMSG dose would produce similar though smaller effects relative to the HMSG dose. Yet, in several situations the LMSG condition altered morphine responses in a different manner from HMSG. These a posteriori findings preclude systematic anatomical or biochemical analysis to focus upon LMSG/HMSG differences. Therefore, the following discussion will focus upon HMSG-induced alterations since most

of the previous anatomical and biochemical data used this MSG dose regimen.

Gender was also found to critically influence the MSG-induced alterations upon morphine responses. As described previously, neonatal treatment with MSG differentially affects males and females on several biochemical and physical measures (Conte-Devolx, 1981; Dawson and Lorden, 1981; Nemeroff et al., 1976; Olney, 1969). In this experiment, MSG-treated females displayed a significantly potentiated analgesic response following morphine on the jump test relative to their control group, while morphine analgesia of MSG-treated males was significantly smaller than controls on the jump test. Conversely, MSG-treated females displayed significantly less analgesia on the jump test throughout the chronic morphine injection sequence as compared to their control group while HMSG-treated males showed potentiated morphine analgesia over the chronic injections. Morphine-induced hyperthermia was significantly greater in MSG-treated females than in MSG-treated males with the latter displaying significantly less hyperthermia than their control group.

Moreover, MSG induced alterations that varied as a function of the nociceptive test employed. While MSG treatment lowered baseline jump thresholds, it increased hot-plate latencies. Such effects were also evident for MSG-induced changes in morphine analgesia. Bodnar and co-workers (1980) showed that MSG male

rats displayed attenuations in morphine analgesia as measured by the jump test. These effects were accompanied by decreases in ACTH and beta-lipotropin immunoreactivity in MBH and in periaqueductal grey terminals. In contrast, Simantov and Amir (1983) demonstrated potentiations in morphine analgesia as measured by the hot-plate test, effects accompanied by potentiations in opiate receptor density in the periaqueductal gray. It would appear that the decrease in beta-endorphin terminals in the midbrain is responsible for the up-regulation in opiate receptors in the midbrain (Simantov and Amir, 1983), but the present study clearly elucidates the importance of test-specificity in assessing the dose- response relationship of MSG effects across a morphine dose range. Male rats treated with HMSG showed decreased morphine analgesia on the jump test and increased morphine analgesia on the hot-plate test across doses, with the most potent effect observed at the 5 and 10 mg/kg doses. In contrast, female HMSG rats displayed analgesic potentiations on both the jump test and hot-plate tests following the higher morphine doses and attenuated morphine analgesia on the hot-plate test following the low dose. Thus, it appears that gender, morphine dose and nociceptive test are all critical variables in determining changes in morphine analgesia in MSG-treated animals.

Such variables also interacted differentially to affect morphine tolerance responses. Control male rats appeared to be more analgesic initially on the jump-test than control females

and subsequently displayed a sharper decline in analgesic magnitude over the chronic morphine injection sequence. In contrast, MSG-treated males displayed a smaller analgesic response than control males after the first injection, but subsequently exhibited potentiated analgesia by the fifth injection. Although the MSG-treated males show a delay in analgesic reaction and in the subsequent development of tolerance, the rate of decline of analgesia over the injection sequence was similar to that of control males. Like MSG-treated males, MSG-treated females initially showed depressed morphine analgesia relative to control female. However, unlike their male counterparts MSG-treated females continued to show attenuated analgesic responsivenes over the entire chronic injection sequence.

A similar pattern emerged with the hot-plate measure: males displayed a greater analgesic effect than females throughout the injection sequence. Yet, although animals of both genders displayed a slower decline of analgesia than observed on the jump test, the decline was faster and more consistent in females than the erratic, inconsistent decline in analgesia exhibited by males. HMSG treatment exerted a considerably greater effect upon chronic morphine effects when the jump test, rather than when the hot-plate test was used as the nociceptive measure. While LMSG treatment displayed a rate of analgesic decline over the

injection sequence similar to that of controls and HMSG rats, the magnitude of analgesia was significantly smaller on both nociceptive measures.

Furthermore, other behaviors altered by chronic morphine injections were found to be significantly changed in the HMSG group. In males, HMSG treatment markedly reduced morphine-induced hyperthermia while LMSG treatment significantly potentiated morphine hyperthermia. Thus as with changes in CWS hypothermia, disruptions in thermoregulation following MSG are observed. Yet, the present results fail to covary directly with observed analgesic disturbances observed in the MSG-treated males and females. As with thermoregulation, weight regulation was disturbed across the injection sequence and critically influenced by gender variables. While control males lost significant amounts of weight over the chronic morphine injection sequence, control females remained largely unaffected by this treatment. In contrast, significant weight loss following chronic morphine was observed in MSG rats of both genders with MSG-treated males displaying greater weight loss than control males following morphine. Contrary to reports that relate activity to changes in body temperature (Martin and Papp, 1980), neither the excessive weight loss or thermoregulatory aberrations are accounted for by differences in gross activity level. The similarity of the potency of the analgesia among groups following the initial delayed peak analgesia observed in MSG animals suggests that the

MBH system is not predominantly involved mediating the tolerance effects of morphine. Moreover, although the groups show similar rates of tolerance, there is clear evidence of disruptions in other coping processes. This further suppports reports of a dissociation between acute morphine analgesia and morphine tolerance (Bhargava, Afifi and Way, 1973; Elchisak and Rosecrans, 1979) as well as between morphine tolerance and coping behaviors induced by morphine injections. Therefore, while this study documents a number of MSG-induced changes in morphine behavioral responses both following acute or chronic administration, our knowledge of MSG-induced alterations of the endogenous opioid system cannot cohesively describe the results under one simple parsimonious model.

Experiment III

Developmental Measures: To assess physical growth during early development, the body weights (0.1 g) and naso-anal lengths (0.5 cm) of 47 SAL treated, 62 LMSG treated and 39 HMSG treated rats were measured on the second, fourth, sixth, eighth, tenth and twenty-first day after birth. As the rats were not assessed for gender until after day 21, the earlier developmental indices will be statistically analyzed on the basis of treatment group. The body weight and naso-anal lengths of these same animals were also assessed at ages 30, 45, 60 and 80 days after birth. However, at these ages, they were grouped according to gender and treatment: SAL (16 males, 23 females), LMSG (24 male, 35 female), and HMSG (19 male, 21 female).

Pain Threshold Measures: Beginning at 45 and 80 days of age respectively, four days of flinch-jump thresholds were obtained for each SAL (13 male, 15 female), LMSG (17 male, 18 female) and HMSG (14 male, 17 female) animal.

The majority of these animals were also tested for hot-plate latencies at the age of 21, 50 and 90 days of age: SAL (6 male, 11 females), LMSG (7 male, 16 female), and HMSG (7 male, 12 female). In this paradigm, the temperature of the floor was adjusted to either 45, 50, or 55 °C (+ 0.3°C). Each rat was exposed to 6 consecutive days of testing with a 24 h interval between each trial. A trial consisted of one exposure to one of

the temperature settings and each rat was exposed to two trials at each temperature. Temperatures were presented in an incompletely counterbalanced order. If an animal failed to emit an appropriate response within 180 sec, the trial was automatically terminated to prevent tissue damage.

Activity Measures: Activity levels of SAL (10 males, 8 females), LMSG (6 males, 6 females) and HMSG (8 males, 4 females) were recorded at ages 45 and 90 days of age. In this paradigm, two rats that had been housed in the same home cage and who were of the same treatment group and sex, were transferred to the test cage set atop the activity meter. After initial adaptation period (16 h) in the dark, the house lights were turned on and activity levels were recorded in 2 h blocks over an 8 h period. Then, activity levels were recorded again at the end of a 16 h dark period. Activity level assessments were paired across neonatal treatment and gender.

Osmolarity Effects: Since MSG possesses a higher osmolarity than saline, a fourth treatment group (HSAL 7 male, 13 female rats) received SC injections of hypertonic saline (2.37 M) as described previously. As before, body weights (0.1 g) and naso-anal lengths (0.5 cm) were determined on the second, fourth, sixth, eighth, tenth and twenty-first day after birth. Again at ages 30, 45, 60 and 80 days gender-specific developmental measures were assessed. Flinch-jump thresholds were measured as before at 45 and 80 days of age.

Results

Body Lengths: As summarized in Table 24, significant differences in body lengths were observed among groups at 30 ($F(3,175)= 19.21$, $p< .0001$), 45 ($F(3,187)= 30.41$, $p< .0001$), 60 ($F(3,186)= 51.37$, $p< .0001$), 80 ($F(3,174)= 51.82$, $p< .0001$) and 100 ($F(3,118)= 10.66$, $p< .0001$) days of age and between genders at 30 ($F(1,175)= 8.55$, $p< .005$), 45 ($F(1,187)= 28.75$, $p< .0001$), 60 ($F(1,186)= 112.79$, $p< .0001$), 80 ($F(1,174)= 211.08$, $p< .0001$) and 100 ($F(1,118)= 236.32$, $p< .0001$) days of age. Both MSG groups of both sexes were significantly shorter than their SAL counterparts at 30, 45, 60 and 80 days of age. At 100 days of age, HMSG males, LMSG males and LMSG females were significantly shorter than their SAL counterparts. In contrast, HSAL males, but not females were significantly shorter than SAL rats at 30 days of age. As the HSAL group developed, males (days 45, 80 and 100) and females (days 45, 60, 80 and 100) were significantly longer than their SAL counterparts.

Body Weights: As summarized in Tables 25 and 26, significant differences in body weight were observed among groups at 10 ($F(3,241)= 14.16$, $p< .0001$), 21 ($F(3,196)= 6.26$, $p< .0005$, 30 ($F(3,211)= 24.59$, $p< .0001$), 45 ($F(3,203)= 50.90$, $p< .0001$), 60 ($F(3,205)= 88.82$, $p< .0001$), 80 ($F(3,210)= 59.96$, $p< .0001$) and 100 ($F(3,173)= 43.82$, $p< .0001$) days of age and between genders at 45 ($F(1,203)= 42.58$, $p< .0001$), 60 ($F(1,205)= 83.21$, $p< .0001$), 80 ($F(1,201)= 315.54$, $p< .0001$) and 100 ($F(1,173)=$

Table 24. Length (cm) of MSG-treated and Control Male and Female Rats During Development

Group		Age (days) 30	45	60	80	100
Male:						
HMSG	$\bar{x}$	13.64*	16.31*	18.63*	20.50*	22.50*
	SEM	.25	.27	.21	.24	.50
LMSG	$\bar{x}$	13.42*	16.15*	19.10*	21.05*	22.85*
	SEM	.23	.24	.25	.25	.17
SAL	$\bar{x}$	14.87	18.44	21.04	22.33	23.24
	SEM	.17	.25	.25	.28	.23
HSAL	$\bar{x}$	14.11*	17.64+	20.89	23.21+	24.03+
	SEM	.31	.42	.24	.18	.11
Female:						
HMSG	$\bar{x}$	12.93*	14.91*	16.73*	18.21*	20.17
	SEM	.19	.26	.19	.22	.25
LMSG	$\bar{x}$	12.79*	15.52*	17.24*	18.78*	19.91*
	SEM	.18	.22	.17	.12	.16
SAL	$\bar{x}$	14.20	16.74	18.76	19.86	20.42
	SEM	.21	.21	.20	.17	.16
HSAL	$\bar{x}$	14.00	16.94+	19.27+	20.96+	21.12+
	SEM	.21	.19	.18	.12	.21

Note: Significantly less (*) or greater (+) than same-sex SAL control ($p < .05$, Dunnet comparisons).

Table 25. Weights (g) of MSG-treated and Control Rats at 10 and 21 days of Age

Group		Age (days) 10	21
HMSG	$\bar{x}$	17.59*	36.14*
	SEM	.44	1.26
LMSG	$\bar{x}$	20.31*	40.47*
	SEM	.55	1.67
SAL	$\bar{x}$	22.56	44.73
	SEM	.65	1.32
HSAL	$\bar{x}$	19.40 *	40.73 *
	SEM	.87	1.14

Note: Significantly less (*) than SAL control value ($p < .05$, Dunnett comparisons).

Table 26. Weight (g) of MSG-treated and Control Rats During Development

	Age (days)				
Group	30	45	60	80	100
Male:					
HMSG $\bar{x}$	76.15*	133.86*	159.47*	263.20*	315.32*
SEM	2.01	6.10	8.34	10.41	10.09
LMSG $\bar{x}$	72.66*	148.93*	229.10*	305.40*	371.44*
SEM	3.35	4.62	5.73	6.60	9.28
SAL $\bar{x}$	95.03	193.98	288.96	371.91	431.46
SEM	3.24	4.91	9.51	6.05	9.12
HSAL $\bar{x}$	85.33*	169.10*	261.04	358.13*	427.51
SEM	3.69	8.24	8.17	10.60	4.13
Female:					
HMSG $\bar{x}$	69.12*	107.83*	135.53*	204.92*	240.72*
SEM	2.99	4.82	8.13	5.16	5.88
LMSG $\bar{x}$	70.95*	131.87*	175.57*	211.49*	244.25*
SEM	2.61	3.21	4.12	4.76	4.31
SAL $\bar{x}$	91.15	154.84	207.78	248.00	288.97
SEM	2.54	3.36	4.51	3.36	8.11
HSAL $\bar{x}$	81.58*	150.19	230.23+	258.18	279.30
SEM	4.13	5.14	3.22	6.15	5.39

Note: Significantly less (*) or greater (+) than same sex SAL control value ($p < .05$, Dunnett value.

379.90, p< .0001) days of age. Both MSG groups of both sexes displayed significantly lower body weights than the SAL group at days 10, 21, 30, 45, 60, 80 and 100 days. While the HSAL rats of both sexes also weighed significantly less than SAL animals at days 10, 21, and 30 days of age, they weighed significantly more than HMSG rats at these ages. Male HSAL rats weighed significantly less than SAL males at days 45 and 80, while HSAL females weighed significantly more than SAL females at 60 days of age. Furthermore, while MSG rats weighed less than SAL rats at 100 days of age, HSAL rats failed to differ from SAL rats.

Flinch-Jump Thresholds: As summarized in Table 27, significant developmental changes in jump thresholds were observed among groups ($F(3,106)= 4.08$, $p<.01$), between males and females ($F(1,106)= 51.50$, $p< .0001$), and for the interactions between test age and groups ($F(3,106)= 17.23$, $p< .0001$) and test age and gender ($F(1,106)= 9.97$, $p< .005$). While HMSG male rats, HMSG female rats and LMSG female rats displayed significantly lower jump thresholds at 80 days of age as compared to 45 days of age, HSAL rats of both sexes, and SAL males displayed significantly higher jump thresholds at 80 days of age than at 45 days of age. Jump thresholds of SAL and HMSG males failed to differ from each other at 45 days of age, while the LMSG and HSAL males exhibited significantly lower jump thresholds than the SAL males. In contrast, HMSG and LMSG males displayed significantly lower jump thresholds at 80 days of age than either SAL or HSAL

Table 27. Jump Thresholds of 45 and 80 day MSG-Treated and Control Rats

Group		Age (days) 45	80
Male:			
HMSG	$\bar{x}$	.48	.43*
	SEM	.01	.02
LMSG	$\bar{x}$	.43*	.43*
	SEM	.02	.02
SAL	$\bar{x}$	.46	.50
	SEM	.02	.02
HSAL	$\bar{x}$	.40*	.50
	SEM	.02	.01
Female:			
HMSG	$\bar{x}$	.41	.33*
	SEM	.02	.01
LMSG	$\bar{x}$	.39	.33*
	SEM	.02	.01
SAL	$\bar{x}$	.40	.41
	SEM	.02	.02
HSAL	$\bar{x}$	.35*	.39
	SEM	.10	.11

Note: Significantly less (*) than SAL group of same sex ($p < .05$, Dunnett comparisons).

males. Jump thresholds of 45 day old HMSG, LMSG and SAL females failed to differ from each other while HSAL thresholds were consistently lower than all three groups. In contrast at 80 days of age, HMSG and LMSG females exhibited significantly lower jump thresholds than either SAL or HSAL females which in turn failed to differ from each other.

Flinch thresholds were significantly altered among groups ($F(3,106)= 10.70$, $p< .0001$), between males and females ($F(1,106)= 12.61$, $p< .001$), between test ages ($F(1,106)= 6.35$, $p< .05$) and for the interaction between test age and groups ($F(3,106)= 5.04$, $p< .005$). HMSG males, HMSG females and LMSG females displayed significantly lower flinch thresholds at 80 days of age than at 45 days of age; all other groups failed to differ across ages. Flinch thresholds of HMSG males and females, but not those of HSAL or LMSG were significantly higher than SAL rats. Moreover, SAL thresholds were also significantly higher than the HSAL rats. At 80 days of age, HMSG male and female thresholds continued to be higher than HSAL. In turn, the LMSG male displayed greater flinch thresholds than HSAL males, while the male and female LMSG flinch thresholds were smaller than SAL. Furthermore, SAL male and female thresholds were significantly greater than male and female HSAL.

Hot-Plate Latencies: As summarized in Tables 28, 29 and 30 significant developmental changes in hot-plate latencies were

Table 28. Hot-Plate Latencies (sec) at 45 °C of 21, 50 and 80 Day Old MSG-treated and Control Rats

Group		Age (days) 21	50	80
Male:				
HMSG	$\bar{x}$	68.08*	55.21+	88.23+
	SEM	12.73	10.14	10.48
LMSG	$\bar{x}$	76.62	31.91	55.50
	SEM	15.49	4.22	7.87
SAL	$\bar{x}$	87.43	42.40	58.72
	SEM	17.64	12.66	6.16
Female:				
HMSG	$\bar{x}$	97.04	79.15+	86.00+
	SEM	10.72	14.23	11.10
LMSG	$\bar{x}$	82.68	50.33	84.32+
	SEM	8.74	7.25	5.92
SAL	$\bar{x}$	87.15	43.93	68.82
	SEM	13.28	9.81	9.74

Note: Significantly less (*) or greater (+) than same sex SAL control value ($p < .05$, Dunnett comparisons).

Table 29. Hot-Plate Latencies (sec) at 50°C of 21, 50 and 80 Day Old MSG-treated and Control Rats

Group		Age (days) 21	50	80
Male:				
HMSG	$\bar{x}$	32.61	27.84 +	20.91
	SEM	3.19	2.75	1.57
LMSG	$\bar{x}$	17.63	19.79	12.29
	SEM	2.84	1.40	1.16
SAL	$\bar{x}$	22.44	14.70	13.85
	SEM	3.09	1.72	2.61
Female:				
HMSG	$\bar{x}$	23.69	25.45	23.29
	SEM	1.88	1.91	3.05
LMSG	$\bar{x}$	22.26	23.66	24.74
	SEM	1.70	2.17	1.73
SAL	$\bar{x}$	24.15	19.92	22.50
	SEM	2.36	1.73	1.06

Note: Significantly greater (+) than same sex SAL control value ($p < .05$, Dunnett comparisons).

Table 30. Hot-Plate Latencies (sec) at 55 °C of 21, 50 and 80 Day Old MSG-treated and Control Rats

Group		Age (days) 21	50	80
Male:				
HMSG	$\bar{x}$	9.04	7.54	5.53
	SEM	.81	.94	.60
LMSG	$\bar{x}$	9.87	4.94	3.68
	SEM	2.08	.33	.54
SAL	$\bar{x}$	8.09	4.63	4.76
	SEM	.70	.13	.47
Female:				
HMSG	$\bar{x}$	8.75	6.81	4.94
	SEM	.68	.40	.56
LMSG	$\bar{x}$	7.21	7.05	4.04
	SEM	.54	.47	.23
SAL	$\bar{x}$	8.18	6.36	5.25
	SEM	.81	.49	.34

observed among groups ($F(2,53)= 4.36$, $p < .05$), between male and female ($F(1,53)= 5.25$, $p < .05$), among test ages ($F(2,106)= 16.14$, $p < .0001$), temperatures ($F(2,106)= 354.34$, $p < .0001$), and for the interactions between temperature and gender ($F(2,106)= 3.61$, $p < .05$), and test age and temperature ($F(4,212)= 14.34$, $p < .0001$). Dunnett comparisons revealed no group-dependent or age-dependent alterations in hot-plate latencies at plate temperatures of either 55 °C or 50 °C, except for a transitory increase in latencies elicited by the 50 °C stimulus in HMSG male rats at 50 days of age. At the 45 °C stimulus, HMSG rats of both genders exhibited significantly longer latencies than controls at 80 and 50 days of age. In contrast, male HMSG rats displayed significantly shorter latencies than controls at 21 days of age. Finally, female LMSG rats exhibited significantly longer latencies than controls at 80 days of age. The results at the 45 C temperature (Table 28) should be interpreted in terms of age-dependent effects. Typically, in the SAL control group, a V-shaped function emerged with shorter latencies observed at 50 days of age as compared to either 21 or 80 days of age. This function in female HMSG rats was flattened across ages, the age-latency relationship in male rats was reversed between the SAL and HMSG groups; that is, the highest obtained latency for HMSG animals occurred at 80 days of age, while the highest obtained latency for SAL animals occurred at 21 days of age. It should be noted however, that all of the above effects occurrred at a temperature setting which is

typically considered to be minimally affecting primary nociceptive afferents (see review: Price and Dubner, 1977).

Activity: Significant differences in activity failed to occur among groups at the second ($F(2,15)= .15$, $p < .85$), fourth ($F(2,15)= .00$, $p < .99$), sixth ($F(2,15)= .33$, $p< .72$), or eighth ($F(2,15)= .10$, $p< .90$) diurnal hours, nor after sixteen ($F(2,15)= .68$, $p< .52$) hours of dark. At age 90 days diurnal locomotor activity was significantly less than at age 45 days in all groups after two hours ($F(1,15)= 13.27$, $p< .005$), four hours ($F(1,15)= 13.05$, $p< .005$), six hours ($F(1,15)= 13.45$, $p< .005$), and eight hours ($F(1,15)= 15.54$, $p< .005$). Similarly, nocturnal activity was significantly less at age 90 days than at 45 days ($F(1,15)= 15.46$, $p< .005$).

Discussion

The present findings of stunting and obesity in spite of lower body weight verifies the neurotoxic effects of neonatal treatment with MSG reported in other studies (Olney, 1969; Dawson and Lorden, 1981; Kanarek et al., 1979). This effect was specific to MSG in that an equimolar solution of saline affected the developmental pattern differently. The animals of the HSAL group were longer than those treated with either SAL or either MSG dose. Although HSAL rats weighed less than vehicle-treated animals at early points, this effect was not an enduring one. Therefore, it appears that the effects noted in MSG animals are due to the neurotoxic effects of MSG and not nonspecific results of injections of hypertonic solutions with subsequent changes in osmolarity. Moreover, as in experiments one and two, MSG induced changes in basal nociceptive thresholds which were manifest after sexual maturity. Furthermore, as in experiment two, these changes were a function of the pain test. On the jump test, MSG induced hyperalgesia, while on the hot plate, the thermonociceptive response in MSG-treated animals was significantly greater than for the vehicle group.

Recent data suggest that during critical periods of development, hormones, and gonadal hormones in particular, influence the CNS to organize and program adult neuroendocrine activity that are later reactivated during sexual maturation (see reviews: Harris, 1964; Levine, 1966). This organization is said

to include the neuroendocrine activity elicited under conditions of stress (Levine, 1969). MSG-induced damage to the arcuate nucleus and median eminence, which depletes this area of various neurotransmitters and neuropeptides, is thought to account for the subsequent neuroendocrine and behavioral deficits that comprise the MSG syndrome (Olney, 1969; Nemeroff et al., 1981). In view of the influences that hormones exert on development, this study had assumed that any MSG-induced disruption of the normal organization generally induced by gonadal and other hormones would occur early in development. To this end, a longitudinal assessment of the nociceptive thresholds in MSG treated animals examined whether later hormonal changes influenced basal nociceptive alterations, or rather, if such alterations were the result of long-standing insults caused by the MSG-treatment early in development. MSG induced a hyperalgesic response on the jump test after sexual maturity, while SAL and HSAL rats exhibited jump thresholds that increased after sexual maturity. Since MSG did not alter jump thresholds before maturity, this suggests that longer- standing hormonal changes may be responsible for this effect. These results are in agreement with a temporary hyperalgesia noted on the tail-flick test following electrolytic lesions placed in the arcuate nucleus (Millan, Gramsch, Przewlocki, Hollt and Herz, 1980). However, changes in basal nociceptive responses were test specific, since MSG animals displayed elevated thermonociceptive thresholds on the hot-plate after sexual maturity, an effect opposite to the

decreased latencies observed following sexual maturity in vehicle-treated rats.

That hot-plate latencies only differed in MSG-treated rats at the 45 °C, and not at the higher temperatures, suggests that this alteration involves more general somato-sensory processes, rather than nociception specifically (Dubner and Price, 1977). Although Simantov and Amir (1983) reported normal hot-plate latencies in MSG-treated mice, this discrepancy may be accounted for by the use of a different species, age (60 days) or hot-plate temperature (52°C). However, as for the jump test, the change after sexual maturity suggests hypothalamo-hypophyseal hormonal influences may be critical for proper development of sensory nociceptive processes. These effects are not accounted for by differences in locomotor activity as MSG animals displayed a significant reduction in activity with age that was similar to that noted in vehicle-treated rats. Thus, while the results point to the relative independence between sensory modalities, it is important to note that MSG induces long term effects through possible hormonal changes, as well as short term effects, attributable to the preexisting neurotoxicity.

General Discussion

These experiments show that neonatal administration of high doses of MSG: 1) Alter a range of responses following CWS and 2-DG. MSG rats showed attenuated analgesia and hypothermia following CWS, potentiated 2-DG analgesia and reduced 2-DG hyperphagia. 2) Alters a range of opiate mediated responses were altered. Following acute morphine injections, test-specific and gender-specific effects were observed in MSG-treated rats. Male MSG-treated rats showed lowered analgesic response on the jump test, and increased analgesia on the hot-plate test, whereas female MSG-treated rats displayed potentiated analgesia on both tests after a high dose, but attenuated hot-plate analgesia following a low dose. Moreover, HMSG altered morphine tolerance on the jump test significantly more than on the hot-plate and disrupted morphine coping responses: hyperthermia was decreased and weight loss was increased. 3) Alter the normal physical development as well as nociceptive responses. While nociceptive thresholds were test-specifically altered, these changes were only evident after sexual maturation suggesting long-standing hormonal effects of the MSG induced neurotoxicity.

These results indicate that MSG-treatment alters a number of stress responses and that interpretation of the analgesic alterations in terms of a specific role for the circumventricular system in pain-inhibitory systems should be evaluated in light of the multifaceted effects of MSG. Given that MSG induces damage to the circumventricular system and to the MBH particularly, it

might be assumed that this structure may be integrally involved in the mediation of a variety of coping responses. While it is at present difficult to ascribe the mediation of the affected behaviors to any of the peptides or transmitter disruptions induced by MSG, the present data presents an opportunity to distinguish among the medial-basal hypothalamic substances and elucidate their respective functional roles. Therefore in future work one can systematically and centrally replace peptides or a combination of peptides in an effort to selectively assess the behavioral changes. This strategy therefore, permits investigating whether a given localized peptide system is integral for a given function rather than analyzing effects which deplete the peptide system throughout the brain. However, the present study demonstrates that such work should also take into account differences among gender, behaviors and test measures. Since the behavioral deficits can be clearly observed in the MSG-treated rat, replacement of a given peptide or neurotransmitter can allow one to observe whether a given impairment can be corrected. This replacement strategy is of heuristic importance because it can specify the functional involvement of peptides and transmitters in an organism incapable of behaving normally.

In studies employing stress as an independent variable, it is crucial in their interpretation of results to recognize that any change in responsivity in terms of the dependent variable may

not only be attributable to effects upon systems mediating the dependent variable, but alternatively to effects upon other systems that may impinge upon and/or modulate the consequences of the stressful stimulus.

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