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LOCUS COERULEUS LESIONS DIFFERENTIALLY ALTERS MORPHINE'S EFFECTS ON HYPOTHALAMIC SELF-STIMULATION IN RATS

City University of New York PH.D. 1982

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LOCUS COERULEUS LESIONS DIFFERENTIALLY ALTERS MORPHINE'S EFFECTS ON HYPOTHALAMIC SELF-STIMULATION IN RATS

by

ANN TEMPEL

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.

1982

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

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Abstract

LOCUS COERULEUS LESIONS DIFFERENTIALLY ALTERS MORPHINE'S EFFECTS ON HYPOTHALAMIC SELF-STIMULATION IN RATS

by

Ann Tempel

Advisor: Professor Steven J. Ellman

Studies have reported that morphine at low doses, facilitates some self-stimulation sites but not others. These sites are consistent with areas of high opiate receptor density. Farber (1976) showed that unilateral locus coeruleus lesions differentially altered ICSS rates. It was postulated that morphine exerts its effects on the reward system via the locus coeruleus. The following study explored the effects of morphine on ICSS from various sites before and after a discrete unilateral locus coeruleus lesion.

Rats were implanted with electrodes aimed at ICSS sites and were trained to bar press for brain stimulation. After rates stabilized, subjects entered the paradigm which consisted of 7 days saline, 1 day naloxone, 7 days saline, 7 days morphine, 1 day morphine + naloxone, 7 days saline, 1 day d-amphetamine, 2 days saline, 1 day L-amphetamine, 2 days saline, 1 day L-amphetamine, 2 days saline, 1 day d-amphetamine and 7 days saline. Animals were then anesthetized and acutely lesioned in the left locus coeruleus. The paradigm post-lesion was identical

to the pre-lesion paradigm.

Locus coeruleus (LC) lesions reduced ICSS response rates in subjects whose electrodes were located in the H_2Fields of Forel(FF), Zona Incerta (ZI), Internal Capsule (IC), Mammillothalamic Tract (MT) and thalamic nuclei. ICSS in subjects whose hypothalamic electrodes were located in the Medial forebrain bundle (MFB)-Perifornical (PF) area were not affected by these lesions. Morphine facilitated ICSS rates from electrodes in the H_2FF, ZI, MT, thalamic nuclei and MFB-PF area. ICSS rates in the IC were not altered by morphine administration. Post-lesion ICSS rates from the H_2FF, ZI, MT and thalamic nuclei which were depressed following the lesion were facilitated to pre-lesion saline levels under morphine administration but not pre-lesion morphine levels. Post-lesion ICSS rates from the IC that were depressed following the LC lesion, were still not altered by morphine administration. Morphine administration produced comparable facilitations in ICSS rates in the MFB-PF area post-lesion, as it did pre-lesion. ICSS rates in this group were not altered by the LC lesion.

These results support the idea that there are several reward-ICSS systems and that these systems can be differentially affected by LC lesions and morphine administration.

...in loving memory of my father,

Abraham Tempel

Acknowledgements

I would like to thank Steven Ellman and Solomon Steiner for teaching me the art and nature of scientific research. I wish also to thank them for giving me the freedom to work independently. What they both have taught me will always be of help to me in my future endeavors.

I also wish to thank my committee members, Louis Gerstman, Donald Mintz and Richard Kestenbaum, for their useful comments and constructive criticisms. I would like to thank Richard Bodnar for his hours spent localizing the lesions and electrode placements.

Furthermore, I would like to acknowledge Douglas Ocheret, Gus Pavlides, Demetrious Zafirides, Steven Berman and Yaakov Stern for their hard work and dedication.

I would especially like to thank my family and friends whose support, love and patience helped me through the most difficult times of this experience.

And finally, I would like to acknowledge my rats for their cooperation and patience, since without them this research would have been impossible.

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One of the most prominent methods for assessing morphine's effects on central reinforcing systems has been to allow animals to self-administer morphine through indwelling catheters to areas in the hypothalamus that support self-stimulation behavior. Numerous studies have demonstrated that animals will self-administer morphine given orally (Amit et. al., 1976), intraventribularly (Deneau, G.A. et. al., 1969), or intraperitoneally (Collins, R.J., 1964, 1965) to specific sites. It has also been reported that rats will self-administer morphine infused into the lateral cerebral ventricles (Amit, Z., 1976; Belluzzi, 1977) and they will also self-administer the enkephalins (Meek, J.L., 1977; Yang, H.Y., 1977).

Discrete lesions in the lateral hypothalamic - MFB area have been shown to abolish self-administration of morphine, suggesting that these structures play an important role in the mediation of positive reinforcing properties of morphine (Glick, 1974, 1975).

The hypothalamus and specifically the MFB within it, have also been viewed as likely sites for the mediation of the reinforcing effects of morphine because morphine will facilitate ICSS from this site (Olds, 1962). Studies have reported that morphine facilitates self-stimulation behavior when given systemically (Lorens, 1976; Esposito, 1977). Moderate doses (5-10 mg/kg) produce initial inhibition of response rates for a period of 1-3 hours post-injection (Bush, 1976; Wauquier, 1976). It has also been demonstrated

that low to moderate doses of morphine (4-8 mg/kg) reduce the threshold for self-stimulation to the MFB-LH area in rats (Esposito, 1977) as well as to other areas in the brain (Liebman, 1977; Lorens, 1976; Nelson, 1977). Jackler et. al. (1979) and Nelson (1978) showed that at doses as low as 1.25 mg/kg, morphine selectively facilitates self-stimulation behavior at some sites but not at others. These sites which show facilitations are also consistent with areas of high opiate receptor density (Nelson et. al., 1981).

Stein (1978) reported that morphine and leu-enkephalin, when infused into the lateral ventricle of rats faciliatates self-stimulation behavior. He has proposed that the reinforcing effects of morphine and the enkephalins are produced because these substances directly activate the neural pathway subserving self-stimulatin behavior. They activate a central reinforcing mechanism of which the hypothalamic - MFB system is a main component. In support of this theory, Olds, (1979) showed that rats will self-administer morphine infused directly into the LH self-stimulation site and that naloxone + morphine reduced self-administration behavior. Collectively, these studies support the hypothesis, based on lesion data and morphine self-administration studies, that the hypothalamus plays a crucial role in the mediation of the reinforcing properties of morphine.

The nucleus locus coeruleus (LC) is the main supplier of

brain NE. Systemic or iontophoretic application of morphine to these cells produce a naloxone reversible depression of firing (Bird, S.J. and Kuhar, M.J., 1977). The sensitivity of the LC neurons to morphine is not unexpected in view of the fact that there is a high density of opiate receptors in this area (Atweh, S.F. and Kuhar, M.J., 1977). It has also been suggested that morphine inhibits release of NE from axon terminals originating with LC (Sasa, Munekiyo, K. and Takaori, 1975).

Farber et. al., (1976) showed that unilateral LC lesions differentially altered self-stimulation behavior. ICSS from the crus cerebri (cc) was reduced or completely abolished following discrete unilateral LC lesions, while MFB and perifornical stimulation were either unaltered or facilitated as a result of the lesion. Mattiace (1981) demonstrated facilitation in ICSS responding from the septal area following unilateral LC lesions. These data clearly show that LC lesions differentially alters ICSS behavior depending on the neuroanatomical locus of the stimulating electrode.

In summary, morphine at low doses, facilitates some self-stimulation sites but not others and these ICSS responses can be altered by unilateral lesions to the LC area. The following study was an attempt to assess the effects of morphine on self-stimulation from varying sites before and after a discrete unilateral LC lesion.

Olds and Milner's (1954) discovery that animals will

electrically self-stimulate certain regions of their own brains lead to the notion of a reward system. Since then numerous researchers have attempted to identify the structures and substrates of this reward system. Like all operant behaviors, self-stimulation requires a source of reinforcement for its maintenance. Electrical stimulation of discrete regions of the brain is a sufficient condition to produce reward. This probably represents a direct activation of the brain's normal reinforcement system (Deutsch, 1960; Olds, 1962; Stein, 1964, Gallistel, 1973). If these assumptions are true, then identification of the pathways that subserve SS would reveal the pathways subserving reward.

In an attempt to answer these questions, numerous mapping and pharmacological studies have been done. Anatomical and pharmacological evidence has produced agreement that catecholamine (CA) - containing neurons play a critical role in SS (Stein, 1962; 1968, Poschel & Ninteman, 1963; Arbuthnott, Fuxe & Ungerstedt, 1971; Crow, 1972, Stinus & Thiery, 1973; Phillips & Fibiger, 1973; Wise, Berger & Stein, 1973; Clavier & Routtenberg, 1974; German & Bowden, 1974; Herberg, Stevens & Franklin, 1976). Acetylcholine or serotonin systems seem to be associated with the suppression, rather than the facilitation of SS (Stein, 1968; Wise et al ; 1973).

I. Catecholamine Theories of ICSS

A. Pharmacological Evidence Implicating NE

In early studies it was found that substances that release CAs, such as amphetamine or alpha-methyl-m-tyrosine or phenethylamine in combination with a monoamine oxidase inhibitor facilitate SS. Drugs that deplete CA stores such as reserpine, or block CA receptors (Chlorpromazine, Haloperidol) or inhibit CA synthesis (alpha-methyl-p-tyrosine) suppress SS (Stein, 1962, 1964; Poschel & Ninteman, 1963).

Later studies tried to delineate which CA was actually responsible for the SS behavior. An important role for NE, was suggested by work with inhibitors of dopamine-B-hydroxylase, the enzyme that converts DA to NE. Systemic administration of disulfira or intraventricular administration of diethyldithiocarbamate abolish SS and eliminate the rate-enhancing action of amphetamine (Wise & Stein, 1969, 1970). Intraventricular administration of l-NE after DBH inhibition reinstated SS and restored the facilitatory action of amphetamine. Injections of d-NE and DA were ineffective. These observations were also observed using the more specific DBH inhibitors U14 and fusaric acid.

On the other hand, FLA-63, a drug with similar biochemical actions, did not have the same effect (Lippa et al 1973; Fuxe et al, 1970). Franklin et al (1975) has suggested a possible reason for this drug's failure to suppress ICSS. ICSS was supressed with FLA-63 only after

pre-treatment with reserpine. Franklin et al (1975) have suggested a possible reason for FLA-63's failure to suppress ICSS, when given alone, without pre-treatment.

It takes three days for reserpine to totally deplete CA reserve pools. Functional pools are intact and can maintain SS behavior. If you've already depleted reserves with reserpine and then you administer FLA-63, FLA-63 will work on the functional pools to deplete NE, thereby causing a decrease in SS behavior. Breese and Cooper (1974) conducted similiar experiments with reserpine and U-14, 624 and found no blockade of ICSS, but their reserpine dose may have been too low.

DBH inhibitors leave brain DA levels unaffected or slightly increased. Replenishment of depleted transitter stores by intraventricularly administered NE produces behavioral recovery and thus lend support to the notion that NE neurons are specifically involved in SS. Researchers have challenged this conclusion on the grounds that DBH inhibitors cause drowsiness, thereby decreasing SS behavior. Rolls 1970; Rolls, Kelly & Shaw, 1974 observed that disulfiram (a DBH inhibitor) had a greater depressant effect on spontaneous locomotor activity and rearing than on SS so they concluded that disulfiram's effects "on SS reward are relatively non-specific". However, these 2 measures of arousal are not independent of reward effects. Stein, Wise & Belluzzi, 1975 suggest that disulfiram's depressant action on locomotor activity and rearing may reflect a

"depreciation of the rewarding effects of novel stimulation, due to depletion of reward transmitter". Also, Stein argues that sedation itself is not adequate to reduce ICSS since rats heavily sedated with barbiturates still self-stimulate (Stein, 1964).

The NE receptor involved in behavioral reinforcement seems to be of the alpha-type. Intraventricular administration of the alpha-NE antagonist phentolamine, reduces rates of SS and block the facilitatory effects of amphetamine (Wise, Berger & Stein, 1973). The B-antagonist, propranolol, was ineffective. Systemically-administered thymoxamine (an alpha-antagonist) also reduces SS behavior (Herberg, Stevens & Franklin, 1976). In a study in which rats were reinforced for each pedal press, phenotolamine did not suppress SS rates (Lippa et al, 1973). The above mentioned studies used a variable interval schedule decreasing the number of stimulated neurons. Decreasing the density of NE neurons, decreases the concentration of NE available, thereby causing a decrease in SS rates. Increasing the density of NE neurons (CR Schedule) increases NE availability and thereby does not suppress SS behavior (Stein, Wise & Belluzzi, 1975).

B. Anatomical Evidence Implicating NE

Histochemical mapping studies have identified 3 major ascending NE fiber systems in rat brainstem (Fuxe, Hokfelt &

Ungerstedt,1970; Ungerstedt 1971b; Jacobowitz 1973; Lindvall & Bjorklund 1974). A dorsal pathway originates mainly in the principal locus coeruleus (NE cell group A6 according to Dahlstrom & Fuxe 1964) and innervates neocortex, cerebellum, hippocampus and thalamus. A ventral pathway originates from NE cell groups in medulla oblongata and pons (A1, A2, A5, A6 & A7) and innervates hypothalamus and ventral parts of limbic system. The midway periventricular pathway originates in NE cell bodies in central gray matter and innervates medial regions of thalamus and hypothalamus. SS mapping studies were carried out in each of these pathways. Electrodes in the dorsal bundle or LC support high rates of SS (Crow, Spear and Arbuthnott 1972; Ritter and Stein 1973; Farber et al 1971 + 1972; Wanquier and Rolls 1976; Steiner and Ellman 1972, Ellman et al, 1974 & 1975). Studies which failed to produce SS in the LC area may have had too low current intensities and shaping procedures were not adequate for this area (Amaral and Routtenberg 1975; Simon 1975; Corbett and Wise, 1979).

SS rates have been obtained in the mesencephalic central gray in the dorsal raphe nucleus (Margules 1969; Routtenberg & Malsbury 1969; Liebman, Mayer and Liebeskind 1973; Ellman et al 1976) and The DNB arising from the LC (Ritter & Stein 1973). SS has also been obtained in the ventral tegmental nucleus of Gudden (Simon et al, 1975) and nucleus paraventricularis (Atrens 1973) of the medial hypothalamus. Some rostral central gray sites which contain noradrenergic

neurons do not support SS behavior or have been reported to be aversive (Liebman, Mayer and Liebeskind 1973). However, as noted previously, some areas of the NE periventricular system do support SS behavior.

The role of the ventral NE pathway in SS is still not clear. Arbuthnott, Fuxe and Ungerstedt (1971) obtained SS from the ventral bundle at the level of the interpeduncular nucleus. They also observed an increased turnover of NE on the stimulated side in hypothalamic and limbic system areas innervated by terminals of the ventral bundle, Stinus and Thierry (1973) found similar results in the ventral tegmental area. Some investigators have failed to find SS behavior in ventral bundle areas. Anlezark et al (1974) and Clavier and Routtenberg (1974) failed to obtain SS from areas A1 or A2 or from the ascending fibers of the VB at the level of the LC. Ritter and Stein (1974) found that electrodes localized in the VB at sites caudal to all known DA cell groups in the mesencephalon do support SS rates. Carter and Phillips (1975) found positive electrodes in the dorsal medulla oblongata ventral to and within the solitary nucleus, area A2. Stimulation parameters were altered, however, since the conventional 60Hz frequency did not yield SS rates. Stimulation frequency was raised to 200Hz to obtain SS rates. Recently, area A7 was shown to support high rates of SS (Mattiace, L., 1981). The above studies present evidence that fibers in all 3 major ascending NE systems yield positive reinforcement.

C. Anatomical Evidence Implicating DA

Other investigators have suggested a role for DA in SS. Mapping studies suggest that DA tracts in the MFB and internal capsule can support SS. Kojima et al (1973) obtained SS from the I.C., whose rates were facilitated by both isomers of amphetamine, but d-amphetamine was more potent. Crow (1972) suggested there are DA systems which yield SS after ICSS was obtained in the DA cell groups of the SN and the area around the interpeduncular nucleus (A10). These areas also contain ascending NE tracts in close proximity of these DA cell groups (Ungerstedt 1971: Lindvall and Bjorklund 1974).

SS of the SNC has been reported by many investigators (Routtenberg & Malsbury; 1969 Arbuthnott et al 1970; Crow 1972; Phillips and Fibiger 1973) and constitutes one of the strongest arguments that stimulation of a DA system may itself be reinforcing. Corbett and Wise 1980 recently mapped DA systems for ICSS. They obtained ICSS from I.C., optic tract, ZI,Fornix, SNC, Tsai. No ICSS was obtained from A8, A9, A10.

Surgical, chemical, and pharmacological techniques were used to access the independent contributions of NE and DA in SN SS. Belluzzi et al (1975) used knife cuts to transect the dorsal periventricular and ventral NE fiber bundles at the level of the interpeduncular nucleus, caudal to all known DA cell groups (Ungerstedt 1971). Ipsilateral knife

cuts decreased SN SS for weeks. In another experiment, NE bundles were lesioned by local application of 6-OH. This also caused decreased ICSS rates in the SN. They also injected diethyldithiocarbomate (DDTC), an inhibitor of DA-B-hydroxylase, and observed decreased rates of SN ICSS. However, it is known that this chemical causes decreased locomotor behavior in rats. Intraventricular administration of l-NE restored SS rates. Injections of ringer solutions, DA, or clonidine were ineffective. This lent support to the notion that NE fibers of passage play a role in SN SS and that stimulation cannot depend on the activation of DA neurons alone.

Franklin et al (1975) have drawn similar conclusions on the basis of experiments in which Thymoxamine, a specific alpha-adrenergic receptor-blocking agent, reduced SS of DA sites more than NE sites. They used the alpha-blocking agent since Wise et al (73) showed that it was the alpha-and not the B-NE receptor that was involved in ICSS. Intraventricular injections of phenotolamine, an alpha-NE antagonist, suppressed ICSS and blocked the facilitatory effect of amphetamine while propranolol, a B-NE antagonist, did not.

In view of this evidence, it seems difficult to favor 1 CA over another. "Mixed Theory" models have therefore arisen (Herberg, Franklin and Stevens, 1976) which suggest that it is necssary to have the activation of both systems, for the most reinforcing effects. In support of the mixed theory

models Ritter and Stein (1974) found that electrodes placed in the ventral NE bundle, more rostrally where NE & DA systems overlap, yielded higher rates of SS than pure NE sites. Ackermann, R. F., (1975) found that simultaneous stimlation of the DA & NE system yielded higher SS rates than when only 1 system was being activated. Bodnar R.J., (1976) reported increased ICSS rates when the LC and IC areas were simultaneously stimulated in contrast with stimulation of either site alone.

D. Pharmacological Evidence Implicating DA in ICSS

Haloperidol and Pimozide, 2 drugs that block DA receptors, suppressed ICSS of the MFB (Wauquier and Niemegeers 1972). Lippa et al (1973) Liebman and Butcher (1973) Fuxe et al (1974) Rolls et. al. (1974) found that spiroperidol,a more specific DA receptor-blocking agent suppressed SS in the nucleus accumbens, septal area, hippocampus ventral tegmental area, and anterior and lateral hypothalamus. Breese and Cooper have used 6-OH in conjunction with other drugs to selectively destroy NE or DA containing neurons in the CNS (Breese and Taylor, 1970). When 6-OH-DA is administered intraventricularly to rats in 3 small doses, 4 - 8 hours apart, brain NE is depleted 60% whereas DA is reduced less than 20%. Greater depletion of brain DA can be achieved by pretreating with desipramine to prevent the uptake of 6-OH-DA by Ne neurons (protecting NE

content) and by administering 6-OH-DA in a single large dose. Maximum non-selective depletion of both CAs is achieved by pretreatment with pargyline, a monoamine oxidase (MAO) inhibitor, and a single dose of 6-OH-DA.

Depletion of both NE and DA or of DA alone drastically reduced SS of the MFB (Cooper et al 1974; Koob et al, 1978). NE depletions had no effect on SS. The same effects are seen in the L.C., a purely noradrenergic structure (Koob et al, 1978). There was actually a significant increase in LC SS rates in the condition that produced the largest depletions of NE. Fuxe et al (1974) also reported an increase in ICSS following administration of FLA-63, the DBH inhibitor (decreases NE levels). The depletion of NE resulting from multiple injections of 6-OH DA was not complete and it might be argued that the remaining NE neurons were able to support ICSS. In an attempt to reduce NE levels even further, Cooper and Breese used the DBH inhibitor U-14, 624 in conjunction with 6-OH DA treatments. NE levels were reduced to 8% of normals but ICSS from the lateral hypothalamus and L.C. were not affected. These results are not in accordance with those of Stein et al,. Breese and Cooper did find suppression of ICSS with disulfiram and DDC as had Stein et al. However, Stinus and Cardo (1975) reported that FLA-63, U-14,624 and disulfiram all had no effect on LH and ventral tegmentum SS. These pharmacological studies have actually added to the confusion rather than answering any questions.

Phillips et al (1976) Rolls, as well as Breese and Cooper caution about data obtained from 6-OH-DA experiments. These animals do not display normal behavior and are probably ill when ICSS is suppressed. There are confounding motor effects and impairments following pharmacological manipulations of DA as is seen in Parkinsonism. When animals recover, ICSS behavior recovers as well.

Although Breese and Cooper (1974) do not really offer an explanation for why they fail to find a role for NE in ICSS, they suggest that conflicting data is evidenced because neither transmitter is directly involved in ICSS and some unidentified pathway closely associated with CA pathways mediates reinforcement and the CA system modifies it.

E. MAPPING STUDIES OF DOPAMINERGIC ICSS SITES

Phillips, Carter and Fibiger (1976) found many sites scattered throughout the caudate nucleus that support high rates of SS. Although more shaping was needed than for areas like the MFB and SN. This may explain why others fail to find SS behavior in the caudate (Prado-Alcala et al (1975) made lesions in the SN using 6-OH-DA and desipramine to protect NE neurons. Caudate SS rates were severely reduced as was DA levels indicating a role for DA in caudate SS.

Caudate ICSS was also depressed following injections of P-chlorophenylalanine (PCPA), an inhibitor of 5-HT biosynthesis. ICSS of the hypothalamus was facilitated

under this treatment and both effects were correlated with the inhibition and recovery of 5-HT levels in the brain. Clavier et al (1976) found that lesions of the nigrostriatal bundle, using 6-OH-DA injections at the level of the hypothalamus, reduces SNC SS. He, therefore, interpreted his data to mean that SS is not dependent on the activation of the NE system.

Self-administration studies also lend support to the notion that DA is implicated in ICSS. Stein et al (1973) Baxter et al (1976) reported that apomorphine, which stimulates DA receptors, is reinforcing for rats when it is administered intravenously. The self-administration was blocked by pimozide, a DA receptor blocker.

Apomorphine facilitates SS of the nucleus accumbens, lateral hypothalamus, L. C. and ventral tegmentum in half of the rats tested, but reduced it in the other half (Broekkampt and Van Rossum, 1974). These bidirectional results suggest that ICSS may not always be mediated by the same system.

SS sites were found in A9, A1Ø. Huang and Routtenberg (1971) found degeneration in A9 (SNC) after lesions in the MFB and Routtenberg and Malsbury (1969) reported SS of the SN. Dreese (1966) reported SS of the A1Ø area.

F. Epinephrine as a Substrate for ICSS

A number of investigators have also reported the

detection of small amounts of epinephrine in a variety of species. Martha Vogt (1954) demostrated the presence of epinephrine in the hypothalamus of dogs and cats. In 1969, Gunne used a combination of biochemical and bioassay procedures and quantified the epinephrine levels in the hypothalamus and brainstem. In rat brainstem, epinephrine accounted for 4.5% of the total CAs present. In 1974, using immunohistochemical techniques, Hokfelt et al localized Phenylethanolamine-N-Methyltransferase (PNMT) in the CNS of the rat. PNMT is the enzyme that converts NE to E. PNMT was localized in areas A1 and A2, L.C., periventricular gray and the MFB-LH area of the hypothalamus.

Epinephrine containing cells are known to innervate a number of brain sites which support SS such as the L.C., and a number of hypothalamic sites (Hokfelt et al 1974; Saavedra et al, 1974), as well as the A2 area (Carter and Phillips, 1975).

Inhibitors of PNMT have been developed (Fuller et al, 1973 Lew et al 1976; Pendelton et al 1976) which allow for behavioral testing following PNMT synthesis inhibition. Systemic injections of these drugs have been shown to decrease ICSS elicited from the MFB-LH area (Katz and Carroll, 1977 & Mickley and Teitelbaum, 1979). In addition, these drugs, injected intracranially into the LH area, also decreased ICSS rates in this area (Mickley et al 1979).

The signficance of small amounts of epinephrine in the brain has been questioned since it can enter through the

blood from other parts of the organism. However, it has been demonstrated that there is enzymatic synthesis of epinephrine within the CNS (Barchas et al 1962; McGeer et al 1964; Poharecky et al, 1969). This sythesizing envyme could not have leaked into the CNS, since enzymes cannot cross the blood brain barrier. The fact implies that the enzyme is present in brain as well. Epinephrine has been implicated in states of arousal and activation and this suggests a possible role as a neuroregulatory agent for epinephrine. Since the LC which gives rise to the dorsal NA pathway is innervated by adrenergic terminals originating in A1 and A2, there is a possibility of an interaction between adrenergic and nor-adrenergic neurons in the L.C.

Do any Non-Catecholamine Systems Support ICSS ?

Halloway (1975) found release of serotonin as well as NE, with LH self-stimulation. Miliaressis et al (1975) found high rates of SS of the median raphe nucleus where only moderate SS (Saint-Laurent et al, 1973; Simon et al, 1973) or none at all (Routtenberg and Malsbury, 1969) had been found previously. The ICSS described by Miliaressis was abolished by PCPA and chlorpromazine. It is possible that the serotonergic raphe nuclei support ICSS through noradrenergic activation of the LC since ascending and descending pathways from raphe to LC have been mapped (Hokfelt et al, 1974). Antidromic activation of the LC may cause release of NE, activating the raphe and causing release of sertonin.

In summary, most of the neurochemical hypothesis of ICSS involve NE and/or DA. There has also been some behavioral and biochemical data suggesting that these nor-adrenergic and dopaminergic ICSS sites can be differentiated by the effects of the d- and l- isomers of amphetamine. Coyle and Snyder (1969, Taylor & Snyder, 1970, 1972 showed that the d- and l- isomers of amphetamine have differential effects on the uptake of DA and NE in the brain. The d- isomer was 10X more potent in blocking CA uptake in NE neurons than l-amphetamine, but they were equipotent in blocking uptake in striatal DA neurons. Using these data as a basis, Phillips and Fibiger (1973) showed that the 2 stereoisomers were equally effective in facilitating ICSS rates from SNC (DA site) but that d-amphetamine was 4 - 8X as potent as the l-isomer in facilitating ICSS rates from the MFB and DNB (NE site). This seemed logical at the time since d-amphetamine was assumed to be working on noradrenergic neurons. Subsequent studies have shown that it is possible to differentiate many loci using these isomers of amphetamine. Ellmanet al (1976) found d-amphetamine sensitive electrode tips in the L.C. dorsal NE bundle and dorsal PAG. Stephens and Herberg (1975) and Herberg, Stephens and Franklin (1976) reported that the far-lateral hypothalamus including the nigrostriatal bundle in the area of the CC had ICSS rates that were equally enhanced by both isomers of amphetamine, while the LH-MFB area was more responsive to the d- than the l-isomer of amphetamine. Phillips Brooke and Fibiger

(1975) found the d-isomer more potent than the l-isomer in the DNB, whereas the 2 isomers were equipotent in the nucleus accumbens (DA). Studies concerning the SNC area, revealed more conflicting data. Liebman and Butcher (1974) used a shuttle box avoidance paradigm and found, again, that the d-isomer was more potent in the LH area. The 2 isomers were equipotent in the SNC at a dose of 1mg/kg, but at lower doses, sometimes the d-isomer was more potent and sometimes the l-isomer was more potent. However, this data is difficult to interpret since no animal received both isomers of amphetamine. Taylor and Snyder (1970) found the d-isomer of amphetamine more potent in increasing locomotor behavior than the l-isomer. Carey, Goodall and Lorens (1975) found a similar effect in the SNC, while the medial frontal cortex was not affected by either isomer. The L.C. was found to be d-sensitive (Herberg, Stephens and Franklin, 1976) while the SN was equally sensitive to both isomers. In 1973, contrary to Coyle and Snyder's original biochemical findings the two stereoisomers were found to be equal in inhibiting NE uptake while the d-isomer was 4 - 6X more potent than the l-isomer in inhibiting DA uptake causing an increase in DA levels (Ferris and Thornberg and More 1973). This was exactly opposite to the original findings of Coyle and Snyder presumably because they had pretreated all animals with reserpine which depletes CA stores. Assays emphasizing the release of DA and NE showed the d-isomer to be 2 - 10X more potent than the l-isomer in releasing DA presynaptically but

the 2 isomers were equal in releasing NE (Holmes and Rutledge 1976; Peterson 1976; VonVoightlander and Moore, 1973).

In summary, the evidence now supports the notion that d-amphetamine is a more potent releaser of DA than l-amphetamine and the 2 isomers are equipotent in releasing NE. The new biochemical data does not negate the usefulness of the isomers of amphetamine as a tool to differentiate ICSS loci. The ICSS data is still valid, only the interpretation changes. The mixed theory models of ICSS presented earlier can explain the differentiation nicely. Electrodes located in NE systems (L.C.) should be more sensitive to the d-isomer (since this releases DA) thereby activiating both systems involved in ICSS. Electrodes located in DA sites (SNC) should behave equally to the 2 isomers since the dopaminergic system had already been maximally activated by the stimulation and there is no further activation of the reward system through the nonadrenergic system. This interpretation is in agreement with all the behavioral ICSS data cited previously.

One interesting feature of the CA systems is their similarity in laboratory animals. The similarity of the pathways among mammalian species and the presence of homologous pathways in lower vertebrates suggest that these systems are phylogenetically old & stable (Moore et al, 1977).

II. Anatomy of the CA Pathways

With the description of the CA pathways in the brain, there appeared an important relationship between brain catecholamines and ICSS. Before considering these hypothesis it will be helpful to review the anatomy of the CA pathways, as well as the L.C. area.

The L.C. is a densely packed nucleus of large cell bodies, about 1400 in number (Descarries and Saucer 1972). It lies at the floor of the fourth ventricle and is bordered by the dorsal tegmental nucleus on its medial side and by the nucleus of the mesencephalic V on its lateral side (Zeman and Innes, 1963). By use of the histochemical fluorescence technique of Falck, Hillarp, Thieme and Torp, (1962) it has been shown that the cell bodes of the LC of the rat are catecholaminergic (CA) (Dahlstrom and Fuxe, 1964), a large amount of which is NE (Corredi et al 1970; Fuxe et al, 1970, Hillarp et al, 1966). The area just ventral to the anterior aspects of the LC have been referred to as the "subcoeruleus" (SC) (Maeda and Shimizu 1972; Olson and Fuxe 1971) and is an integral part of the coeruleus system. The cell bodies of the SC, also containing NE, form a row of multipolar cells that pass from the antero-ventral LC towards the more ventrally located NA cell bodies in the pons (described by Dahlstrom and Fuxe as areas A5 and A7).

Dalhstrom and Fuxe (1964) have postulated that the monoaminergic-nuclei, which seem exclusively located in the

lower brainstem and mesencephalon, are an important part of the "afferent link to the limbic system". A number of studies have shown that the LC and other hindbrain nuclei are accountable for a large percentage of the NE supplied to the brain (Anden, Dahlstrom, Fuxe and Larrson 1965; Anden et al 1966, Anden et al, 1970). Ungerstedt (1971) has reported that LC innervation is minimal in areas of the hypothalamus associated with ICSS (LH & MFB). He has identified 2 ascending NE systems. The dorsal bundle (DB) originates from cell bodies in the LC and ascends parallel and lateroventral to the central gray of the mesencephalon. The DB innervates the geniculate bodies and enters the thalamic nuclei. It then joins the other CA pathways passing through the MFB to septum and it then innervates the entire cerebral cortex. The cell bodies in the lateral aspects of the LC give rise to cerebellar NE terminals.

The ventral bundle (VB) originates from NE cell bodies in the medulla and pons (areas A1, A2, A5 and A7). This pathway takes a ventro-medial direction along the mesencephalon and diencephalon and innervates the ventral tegmentum, the entire hypothalamus, including the perifornical region.

Although Ungerstedt's results indicate that the hypothalamus is mainly innervated by the VB with minor contributions of the LC, other studies have reported contrary findings. Maeda and Shimizu (1972) identified a third, intermediate bundle from cell bodies arising from the

S.C. This pathway innervates the periventricular hypothalamus and travels between the VB and DB. Olson and Fuxe (1971) reported virtually the same finding with the difference that the SC sends its fibers together with the VB, rather than a third distinct pathway. According to both studies, the DB stems from the principal LC (dorso-lateral LC) and innervates all cortices. The VB stems from cell bodies in the medulla and innervates the ventral tegmentum and hypothalamus.

Ross and Reis (1974 & 1975) looked at the levels of dopamine-beta-hydorxylase in different brain areas after LC lesions. They found that the LC innervates virtually the entire neuroaxis. They found a 40% to 60% decrease of this enzyme's activity in the medial and lateral hypothalamus. This level was reached within 12 days after the lesion.

In 1974, using a more sensitive fluorescence technique using glyoxylic acid, Lindvall and Bjorklund found that the CA systems are more numerous and complex than previously believed.

They described a third periventricular NE system. It originates in the area of the dorsal raphe nucleus, ascend in the DLF of Schutz. Cells in the mesencephalic central gray and the periventricular gray also contribute to this system whose division projects to the medial thalamic nuclei.

The afferent connections of the MFB arising from the lower brain stem have recently been investigated by means of

horse-radish-peroxidase (HRP). The injection was made iontophoretically into the MFB. After injections, a number of HRP labeled neurons were observed in 1) raphe nucleus, 2) L.C. 3) parabrachial nuclei 4) A1, A2, A4, A5 and A7, 5) A8, A9, A1Ø. Projections are primarily ipsilateral except for the L.C. projections, which was bilateral.

A. Dopaminergic Systems

A major ascending DA system, the nigrostriatal system, has been implicated in ICSS. It originates in SNC (cell group A9 in classification of Dalhstrom and Fuxe) and travels rostrally as the nigrostriatal bundle through the dorsolateral part of the hypathalamus.

The second major DA system implicated in ICSS is the mesolimbic system of Ungerstedt. Cells of origin are dorsal and lateral to the interpeduncular nucleus groups A8 and A1Ø of Dahlstrom and Fuxe. They ascend together with the NSB, through the lateral MFB and adjacent parts of the internal capsule to terminate in the amygdala, septum, nucleus accumbens, olfactory tubercle and frontal cortex.

B. Adrenergic Systems

Epinephrine containing neurons have been added to CA pathways in the brain (Hokfelt, 1974). The cells of origin form 2 groups. The largest group, C1, is in the rostral

part of the lateral.reticular nucleus near the inferior olive and their distribution resembles that of the A1 NE cells. The smaller group, C2, is in the dorsomedial reticular formation, lying below the medial part of the fourth ventricle. One axon bundle of these E- containing cells travels with the VNB. In the brainstem, terminals of E fibers are found in the dorsal motor nucleus of the vagus, the nucleus of the solitary tract (A2) and L.C. There are projections to certain hypothalamic nuclei (dorsomedial nucleus) and descending projections terminate in the central gray of the spinal cord.

III. Brain Lesions and ICSS

One method to critically evaluate the specific contributions of a neuroanatomical locus to a maintenance of a behavior has been to introduce a lesion in that structure. One area yielding the highest rates of SS is the posterior MFB at the level of the ventromedial nucleus (Olds et al, 1960). Some areas of SS are also involved in hunger and reproductive functions. It was generally believed that these areas involved in SS form a system which is related to basic drive mechanisms and that their major pathway was the MFB (Miller 1963; Morgane 1962, Olds et al, 1964, Olds and Olds, 1964, Olds et al, 1960). One way of ascertaining the MFB's contribution to SS behavior has been to lesion this area, and observe the resulting behavior. Olds and Hogberg

(1964) reported that bilateral lesions in the anterior MFB caused a 46% decrease in response rates with electrodes in the posterior MFB. Olds and Olds (1964) replicated these results but found that rates recover over time. However, if the stimulating electrode was in the anterior MFB, bilateral lesions of the more posterior MFB produced long lasting decrements in ICSS. Miller (1963) reported that bilateral lesions in the septal area had no effect on SS rates in the hypothalamus but that bilateral lesions of the MFB abolished SS rates in the Septal area. Valenstein and Campbell (1966) reported that bilateral lesions of the MFB actually facilitated ICSS rates of the septal and olfactory areas. However, some of these lesions were extensive and were accompanied by a loss of body weight. The response rates returned to normal rates as weight was regained. They concluded that the MFB was not an essential route between telencephalic and mesencephalic structures in mediating SS behavior. The system contained "redundancy or a capacity for reorganization". Boyd and Gardner (1967) placed unilateral RF lesions in the preoptic area, mammillothalamic tract, fornix or the interpeduncular/ ventral tegmental nuclei. Stimulating electrodes were in the posterior MFB. These lesions caused a reduction of response rates with recovery over time indicating again, that these 4 pathways were not essential to SS behavior and that this behavior contains "both redundancy and a significant capacity for reorganization". Similarly, Lorens

(1966) reported that bilateral electrolytic lesions of the anterior or posterior MFB had little effect on MFB SS rates. Lesions in the anterior MFB did not abolish ICSS. Lesions caudal to the MFB had no effect. When anterior lesions of the ipsilateral anterior hypothalamic area or medial preoptic area were combined with the various caudal tegmental lesions, no effects other than those obtained individually were evidenced. Therefore, it seemed that the maintenance of lateral hypothalamic ICSS was not dependent upon MFB projections caudally to the tegmentum or rostrally to the lateral preoptic, septal, and basal telencephalic area. However, Lorens does report a faciliation in MFB ICSS rates from septal lesions. Keesey and Powley (1973) also found that bilateral electrolytic lesions in the posterior septum produced a permanent decrese in the threshold for MFB-LH ICSS, again indicating that the septum appears to have an inhibitory influence on LH ICSS.

However, Olds and Olds (1969) have obtained different results. Electrolytic lesions of varying sizes were placed either in the anterior or posterior MFB. Posterior MFB lesions were consistenly more effective in abolishing MFB ICSS than anterior MFB lesions were, suggesting that posterior lesions in the same pathway as the MFB were the most effective in impairing MFB ICSS. The magnitude of this impairment was dependent upon the proximity to the stimulating electrode and the extent of tissue damage incurred by the lesion.

Another area often examined for its possible role in the integration and maintenance of ICSS behavior is the septum, since it has strong connections with the MFB. It has been implicated as a relay station between the limbic forebrain and midbrain which is thought to be the neuroanatomical substrate for a central regulatory mechanism of motivation (Grossman, 1964). These motivational properties include avoidance behavior, hyperemotionality, and rage following septal lesions (Brady and Nauta, 1953). Ward (1960, 1961) showed that rats with bilateral ablations of either the septal area or the amygdala would still self-stimulate via eletrodes in the basal tegmentum. Ablations of septum cause increased seizure activity of the hippocampus accompanied by increased grooming (Ward, 1960). The septum also maintains stimulus bound eating and drinking as well as ICSS.

In one of the only studies to successfully abolish septal ICSS, Schiff (1964) reported that bilateral ventral tegmental electrolytic lesions permanently abolished septal ICSS while dorsal tegmental lesions had no effect. However, upon close examination, his dorsal tegmental group shows ICSS rate facilitations. Asdourian et al (1968) reported that the dorsal areas of the hippocampus and thalamus when lesioned bilaterally (RF) produced differential effects on ICSS with no consistencies. Only 9 of his 21 subjects demostrated an increase in septal ICSS rates. As previously mentioned, these results are in direct disagreement with the findings of Valenstein and Campbell (1966) who found that

unilateral-electrolytic lesions of the MFB, including the preoptic area, anterior and posterior hypothalamus and the ventral tegmental area of Tsai, had no permanent effects on ICSS rates. By the second week, rates recovered to normal. Valenstein and Campbell attributed the effects reported by Schiff and Asdourian to non-specific effects since there was insufficient post-lesion testing to pick up recovery of ICSS.

Boyd and Celso (1970) found that RF lesions in the anterior hypothalamus and preoptic area, mammillothalamic tracts, or in the area anterior or drosal to the interpeduncular nucleus yielded no consistent effects on septal ICSS. Where there were decrements over time, ICSS rates recovered to baseline levels. These authors, in agreement with Valenstein and Campbell (1966), concluded that the ICSS system is redundant and capable of reorganization and recovery over time.

Kant (1969) reported that bilateral electrolytic lesions of the amygdala produce an increase in septal ICSS rates. Following MFB lesions, septal ICSS was unchanged. However, stimulation of the anterior MFB during septal ICSS produced both increases and decreases in septal ICSS with no apparent consistencies. Kant proposed that the MFB contains both an exitatory and an inhibitory fiber system and the behavioral results depended upon which system was damaged. If equal proportions of both systems were damaged, no behavioral effect would be observed. He then concluded that the

amygdala exerts an inhibitory influence on the septum while the MFB exerts both facilitatory and inhibitory influence.

Madryga and Albert (1971) found that bilateral injections of procaine along the neuroaxis of the MFB-LH ipsilateral to the stimulating electrode produced decrements of septal ICSS in comparison to contralateral injections. They conclude that their findings are consistent with those of Olds and Olds (1969) in which posterior MFB lesions abolished ICSS from ascending sites within the same pathways as the MFB as well as the septum.

In summary, the above studies, although presenting inconsistent data, indicate that it is not possible to disrupt ICSS from either the MFB or the septum with one lesion. The conclusion reached was that the ICSS system is highly redundant and capable of reorganization. Olds and Olds (1969) presented the only evidence for abolition of MFB ICSS but these lesions were so large that damage extended to the area of stimulation.

There is now a good deal of evidence implicating an important role for NE in SS behavior although the specifics are still not clear. The locus coeruleus is a unique structure since it is responsible for most of the brain's production of NE. It is also the origin of the DHNB. The association between the LC and ICSS was strengthened by the demonstration of increased neocortical levels of NE metabolites following one hour of passive stimulation near the L.C. (Anlezark, G. M., Arbuthnott, G. W., Crow, T. J.,

Eccleston, D., and Walter, D. S. 1973). The conclusion drawn from this last experiment was "that stimulation of the noradrenergic nerves arising from the L.C. is necessary for the phenomenon of SS". Ritter and Stein (1973) demonstrated that ICSS in the vicinity of the L.C. was facilitated by d-amphetamine. However, the role of the LC in ICSS is not entirely certain. Amaral and Routtenberg (1975) did not find ICSS in the L.C. proper. Cooper and Breese (1975) have shown that LC ICSS is reduced by pharmacological depletion of brain DA, but not by depletion of brain NE.

In an attempt to further explore the role of the noradrenergic system in ICSS, a series of studies were done lesioning the L.C. area. Clavier and Routtenberg (1976) made LC lesions in 27 rats. Seventeen out of 27 animals with extensive ipsilateral LC lesions had reduced ICSS rates in the midbrain tegmental area. Ten animals had ICSS faciliations, However, all animals in their study recovered to baseline levels by day 3-4. In spite of this ICSS recovery, ipsilateral cortical NE depletions remained at less than 80% of normal levels. The initial ICSS decrement could be due to NE depletions, with recovery occuring because of a supersensitivity phenomenon.

Eight animals in their study received ventral NE system lesions. Again, animals showing ICSS reductions recovered to baseline levels by day 3. In an attempt to reduce midbrain tegmental ICSS, the MFB was lesioned. All MFB lesioned animals had reduced ICSS rates. These authors

concluded that the majority of the dorsal NE or VB bundle cells can be destroyed without permanently attenuating ICSS. However, they report that midbrain tegmental ICSS depended upon the integrity of the descending fiber systems of the MFB, the origin of which may be the frontal cortex (Routtenberg, 1971; Maeda and Shimizu (1972)). Rolls and Cooper (1974) reported temporary attenuation of LC ICSS after bilateral injections of procaine into the sulcal prefrontal cortex.

In another attempt to define the role of the L.C. in ICSS, Clavier, Fibiger and Phillips (1976) examined the effects of 6-OHDA induced lesions of the dorsal noradrenergic bundle (DNB) on ICSS from the LC. These lesions did not significantly reduce LC ICSS. However, 3 out of these 21 cases, showed severe and permanent ICSS reductions. They conclude that their results raise the possibility that there exists non-noradrenergic neurons responsible for ICSS. Rolls and Cooper (1974) suggested that LC ICSS is mediated by descending efferents from the sulcal prefrontal cortex. However, Clavier and Corcoran (1976) were unable to attenuate SN ICSS or to demostrate prograde degeneration in the LC after bilateral lesions of sulcal cortex. Simon et al (1975) suggested the descending limbic axons that innervate the periventricular gray may support brainstem ICSS, a notion similar to Clavier and Routtenberg's.

Corbett, Skelton and Wise (1977) attempted to lesion the

DNB to disrupt LC ICSS. They found that unilateral DNB lesions did not disrupt LC ICSS but they did disrupt LHA ICSS. However, LHA SS rates returned to normal by day 5. Bilateral DNB lesions also failed to attenuate LC ICSS. Again, LHA rates were reduced, but returned to normal by the second post-lesion day. After day 2, a significant facilitation in LHA ICSS rates was observed. This is not surprising, since LC lesions have this same effect on LHA SS rates (Corbett (1974), Koob et al, 1976). These findings are in agreement with those above of Clavier et al (1976). They conclude that the DNB is not critical for LC SS and that it contributes nothing the LC ICSS. However, other noradrenergic fibers from the LC may mediate LC SS. The LC sends projections into both the central tegmental tract (VNB of Ungerstedt, 1971) and into the dorsal periventricular system (Lindvall and Bjorklund, 1974). Also, the LC produces NE and may thereby mediate its own ICSS behavior.

In summary, the effects of LC lesions have generally supported the view that LC fibers are not responsible for LH self-stimulation. In most cases, an increase in responding has been found (Corbett 1974; Koob et al, 1976; Mattiace et al, 1981) rather than the decrease one would expect if LC activation were important. However, it has been shown to be important for other areas of brain stimulation. Farber et al (1974); Farber (1975); Farber et al (1976) found that unilateral LC lesions permanently abolished or reduced ICSS rates from the crus cerebri,-internal capsule area and the

fields of forel. LÇ lesions had no effect or facilitated ICSS rates from the MFB-perifornical area. ICSS rates from the SN were also reduced suggesting a role for noradrenergic systems in SN SS. This is in agreement with the findings of Belluzzi et al (1975).

However, one cautionary note should be made when comparing data across lesion studies; there have been different behavioral measures in varying studies. Valenstein (1962) showed that along a continuum of increasing stimulation strength, an "inverted U-shaped" function of response rates for ICSS is generated and that the measures of ICSS taken at only one intensity does not represent the range of possible behavioral effects. In support of this idea, Steiner and Stokely (1973) showed that methamphetamine effects are not uniform across a rate intensity (RI) function. Methamphetamine facilitated ICSS rates at lower intensities, reduced variability of threshold rates and produced decrements in ICSS rates at the higher intensities. The studies by Keesey and Powley (1973), Valenstein and Campbell (1966), Kant (1969) and Olds and Olds (1969) have employed some form of the multiple intensity technique.

Another difficulty with interpretion, lies in the type of lesion technique employed. RF lesions are considered superior to electrolytic lesions since the extent of damage remains stable and discrete since lesioning is due to coagulation from heat. However, only the studies by

Asdourian, (1968), Boyd and Gardner (1967) and Boyd and Celso (1970) used the RF lesion technique. All others used the electrolytic lesion technique. RF lesions produce a large, spherical shaped area of necrotic damage while eletrolytic lesions leave residual metallic deposits causing further spreading of damage to neural tissue (DiCara et al 1974 and Gold 1975). Another problem with electrolytic lesions is that they produce abnormal electrical activity (Reynolds, 1975) which makes evaluation of ICSS data difficult. Electroylytic lesions also produce lesions that are varied in shape and size and therefore it becomes difficult to reproduce results.

Another issue prevalent in lesion data analysis, is the amount of recovery time and post-lesion testing time allowed. These time periods ranged from 5 days to 12 days; 5 days to 14 days; 20 - 25 days to several weeks of post-lesion testing. Ross and Reis (1974) showed that neural degeneration is completed by day 5 but total NE depletion following LC lesions is not complete until day 12. Therefore, any behavioral testing done before 12 days has elapsed, does not allow for total depletion and degeneration. Another issue in lesion analysis is the time course for recovery or reorganization in the CNS. Recovery of behavioral deficits can occur by day 10, but not much sooner. Loesche and Steward (1977) found that deficits in alterhaxion behavior after unilateral entorhinal cortex lesions recovered to normal in 10 days which paralleled the

time course of collateral sprouting re-innervation from the contralateral entorhinal cortex as evidenced by electrophysiological and autoradiographical studies. Septal rage syndrome has also been shown to diminish 2 weeks after surgery also indicating that a 2 week period is sufficient for recovery to have taken place (Gaze and Alton 1976). However, anatomical studies indicate that 2 weeks after a lesion, dead tissue is still being cleaned away and that the nervous system tissue, changes, until 16 weeks - 4 months after surgery (Wolf and DiCara 1969). Raisman and Field (1973) showed that it takes 4 - 6 weeks to reinnervate the septal area to the normal number of synapses after fimbrial lesions. R. Moore (1973) and Bjorklund (1972) demonstrated 2 types of sprouting that adrenergic nerves of the L.C. and MFB are capable of within the CNS. However, the functional significance of this reinnervation still remains to be explored. If behavioral recovery, does in fact, parallel neuronal recovery, then ICSS testing procedures should begin immediately following the lesion, and be prolonged to include all time courses to allow for neuronal recovery.

IV. Behavioral Theories of ICSS

A. Deutsch's Theory

Deutsch and Howarth (1963) maintained that both motivational and reinforcement pathways are exicted by ICSS.

Stimulation of the motivational pathways is necessary for ICSS, but these drives rapidly decay. This decay accounts for the rapid extinction of SS where intracranial reinforcement is withheld. The need for priming follows as a direct consequence of the theory. In a study by Deutsch and Howarth (1963) they present several lines of evidence to support their theory. The number of lever presses during extinction was found to depend on the time elapsed since the last reinforcement.

In an attempt to further elaborate Deutsch's theory of reinforcement, Gallistel has used a runway situation in which running speed is the dependent variable. In this situation, he was able to separate the motivational and reinforcing properties of ICSS. Rats traverse a runway to press a lever at the end of it, which results in rewarding brain stimulation. They receive priming before each trial. What he found (1969 & 1974) was that a change in the rewarding stimulation (varying stimulation for running) leads to a change in behavior that develops over trials mimicking the conventional learning curve. He interprets this to mean that there is some sort of memory for stimulation received on previous trials and it's this memory that mediates the reinforcing properties. The priming effect, however, varies as a function of time since the last priming. When sufficient time is allowed for the priming effect to decay between trials (10 minutes) there is no evidence of learning and no evidence that the priming

process effects running speed. Taking this notion one step further, they presented evidence that the priming and reward effects are mediated by neural systems with distinct refractory periods. Brain stimulation was presented in the form of a train of pulse pairs. The within-pair interval was shortened until there was a decrease in running speed to the level supported by half as many pulses, indicating that the second pulse in each pair fell within the neuronal refractory period. This decrease occured at a within-pair interval (C-T) of 1.Ø Msec when the priming stimulation was the I.V. and at Ø.6 Msec when the reward stimulation was the I.V.

Some of the properties of these results, specifically, the time effects have been interpreted in different manners.

B. Ball's Theory

In Ball's opinion, the poor ICSS rates under condition's of low reinforcement density is due to the disiration of negative, aversive consequences of ICSS. The organism ordinarily self-stimulates in order to avoid these consequences. It is assumed that the aversive effects of one stimulus is obliterated by a succeeding stimulus. The evidence for this is presented in a study by Ball and Adams (1965) where rats avoided ICSS when it was available at long intertrail intervals, but responded to the stimulation when the intertrial interval was shortened or they were placed on

fixed interval schedules, presumably so that the succeeding stimulus came quickly enough to overcome the aversive aftereffects of the preceding stimulus.

Rapid extinction and poor performance under partial reinforcement schedules were the focus of many researcher's investigations. Kent and Grossman (1969) found that overnight decrements in behavior reinforced by ICSS did not occur in every rat. Their differences depended on the site of stimulation. Rats not showing decrements had electrodes localized in the MFB (purely positive site) as opposed to negative and mixed sites. They suggest that sites with strong negative properties require priming, others do not. In mixed systems, the negative effects outlast the positive ones, so you get poor performance with long intervals between reinforcements. This has come to be known as the "conflict theory" in ICSS.

Trowill and co-workers (1969) have presented evidence consistent with the notion that ICSS is not really different from other natural reinforcements. Terman and Terman (1970) and Annau et al (1974) showed that when rats have continuous long term access to ICSS, a diurnal pattern emerges in which the SS does not require priming, it exhibits satiation and displacement by other behaviors and does not show overnight decrements.

The MFB in the lateral-hypothalamus is the most consistently rewarding site and the site where the highest rates of ICSS are usually obtained. However, electrical

stimulation at many sites including the MFB, may have both positive and negative effects. Animals will make one response to turn it on, and another to turn it off (Bower and Miller, 1958; Steiner et al, 1973; & 1976). It is this concept that lead to the theory of Olds and Olds. Positive reinforcement results from excitation of lateral-hypothalamic systems, which are generally involved in appetitive behavior under control of chemosensory and visceral afferents. Sensory inputs via these channels, activated naturally or electrically, are themselves reinforcing. Evidence for this lies in the fact that there are descending components of the MFB that originate in olfactory regions. The medial hypothalamus, including the periventricular system, is aversive and inhibits LH activity. The inhibition is not reciprocal, but one way, from medial hypothalamus to lateral hypothalamus. Since ICSS is evidence against a drive reduction theory of reinforcement, Olds felt animals self-stimulate for the pure pleasure it gives. Other evidence led him to believe that drive and reinforcement pathways are excited by ICSS and that the drives or rewards are specific. In 1958, he found that food deprivation increased ICSS at sites in some animals but not in others, in castrated rats testosterone replacement enhanced ICSS at some sites but not at others and constant stimulation can elicit feeding (Hoebel and Teitelbaum 1962; Margules and Olds 1962) drinking (Mogenson and Stevenson 1966; Mogenson and Morgan 1967) or sexual

behavior (Herberg 1963; Caggiula and Hoebel 1966). In 1969, Hoebel found that operations that increased LH SS also increased eating and vice-versa (Hoebel, 1975).

C. Valenstein's Theory

Valenstein felt that the type of behavior elicited at a particular site is dependent upon situational variables (1970). If stimulation elicits feeding, it may later elicit drinking if food is removed and water substituted. Valenstein proposes that hypothalamic stimulation excites pathways descending to brainstem mechanisms of species-specific behaviors, that are under hypothalamic control. In his view, motor but not motivation mechanisms are the primary substrate of behaviors elicited by hypothalamic stimulation. Valenstein's view of brain reinforcement mechanisms has several features in common with Roll's theory. Activation of particular hypothalamic neurons consitute the reinforcing event by the pleasure that results. It is this kind of event that maintains behavior, mainly through descending pathways into brainstem motor mechanisms. As in Roll's formulation of reinforcement mechanisms, the effectiveness of sensory stimuli in activating the reinforcement system depends on a gating mechanism that reflects the motivational state of the organism. The gate is influenced by physiological cues associated with drives and involves many brain regions.

Reinforcement mechanisms also serve learning and memory, and Valenstein feels that this function is mediated by ascending pathways from the hypothalamus, possibly CA pathways. His principal finding is that SS at hypothalamic sites was elicited more than one kind of motivated behavior such as feeding, depending on a number of situational variables and the organisms previous experience. When food, water and a wood block for gnawing were available stimulation in the LH region initially evoked only drinking, then when the water was removed, the same stimulation elicited eating. Stimulus-bound behavior of this type usually requires time to develop; it does not develop automatically. Animals may also lick the walls of the apparatus or chew inedible objects, if natural reinforcers are not available. This suggested to Valenstein that it is the occurrance of the behavior itself that is reinforcing, not the satisfaction of some drive.

Behaviors elicited by tail pinch also have a number of features in common with the behaviors elicited by hypothalamic stimulation (Antelman and Szechtman 1975; Antelman et al 1975; Rowland and Antelman 1976). Tail pinch elicits eating, gnawing, licking, drinking of palatable fluids, maternal behavior if pups are present or grooming if no goal objects are present. These tail pinch phenomenon also occur gradually over time. There is some evidence that both of these behaviors may depend on the dopaminergic nigorstriatal system. Antelman et al found that tail pinch

behavior was reduced by spiroperidol and pimozide and by 6-OH DA lesions of the SN. Phillips and Nikaido (1975) found that haloperidol (which blocks DA receptors) reduced feeding induced by hypothalamic stimulation. These behaviors also resemble the stereotyped induced by amphetamine which depend on the dopaminergic effects of the drug. Valenstein speculates that these behaviors may all represent an attempt by the organism to cope with a sensory overload and that stereotyped behavior may limit or order the organism's experience.

D. Routtenberg's Theory

Routtenberg's theory attempted to represent an anatomical distinction between reward and reinforcement. He proposes 2 major brain systems Arousal System I & II that have primary functions in controlling appetative behavior and learning a third system was comparable to Old's medial hypothalamic system. Neocortical arousal can occur as the result of activity in either arousal system. Arousal System I, originating in mesencephalic reticular activating system, is responsible for drive and organization of response. System II is the limbic system with its main projections through the MFB. It is a reward system that has inhibitory effects on System I and vice-versa. Activation of System II is rewarding but doesn't lead to learning unless there is an establishment of memories requiring persistent neural

activity which causes reduction in System I.

E. Stein's Theory

Stein's Theory of ICSS was similar to Olds' in that both had a positive reward system centered on the MFB and a negative system centered on the periventricular system. However, in Stein's theory the 2 systems were mutually inhibitory whereas in Olds theory there was an asymmetric inhibitory relationship from negative to positive system.

V. C-T Stimulation Technique

C-T stimulation techniques entail delivery of trains of rectangular electrical pulse pairs. The first pulse of a pair is designated the C (conditioning) pulse, the second is designated the T (test) pulse. Within certain limits, the shorter the interval between C and T pulses, the more effective is the stimulation. If the C-T interval is shortened below a certain critical duration, the stimulation rapidly diminishes and becomes no more effective than single pulse stimulation (T-pulse omitted). A possible explanation for this, proposed by Deutsch (1963), is that the C-T intervals which are shorter than normal refractory periods do not allow neurons sufficient recovery time from C pulses, to be responsive to succeeding T pulses (Smith and Coons, 1970; Coons et al 1976). Deutsch (1964) adapted this

technique for ICSS, to test the hypothesis that the drive and reward fibers might be separable on the basis of refractory period characteristics. He found that ICSS response rates at certain C-T intervals were similar to the excitability characteristics of peripheral nerves. Other explanations, which do not assume, that the difference in response rate at different C-T interval is due to refractoriness, have been offered (Szabo 1972, 1973; and Szabo 1974).

It has been shown that long descending fibers of the MFB terminate in path neurons of the lateral hypothalamic and preoptic region (Millhouse 1969). Dendrites of the path neurons are usually arranged perpendicularly to these long fibers and the medially originating axons of the path neurons bifurcate near the cell bodies to project both rostrally and caudally giving off many short colaterals to other path neurons. Therefore, a reverbatory system of neuronal loops is comprised of the path neurons of the MFB. Szabo maintains that the activation of the reverbatory loops of path neurons of the MFB is responsible for LH SS as the C-T intervals are lengthened, not recovery from absolute refractory periods. Also, axon diameters were measured by light and electron microscopy (Szabo et al, 1974). Most axon diameters ranged between Ø.6 to 1.3 micra. Measurement of both the axon diameters and refractory times in the fornix and anterior comissure suggest that the absolute refractory period of Ø.8 - 1.1 Msec measured by Deutsch

(1964) belong to axons in the lateral hypothalamic SS loci, but the other period of Ø.5 to Ø.6 Msec would require myelinated axons of about 5 - 6 micra in diameter. These findings lend further support to the view that increased SS rates after Ø.5 - Ø.6 Msec is due to the onset of synaptic activation instead of recovery from axonal refractory periods. Yeomans (1975) states that these previous paired-pulse techniques for estimating neural refractory periods of neurons of ICSS are inadequate for characterizing the distribution of refractory periods. One of his findings is that the form of the C-T function varies as one changes the C-C interval and that it's possible to get a flat function at very short C-C intervals with ceiling response rates. Presumably, when the voltage is held constant, the population of fibers which are stimulated above threshold is theoretically constant.

Smith and Coons (197Ø) adopted a modified C-T technique employed by Deutsch to explore the CNS excitability characteristics of neurons. Using 2 criteria for threshold, 5 and 7 presses/minute (Ungerleider and Coons, 197Ø; Coons, Schupf and Ungerleider, 1976) these authors found that the threshold current required to meet criteria varied as a function of the C-T interval. They found that short C-T intervals supported high thresholds for ICSS (refractory periods) longer C-T intervals supported lower thresholds for ICSS (temporal summation) and very long C-T intervals supported a sharp rise in thresholds (recovery from or decay

of temporal summation). These functions were similar to the functions demonstrated for the pain system (Kestenbaum et al 1973).

In order to test summation arising from heterosynaptic stimulation, they applied the C and T pulses to separate sets of fibers that converge onto common post synaptic neurons. They delivered the C pulse to the MFB on one side of the brain and the T pulse to the contralateral MFB and compared these rates with those obtained by delivering both pulses to the same side of the brain. Bilateral stimulation of the MFB eliminated the high latencies at short C-T intervals in unilateral stimulation. The basic finding was the shorter the interval, the greater the response, circumventing the refractory period. These authors also suggest that the data shows that there is convergence of the SS system from the 2 sides of the brain. This suggests that the C-T technique can be used as an anatomical tool to explore neural connections in the brain. Using this idea, Bodnar (1976) and Bodnar et al, (1978) explored the convergence and summation properties of LC stimulation on varying ipsilateral hypothalamic placements. ICSS rates were optimal if the C-pulse was delivered to the LC first, followed by the T-pulse in the CC-internal capsule area (asymmetrical interaction). ICSS rates were equal if the C-pulse was delivered to the LC, the T-pulse to the MFB, versus the C-pulse to the MFB, T-pulse to the LC (Symmetrical or bidirectional interaction).

Another aspect of the C-T technique is that it is sensitive to pharmacological manipulations. Coons et al (1976) used imiprimine a drug that retards presynaptic reuptake of nerve transmitters, such as NE and Diisopropyl fluorophosphate (DFP), a drug that retards the enzymatic breakdown of ACH, thereby increasing synaptic transmitter concentration. imprimine had either no effect or a slightly inhibitory one on the levels of current required to elicit the SS criterion. However, it did change the temporal summation segment of the function to lower thresholds. DFP raised the current level thresholds at the long C-T intervals but had no effect on the short C-T intervals. These authors concluded that this evidence supports the hypothesis that the decreasing effectiveness of longer C-T intervals in maintaining SS is "an expression of certain synaptic processes, namely, the disposal over time of the transmitter mediating the behavior". Bodnar et al (1976) found that strychnine, a glycine inhibitor, and picrotoxin, a GABA inhibitor, increased ICSS response rates, while Nelson (1978) reported that the C-T function is sensitive to the effects of "drugs of abuse such as morphine". Thus, the C-T function may provide a sensitive tool for investigating drug actions on behavior.

VI. Anatomical Localization of Enkephalin

The dramatic effects of opiates on the brain and the

ability of researchers to pharmacologically characterize the actions of opiates within the limits of receptor theory led to the hypothesis that specific receptors may exist within the brain to mediate the opiates effects. The search was on for the naturally occuring endogenous opiate-like compound within the brain.

A. Opiate Receptors

In 1974, John Hughes and Lars Terenius reported the first evidence that a morphine like peptide of unknown structure could be extracted from brain. They reported that the regional distribution of this morphine-like substance was highest in striatum, low in brainstem, absent in cerebellum and intermediate elsewhere and this was in agreement with opiate receptor distribution. Hughes called this substance "enkephalin", the endogenous ligand for opiate receptors. Pert and Kuhar (1975) developed an autoradiographic technique using radioactive diprenorphine, an opiate with high affinity binding to opiate receptor sites, but whose binding was reversible. This lead to fine detailed maps of opiate receptor distribution.

The development of rabbit antibodies against the enkephalin has allowed the immunohistochemical localization of enkephalin containing sites in the brain at the light microscopic level (Hokfelt eta al, 1977; Saretal, 1978; Simantou, 1977; Watson et al 1972) and immunocytochemical

localization of enkephalins at the electron microscopic level (Pickel et al 1979). Many of the sites found to contain enkephalin-like immunoreactivity are also known to contain opiate receptors as measured by biochemical (Pasternak et al, 1975; Pert et al, 1973; Simantov et al, 1976; Simon et al, 1973; Terenius, 1973; Yang, 1977) as well as autoradiographic techniques (Atweh and Kuhar, 1977a,b,c; Pert et al, 1975; Pert et al, 1976).

Electrically-induced contractions of both guinea pig ileum and mouse vas deferens in vitro can be suppressed in a dose-dependent, Naloxone reversible fashion by opiates. However, with the discovery of the structure of enkephalin (Hughes et al, 1975) and the synthesis of analogs, it became apparent that these 2 smooth muscle preparations display different sensitivities to various opiate ligands. Kosterlitz termed the ideal receptor in which morphine is more potent than leu-enkephalin, the mu "M" receptor and termed the vas deferens receptor in which leu-enkephalin is more potent than morphine, the delta receptor (Lord et al, 1977). Kosterlitz's nomenclature was based on experiments done previously by Martin (1967). Another difference between these 2 types of receptors is the concentration of Naloxone required to antagonize opiate effects; the vas deferens receptor is about 10 times less sensitive to Naloxone's potency as an antagonist than the M ideal receptor (Lord et al, 1977). Actually, opiate agonist effects are reversed by Naloxone over a broad spectrum of

antagonist potencies depending on which opiate receptors are being considered (Martin, 1967; Sharma et al, 1977; Way, 1969).

Taylor, Pert and Pert (1978) have been able to identify 2 different patterns of opiate receptor distribution (1980) depending upon the ligand and the conditions used. Opiate-like [3H] morphine and [3H] Naloxone with their higher affinity for Type I receptors produce patterns of islands and clusters in the striatum. Using [3H] diprenorphine, [3H] opiate peptides and [3H] morphine produce Type 2 receptor distribution which is a diffuse pattern in the striatum (Bomen et al, 1979). Not only in the striatum, but at other levels of rat brain, Type I opiate receptor distribution patterns have sharp, discrete borders, while Type 2 receptors are diffuse. For most of the midbrain, Type I binding is 2-3 times as great as Type 2 binding, whereas in frontal cortex, levels of binding are equivalent for both types.

Type I opiate receptors form a number of dense clusters with discrete edges in rats. They have presented evidence that indicates that Type I receptors are postsynaptic,(Creese et al, 1975; Zieglgansberger et al, 1976). It is hypothesized that the Type2 receptors are presynaptic (Lord et al, 1977) but until visualization of both receptors has been accomplished, with points of contact visible, this idea remains speculative.

Highest levels of opiate receptors in brain are in the

amygdala and other parts of the limbic system in monkeys (MacLean, 1972; Kuhar et al, 1973; LaMotte, 1978) as well as humans (Hiller, et al, 1973). Stereospecific [3H] morphine and [3H] Naloxone binding (Type I receptors) can be demonstrated in vertebrate brains but not in invertebrates (Pert et al, 1975). Hall and Pert (unpublished) showed that membranes from heads of fruitfly contain Type 2 opiate receptors. Thus, there may be a phylogenetic progression toward increasing Type I: Type 2 opiate receptor ratios. The Type 2 receptors may be associated with primitive, old brain stem areas.

Areas of high immunoreactivity are in various regions of the hypothalamus including the nucleus dorsomedialis, caudal aspect of nucleus periventricularis and nucleus paraventricularis, rostral portions of the mamillary nucleus and surrounding portions of the columns of the fornix. Another area containing a large number of immunoreactive cell bodies was the amygdala nucleus.

Areas of moderate immunoreactivity were seen in the preoptic nuclei, ventromedial nucleus, and arcuate nucleus of the hypothalamus. Other areas displaying this amount of immunoreactivity were the lateral geniculate nucleus, lateral septum, stria terminalis and caudate-putamen.

A few enkephalinergic immunoreactive cell bodies were seen in the supraoptic nucleus and lateral hypothalamus and various nuclei of the thalamus and SNC.

Enkephalin immunoreactive fibers were seen in several

fiber tracts in the forebrain. Moderate numbers of these fibers were seen in the mammillothalamic tract. The amount of immunoreactive fibers dropped off through the hypothalamus although moderate numbers of immunoreactive fibers were seen crossing the crus cerebri and running along the border of the internal capsule (Hokfelt et al, 1977; Sar et al, 1978; Simantov et al, 1977; Watson et al, 1977).

Areas shown to display opiate receptors also shown enkephalin containing cell bodies as well as fibers (Uhletal, 1978; Atweh et al, 1977). The localization of enkephalin containing cell bodies in the mammillary nucleus combined with the localization of fibers in the mammillothalamic tract may indicate an enkephalin pathway projecting to the anterior thalamus. Biochemical studies have demonstrated large amounts of opiate receptors in the midline nuclei of the thalamus (Snyder et al, 1975) and light microscopic autoradiograhic studies have indicated moderate concentration of opiate receptors in this area (Atweh, 1977). This possible enkephalin containing mammillothalamic tract could indicate a behavior role for the enkephalins.

Many fiber bundles are associated with enkephalin containing cell bodies. These areas include the MFB, and the mammillothalamic tract. Atweh et al (1977 a,b, 1978) have indicated that small unmyelinated (c) (pain) fibers may have opiate receptors along their axons. This axo-axonic synapse may be taking place within fiber bundles between

enkephalinergic neurons and other neurons.

VII. Enkephalinergic Interaction with CA Pathways

Since the discovery of the opioid pentapeptides known as the enkephalins and related larger opioid peptides of the endorphin class (Guillemin, 1978; Hughes et al, 1975) intensive investigation into the localization and neurobiological properties of these substances has taken place. There is good reason to believe that the enkephalins act as some type of neurotransmitter or neuromodulator. Electron microscopic loalization has revealed that the enkephalins are localized in granules in nerve endings (Pickel et al, 1979) and gut endocrine cells (Alumets et al, 1978). They may be released by depolarizing stimuli from neural tissue in a calcium-dependent fashion (Bayon et al, 1978; Henderson et al, 1979). Micro-iontophoretic application of these substances onto opiate-sensitive neurons produces modulatory effects (Nicoll et al, 1977). Some researchers have suggested that endorphins and enkephalins exert their effects via actions on dopaminergic systems. Their cataleptic (Bloom et al, 1977) and neuroendocrine effects (Meites et al, 1979) are indicative of this.

Localization of enkephalinergic systems has revealed that they exist in close proximity to previously known catacholmine- containing systems. Enkephalins may even be

found within the same cells as certain biogenic amines. This is the case in the adrenal medulla and in SIF cells in superior cervical ganglion (Schultzbert et al, 1978). Endocrine cells in the gut mucosa stain for enkephalin and serotonin (Alumets et al, 1978). Adrenal Medulla exhibits enkephalin immunohisto-chemical reaction where epinephrine is localized (Viveros et al, 1979). It has been shown that cholinergic stimuli release enkephalin and epinephrine from the adrenal medulla of dogs (Viveros et al, 1979). With respect to the CNS, it is clear that in certain areas catecholamine-containing and enkephalin-containing neurons exist in close proximity. This is particularly true in areas of the median eminence of the hypothalamus, the basal ganglia, nucleus locus coeruleus, area postrema and in other areas of the limbic system. The existence of high concentrations of enkephalins in most of these areas has been confirmed by radioimmunoassay (Hong et al, 1977; Kobayashi et al, 1978).

A. Nucleus Locus Coeruleus

Enkephalinergic fibers interact with noradrenergic systems in the nucleus L.C. and the A2 region (Pollard et al, 1977). Immunocytochemical localization of enkephalin at the light microscopic level indicates that the L.C. and A2 nuclei contain neuronal varicosities which are positive for enkephalin and substance P. Immunocytochemical staining

with antibodies against tyrosine hydroxylase (TH) shows that in the LC and the A2 area, TH is localized to perikarya and dendrites of intrinsic neurons. Axon terminals showing positive reactions for substance P and enkephalin are morphologically similar to each other. This type of axon terminal always forms asymmetrical synaptic junctions and contains large dense vesicles and many small clear vesicles. The L.C. has also been found to be rich in opiate receptors as shown by autoradiography. Microiontophoresis of opiates onto L.C. causes a depression of neurons firing which neurons can be blocked by Naloxone (Aghajanian, 1978). Thus, it seems possible that incoming enkephalinergic fibers regulate the activity of noradrenergic neurons in this nucleus.

B. Basal Ganglia

The profound cataleptic effects produced by many opiates and opioid peptides are similar to those produced by neuroleptics (Bloometal, 1977). The finding that the basal ganglia and in particular the globus pallidus are very rich in enkephalin-like immunoreactivity (Hong et al, 1977; Kobayashi et al, 1978; Sar et al, 1978) suggests that these behavioral-like effects of narcotics may be produced by interaction with dopaminergic systems, particularly those of the nigrostriatal pathway. A good deal of enkephalin has also been found in the nucleus accumbens and amygdaloid

nucleus where dopaminergic systems are also located (Sar et al, 1978). It was shown that a pathway running from the caudate nucleus to the globus pallidus in the rat contains enkephalin. Cuello and Paximos (1978) showed that by making a cut between the caudate and the globus pallidus most of the enkephalin-like immunoreactivity in the pallidum is lost.

There is some evidence that dopamine agonist and antagonist drugs may affect the concentration of enkephalin found within the basal ganglia. Costa et al observed that long-term neuroleptic treatment selectively increases the enkephalin content of the rat striatum and nucleus accumbens (Hong et al, 1978). This chronic treatment also accelerates the biosynthesis of enkephalin in the striatum (Hong et al, 1979). Several researchers showed that opiates and opioid peptides accelerate the turnover rate of dopamine in the nigrostriatal pathway (Deyo et al, 1979). Tolerance to this effect is seen in animals made tolerant-dependent on the action of opiates.

C. Hypothalamus

Many enkephalinergic cell groups and nerve terminals are found within the hypothalamus. Many enkephalin nerve terminals are localized within the external layer of the median eminence of the rat (Sar et al, 1978). The narcotic drugs such as morphine have a variety of neuroendocrine

effects; including the ability to increase the secretion of vasopressin, growth hormone and prolactin from the pituitary gland (Meites et al, 1979). The localization of enkephalinergic terminals in the median eminence provides a neuroanatomical basis for these effects and suggests the hypothesis that one role for enkephalinergic systems may be a neuroendocrine modulatory one. It is hypothesized that enkephalin act via some mechanism in the hypothalamus. It was found that there is a close opposition at the light microscope level between enkephalinergic and dopaminergic nerve terminals in the median eminence. This suggests the possibility that the release of dopamine into the hypophyseal portal system may be modulated by enkephalinergic neurons. Pickel et al (1979) observed that morphine and the opioid peptides are able to slow the turnover of dopamine, implying that they decrease the release of dopamine from the nerve terminals of the tuberoinfundibular dopaminergic neurons. Morphine tolerant animals also show a decreased ability of a dose of morphine to increase pituitary prolactin release. Morphine is also unable to slow the turnover of dopamine in this system. Thus, tolerance to the prolactin-releasing effects and the dopamine-turnover-modulating effects of opiates develops at the same time, indicating a connection between the two.

Another effect of narcotic agents is that they are powerful emetics (Jaffe, 1976). In this connection, enkephalin-containing neurons were localized within the area

postrema of the rat. This area, known to be concerned in the production of emetic effects, and is noradrenergic, and is another point of interaction between enkephalinergic and catecholminergic systems.

The above evidence implies that some of the pharmacological effects of exogenous opiates may be mediated by interaction with catecholamine-containing systems.

VIII. Narcotic Analgesics and CA Interactions

Narcotic analgesics have been found to increase the turnover of dopamine and 5-hydroxytryptamine in the brain in vivo and Naloxone antagonizes these effects (Ahtee et al, 1979; Kuschinsky, 1977). The effects of B-endorphin on brain monoamine synthesis are very similar to those of morphine. The antagonists naloxone and naltrexone decrese the synthesis of cerebral catecholamine and 5-HT (Garcia - Sevilla et al, 1978). Thus, it is possible that opiate receptors and their endogenous ligands are involved in the regulation of cerebral monoamine synthesis. Chronic morphine treatment produces tolerance toward several effects of exogenous B-endorphin (Tseng et al, 1977). Przewlocki et al (1979) reported that chronic morphine administration decreases the cerebral concentration of opioid peptides.

Ahtee and Attila (1979) found that dopamine neurons in the limbic forebrain are more easily affected by chronic administration of narcotic analgesics than those of the

striatum. However, long enough treatment seems to affect these neurons, too (Ahtee, 1974). Rosenman and Smith (1972) found that the rate of synthesis of catecholamines from labeled tyrosine in the whole brain of mice treated chronically with morphine was decreased at 18 - 54 hours after withdrawal of morphine. They also found that acute administration of morphine to chronically treated mice still increased the synthesis of cerebral catecholamines (Rosenman and Smith, 1972).

Chronic morphine administration for 8 weeks, significantly decreases the cerebral 5-HT and 5-HIAA concentrations. These findings suggest that endogenous opioid mechanisms which are weakened by chronic morphine administration are involved in the regulation of synthesis and release of cerebral 5-HT.

IX. Opiate Interaction with Endorphins

It has been postulated that prolonged stimulation of opiate receptors might produce a feedback inhibition of endorphin synthesis (Goldstein, 1977; Kosterlitz et al, 1975). This reduced synthesis might result in a deficiency of endorphins at the receptors, perhaps contributing to the appearance of withdrawal signs after discontinuation of the exogenous opiate supply.

A number of investigations have been unable to discover significant changes in the enkephalin content of various

areas of rat brain after chronic morphine treatment (Childers et al 1978; Fratta et al, 1977 Wesche et al, 1977; Wuster et al, 1979). There were also no changes in enkephalin content after naloxone- precipitated withdrawal in tolerant/dependent rats. such negative results, however, do not exclude the possibility that morphine dependence is associated with changes in enkephalin turnover in the brain.

Some data has emerged showing effects of chronic opiate treatment upon the B-endorphin systems (Hollt et al, 1978 a; Przewlocki et al, 1979b: Hollt et al, 1978b). In rats chronically treated with morphine pellets for 10 days, no changes were observed in levels of B-endorphin immunoreactivity. However, there was an increase in plasma levels and a decrease in anterior pituitary lobe levels after naloxone-precipitated withdrawal, as well as in the hypothalamus. This effect, however, may be due to nonspecific stressor effects (Guillemin et al, 1977). A different pattern of results was obtained with long-term (1 month) drug treatment. This treatment caused a 60% decrease in B-endorphin levels in the intermediate/posterior lobe, the septum, midbrain, and the striatum (Przewlocki et al, 1979b).

After chronic etorphine (morphine agonist) treatment, no changes in B-endorphin or enkephalin content in pituitary or brain were found, although tolerance formed (Wuster et al, 1979). From these data, it was concluded that the changes in endorphin content after prolonged morphine treatment are

not related to feedback inhibition of endorphin synthesis. This is in agreement with the results obtained from enkephalin release studies in vitro (Osborne et al, 1979).

X. Relationship Between the Enkephalins and B-LPH

Shortly after the discovery of the pentapeptides methionine and leucine-enkephalin (Hughes et al, 1975) the longer opiate peptide, B-endorphine (Bradbury et al, 1976; Guillemin et al, 1978; Li et al, 1976), was discovered by several investigators. It was soon realized that the entire structure of methionine-enkephalin and endorphin were to be found in the C terminal portion of the 91 amino acid peptide known as B-lipotropin (Hughes et al, 1975). B-LPH had been sequenced by Li et al (1966) over a decade earlier, but no specific biological function had been assigned to this molecule. In 1973, Moan, Jennings and Li (1973) were able to map the localization of B-LPH in the rat pituitary and found that it was located in some of the cells of the anterior lobe and all cells of the intermediate lobe. Stress was shown to result in release of B-endorphin, B-LPH and ACTH from the anterior pituitary (Pelletier et al, 1977). A biochemical relationship between B-endorphin, BLPH and ACTH was demonstrated by Mains, Eipper and Ling (1977) such that they were all derived from a common precursor molecule (Nakanishi, 1979). Bloom et al (1977) were also able to visualize B-endorphin-like immunoreactivity in cells which

also contained ACTH and B-LPH. Thus, there were several lines of work leading to the conclusion of a strong relationship between B-endorphin B-LPH, and ACTH.

It soon became evident by radioimmunoassay and extraction techniques that brain also contained B-endorphin and B-LPH size peptides (Rossier et al, 1977). Several researchers (Boch et al, 1978; Bloom et al, 1978; Watson et al, 1979; 1977; Zimmerman, 1978) began the study of the brain B-endorphin/B-LPH system simultaneously, using immunocytochemical techniques. These anatomical studies located B-endorphin and B-LPH in a single major neuronal cell group in the basal arcuate nucleus of the hypothalamus. In contrast to the large number of widely spread enkephalin cell groups and fibers, B-endorphin and B-LPH were contained within the single arcuate cell group but had a large fiber system associated with those cells. The fibers were distributed throughout the limbic system to the thalamus, amygdala, nucleus accumbens, septum, periaqueductal central gray, locus coeruleus and nuclei in medulla oblongata. This system was distinctly different from the enkephalin system and tended to reinforce the idea that enkephalin and B-endorphin neuronal pools represent 2 distinct systems. All cells in the arcuate nucleus which contained ACTH immunoreactivity also contained B-endorphin and B-LPH (Watson et al, 1978; Nilaver et al, 1979; Sofroniew, 1979).

XI. Evidence from Experiments on the Self-administration of

Drugs

Much of the evidence indicates that drugs self-administered by man and animals are those that significantly affect brain CAS. Baxter et al (1974) showed that rats self-administer apomorphine, a DA receptor stimulant, and that this self-administration can be blocked by pimozide. Yokel and Wise (1975) showed that rats self-administer amphetamine, a drug of abuse, which depends on DA pathways. Smith et al (1970; 1972) Rethy et al (1971) and Sheldon et al (1975) found that narcotic analcensigs such as morphine and levorphanol lead to increases in CA turnover and then to reduced brain CA levels. Smith et al, also found that the development of tolerance and withdrawal were paralleled by changes in the CA response to the drug; increased synthesis of CAs with nontolerant animals diminishes as tolerance develops but recovers with withdrawal.

The self-administration phenomena are very complex functions of pharmacological and behavioral variables, altered physiological states and biochemical changes and their interactions. In morphine self-administration for example, the pleasures of the initial rush relief from withdrawal symptoms and relief from the fear of withdrawal symptoms may all contribute to morphine's reinforcement power. How these various aspects of reinforcement are tied to CA mechanisms remains to be explored.

The concept of a drug having positive reinforcing characteristics is a complex one and is related to some fundamental properties of the brain. Part of reinforcment is related to need reduction. The problem of whether the conscious experience of feelings of pleasure and displeasure is a fundamental property of the brain of mammals has concerned all researchers, including philosophers. The first experiments of Olds (1956, 1958) showed that there are parts of the brain which when electrically stimulated give rise to self-stimulation, while other areas produce avoidance. The discovery that some drugs of abuse can have positive reinforcing properties in operant studies has led to the general belief that drugs that are positively reinforcing in animals are positively reinforcing in man.

A wide variety of drugs including cocaine, amphetamines, nicotine, barbiturates, ethyl alchol, as well as opioids can act as reinforces for operant behavior in the monkey (Yanagita et al, 1965) and the rat (Pickens et al 1968; Pickens et al 1968). As a general rule, those drugs which have high abuse potential in man are self-administered by the monkey. Conversely, drugs with low abuse potential in man (chlorpromazine and nalorphine) do not act as reinforcers in the monkey.

One of the earliest experimental attempts to study the behavioral aspects of opiate dependence was that of S.D.S. Spragg (1940). He demonstrated that physically dependent chimpanzees, who had been deprived of morphine (undergoing

withdrawal) would choose a box with morphine, in a choice-task. This type of behavior was considered escape (from the withdrawal state).

Headlee et al (1955) first demonstrated that rats exhibit a preference for I.P. administration of morphine, once physically dependent.

In 1957, Beach made rats physically dependent on morphine and they learned to self-administer. Beach interpreted his experiment as showing that morphine has 2 reinforcing effects, it acts as a reinforcer by reducing the aversive properties of withdrawal and second, it has longer lasting "euphoric" effects.

Subsequently, Weeks (1962) showed that morphine-dependent rats would bar-press for morpine. Collins and Weeks (1965) then showed that rats that had been passively made dependent on morphine would also bar-press for dihydromorphine methadone and morphine. Trojular et al (1974) found that morphine-dependent rats would self-administer morphine intragastrically, as well.

Thompson and Schuster (1964) first showed that the morphine-dependent rhesus monkey would self-administer morphine when abstinent. Deneau et al (1969) found that 75% of naive rhesus monkeys would self-administer morphine and codeine to the extent that they would become physically dependent. The rhesus monkey has been shown to self-administer propiram, d-propoxyphene, meperidine, methadone, dihydromorphinone, pentazocine, and

dextromethorphan (Deneau et al 1969; Yanagit 1975) but not nalorphine or saline (Deneau 1969). Woods and Tessel (1974) reported that fenfluramine was not self-administered by monkeys and Griffiths et al (1976) found the same effect in baboons, while they did administer d-amphetamine and cocaine.

Schuster and Woods (1967) allowed monkeys to self-administer morphine through chronic indwelling jugular catheters. The morphine dose was below that necessary to produce detectable signs of physical dependence (10 or 25 mcg/kg). They concluded therefore, that morphine can act as a reinforcer independently of its ability to relieve the abstinence syndrome yet its efficacy is greatly enhanced when animal's are undergoing withdrawal.

The first demonstration of relapse was done by Nichols (1956). After his rats were drug-free and no longer physically dependent upon the drug, they again chose to self-administer morphine. The conclusion again is that rats and monkeys self-administer morphine for its reinforcing, euphoric effects. Martin et al (1963) showed, in rats, that there are 2 phases to the abstinence syndrome. The first phase of primary abstinence lasts for 7 days. Then there is a second phase which lasts for 4 - 6 months. Wikler and Pescor (1965) showed that the tendency of rats to relapse follows a similar time curve to that of the secondary abstinence syndrome. Martin et al (1967) demonstrated a similar time course of the morphine abstinence syndrome in

man. The primary phase of abstinence lasts for several months. The secondary phase lasts for an additional 4 months.

Morphine has rate-limiting effects on self-injection behavior to which tolerance develops (Woods and Schuster, 1971). Goldberg et al (1971) and Downs et al (1975) found that morphine dependent monkeys would terminate bar-pressing if it resulted in the administration of nalorphine or naloxone. Hoffmeister et al showed that naive rhesus monkeys can distinguish morphine-like drugs which are euphoriants in man, from the nalorphine like agonists which produce dysphoric subjective effects again demonstrating that animal's will self-administer "drugs of abuse", but not drugs which have low abuse potential in man. Tricylic antidepressants and major tranquilizers are classes of centrally active agents, represented by drugs such as imipramine and chlorpromazine, that do not maintain self-administration behavior (Hoffmeister et al 1973)). Hoffmeister and Wuttke (1975) have provided data indicating that chlorpromazine administration will be terminated by monkeys.

Prior experience with narcotics can produce alterations in drug self-administration. Downs and Woods (1975) found that both morphine-dependent and nondependent monkeys respond to terminate an infusion of naloxone, whereas the dependent monkeys terminate a much lower dose of naloxone than the morphine-naive monkey. Naloxone can also be used

to punish or reduce narcotic self-administration. The higher the naloxone dose, the greater the suppression.

With the discovery of endogenous opiates and the localization of opiate receptors, researchers have begun to investigate self-administration of drugs infused directly into reinforcing brain sites. It has been reported that rats will self-administer morphine infused into the lateral cerebral ventricles (Amit 1976; Belluzzi, 1977) and they also will self-administer the enkephalins (Meek, J.C. 1977; Yang, H.Y., 1977, Belluzzi and Stein 1977). Leu- rather than met- had a higher rate of self-administration. To assess rewarding effects on self-administration behavior, lesions were made in the hypothalamus and MFB (Glick, 1974 and 1975). Results showed that lesions in the hypothalamus reduced or abolished self-administration of morphine, suggesting this structure has an important role in the mediation of positive reinforcing properties of morphine.

XII. Drugs of Abuse and ICSS

A number of investigators have reported a facilitation of SS behavior in the rat following morphine administration (Adams, et al 1972; Lorens and Mitchell, 1973; Maroli et al, 1978; Nelson, 1978). These observations have been accompanied by findings that morphine lowers positive reinforcement thresholds for electrical stimulation of the MFB (Marcus and Kornetsky 1974; Esposito and Kornetsky,

1977). Also consistent are the earlier findings which show that morphine decreases the amplitude of EEG waves recorded from sites in the MFB (Nelson and Kornetsky 1972) indicating that morphine increases the excitation of neural elements in the system. Maroli et al (1978) provided behavioral evidence indicating that morphine's faciliation of SS is due to a potentiation of the activity of the system. Taken together, these results lead to the speculation that the mechanism through which morphine enhances SS may be related to the neural process which mediate the positively reinforcing characteristics of the drug (euphoria) (Marcus and Kornetsky 1974). This hypothesis is supported by a number of pharmacological and behavioral studies which indicate that CA containing neurons may have a critical role, perhaps providing a final common pathway, in mediating the reinforcing effects of both opiates and SS. It has been shown that both morphine (Smith et al, 1970, 1972) and SS (Stein and Wise 1973 Arbuthnott et al 1971, Saint-Laurent et al 1975) produces an increase in the turnover of CAs in many of the brain structures which are anatomically related to the the MFB. Administration of AMPT, (a tyrosine hydroxylase inhibitor which depletes CAS) has been found to suppress SS (Gibson et al, 1970; Saint-Laurent et al, 1973) and to block the self-administration and reinforcing properties of I.V. injections of morphine (Davis and Smith 1972, 1973). Pretreatment with AMPT has also been found to attenuate morphine's facilitation of SS (Pert and Hulsebus

1975). Therefore, it seemed reasonable to suspect that techniques employing EBS might help bridge the gap between behavioral theories of drug addiction and underlying neurophysiological processes. To the degree that morphine acquires reward value through the SS system, one would expect to find changes n ESB as a result of drug administration.

The effects of morphine are not unidirectional. The effect is not always a potentiation of SS. Liebman and Segal (1977) showed that morphine does reliably inhibit SS with certain electrode placements.

Amphetamine, cocaine, and apomorphine are central stimulants inducing stereotyped behavior and agitation in various animal species. All 3 drugs are self-administered in animals and cocaine and amphetamines possess abuse liability in humans (Wauquier and Niemegeers 1973, 1974a and b) Stein (1962) and Benesova (1969) reported a weak facilitation on threshold intensity stimulation while Crow (1972) found a doubling of the SS rate after i.p. injection of 5 mg/kg of cocaine. A potentiation of the effects of cocaine was found with d-methamphetamine (Stein 1962a) atrophin, imipramine, and amitriptyline (Benesova, 1969). Wauquier and Niemeegers (1974b) found that different doses of cocaine (Ø.63, 1.25, 2.5Ø, and 1Ø.Ø mg/kg) given S.C. one half hour before the ICSS session produced a dose-related facilitation of SS.

Amphetamine and its derivatives has been found to lower

the threshold for SS (Stein and Ray, 1960; Steiner and Stokely, 1973), reduce the amount of pausing in rats responding intermittently (Stein, 1962b), facilitate low response rates (Olds 1970) and decrease high response rates (Stark et al, 1969). Antagonism to the effects of amphetamines were found with chlorpromazine, reserpine and AMPT (Stein, 1962a and 1964) and partially with tetrabenazine and physostigmine (Olds,1972a). Wauquier and Niemegeers (1974a) found a dose-related response rate facilitation to different doses of amphetamine with the higher doses producing facilitations later on in the ICSS session.

A. Apomorphine

Liebman and Butcher (1973 & 1974) found a slight increase in ICSS. Broekkamp and van Rossum (1974) showed that response facilitation was independent of the eletrode localization (Their placements were in the lateral hypothalamus, nucleus accumbens, A 10 area and L.C.) Wauquier and Niemegeers (1973) found that apomorphine induced response rate facilitations as well as decreases. Highest facilitations were found with low doses and low responders were more sensitive to this than high responders. The depressions were highest during the second-half hour session and corresponded with the time-course of the stereotypy-inducing effect of apomorphine.

In the study of the function of Ach at at the periphery, a distinction has been made between a muscarinic and a nicotinic receptor. Evidence for a central representation of both cholinergic-sensitive systems was given (Bradley, 1968). A central cholinergic modulation was implicated in SS (Olds and Domino, 1969b). Cholinergic muscarinic agonists exert response depressant effects on SS behavior. With pilocarpine, an ACH analogue, the decrease was does-related (Newman, 1972). The cholinesterase inhibitor, physostigmine induced a time and dose related depression (Newman, 1972 Olds and Domino 1969b). With nicotine, Olds and Domino (1969b) found a transient and variable decrease, while other authors were able to demonstrate facilitation (Bowling and Pradhan, 1967) which was most prominent in low self-stimulators and which was related to time and dose (Newman, 1972).

Others studied the effects of anticholinergics such as atropine and scopolamine. Scopolamine antagonizes the depression of SS brought about by tetrabenazine, chlorpromazine and physostigmine (Olds, 1972a). Slight antagonistic effects were shown against pentobarbital-induced inhibition (Olds, 1972a).

In general, muscarinic agonists cause response rate depressions, whereas antagonists mainly produce facilitations. Nicotine causes facilitation of SS responding and antagonizes barbiturate-induced depression. However, the doses needed to show measurable effects on SS,

are extremely high (Janssen and Niemegeers, 1967; Wauquier et al, 1975).

B. Narcotic Analgesics

Narcotic Analgesics cause depression or facilitation which is species, time and dose-related. Some of these, such as morphine, are self-administered by animals, cause dependence and are abused in humans.

The effects of morphine have been studied by many authors. The main effect, occuring within a period of 2 - 3 hours after the administration of morphine, is depression. Response depression was found after i.p. or s.c. injections of doses ranging from 5 - 20 mg/kg in rats SSing in the forebrain. Response rate depressions have been observed with as little as 10 mg/kg of morphine (Adams, Lorens and Mitchell, 1972 Bozarth and Reid, 1977; Bush, Bush, Miller and Reid, 1976; Evers, Stilwell and Levitt, 1977; Glick and Rapaport, 1974; Holtzman 1976; Kelley and Reid, 1977; Levitt, Baltzer, Evers, Stilwell and Furly, 1977; Lorens and Mitchell, 1973; Magnuson, Tadeusik and Reid, 1976; Maroli, Tsang and Stutz, 1978; Pert and Hulsebus, 1975; Schaefer and Holtzman, 1977; Terando, Mirza, Zipnick, Overweir, Rossi and Reid, 1978; Wauquier and Niemegeers, 1976a; VanderKooy, Sciff and Steele, 1978); as well as with 15 mg/kg (Bush et al, 1976; Farber and Reid, 1976; Lieberman and Segal, 1975,; 1976,; 1977; Lorens, 1976). The lower doses tend to show

facilitations following these depressions (Glick et al, 1973,; Glick and Rapaport, 1974; Lorens 1976; & 1977; Ornstein and Huston, 1977; Wauquier and Niemegeers 1976; Schaeffer and Holtzman, 1977.) Other researchers, however, report only depressions (Bush et al, 1976; Glick et al, 1973; Holtzman, 1976; Lorens 1976; Makaenko, 1969; Olds and Travis, 1960; M. E. Olds, 1976; Wauquier and Niemegeers, 1976). Slight excitatory effects were reported when 7mg/kg was injected in rats SSing in the tegmental area (Olds, 1959; Olds and Travis, 1960). Excitatory effects were seen in the lateral hypothalamus, 5 - 6 hours after the injection (Adams et al, 1972; Lorens and Mitchell, 1973).

With chronic injections tolerance to the suppressive effects of 10mg/kg of morphine developed as early as 3 days afterwards (one injection daily). The excitatory effects appeared on the fifth day of administration. Dose-response effects have been described by Lorens and Mitchell (1973). Wauquier et al, (1975) found response rate depressions at the doses of 10 and 20mg/kg and slight enchancements at lower doses. Naloxone at a dose of 5mg/kg above, was ineffective, but reversed the morphine-induced depression (40 mg/kg) of SS rates, as well as the muscle rigidity and loss of righting reflex (catatonia) (Wauquier et al, 1974). Koob et al (1975) showed that heroin - induced facilitations were naloxone reversible. Bozarth and Reid (1977) reversed morphine-induced facilitations to saline levels with naloxone (1mg/kg). Other researchers have tried to assess

the effects of naloxone alone, on ICSS. Holtzman (1976) showed that naloxone at doses from Ø.3 to 3Ø mg/kg had no effect on lateral hypothalamic ICSS while naloxone (1mg/kg) reversed ICSS rate depressions produced by morphine. He also demonstrated that naloxone could reverse facilitation produced by d-amphetamine (Ø.3 & 1.Ø mg/kg). Morphine has been implicated in dopaminergic transmission. Since d-amphetamine has its effects by releasing dopamine, it is possible that they interact on the DA system. Naloxone (2Ømg/kg) has also been found to reverse ICSS decreases induced by substance P (Goldstein and Malick, 1977). Similarly, substance P and the enkephalins are localized in similar areas of the brain (Hokfelt et al, 1977) and it is possible that they interact in this system. Pradhan (1975) found depressions and facilitations with morphine administration.

Part of the variability of the type of response that is observed under morphine administration may be accounted for by the electrode locus. The majority of these studies have examined morphine's effects on MFB-LH self-stimulation. Olds and Travis, (196Ø) were the first to report morphine neuroanatomical specificity. They reported response rate facilitations in the tegmental area and variable effects in the anterior and posterior hypothalamic area. Lorens (1973 & 1976) found only facilitations in the cingulate and medial frontal cortices without the initial depression. Liebman and Segal (1975, 1976, 1977) found that morphine facilitates

ICSS from dorsal SNC sites. Esposito and Kornetsky (1977b) found decreased thresholds for the A1Ø area and the anterior L.C. area. Broekkamp, in a series of studies, (Broekkamp and van Rossum, 1975; Broekkamp, van den Bogaard, Heijenen, Rops, Cools and van Rossum, 1976) showed that microinjections of morphine into the neostriatum and anterior and posterior hypothalamus produced ICSS response rate facilitations from stimulating electrodes in the A1Ø area and the hypothalamus. Injections into the dorsal raphe and L.C. produced response rate depressions in the A1Ø area. Nelson (1978) reported that electrode tips lateral to and within the L.C., as well as in the MFB area, produced response rate faciliatations, while placements medial to the L.C. produced depressions. Placements in the SNC also produced depression in ICSS rates, again showing that morhpine's effects on ICSS are site-specific.

In general, response rate depressions have usually been observed with acute morphine administration of high doses. (Goldstein and Malick, 1977; Holtzman, 1976; Makarenko, 1969; Olds and Travis, 196Ø; M. E. Olds, 1976).

Longitudinal studies have demonstrated a biphasic effect of morphine administration thus helping to clarify contradictory results. The biphasic effect consists of an initial depression followed by a facilitation that usually returns to baseline (Adams et al, 1972; Lorens, 1973, 1976 Lorens and Mitchell, 1973). Jackler et al (1978) showed that not all reponse rate depressions turn into

facilitations. Depending on neuroanatomical locus, ICSS rate depressions return to baseline rates without any facilitation.

Facilitations, however, are seen with low enough doses or after chronic administration. Studies that have examined the effects of single or double injections of morphine over long exposures of time have observed response rate facilitations in most animals (Lorens, 1973, 1976; Adams et al, 1972; Glick 1973; 1974; Koob et al, 1976; Lorens and Mitchell, 1973; Liebman and Segal, 1975; 1976; 1977; Bush et al, 1976; Farber and Reid 1976; Zvartau, 1977; Schaefer and Holtzman, 1977; Ornstein and Huston 1977; Bozarth and Reid, 1977; Maroli et al, 1978; Terando et al, 1978; Nelson, 1978). Low to moderate doses cause towered ICSS thresholds, while higher doses are either ineffective or elevate ICSS thresholds (Kornetsky and Esposito, 1979) Espositi et al, 1979.

The facilitatory effects are usually not observed because of the high doses and because the animal is usually only tested shortly after injection. The depressions found are not necessarily related to the rewarding value of brain stimulation. The doses used produced rigidity and catatonia and the inhibition results from motor incapacitation.

Some hypotheses relate the effects of narcotic analgesics to their interaction with dopamine receptors (Fuxe and Ungerstedt, 1970; Sasame et al, 1972) although Broekkamp and van Rossum (1975) found no evidence that

morphine interferes with dopaminergic transmission within the neostriatum.

Since morphine is self-administered by animals and abused by humans, they act as reinforcers and can increase the sensitivity of pathways involved in reinforcement mechanisms. Glick et al (1973) reported that morphine affected the reward structure involved in SS, which in turn altered the degree of dependence. Marcus and Kornetsky (1974) also provided evidence for threshold-reducing effects of morphine on SS. Other opiates, besides morphine, have been tested for their effects on ICSS. Some of these drugs Heroin - (Koob et al, 1976) oxymorphone (Schaefer, 1977) fentanyl and piritramide (Wauquier and Niemegeers, 1976) produce ICSS facilitations, while others cyclazocine and pentazocine (Holtzman, 1976) levorphanol, meperidine and methadone (Schaefer and Holtzman, 1977) produce dose-related ICSS depressions.

In summary, it is possible to find ICSS response rate depressions and facilitations to morphine administration depending on the placement of the stimulating electrode, the time of the testing interval and the dosage of the drug. It is also possible to reverse opiate drug effects with naloxone an antagonist.

XIII. Endogenous Substances and ICSS

If enkephalin - rich brain areas activate the reward

system, they should be capable of sustaining ICSS. Using this notion Stein and Belluzzi (1978) found that the nucleus paratenialis of the thalamus, an area rich in enkephalins, did indeed support ICSS. Belluzzi and Stein (1977) showed that animals self-stimulating in the MFB, had dose-related response rate depressions after intraventricular injections of leu and met- enkephalin. This was surprising since a facilitation was expected but it is possible that they missed the facilitations since the test interval was not long enough (20 min. post injection) and the doses may have been too high (100 and 200 mug). Belluzzi and Stein (1977) also reported self-administration behavior of leu, and met enkephalin. They have proposed that the reward functions may be mediated by the enkephalins or a related opioid peptide. Microinjections of met-enkephalin into the ventral tegmental area also produced facilitations in hypothalamic ICSS rates (Broekkamp et al, 1975). D-Ala 2-met-enkephalinamide, a synthetic analogue of met-enkephalin, was self-administered in the lateral hypothalamus. This self-administration behavior was naloxone reversible (Olds and Williams, 1980). In a further attempt to study the interactions of the opiate system and ICSS system, the effects of naloxone alone on ICSS have been studied. D. Van der Kooy et al, (1977) found that only doses of 40 mg/kg of naloxone reduced ICSS in caudate and LH although the caudate is high in opiate receptors and activity while Mayer et al (1971) found that naloxone at

doses as low as 0.1 to 10 mg/kg suppressed SS behavior in the central gray. Gimino et al (1979) found site-specific effects of naloxone on ICSS. At the higher doses of 10 and 40 mg/kg, most rats demonstrated ICSS rate depressions that had facilitations under morphine administration. Lower doses of 1.0 mg/kg produced either no effect or facilitations in response rates (had no effect under morphine administration).

These data indicate that although the opiate system and ICSS systems appear independent, the ICSS system may be regulated by enkephalin or related opioid peptides through their actions on CAs.

Method

Subjects

Subjects were male, Albino, Sprague, Dawley rats (Holtzman), weighing between 300 - 550 grams at the time of surgery. All subjects were housed in individual cages with ad libitum access to food and water throughout the experiment. Animals were maintained on a 12 hour light-dark schedule (light period + 0700 - 1900 hours).

Surgery

Animals were anesthetized with nembutal and stereotaxically implanted (Kopf) with two chronic bipolar electrodes (plastic products: MS 303/1) aimed at one of the following combinations: medial forebrain bundle (MFB) and crus cerebi (CC) MFB and fields of forel (FF) cc and FF. All electrodes were ipsilaterally placed in the left hemisphere. Each stainless steel electrode was insulated except for the tips which were separated by a maximum of 0.24 mm. Tips were aligned medio-laterally (perpendicular to the mid-sagittal suture). In addition, two screws serving as an indifferent skull screw were also implanted. A bipolar stainless steel electrode was unwound, stripped of the insulation and each pole was tightly wound around a

screw. Both electrodes and screws were fixed to the skull with dental acrylic.

Coordinates used were developed from the Konig and Klippel rat atlas and from adjustments made from histological examination using the bregma and lambda sutures as points of reference. Coordinates for the MFB implants were: 1.Ø mm anterior to the midpoint between lambda point and bregma, 1.5 mm lateral to the midsagittal suture and 8.8mm ventral from the surface of the skull.

Coordinates for the FF implants were: the midipoint between lambda point and bregma, 1.2 lateral to the midsagittal suture, 8.3 mm ventral from the surface of the skull.

Coordinates for the crus cerebri implants were: the mid-point between lambda point and bregma, 2.4 mm lateral to the midsagittal suture, 8.5 mm ventral from the surface of the skull.

To prevent the rupture of the transverse sinus located beneath the lambda suture, the incisor bar was set at 5mm. After implantation subjects were sutured and allowed to recover from 1Ø - 14 days.

Apparatus

Brain stimulation was delivered in an operant conditioning chamber on a continuous reinforcement schedule (CRF). Depression of a BRS/LVE retractable lever delivered

trains of electrical stimulation. A force of 20 grams was sufficient to activate a micro switch to fulfill the response requirement. Stimulation consisted of 700 Msec trains of negatively-going, monophasic rectangular pulse-pairs of 0.1 msec durations each. Constant current was optically isolated from ground in a new stimulator designed and built in our laboratory. It was interfaced with BRS/LVE Digi-bit logic modules so that the experimenter could manipulate all the parameters of the stimulation. The first pulse in the pair is designated the C-pulse and the second pulse, the T-pulse. The time interval between the C and T pulse is called the C-T interval. Their durations were 0.0, 0.5, 0.8, 1.2, 2.5, 5.0 and 15.0 msec. The time interval between the first C-pulse and the next C-pulse is called the C-C interval and was set at a duration of 30 msec for the duration of the experiment. The amperage of the pulses ranged between 150 - 500 ua. Wave form, interpulse interval, pulse and train durations and amperage were continuously monitored by observing a current drop across a 100 Ohm precision resistor on a differential input Hewlett-Packard (1200B) Cathode Ray Oscilloscope.

Procedure

Daily testing began 10 - 14 days after surgery to determine if both electrodes would support ICSS. Stimulation parameters chosen for shaping each electrode

were a C-C interval of 30 msec., a C-T interval of 5Msec, a train duration of 700Msec., and a low current intensity that was adjusted upward if the animal showed no interest in the stimulation. Each animal was tested at a variety of current intensities varying in 20 UA steps until the lowest intensity which elicited peak responding from one of the poles of a bipolar electrode was determined. Only animals who reliably self-stimulated from at least 1 pole of both electrodes (double pressers) were used in the experiment.

All parameters of the stimulation were held constant throughout the paradigm except for the C-T interval. Intervals were presented in an ascending series only; in order to minimize variability in response rates. Once each day animals bar pressed for stimulation set at each C-T interval for 6 minutes. Each interval was separated by a one-minute time-out, during which the lever was retracted from the chamber. Data collected during the first two minutes of every 6 minute interval was treated separately in order to eliminate any carry over effects from the previous interval. All priming and shaping of the response was done during these first two minutes. Only data from the last 4 minutes of each C-T interval were used to plot the C-T function. Subjects were run daily until ICSS rates reached stability. Stabilization was said to have been reached when the means and standard error of the mean (S.E.M.) of 4 consecutive days fell within the range of the means and S.E.M.s of the 4 previous days. When ICSS rates for each

electrode tip reached stabilization criterion, the animal entered the paradigm.

For the next seven days, the animal was injected with Ø.9% normal saline (1m/kg) 4Ø minutes before the beginning of the ICSS session. This was followed by 1 day of naloxone (1 mg/kg), 7 days of saline and 7 days of morphine (either 1.25 mg/kg or 2.5Ø mg/kg). Animals receiving 1.25 mg/kg of morphine also received another 7 days of morphine at a dose of 2.5Ø mg/kg, with 4 days of saline in between. After completion of the morphine days, animals received 1 day of morphine and naloxone and 6 days of saline. The first days of saline and morphine were treated separately to allow for spurious behavioral effects caused by the injections. These animals then entered the d- and l-amphetamine paradigm which consisted of 1 day d-amphetamine, 2 days saline, 1 day l-amphetamine, 2 days saline, 1 day l-amphetamine, 2 days saline, 1 day d-amphetamine and 7 days saline (A-B-B-A sequence). All doses were 1mg/kg, injected S.C., 4Ø minutes before the beginning of the ICSS session. All animals were run 7 days a week and at the same time each day for the duration of the experiment. Following the amphetamine paradigm, all animals were unilaterally lesioned at the left locus coeruleus (LC). Animals were anesthetized, placed in a stereotaxic (Kopf) instrument and acutely lesioned through a monopolar stainless steel electrode, completely insulated, except for the tip. Coordinates for the LC lesion were: Ø.3mm posterior to lambda line, 1.Ømm lateral to the

mid-sagittal suture and 7.3mm ventral from the surface of the skull. Lambda line is a hypothetical transverse line aligned with the lambda suture at 2.Ømm lateral from lambda point and has been established as a more stable point of anterior-posterior reference. Lesions were made with a radio frequency Grass Lesion Maker (LMA 4) and were produced by passing a 2-8ma anodal current (25 volts) through the electrode tip to an indifferent cathode (metal plate on the ventral surface of the animal) for a duration of 3Ø seconds. Animals were monitored for corresponding times and many changes during the duration of the lesion, along with any concommittant behavioral effects. Following the lesion, animals were run for 21 days of saline (Ø.9% normal at 1m/kg) to include a 12 day maximum time course for fiber degeneration and neuroheumoral depletion (Ross and Reiss, 1974 Ungerstedt, 1971). Prior to and following the lesion, and during drug administration days, any evidence of stimulus bound behaviors (motor movements) during ICSS sessions were recorded. Daily weight records were kept to Monitor fluctuations which could confound ICSS data. ICSS saline and drug pardigms post-lesion were identical to the pre-lesion paradigm.

Histology

At the end of the experiment, all animals were overdosed with nembutal and decapitated. Their brains were removed

and placed in a 10% formalin solution for 2 days and then transferred to a 10% sucrose and formalin solution for another 2 days. Brains were then cut using the frozen section method and a sliding microtome (Spencer 860) into 40 micron thick coronal sections. Brain sections were then mounted and stained with Cresyl violet (cell bodies) and Luxol Fast Blue (fibers) according to the Kluver-Barrera method (1953). Each animal was histologically evaluated for both electrode placements and the extent of lesion destruction by an independent rater who was not familiar with the behavioral data. ICSS placements were identified according to the neuroanatomical locus under the electrod tip, and localized on plates of Konig and Klippel (rat atlas 1963). Size and extent of the lesion was evaluated according to plates of Palkovitz and Jacobowitz (1974).

Results

Nineteen subjects completed the experiment. Table I summarizes the extent of the LC lesion in each Ss in terms of the areas affected and destroyed. LC lesions destroyed 100% of the LC cell bodies at the level of the mesancephalic V, at the level of the ant. pons and pons midbrain transition area. Some lesions extended medially to include the dorsal tegmental nucleus of Gudden, laterally to include the edge of the mesancephalic V and ventrally into the ventral LC area (N=10).

In nine subjects the LC area, at all levels was totally spared. These animals formed a separate control group. The lesions in these animals included areas of the superior cerebellar peduncles (pcs) at the level of the midbrain, or posterior medial longitudinal fasciculus (MLF), or the posterior nucleus of Gudden, or the dorsal raphe nucleus (midbrain level). Photomicrographs of histological sections (figure 1) show the extent of the lesions in representative subjects. The spread of these lesions into adjacent areas are described in Table I.

Table II lists the ICSS brain sites impinged upon by the electrodes ipsilateral to the LC lesion and in the lesion control group for all 19 subjects. Reference to Konig and Klippel's (1963) diagrams is also given for each electrode site. Figure 2 illustrates the areas directly under each electrode in an anterior to posterior series of brain

sections. The electrode tips were located in 8 general areas: CC (N=1), IC (N=10), MFB (N=10), MT (=2), ant. vent. thal. (N=5), ZI (N=4) H2FF (N=5) and per F (N=1). These sites were combined and grouped into four general areas to allow for meaningful statistical analysis of the data. Table III summarizes these histological electrode placements in terms of these four areas and the number of subjects in each group. The CC and IC were combined to form one group (N=11). These areas are primarily innervated by the DA nigrostriatal system ascending from the SN (Lindvall and Bjorkland, 1974; Ungerstedt, 1971). Figure 3 shows a photomicrograph of these hypothalamic electrodes. Nine electrodes were localized in the zona incerta (ZI) - H 2 Fields of Forel (H 2 FF) area and formed the second ICSS group since fibers from the FF project to the ZI. Figure 4 shows a photomicrograph of these hypothalamic electrodes.

The third ICSS group was formed by the Perifornical site and the medial forebrain bundle (MFB) group (N=11). The perifornical area electrode was localized just medial to the MFB group and was therefore included with this group. The MFB is heavily innervated throughout by the VB, with contributions of the DB, the DA systems as well as cholinergic systems and is therefore referred to as a "mixed" area of innervation. Photomicrographic representations of these electrodes are shown in Figure 5. The mamillothalamic (MT) electrodes and the thalamic (AV thal.) electrodes were combined to form the fourth ICSS

group (N=7) since the MT projects to the AV thal. These areas are heavily innervated by the DB arising from the LC. Figure 6 shows photomicrographs of these electrode sites.

Table IV lists the breakdown of the LC lesions experimental vs. control group with the corresponding ICSS electrodes placements and the N in each group. In the IC-CC group, 4 Ss were in the control group and 7 were in the LC hit group. In the H2FF-ZI group 4 Ss were in the control group and 5 were in the LC hit group. In the MT and AV thal. group 2 Ss were in the control group and 5 Ss formed the LC hit group. In the MFB and PerF group, 6 Ss were in the control group and 5 Ss formed the LC hit group.

The seven C-T invervals were combined and reorganized in the following manner for the statistical analyses of the data, in order to decrease variability. The first of 4 C-T invervals (Ø.Ø, 9.5, Ø.8, and 1.2 msec) were added together and are called the "sum" statistic for each animal. The response rates for Ø.Ø msec. was then subtracted from the rates at 1.2 msec. giving a "grow" factor for each animal. The third data point was the peak response rate for the C-T intervals of 2.5, 5.Ø and 15.Ø msec. and the fourth data point indicates at which of the 3 C-T intervals the peak response rates occurred. Two-tailed T-tests for matched pairs were performed on pooled data across all Ss and sites.

The Sum Data Point

All groups combined showed a significant facilitation in ICSS response rates under morphine administration - dosages 1.25 mg/kg which were naloxone reversible N=10 (T-test for matched pairs 2 tailed p<.01).

Animals receiving morphine at a dosage of 2.50 mg/kg (N=36) also showed a significant increase in ICSS rates (p<.01) which were naloxone reversible. However, there was no significant effect between the 2 doses of morphine. D-amphetamine at a dose of 1.0 mg/kg and 2.0 mg/kg both produced a significant increase in ICSS rates (p>.01). D-amphetamine at the lower dose of 1.0 mg/kg produced a significantly larger facilitation than the higher dose of 2.0 mg/kg (p>.05) due to the hypersensitivity causing immobility in the animals. L-amphetamine (1.0 mg/kg) also produced a significant increase in ICSS rates (p<0.1) but D-amphetamine at the same dose (1.0 mg/kg) produced a significantly greater facilitation (p<.01) which was nearly two-fold. L-amphetamine (2.0 mg/kg) still did not increase rates as high as D-1.0 did (p<.01) indicating that D-amphetamine (1.0 mg/kg) was the more effective isomer and dose. L-2.0 mg/kg produced a significantly greater increase in rates than did L- mg/kg (p<.01).

Post lesion ICSS rates were significantly increased under morphine administration (1.25 mg/kg) (p<.01). These facilitations were naloxone reversible (p<.01). Response rates under morphine administration (2.50 mg/kg) were also significantly increased post-lesion (p<.01) with no

significant difference between the 2 doses of morphine. Post-lesion, D-amphetamine (1.Ø mg/kg) was still more potent in producing response rate facilitations than was the dose of 2.Ø mg/kg ($p<.Ø1$) or L-amphetamine at either dose ($p<.Ø1$). L-2-Ø mg/kg was more potent than L 1.Ø mg/kg in producing increases in response rates ($p<.Ø1$). All response rates under saline control conditions were not significantly different from one another ($p>.Ø5$) indicating a return to baseline rates before and after every drug manipulation. The same is true for all post lesion saline conditions as well ($p>.Ø5$).

Effect of Lesion

Post-lesion saline rates were significantly lower than pre-lesion saline rates ($p<.Ø1$) indicating an overall lesion effect. This lesion effect stabilized by the third post-lesion saline condition and remained stable and decreased throughout the remainder of the paradigm.

The Grow Data Point

The "grow" data point was obtained by subtracting ICSS rates at Ø.Ø msec. from 1.2 msec. for all subjects. All site groups combined showed a significant increase in rates under morphine administration (dose of 1.25 mg/kg) which were naloxone reversible ($p<.Ø1$). Animals receving morphine

at a dose of 2.50 mg/kg also showed a significant increase in this difference score ($p<.01$) which were naloxone reversible. There was no significant difference between the 2 doses of morphine. D-amphetamine at both doses of 1.0 and 2.0 mg/kg produced a significant increase in ICSS rates ($p<.01$). D-amphetamine at the lower dose was significantly more potent ($p<.05$). L-amphetamine at a dose of 1.0 mg/kg also produced an increase in rates ($p<.01$) but d-amphetamine (1.0 mg/kg) was more potent ($p<.01$). L-amphetamine (2.0 mg/kg) produced a significantly greater increase in rates than did L-amphetamine (1.0 mg/kg) ($p<.01$).

Post-lesion ICSS rates were significantly increased under morphine administration (1.25 mg/kg) ($p<.01$). These facilitations were naloxone reversible ($p<.01$). Response rates under morphine administration (2.50 mg/kg) were also significantly increased post-lesion ($p<.01$) with no significant difference between the 2 doses of morphine ($p>.05$).

Post-lesion, D-amphetamine, (1.0 mg/kg) was still more potent in producing response rate facilitations than was the dose of 2.0 mg/kg ($p<.01$) or L-amphetamine at either dose ($p<.01$). L-2.0 mg/kg was more potent than L-1.0 mg/kg in producing response rate facilitations ($p<.0$). All response rate differences under saline control conditions were <u>not</u> significantly different from one another ($p>.05$).

<u>Effect of Lesion</u>

Post-lesion saline rates were significantly decreased from pre-lesion saline rates ($p<.1$) indicating an overall lesion effect. This decrement stabilized by the third post-lesion saline condition and remained decreased throughout the rest of the paradigm.

"Peak Response Rate" Data Point

There was a significant increase in peak response rate under both doses of morphine ($p<.01$) which were naloxone reversible ($p<.01$). There was no significant difference in peak response rate between the 2 doses of morphine. There was no significant difference in peak response rate between both doses of D-amphetamine ($p>.05$) or both doses of L-amphetamine ($p>.05$). D-amphetamine, at both doses did produce a significant facilitation in peak response rate ($p<.01$). D-amphetamine at 1.0 mg/kg was significantly more effective in increasing peak rates than L-amphetamine at either dose ($p>.05$).

ICSS peak response rates were significantly increased under both doses of morphine, post-lesion ($p<.01$). These increases were naloxone reversible ($p<.05$). Again, the 2 doses of morphine were equipotent in producing peak response rate facilitations. Under post-lesion administration, D-amphetamine 1.0 mg/kg was significantly more potent in producing peak rate increases than either of the doses of L-amphetamine ($p<.01$) and D-amphetamine 2.0 mg/kg was

equipotent with L-amphetamine. ($p>.05$). All peak response rates were not significantly different from one another ($p>.05$) across all pre-lesion saline control conditions ($p>.05$).

Effect of Lesion

Post-lesion saline peak response rates were significantly decreased ($p<0.1$) indicating an overall lesion effect. This decrement stabilized by the third post-lesion saline condition ($p>.05$) and remained decreased thorughout the rest of the paradigm.

"Location" of the peak response rates was defined as the C-T interval at which the peak ICSS response rate occurred for each animal. There were no significant differences in location of peak response rate in any of the drug conditions ($p>.05$) or saline conditions ($p>.05$) pre, and/or post lesion. Since there were significant increases in response rates under various drug conditions, as previously mentioned, the location data would seem to indicate no change in the shape of the function, but an increase in rates, keeping the relative shape of the function in tact.

A 2-tailed T-test for matched pairs was then performed independently for each of the 4 ICSS electrode site groups.

ICSS Group MT and AV Thal - Sum Data Point

This group showed a significant facilitation in ICSS response rates under morphine administration at a dose of 2.50 mg/kg ($p<.05$) (Figure 7). These increase were naloxone reversible ($p<.05$) (Figure 8). This group did not receive the lower dose of morphine (1.25 mg/kg).

D-amphetamine at a dose of 1.0 mg/kg produced a significantly larger facilitation than L-amphetamine (1.0 mg/kg) ($p<.01$) (Figure 9 & 10). The higher dose of amphetamine was not administered to this group. Post-lesion, ICSS rates were significantly increased under morphine administration at 2.50 mg/kg ($p<.05$) (Figure 11 and 12). D-amphetamine again showed a significantly larger facilitation than L-amphetamine ($p<.01$) (Figure 13 & 14). All response rates under saline control conditions were not significantly different from one another ($p<.05$) indicating a return to baseline rates before and after every drug manipulation. The same is true for all of the post-lesion saline conditions as well ($p>.05$).

Effect of Lesion

Post-lesion ICSS rates during the saline conditions were significantly decreased by the lesion ($p<.05$) indicating a lesion effect (Figure 15).

The Grow Data Point

The grow data point was significantly increased under morphine administration ($p<.05$)(Figure 7). This increase was naloxone reversible (Figure 8). ICSS rates for this data point were also increased with D-amphetamine but not L-amphetamine ($p<.05$) (Figure 9 & 10). Post-lesion, the grow data point was significantly increased under morphine administration ($p<.05$) (Figure 11 & 12). D-amphetamine produced a significant increase in rates as opposed to L-amphetamine ($p<.05$) (Figure 13 & 14). All response rates under saline control conditions were not significantly different from one another for pre-lesion ($p>.05$) as well as post-lesion conditions ($p>.05$).

ICSS rates for the grow data point were significantly decreased (pL.05) by the lesion indicating a lesion effect (Figure 15).

"Peak" Response Rate Data Point

There was a significant increase in peak response rate under morphine administration (2.50 mg/kg ($p<.05$) which was nalaxone reversible ($p<.05$) (Figure 7 & 8). D-amphetamine (1.0 mg/kg) produced a greater increase in peak response rate than L-amphetamine (1.0 mg/kg) ($p<.05$) (Figure 9 & 10). Post-lesion, the peak ICSS response rate was significantly greater under morphine administration (2.50 mg/kg) ($p<.05$) (Figure 11 & 12). D-amphetamine (1.0 mg/kg) produced a larger increase in peak response rate than did L-amphetamine

(1.Ø mg/kg) ($p<.Ø1$) although both isomers produced a facilitation (Figure 13 & 14). All pre-lesion peak response rates were not significantly different from one another ($p>.Ø5$) as were the post-lesion saline conditions ($p>.Ø5$).

Effect of Lesion

Post-lesion ICSS peak response rates were significantly decreased from pre-lesion rates ($p<.Ø1$) indicating that the lesion was effective in altering ICSS rates (Figure 15).

"Location" of Peak Response Rates

There were no significant differences in location of peak response rate in any of the drug conditions ($p>.Ø5$) or saline conditions ($p>.Ø5$) pre and/or post-lesion. Since there were significant increases in response rates under various drug conditions, the location data would indicate no change in the shape of the function, but an increase in rates, keeping the relative shape of the function in tact (Figure 7 - 15).

In summary, pre-lesion rates were facilitation under morphine administration at a dose of 2.5Ø mg/kg. These facilitation were naloxone reversible. Both isomers of amphetamine (D and L) at a dose of 1.Ø mg/kg significantly increased pre-lesion rates, with the d-isomer being more

potent.

The LC lesion produced decreases in saline control rates. Post-lesion drug administration produced comparable effects to pre-lesion effects.

ICSS Group IC and CC - Sum Data Point

This group did not have any significant effects in ICSS response rates under either dose of morphine ($p>.05$) (Figure 16 - 19). There were no significant differences between the 2 doses of morphine ($p>.05$). D-amphetamine at both doses of 1.0 and 2.0 mg/kg significantly increased ICSS rates ($p<.01$) (Figure 20 & 21). However, the 2 doses did not produce a different effect ($p>.05$). L-amphetamine only at the dose of 2.0 mg/kg produced a significant increase in rates ($p<.01$) (Figure 22 & 23) and D-amphetamine (1.0 mg/kg) was more potent ($p<.01$). L-amphetamine (1.0 mg/kg) was ineffective ($p>.05$) (Figure 23).

Post-lesion, morphine was still ineffective in altering ICSS rates at both doses ($p>.05$) (Figure 24 & 25). Both doses of d-amphetamine produced rate increases ($p<.01$) while only L-amphetamine at 2.0 mg/kg was effective ($p<.05$) (Figure 26, 27, 28, 29).

All response rates under saline control conditions were not significantly different from one another for pre-lesion ($p>.05$) as well as post-lesion ($p>.05$) conditions.

Effect of Lesion

Post-lesion saline ICSS response rates were significantly decreased as a result of the lesion ($p<.05$) (Figure 30). This decrease stabilized by the third post-lesion baseline condition and remained stable and decreased throughout the rest of the paradigm.

The Grow Data Point

The grow data point was also not affected by either dose of morphine ($p>.05$), pre-lesion (Figure 16 - 19). D-amphetamine, and both doses significantly increased rates ($p<.01$) (Figure 20 & 21). L-amphetamine only at the dose of 2.0 mg/kg produced a significant increase in rates ($p<.01$) (Figure 22 & 23). Post-lesion morphine at both doses, was still ineffective in altering ICSS response rates ($p>.05$) (Figure 24 & 25). Post-lesion amphetamine effects were comparable to pre-lesion effects (Figure 26, 27, 28, 29).

All response rates under saline control conditions were not significantly different from one another for pre-lesion ($p>.05$) as well as post-lesion ($p>.05$) conditions.

Effect of Lesion

The grow data point was significantly decreased ($p<.01$) after the LC lesion by the second saline baseline condition

and remained stable and depressed throughout the remainder of the paradigm (Figure 30).

"Peak" Response Rate Data Point

The peak response rate was not affected by either dose of morphine (1.25 and/or 2.50 mg/kg) ($p>.05$) Figure 16 - 19). D-amphetamine at both doses of 1.0 and 2.0 mg/kg did increase the peak response rate ($p<.50$) (Figure 20 & 21). L-amphetamine was ineffective at a dose of 1.0 mg/kg (Figure 22 & 23). Post-lesion, the peak response rate was also not affected by morphine (Figure 24 & 25). Both doses of D-amphetamine produced a significant increase in peak reonse rate ($p<.01$) (Figure 26, 27) although there was no significant difference between the 2 isomers ($p>.05$). L-amphetamine (2.0 mg/kg) also produced a facilitation in rates ($p<.05$) (Figure 28 & 29). All pre-lesion peak response rates were not significantly different from one another ($p>.05$) as was the case for the post-lesion salines ($p>.05$).

Effect of Lesion

Post-lesion ICSS peak response rates were significantly depressed following the lesion ($p<.01$) (Figure 30).

"Location" of Peak Response Rates

There were no significant differences in location of peak response rate in any of the drug conditions ($p>.05$) or saline conditions ($p>.05$) pre and/or post-lesion. Most animals peaked at the C-T interval of 15.0 msec. even after the lesion.

In summary, pre-lesion morphine administration at both doses was ineffective in altering ICSS rates. Rates were increased with D-amphetamine (1.0 and 2.0 mg/kg) and L-amphetamine (2.0 only). Post-lesion saline rates were significantly depreesed following LC lesions. Post-lesion, drug effects were similar to pre-lesion drug effects.

ICSS Group FF and ZI - Sum Data Point

This group showed a significant facilitation in ICSS response rates under morphine administration at a dose of 2.50 mg/kg ($p<.05$) (Figure 31). The lower dose of morphine was not administered to these Ss. The morphine facilitation was naloxone reversible ($p<.05$) (Figure 32). D-amphetamine 1.0 mg/kg produced a very large increase in rates ($p<0.01$) (Figure 33) as opposed to L-amphetamine at either dose ($p>.05$) (Figure 34 & 35). The N for D-amphetamine 2.0 mg/kg was too small to allow for meaningful analysis. Post-lesion, morphine produced significant increases in rates ($p<.01$) (Figure 36) which were naloxone reversible ($p<.01$) (Figure 37). D-amphetamine at 1.0 mg/kg again

produced facilitations ($p<.01$) (Figure 38 & 39). All response rates under saline control conditions, pre and post-lesion, were not significantly different from one another ($p>.05$) indicating a return to baseline between drug conditions.

Effect of Lesion

Post-lesion saline ICSS response rates were significantly depressed ($p<.05$) as a result of the lesion (Figure 40). These depressions stabilized by the third post-lesion saline condition and remained decreased and stable throughout the rest of the paradigm. Pre and post-lesion morphine rates were not significantly different from one another ($p>.05$).

The Grow Data Point

There was a significant increase in the "grow" data point under morphine administration at a dose of 2.50 mg/kg ($p<.01$) which was naloxone reversible ($p<.10$) (Figure 31 & 32). D-amphetamine at 1.0 mg/kg produced facilitations ($p<.05$) (Figure 33, 34, 35). Post-lesion, morphine (2.50 mg/kg) increased this difference score ($p<.05$). This increase was naloxone reversible ($p<.05$) (Figure 36 & 37).

D-amphetamine, again produced increases ($p<.05$) in the grow factor (Figure 38, 39). All pre-lesion saline rates

were not significantly different from one another (p>.05).

Effect of LC Lesion

Post-lesion, the grow data point was significantly lower than the pre-lesion data point (p<.01). This decrease stabilized by the third post-lesion saline condition and remained stable and decreased throughout the responset of the paradigm (p>.05).

Peak Response Rate Data Point

The peak response rate increased under morphine administration (2.50 mg/kg) (p<.01). This increase was naloxone reversible (p<.01). Both doses of D-amphetamine significantly facilitated the peak ICSS rate (p<.01) with no difference between the 2 doses (p>.05). L-amphetamine (2.0 mg/kg) and L-amphetamine (1.0 mg/kg) were not effective in altering ICSS rates (p>.05).

Post-lesion, morphine also produced in increase in peak response rates (p<.01) which was no different from pre-lesion morphine rates (p>.05). Post-lesion amphetamine effects were similar to the pre-lesion effects (p>.05).

All pre and post-lesion peak response rates under saline control conditions were not significantly different from one another (p >.05). The same was true for all post-lesion saline control conditions as well (p>.05).

Effect of LC Lesion

Post-lesion saline peak response rates were significantly decreased following the lesion ($p<.05$). This decrease was stable by the second post-lesion saline condition ($p>.05$) and remained depressed for the rest of the paradigm.

"Location" of Peak Response Rates

There were no significant differences in location of peak response rate in any of the saline conditions pre and/or post-lesion ($p>.05$) and most of the drug conditions ($p>.05$). Most animals peaked at the C-T inverval of 15.0 msec. even after the lesion. However, the location of the peak response rate shifted to the C-T inverval of 2.50 msec. under the administration of the D-isomer of amphetamine both pre and post-lesion ($p<.05$). This group showed a sensitivity shift to the left of the function meaning decreased ICSS threshold and increased rates.

In summary, ICSS rates from the H2FF area and the ZI were facilitated with the administration of morphine (2.5 mg/kg), pre-lesion. This increase was naloxone reversible. Pre-lesion rates were increased with D-amphetamine but not L-amphetamine. The lesion in LC produced a decrease in ICSS rates which were facilitated to pre-lesion saline levels under post-lesion morphine administration (2.5 mg/kg).

Post-lesion amphetamine rates were also facilitated. There was also a shift, to the left, of the C-T function, indicating a lowering of ICSS thresholds under D-amphetamine administration both pre and post-lesion.

ICSS Group MFB and Perf - Sum Data Point

ICSS rates in this group showed a significant facilitation under morphine administration at a dose of 1.25 mg/kg ($p<.05$, N=3) and a dose of 2.50 mg/kg ($p<.01$, N=11). These facilitations were naloxone reversible ($p<.05$) (Figure 40 - 43). There was no significant difference between the 2 doses of morphine ($p>.05$), although there was a tendancy for a larger increase with the higher dose of morphine. It is possible, significance was not reached because of the small N. D-amphetamine 1.0 mg/kg and 2.0 mg/kg produced an even larger facilitation ($p<.01$) (Figure 44 & 45). D-amphetamine (1.0 mg/kg) produced a significantly larger facilitation than the dose of 2.0 mg/kg ($p<.05$).

Post-lesion, morphine at both doses produced an increase in rates ($p<.01$) (Figure 46 - 49). D-amphetamine (1.0 mg/kg) and both doses of L-amphetamine increased post-lesion ICSS rates ($p<.01$) (Figure 50 - 53).

Effect of Lesion

There was no significant difference in post-lesion

saline rates vs. pre-lesion saline rates as a result of the lesion ($p>.05$) (Figure 54). All pre-lesion ICSS rates under saline control conditions were not significantly different from each other ($p>.05$). The same was true for all the post-lesion saline control conditions ($p>.05$).

The "Grow" Data Point

The difference score was significantly increased ($p<.05$) under morphine administration at both doses. The lower dose was more potent ($p<.05$) than the higher dose. These increases were naloxone reversible ($p<.01$). L-amphetamine at both doses was ineffective ($p>.05$). D-amphetamine at both doses produced significant facilitations ($p<.01$).

Post-lesion, morphine rates were lower than those of pre-lesion scores, but the increase was still significant ($p<.05$) and naloxone reversible ($p<.05$). Post-lesion, both isomers of amphetamine produced increases in rates ($p<.01$). All pre-lesion ICSS rates and post-lesion rates under saline control conditions were not significantly different from one another ($p>.05$).

Effect of LC Lesion

There was no significant effect in saline baseline rates following the LC lesion ($p>.05$).

"Peak" Response Rate Data Point

Morphine at both doses significantly facilitated peak ICSS rates ($p<.01$). There was no significant difference between the 2 doses of morphine ($p>.05$). These increases were naloxone reversible ($p<.01$).

Both doses of D-amphetamine produced increases in peak rates ($p<.01$) although the lower dose of 1.0 mg/kg was significantly more effective ($p<.01$) than the higher dose of 2.0 mg/kg.

Post-lesion morphine peak rates were lower than pre-lesion morphine rates ($p<.50$) although still higher than post-lesion saline rates ($p<.05$). This increase was naloxone reversible ($p<.05$). Post-lesion both isomers of amphetamine produced increases in peak rates ($p<.05$). Peak response rates pre and post-lesion under saline control conditions were stable throughout the paradigm ($p>.05$).

Effect of LC Lesion

There were no significant differences in the peak response rate under the saline baseline condition following the LC lesion ($p>.05$).

"Location" of Peak Response Rates

Post-lesion, under morphine drug conditions, there was a

significant shift in location of peak response rate ($p<.05$). Saline peak rates were located at the C-T interval of 15.0 msec. This location shifted to the left, to the C-T interval of 5.0 msec. under drug conditions. There was no significant difference in location of peak response rates ($p>.05$) in any of the pre-lesion conditions, as well as in any of the saline conditions across all pre and across all post-lesion saline control conditions ($p>.05$).

In summary, ICSS rates from the MFB-Perf group were facilitated with both doses of morphine, pre-lesion. All isomers and doses of amphetamine increased rates except for L-amphetamine at a dose of 1.0 mg/kg and 2.0 mg/kg which was ineffective. The LC lesion did not produce any significant alterations in saline baseline rates. Post-lesion morphine rates were comparable to pre-lesion drug rates. Post-lesion ICSS rates were increased under administration of both isomers of amphetamine. The LC lesion produced a shift to the left in the ICSS function under morphine drug conditions. Although there were no significant changes in rates, the LC lesion seemed to increase the animals' sensitivity to morphine and amphetamine by decreasing the ICSS threshold.

Overall Summary - Pre-lesion Drug Effects

Pre-lesion ICSS rates from electrodes in the MT, AV thal., H2FF, ZI and MFB were facilitated under morphine

administration at both doses. There was no significant difference between the 2 doses of morphine although there were with individual animals. All morphine facilitations were naloxone reversible. ICSS rates from the IC area were not significantly altered with morphine administration.

Pre-lesion ICSS rates from the MT and Av thal. group, IC group and MFB and Perf group were facilitated with both isomers of amphetamine. ICSS rates from the FF and ZI group were increased by the d-isomer of amphetamine only. The L-isomer was ineffective in altering ICSS rates.

LC Lesion Effect

Post-lesion ICSS rates were significantly depressed following an LC hit lesion when stimulating electrodes were located in the areas of the IC, H2FF MT, ZI, and thalamus. ICSS rates were not altered by LC lesions when the electrodes were located in the Perf. area and MFB. However, some animals tended to have facilitations following the lesion from the MFB electrodes. These facilitations did not reach statisitical significance since most animals in this group were not affected by the lesion.

Post-lesion Drug Effects

ICSS rates from the H2FF, ZI, MT & thalamus which were depressed following the lesion, were facilitated to

pre-lesion saline, but not pre-lesion morphine levels under post-lesion morphine administration. Although rates from the IC area were decreased following the lesion, morphine was ineffective in altering ICSS rates.

The Perf area and MFB electrodes produced comparable ICSS rates to pre-lesion rates under morphine administration. The LC lesion had no effect in altering ICSS rates in these sites. Therefore, if morphine produced an increase in rates pre-lesion, it did so post-lesion.

Post-lesion amphetamine increases were always comparable to pre-lesion amphetamine increases, indicating a different sensitivity to amphetamine and morphine.

In most cases, pre-lesion ICSS rates under amphetamine administration were always higher than rates under morphine administration, indicating an overall difference in the sensitivity to morphine and amphetamine administration.

Discussion

In summary, the following results were found in this experiment: (1) LC lesions which destory at least 90% of the LC or its ascending bundles markedly reduce ICSS response rates in subjects whose electrodes are located in the H2FF, ZI, IC, MT and ant. vent. thalam. These areas are innervated primarily by the DNB, the nigrostriatal bundle or both. (2) ICSS in subjects whose hypothalamic electrodes were located in the MFB-PF area were not affected by these lesions. These areas are heavily innervated by the VNB as well as having serotonergic and cholinergic input. (3) Morphine altered ICSS rates differentially; morphine facilitates ICSS rates from electrodes in the H2FF, ZI, MT, ant. vent. thalamus and MFB-PF areas. ICSS rates in the IC-CC areas are not altered by morphine administration. (4) All morphine facilitations are naloxone reversible indicating an opiate agonist-antagonist relationship. (5) D-amphet (1.0 mg/kg) enhanced ICSS rates in all electrode sites. (6) L-amphet. enhanced ICSS rates only at the dose of 2.0 mg/kg. However, D-amphet always produced a significantly greater facilitated in rates than L-amphet. did. (7) Post lesion ICSS rates from the H2FF, ZI, MT and ant. vent. thalamus which were depressed following the lesion were facilitated to pre-lesion saline levels under morphine administration, but not to pre-lesion morphine levels. (8) Post lesion ICSS rates from the IC-CC area that

were depressed following the LC lesion, were still not altered by morphine administration. (9) Morphine administration produces comparable facilitations in ICSS rates in the MFB-PF area post lesion, as it did pre-lesion. ICSS rates in this group were not altered by the LC lesion. The LC lesions differentially effect hypothalamic self-stimulation, decreasing rates in some sites and not altering rates in others. Although the LC is primarily noradrengeric and gives rise to noradrenergic bundles, its destruction causes decrements in dopaminergic self-stimulation sites. These findings are in accord with Belluzzi and Stein (1975) and Farber et. al. (1976). These decrements were produced by relatively small, discrete unilateral lesions, distant from the stimulation site, again showing that self-stimulation can be decreased and/or affected and that the reward system is not necessarily "redundant and capable of reorganization and recovery."

Some of the problems that may arise with unilateral LC lesions may include, weight loss, hypophagia, loss of grooming and behavioral deficits. All of the subjects were closely monitored before and after the LC lesion to assess these deficits. Weight loss occurred in all animals immediately following the LC lesion. However, normal weight was regained by the fourth post-lesion day and remained stable throughout the rest of the paradigm. This weight loss, then cannot explain the reduced ICSS rates. Also, subjects who showed no effect in ICSS rates following the LC

lesion also displayed this pattern of weight loss and gain. All other behaviors (i.e. grooming, bowel movement, meal pattern and size) were normal. Thus, the obtained results were not artifactual, non-specific side effects caused by neurological injury due to the lesion.

A second issue in evaluating lesion data might be to try and correlate the size of the lesion with the size in the behavioral effect. The size of the lesion did not correlate with the size in behavioral effect. The same lesion produced decrements in ICSS rates from the IC area and produced no effect in the MFB, in the same subject. Since all subjects had 2 stimulating electrodes, this allowed for contrast and specificity of effect due to either the LC lesion or the drug manipulation.

Contrary to many lesion studies, subjects were tested for long periods of time after the lesion (3 months). This revealed valuable information about recovery and/or patterns of recovery. ICSS from some placements were immediately affected, while other sites showed gradual decrements or gradual recovery.

The finding that ICSS from areas rich in dopamine requires the integrity of the noradrengeric LC area is in direct conflict with data from Cooper's laboratory but is in agreement with the findings of Belluzzi et. al. (1975), Farber et. al 1976 and Bodnar et. al 1978. This hypothesis was formulated based on these previous findings and was confirmed. The hypothesis was that the activation of both

the DA and NE systems is necessary to maintain SS behavior. Therefore, if the noradrenergic input is removed, it follows logically, that dopaminergic activation would be insufficient for maximum ICSS behavior. There should be a decrease in ICSS rates. This constitutes one of the reasons why the lesions in this experiment were placed in the LC area. The prediction that ICSS from the anatomical sites which receive fibers from this system would be affected by the LC lesion was confirmed.

The difficulty with previous lesion studies were that they searched for one ICSS center. These studies were based on the hypothesis that such a "reward center" would mediate all ICSS behavior. The MFB was thought to interconnect all ICSS sites and also ICSS from the MFB-LH area seemed most sensitive. Therefore, most previous lesion studies tried to abolish MFB ICSS almost in a hit and miss fashion.

In some of the old ICSS studies lesions did produce ICSS decrements with electrodes in the hypothalamus. These lesions destroyed parts of the CA bundles which innervate the ICSS sites. The Swedish investigators (Lindvall and Bjorklund, 1974, Ungerstedt, 1971) with their CA maps lead the way to new thinking or organization of the ICSS system. Farber (1974) combined this new knowledge of CA maps with knowledge of neuronanatomical connections and was able to predict differential effects in hypothalamic ICSS following lesions.

Belluzzi et. al. (1975) also along these lines, lesioned

the DNB and found reduced ICSS rates in the dopaminergic SN. These findings along with the results predictd here indicate that the hypothalamus as well as other sites, are combinations of different ICSS systems that can be defined in terms of neuroanatomical connections and specific CA nuclei and fibers of passage.

The results of the amphet paradigm clearly shows the importance of the d-isomer in ICSS. In all sites except for the MFB area, the d-isomer at a dose of 1.Ømg/kg produced facilitations equal to or better to l-amphet at a dose of 2.Ømg/kg. The d-isomer was always more potent. ICSS from the MFB, however, was equally affected by both isomers of amphet. This is not so surprising since the MFB really is quite a unique ICSS area since it is made up of many different trasmitter systems with descending and ascending contributions. This then can be another tool for differentiating ICSS hypothalamic sites.

One interesting result of the LC lesion was its effect on the ant. vent. -thalamus. ICSS rates from this group were decreased following the lesion. This is really not unusual since these areas of the thalamus receive numerous projections from the DNB arising from the LC and these results could have been predicted.

Another interesting ICSS group was the MFB-PF group. If all Ss were grouped together, no significant differences in ICSS rates post lesion are found ($p>.Ø5$). However, ICSS patterns in this group were not uniform, as they were in the

other ICSS site groups. Immediately following the lesions, some subjects showed a reduction in rates which recovered by the fourth day post lesion. Some Ss had slightly reduced ICSS rates post-lesion for the remainder of the paradigm, and still other subjects had increased rates as a result of the LC lesion. When Ss were grouped together, these individual differences were cancelled out and there was no signficant lesion effect in this group. These individual differences may be due to the very high response rates normally elicited from this area. MFB Ss responding 90 or more times/minute tended to show initial decrements in rates with recovery over time. Some responding MFB Ss (40 - 50 presses/minute) tended to increase rates as a result of the lesion. It is possible that low responders tended to overcompensate after the LC lesion, thereby causing a facilitation in rates, while high responders may have reached a ceiling effect which was removed by the lesion. Another explanation for the facilitation in response rates following LC lesions may be CNS recovery of function. We can assume that this VB-MFB ICSS system is different than the LC-DA ICSS system. However, both ICSS systems function together perhaps via a feedback loop. If the LC-DA system is damaged, supersensitivity may result in the second ICSS system, namely the VB-MFB system, which is demonstrated by ICSS rate facilitations. This type of facilitation in response rates following LC lesions and VLC lesions have been reported by Mattiace (1981).

Another explanation for the facilitatory effect at some MFB ICSS sites is that the LC input to the MFB is inhibitory. Removing this inhibitory influence, causes release and activation in the MFB causing facilitation in rates.

Analysis of Morphine Effects

Morphine administration differentially effects ICSS by facilitating rates in some sites and not altering rates in others. Morphine facilitated ICSS rates with stimulating electrodes in the MFB-PF area, H2FF, ZI, MT and ant. ventral thalamus. ICSS rates from the IC area were not altered by morphine. These results are not really surprising. There is high enkephalin immunoreactivity in various regions of the hypothalamus including rostral portions of the mamillary nucleus and in the perifornical area, surrounding the Fornix. Moderate amounts of immunoreactive fibers are seen in the mamillothalamic tract, lateral hypothalamus and various nuclei of the thalamus. What was surprising was that the IC-CC area was not affected by morphine. Moderate numbers of immunoreactive fibers have been seen crossing the crus cerebri and running along the border of the internal capsule. However, it is possible that the electrodes did not impinge on these enkephalin-containing neurons. Also, since the reactivity was only found along the borders of the IC, it is possible that a higher dose of morphine (>2.5mk)

would have elecited a change in behavior.

Areas containing opiate receptors also show enkephalin containing cell bodies as well as fibers (Uhl et al 1978; Atweh et al, 1977). The localization of enkephalin containing cell bodies in the mamillary nucleus combined with the localization of fibers in the mamillothalamic tract may indicate an enkephalin pathway projecting to the ant. thalamus. Biochemical studies have demonstrated large amounts of opiate receptors in the midline and ventral nuclei of the thalamus (Snyder et al, 1975) and light microscopic autoradiograhic studies have indicated moderate concentrations of opiate receptors in these areas (Atweh, 1977). This would explain the mor facilitations from the thalamic and MT areas.

The MFB area, although it is a fiber bundle, is associated with enkephalin containing cell bodies (Atweh et, al (Atweh et al 1977a,b, 1978), again indicating an area of interaction for morphine and ICSS.

According to the Taylor, Pert and Pert (1978) classification there are 2 different patterns of opiate receptor distribution, type 1 and type2. They have presented evidence that type 1 receptors are post synaptic (Creese et al, 1975; Zieglgansberger et al, 1976) while Type 2 receptors are presynaptic (Lord et al, 1977). Although visualization is still not technically possible, this hypothesis would seem intuitively possible since for most of the brain, type 1 binding is 2 - 3 times as great as type 2

binding. It seems likely that most opiate receptors would be postsynaptic and follow the distribution and characterization of the Dopamine systems (Gardner et. al. 1980).

Another possible means of interaction between the opiate system and ICSS system may be through regulation of CAS. Localization of enkephalinergic systems has revealed that they exist in close proximity to previously known catechloamine-containing systems. Enkephalins may even be found within the same cells as certain biogenic amines. This is particularly true in areas of the median eminence of the hypothalamus, the basal ganglia and the nucleus locus coeruleus.

The enkephalinergic fibers interact with noradrenergic systems as well, in the LC and the A2 area (Pollard et al, 1977) as shown by immmunocytochemical and light microscopic techniques. The nucleus LC has also been found to be rich opiate receptors as shown by autoradiography. Microiontophoresis of opiates onto LC neurons causes a depression of neuronal firing which can be blocked by naloxone (1). Thus, it seems possible that incoming enkephalinergic fibers to the LC regulate the activity of noradrengergic neurons in this nucleus.

Using this information we predicted that morphine's effects on the reward system would be via the LC. Morphine administration would activate this endogenous opiate system which in turn would stimulate the high number of opiate

recpetors in the LC area. The stimulation of these opiate receptors would in turn excite or inhibit the CA systems from the LC area that were necessary for sustaining hypothalamic ICSS. If we assume that the LC is one possible area for the interaction of the opiate system and ICSS system, then lesioning the LC would remove the area of interaction and should render morphine ineffective in ICSS areas that are dependent upon the intact LC. This prediction however, was not totally confirmed. Surprising results did emerge. Post-lesion ICSS rates from the H2FF, ZI, MT and ant. and vent. thalamus which were depressed following the lesion were facilitated to prelesion saline levels under morphine administration, but not prelesion morphine levels.

One can theorize that destroying the LC removed the site of interaction for the opiate and ICSS system and thereby rendered morphine not as effective as it was prelesion. The fact that morphine was still capable of exerting some effect of ICSS rates can be explained in the following way: (1) the DA nigrostriatal system was left intact and it is possible that morphine exerted its influence via this system when stimulating electrodes were in the H2FF and ZI. (2) When stimulating electrodes were in the MT and ant. and ventral thalamic nuclei morphine may have been exerting its effects directly on this enkephalinergic pathway since these areas are high in opiate receptor density and have already been postulated as forming a separate opiate system (Snyder et

al, 1975; Uhl et al, 1978; Atweh, 1977). (3) Post-lesion ICSS rates from the MFB were unaltered by the LC lesion. Morphine facilitations post-lesion was comparable to prelesion effects. This area then would seem to rely on a different system, namely the ventral LC system. Mattiace (1981) has shown that MFB stimulation rates are increased after ventral bundle lesions. The ventral bundle (areas A1, A2, and A5) does send efferents to the LC area but contributions are minimal. The MFB is comprised of a massive fiber system but it has been shown to be assoicated with enkephalin containing cell bodies (Atweh et al 1977). Also, the ventral bundle A2 area has been shown to contain opiate receptors. it is possible that the interaction of the ICSS and opiate systems for the MFB is in the ventral bundle and constitutes yet another, separate reward system.

(4) The one truly surprising result was that morphine administration was ineffective in altering ICSS rates in the CC-IC area pre and post lesion of the LC. It is possible that this area is simply not part of the endogenous opiate system. Since there are very few enkephalin cells or opiate receptors in this area, activation of the LC area could not cause an interaction in this site postsynaptically since there are no receptors for interaction in the IC-CC area.

ICSS rate facilitations are not a new phenomenon. A number of researchers have reported facilitations in ICSS rates following morphine administration (Lorens and Mitchell 1973, Maroli, 1978, Nelson et. al. 1981, Eposito and

Kornetsky, 1977).

It has been suggested that CA containing neurons may have a critical role, perhaps providing a final common pathway in mediating the reinforcing effects of both opiates and SS. It has been shown that both morphine (Smith et. al, 1970, 1972) and SS (Saint-Laurent et. al., 1975) produce an increase in the turnover of CAS in many of the brain structures which are anatomically related to the MFB. Administration of AMPT, (a tyrosine hydroxylase inhibitor which depletes CAS) has been found to supress SS (Gibson et. al., 1970, Saint-Laurent et. al., 1973) and to block the self-administration and reinforcing properties of IV injections of morphine (Davis and Smith, 1972, 1973). Therefore, it seemed reasonable to suspect that techniques employing ICSS might help bridge the gap between behavioral theories of drug addiction and underlying neurophysiological processes. To the degree that morphine acquires reward value through the ICSS system, one would expect to find changes in ICSS as a result of drug administration.

At high doses, the main effect of morphine has been to depress ICSS rates for 2 - 3 hours after administration. Excitatory effects on ICSS rates follow the depressions. These depressions in rates are not necessarily related to the rewarding value of brain stimulation. These high doses used produce rigidity and catatonia and the depressions in rates results from motor incapacitation. This 2-fold drug effect is known as the morphine biphasic effect and it helps

to clarify seemingly contradictory results that have been obtained from other investigations.

Since the discovery of the opioid pentapeptides known as the enkephalins and related larger opioid peptides of the endorphin class (Guillem, 1978; Hughes et al, 1975) intensive investigation into the localization and neurobiological properties of these substances has taken place. There is good reason to believe that the enkephalins act as some type of neurotransmitter or neuro-modulator. There is now evidence suggesting that endorphins and enkephalins exert their effects via actions on dopamenergic systems. Their cataleptic (Bloom et al, 1977) and neuroendocrine effects (Meites et al, 1979) are indicative of this.

A number of investigators have suggested that one or another type of opioid peptide or endorphin may have a role in psychiatric disorders such as schizophrenia and depression. In schizophrenia, there is evidence for both an excess and a deficiency of endorphin acitivity (Watson et al, 1979b; Verebey et al, 1978). Certain opioid substances are hallucinogenic. Rats given B-endorphin exhibit catatonic behavior (Bloom et al, 1976). Others have reported that endorphin fractions are elevated in the CSF of unmedicated schizophrenic patients and return toward normal when the patients are medicated (Wahlstrom et al, 1976; Terenius et al, 1976; Lindstrom et al 1978). There is also a report of increased CSF concentrations of B-endorphin in

acute, but not in chronic schizophrenic patients (Domschke, W., 1979).

Others found improvement in schizophrenic patients following naloxone, a short acting opioid antagonist (Watson et al, 1978; Emrich et al, 1977; Usdin et al, 1979; Lehman et al, 1979). Emrich et. al. reported decreased hallucinations, Davis et. al. found general visual thought content, while Lehrman et. al. describe general improvement in psychotic behavior after naloxone administration. Others have not found effects (Janowsky et al, 1977; Volavka et al, 1977; Kurland et al, 1977) perhaps because of lower doses of naloxone.

Animal studies with haloperidal have suggested that this antipsychotic increases the amount of enkephalin available in certain brain areas (Hong et al, 1978). Age et. al. (1979) reported that a met enkephalin analog decreased pschotic symptoms. An amelioration of schizophrenic symptoms following B-endorphin was reported by Kline and Lehrman (Usdin et al, 1979).

Fink et. al. (1970) were the first to report that the narcotic antagonists might be beneficial in depressive illness. Terenius et. al. (1977) administered naloxone to depressed patients and found no effects on mood levels. Kline et. al. (1979, 1977) reported transient improvement with B-endorphin, while Angst et. al. (1979) found mania or hypomania with B-endorphin. Terenius et. al. (1976) also reported elevations of CSF fractions 1 and 2 in

manic-depressive illness for both manic and depressive phases. Some researchers report anti-manic effects with naloxone (Janowsky et al, 1978, 1979) while others do not (Emirch et al, 1979; Dewied et al, 1978).

Catatonic schizophrenia has been linked to opiates and B-endorphin (Bloom et al, 1976; Jacquet et al, 1976). Schenk et. al. administered naloxone and reported immediate improvement, while Abrams et. al. (1978) did not observe improvement in catatonia.

Research uncovering the relationships of endorphins to pituitary endocrine function seem relevant to clinical studies. Opiates, narcotic antagonists and endorphins influence ACTH, prolactin, growth hormone, vasopressin and leutenizing hormone. Alterations of each of these hormones have been associated with affective illness or schizophrenia. The relationship of endorphins or hormonal release or irregulation may uncover behavior-dependent symptoms in these illnesses.

B-endorphin has been found to be a potent antinociceptive agent and to exhibit cross-tolerance and cross-dependence to morphine (Li et al, 1977; Loh et al, 1976; Tseng et al, 1976). B-endorphin also produces tolerance in mice and rats (Huidobro et al, 1978; Tseng et al, 1976) and physical dependence in the rat after infusion into the PAG area (Wei et al, 1976). It has been of interest, therefore, to study the effects of b-endorphin in humans and examine its ability to surpress the signs and

symptoms of opiate withdrawal (Su et al, 1978).

As little as 2 mg. of naloxone induce an inconsistent improvement in tremor and ridigity of Parkinson patients while bradykinesia tends to worsen (Ruggieri et al, 1979). A higher dose of 8 mg. induces a constant improvement. In parkinson patients, low doses of naloxone could elevate the release of both DA and ACH release, causing improved symptomotology and worsening of bradykinesia.

Recent data suggest that opiate receptors and opiod peptides play a role in certain seizure phenomena as well. Liebeskind (Urca et al, 1977) reported that met enkephalin injected into the lateral ventricle of awake rats elicited epileptic activity in cortical EEG. This was accompanied by "wet dog" shakes and mioclonic twitches but not by full motor convulsions. In (Frenk et al, 1978) the same activity was found with leucine-enkephalin. Also, morphine injected in the lateral ventricles caused similar behaviors which were naloxone reversible.

Analgesia was never obtained with the enkephalins but was with morphine. Met enkephalin (Frenk et al, 1978) injected into ventral but not dorsal PAG caused analgesia. No thalamic injections of enkephalin caused analgesia, while they did cause seizure activity. These authors suggest that seizures are mediated by enkephalin's interaction with receptors in the forebrain and analgesia by enkephalin's interaction with mu receptors in the PAG area.

Tolerance and cross-tolerance have been found for the

seizure-producing effects of enkephalin and morphine (Elazar et al, 1979; Tortella et al, 1979). When normal regulatory processes are disrupted endogenous enkephalin may play a role in causing epileptic phenomena (Urca et al, 1977). Snead and Beardeu (1980) have demonstrated that petit mal seizures provoked by the GABA metabolite, GABA-hydroxy-butyrate are blocked by naloxone. Also, drugs effective against petit mal epilepsy are potent blockers of enkephalin induced seizures, suggesting that the enkephalins are involved in this disorder.

Hong et. al. (1979) found that repeated ECS blocks caused a 100% increase of met-enkephalin content in the hypothalamus, n. accumbens, septum and amygdala. In other areas, hippocampus and lower brain stem no changes were seen. In the hypothalamus where met-enkephalin levels were doubled, B-endorphin levels were unchanged.

Opiate and opioid seizures are mediated by opiate receptors that are pharmacologiaclly different from those mediating analgesia. Mudge (1979) reported that enkephalin decreases calcium influx in dorsal root ganglion neurons. Chapman and Wey (1980) present evidence on the calcium depleting action of morphine and opiod peptides. Thus, it seems possible that the epileptic properties of morphine and opioid peptides derive from their ability to reduce calcium influx and thereby alter membrane excitability and/or transmitter release in neurons influencing seizure production.

An Endorphin-Mediated Analgesia System

Although the brain may have more than one pain-modulation mechanism (Hayes et al, 1978) we know most about an analgesia system with links in midbrain, medulla and spinal cord. Early studies have shown that the midbrain PAG is a site which when electrically stimulated, can produce supression of responses to noxious stimuli (Stimulation-produced-analgesia - SPA). Thus SPA has been observed in many species (Martin et. al., 1978; Mayer et. al., 1974) including humans (Adams, 1976; Hosobuchi et. al., 1977; Meyerson et. al., 1979; Richardson et. al., 1977; 1977a). The observation that analgesia could be produced by electrical stimuation of certain discrete sites is important in establishing pain modulation as a function of the CNS.

There is evidence that 5-hydroxy tryptamine is involved in analgesia mechanisms (Messing et. al., 1977). Both B-endorphin (Bloom et. al., 1978; Watson et. al., 1977; 1977a) and enkephalin (Elde et. al., 1976; Glazer et. al., 1979; Hokfelt, 1977; Hong et. al., 1977; Sar et. al., 1978) immunoreactivity are present in the PAG. Enkephalin cell bodies are located in PAG and b-endorphin cells are restricted to medial basal hypothalamus (arcuate nucleus). The PAG area also contains a high concentration of opiate receptors (Atweh et. al., 1977; Hiller et. al., 1973; Hokfelt et. al., 1977). Opiate (Yaksh et. al., 1976; 1978) and met-enkephalin (Loh et. al., 1976; Meglio et. al., 1977)

injections in this area produce a naloxone reversible analgesia. Thus, endorphins are present in PAG and can be released upon electrical stimulation.

The spinal cord dorsal horn is relevant to the analgesic enkephalin systems as well. Direct applications of opiates produce analgesia (Yaksh et. al., 1978; 1976; Wang et. al., 1979).

An early finding of considerable interest was the demonstration that opiates induce analgesia from the rat PAG. This supported the notion that SPA and opiate analgesia share common sites and mechanisms of action. Some researchers confirm this finding (Adams, 1976; Hosobuchi et. al., 1977; Oliveras et. al., 1977) and others do not (Pert, 1976; Yaksh, 1976). Liebeskind et. al (1980) indicates that descrepancies are due to where in the PAG the electrodes are located. In order for naloxone to reverse SPA, the electrodes must be placed in the ventral PAG, not dorsal PAG. This evidence, along with others (Hayes et. al., 1978; Lewis et. al., 1980; Mayer et. al., 1976) suggest that analgesic mechanisms exist that are independent of opioid peptides. Another interesting difference is that b-endorphin containing fibers are found in much heavier concentration in ventral than in dorsal PAG (Bloom et. al., 1978; Watson et. al., 1978), the ventral area being the one which is naloxone sensitive.

The b-endorphin and naloxone have higher affinities for the "u" opiate receptor than do the enkephalins (Lord et.

al., 1977). It has already been suggested that "u" receptors in the PAG are involved in opiate analgesia (Frenk et. al., 1978). Akil et. al. (1980) reported that b-endorphin disassociates from the opiate receptor at a much slower rate than the enkephalins.

In summary, opiates or "morphine-like" drugs exert a wide range of pharmacological effects, in addition to analgesia. They have been implicated in psychiatric disorders such as schizophrenia and depression, seizure and epileptic activity and have been implicated as neuroregulatory agents in CA systems involved in CNS reward. This wide diversity of behavioral effects raises the question as to whether these effects could be mediated by a single class of receptor sites.

Heterogeneous opiate receptor populations were postulated by Martin and coworkers (1976) on the basis of neurophysiological and behavioral evidence. Striking differences in pharmacological responses to different types of narcotic analgesics and their inabilities to substitute for one another in the supression of withdrawal symptoms in addicted animals provided evidence for at least 3 receptor types in the dog CNS. These were termed (1) mu receptors with which morphine-like drugs preferentially interact (2) Kappa receptors with which some benzomorphans such as ketocyclazocine interact and (3) Sigma receptors (SKF-10,047). Effects associated with mu receptors included meiosis, bradycardia, hypothermia and analgesia. Effects

characteristic of the K receptor included pupillary constriction and sedation. The syndrome involved mania or "cannine delirium" which Martin proposed to be the equivalent of psychotomimetic effects in man.

In pharmacological and biochemical investigations of the guinea pig brain and ileum and mouse vas deferens, Kosterlitz et. al. (1978) provided evidence for yet a fourth opiate receptor type. They postulated the delta receptor to be the site at which the shorter enkephalin peptides interact. Recently, further biochemical evidence for mu and delta receptors indicate that these have different distributions throughout the brain (K. J. Chang and P. Cuatrecasas, 1979, Simantov et. al., 1978, Leslie et. al., 1980). The thalamus and hypothalamus were shown to be relatively enriched in mu receptors, while frontal cortex and striatium have equal densities of all types. The high affinity site for the classical opiates such as morphine has been found to be the mu receptor. The sigma receptor seems to interact with phencyclidine (PCP or "angel dust") mimicking signs and symptoms of schizophrenia. This receptor site was unresponsive to morphine, amphetamine and naloxone. Thus, it would appear that opiates much like CAS, exert their diverse pharmacological actions by interacting with multiple receptor sites Morphine is ineffective in binding to delta and kappa sites and these receptor sites do not respond to antagonists either.

It is possible that part of the reason for diverse

opiate effects on ICSS is that different neuroanatomical ICSS areas have different opiate receptor types. The original opiate distribution maps were not able to differentiate between these multiple opiate receptors. In view of the recent findings, it is possible that the lateral hypothalamus, thalamic nuclei, FF and ZI contain mu receptors for morphine-opiate interactions. The IC-CC area did not respond to morphine. A possible explanation for this would be that the fewer opiate receptors that have been localized along the borders of the IC area are not the same receptor type and therefore will not respond to any opiate, including morphine.

It is obvious that the questions raised by this study can only be answered by further experimentation. The new biochemical technology emerging now and still to be developed will aid in our understanding of this complicated issue. One obvious study to be done is to map out the localization of the "4" opiate receptor types throughout the brain. It now seems likely that each opiate receptor type is responsible for one opiate system, i.e. one system for analgesia, one for psychiatric disorders, one for seizure activity and one for morphine and opiate drug interactions. It is this fourth system that would interact with the ICSS reward system perhaps via the catecholamine systems. One place of interaction could be the nucelus locus coeruleus giving rise to the DNB, while yet another place of interaction could be the ventral bundle originating in the

A2 area of the hindbrain and forming its own separate opiate-ICSS network.

To summarize, the LC lesions differentially effected hypothalamic self-stimulation, decreasing rates in some sites and not altering rates in others. These effects were produced by small, discrete, unilateral lesions, distant from the stimulation site. These findings replicate other findings from our laboratory (Farber et. al., 1976) and extend them to a new self-stimulation site, the ventral thalamus. These results again show that self-stimulation can be affected by a distant site and that the reward system is not necessarily "redundant and capable of reorganization and recovery".

The MFB area stands out as a unique self-stimulation site. Not only was the LC lesion ineffective in altering rates in this area, but the MFB area responded differently to the isomers of amphetamine than did the other self-stimulation sites. All other sites were more sensitive to the d-isomer. The MFB area was equally sensitive to both the d- and l- isomers of amphetamine.

Morphine differentially affected varying ICSS sites as well. Facilitations in response rates were found in the H2 FF, ZI, MT, ventral thalamus and MFB-PF areas. The IC area was not responsive to morphine administration. These results, then, lend support to the idea that there may be several reward-ICSS systems and that they can be differentially affected by LC lesions, morphine

administration and amphetamine administration.

TABLE 1

Extent of LC Lesion for each subject.

S#	LEVEL	LC	DB	VB	MLF	MESC V	SCP-BC	DTN
82L	Anterior Pons	-	-	-	-	-	-	-
	Transitional Area	+	-	-	-	-	+	-
	Posterior Midbrain	-	-	-	-	-	-	-
52M	Anterior Pons	+	+	-	-	-	-	-
	Transitional Area	+	+	-	+	-	+	+
	Posterior Midbrain	-	-	-	+	-	+	-
38M	Anterior Pons	-	-	-	-	-	-	-
	Transitional Area	+	+	-	-	-	-	+
	Posterior Midbrain	-	-	-	-	-	-	-
17M	Anterior Pons	+	+	-	-	-	+	+
	Transitional Area	+	+	+	-	-	+	+
	Posterior Midbrain	-	-	-	-	-	-	-
46M	Anterior Pons	+	+	-	-	-	+	+
	Transitional Area	+	+	-	-	-	-	+
	Posterior Midbrain	+	+	-	-	-	-	-
95N	Anterior Pons	+	+	-	-	-	+	-
	Transitional Area	+	+	-	-	-	+	-
	Posterior Midbrain	+	+	-	-	-	+	-
9N	Anterior Pons	+	+	-	-	-	-	-
	Transitional Area	+	+	-	-	-	-	-
	Posterior Midbrain	-	-	-	-	-	-	-
17N	Anterior Pons	+	+	-	-	-	-	-
	Transitional Area	+	+	-	-	-	-	-
	Posterior Midbrain	+	+	-	-	-	-	-

TABLE 1 Con't

S#	LEVEL	LC	DB	VB	MLF	MESC V	SCP-BC	DTN
10N	Anterior Pons	+	+	-	-	-	-	+
	Transitional Area	+	+	-	-	-	-	+
	Posterior Midbrain	+	+	-	-	-	-	-
83N	Anterior Pons	+	+	-	-	-	-	-
	Transitional Area	+	+	-	-	-	-	-
	Posterior Midbrain	-	-	-	-	-	-	-
88L	Anterior Pons	-	-	-	-	-	-	-
	Transitional Area	-	-	-	-	+	-	-
	Posterior Midbrain	-	-	-	-	-	-	-
42M	Anterior Pons	-	-	-	-	-	-	-
	Transitional Area	-	-	+	-	-	+	-
	Posterior Midbrain	-	-	-	-	-	+	-
26M	Posterior Pons	-	-	-	+	-	-	+
	Anterior Pons	-	-	-	-	-	-	
	Transitional Area	-	-	-	-	-	-	-
43M	Anterior Pons	-	-	-	-	-	-	-
	Transitional Area	-	-	-	-	-	-	+
	Posterior Midbrain	-	-	-	D.R.	-	+	-
6N	Anterior Pons	-	-	-	-	-	-	+
	Transitional Area	-	-	-	-	-	-	+
	Posterior Midbrain	-	-	-	-	-	-	-
45N	Anterior Pons	-	-	-	-	-	-	-
	Transitional Area	-	-	-	-	-	-	-
	Posterior Midbrain	-	-	-	-	-	-	+

TABLE 1 Cont

S#	LEVEL	LC	DB	VB	MLF	MESC V	SCP-BC	DTN
61N	Anterior Pons	-	-	-	-	-	-	-
	Transitional Area	-	-	-	-	-	-	-
	Posterior Midbrain	-	-	-	-	-	+	-
91N	Anterior Pons	-	-	-	-	-	-	-
	Transitional Area	-	-	-	-	-	-	-
	Posterior Midbrain	-	-	-	D.R.	-	-	-
4N	Anterior Pons	-	-	-	-	-	-	+
	Transitional Area	-	-	-	-	-	-	-
	Posterior Midbrain	-	-	-	-	-	-	-

TABLE 2

Hypothalamic ICSS Sites Ipsilateral to Lesion

Subject #	Anatomical Site	Monoaminergic Nuclei or Fibers	Konig & Klippel Atlas
82L	Internal Capsule	Nigrostriatal-DA System	36B
	Ventral Thalamus	Dorsal NE Bundle	39B
52M	Ventral Thalamus	Dorsal NE Bundle	39B
	Zona Incerta	Dorsal NE Bundle,Nigrostriatal-DA System	37B
38M	Ventral Thalamus	Dorsal NE Bundle	37B
	Zona Incerta	Dorsal NE Bundle,Nigrostriatal-DA System	38B
17M	H2 Fields of Forel	Dorsal NE Bundle,Nigrostriatal-DA System	36B
	Ventral Thalamus	Dorsal NE Bundle	38B
46M	Internal Capsule	Nigrostriatal-DA System	36B
	MFB	Mixed System	37B
26M	H2 Fields of Forel	Dorsal NE Bundle,Nigrostriatal-DA System	36B
	Mammillothalamic Tract	Dorsal NE Bundle	37B
43M	MFB	Mixed System	37B
	Ventral Thalamus	Dorsal NE Bundle	37B
6N	MFB	Mixed System	36B
	Perifornical Area	Dorsal NE Bundle,Ventral NE Bundle	35B
45N	Internal Capsule	Nigrostriatal-DA System	35B
	MFB	Mixed System	36B
61N	Internal Capsule	Nigrostriatal-DA System	35B
	MFB	Mixed System	36B
91N	MFB	Mixed System	37B
	Zona Incerta	Dorsal NE Bundle,Nigrostriatal-DA System	38B

TABLE 2 Con't

Subject #	Anatomical Site	Monoaminergic Nuclei or Fibers	Konig & Klippel Atlas
4N	Crus Cerebri	Nigrostriatal-DA System	38B
	H2 Fields of Forel	Dorsal NE Bundle,Nigrostriatal-DA System	36B
95N	Internal Capsule	Nigrostriatal-DA System	36B
	Zona Incerta	Dorsal NE Bundle,Nigrostriatal-DA System	34B
9N	Internal Capsule	Nigrostriatal-DA System	37B
	MFB	Mixed System	36B
17N	Internal Capsule	Nigrostriatal-DA System	36B
	Mammillothalamic Tract	Dorsal NE Bundle	38B
10N	Internal Capsule	Nigrostriatal-DA System	36B
	MFB	Mixed System	36B
83N	H2 Fields of Forel	Dorsal NE Bundle,Nigrostriatal-DA System	36B
	Internal Capsule	Nigrostriatal-DA System	36B
88L	H2 Fields of Forel	Dorsal NE Bundle,Nigrostriatal-DA System	36B
	MFB	Mixed System	36B
42M	Internal Capsule	Nigrostriatal-DA System	36B
	MFB	Mixed System	37B

Table 3

Hypothalamic ICSS Groups

GROUP	AREA	N	SUBJECT #'s
IC-CC Group	Internal Capsule & Crus Cerebri	11	82L,46M,95N,9N,17N,1ØN, 83N,42M,45N,61N,4N
H2 FF-ZI Group	H2 Fields of Forel and Zona Incerta	9	52M,38M,17M,95N,83N, 88L,26M,91N,4N
MFB Group	Perifornical Area and MFB	11	46M,9N,1ØN,88L,42M,43M, 6N,45N,61N,91N,6N
MT and Ventral Thalamic Group	Mammillothalamic Tract and Ventral Thalamus	7	82L,52M,38M,17M,17N,26M, 43M

TABLE 4

Hypothalamic ICSS Group - Lesion vs. Control Group

Group	LC Lesion	Control
IC-CC Group	N=7	N=4
Ss#	95N,83N,1ØN,17N,46M 82L,9N	42M,45N,61N,4N
H2 FF-ZI Group	N=5	N=4
Ss#	52M,17M,83N,95N,38M	26M,88L,91N,4N
MT and VT Group	N=5	N=2
Ss#	17M,82L,38M,52M,17N	26M,43M
MFB and Perf Group	N=5	N=6
Ss#	1ØN,46M,6N,6N,9N	91N,88L,42M,45N,61N,43M

Figure 1

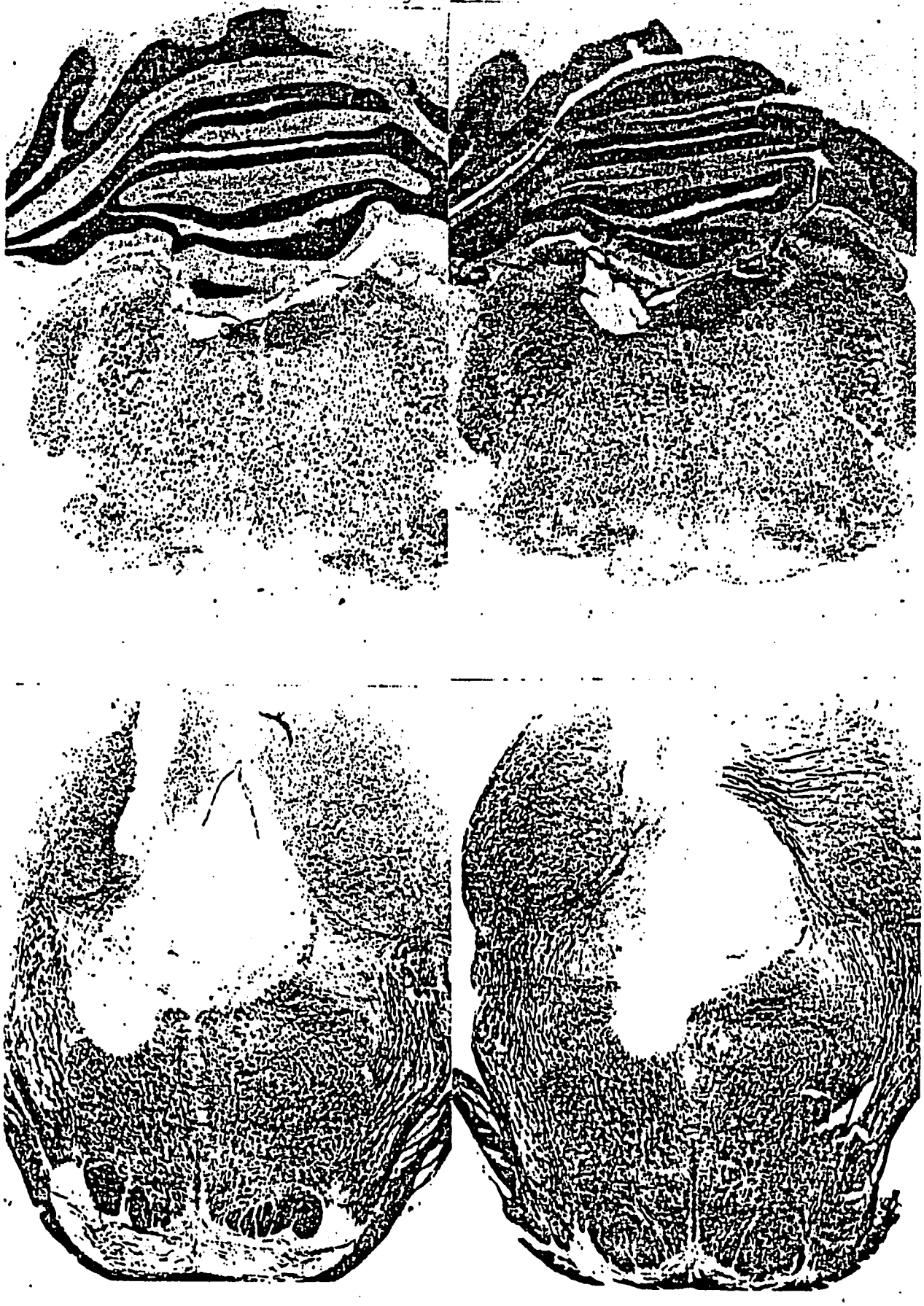


Figure 1 (cont'd)

Figure 1

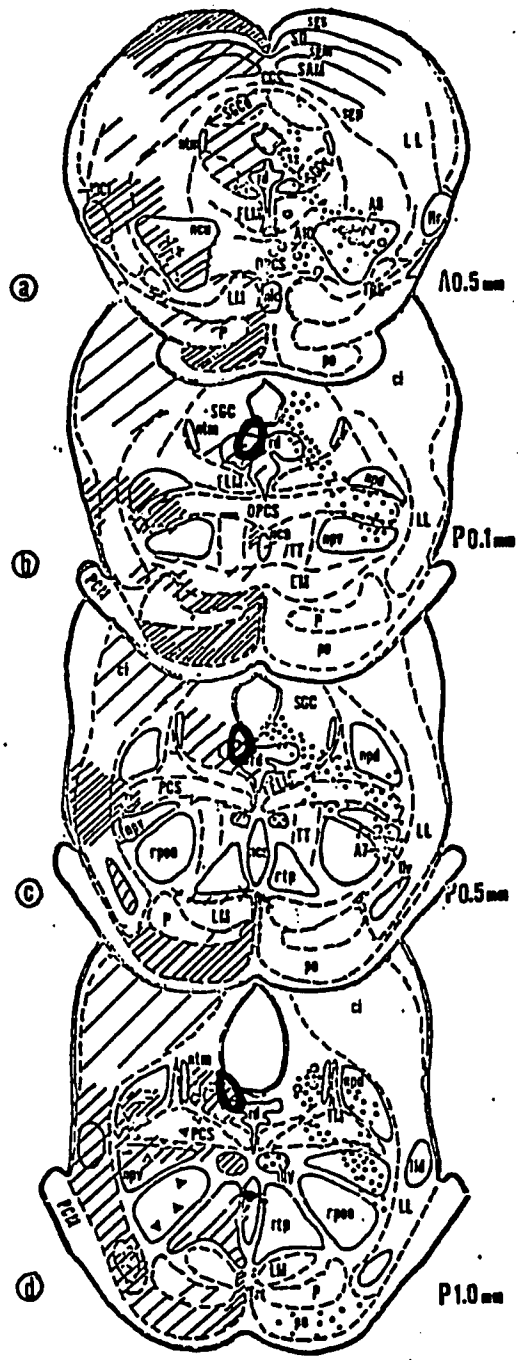


Figure 2

Figure 1

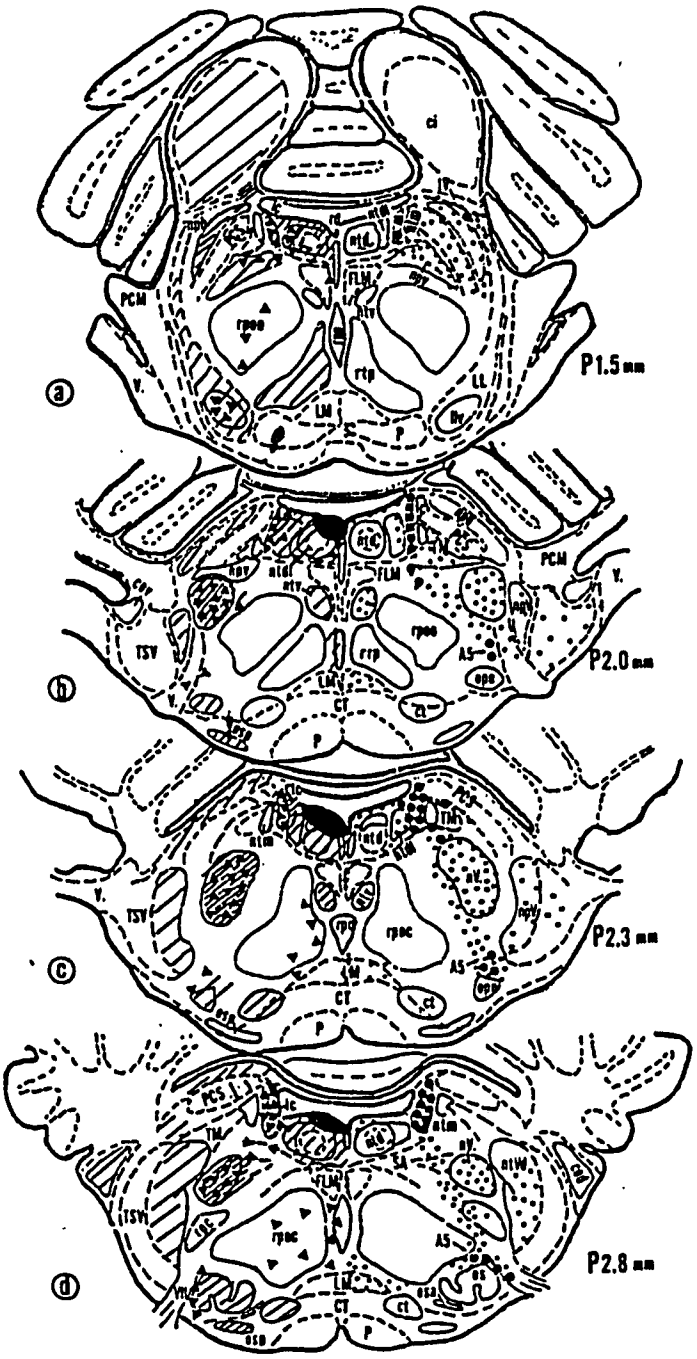


Figure 3

Figure 1

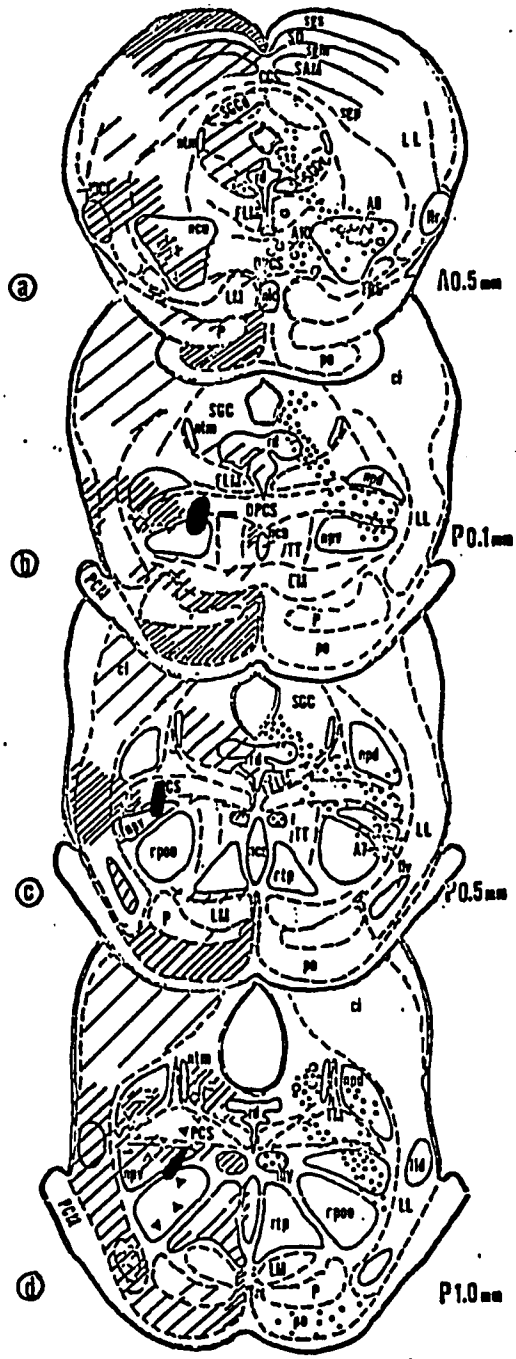


Figure 2

61N

Figure 1

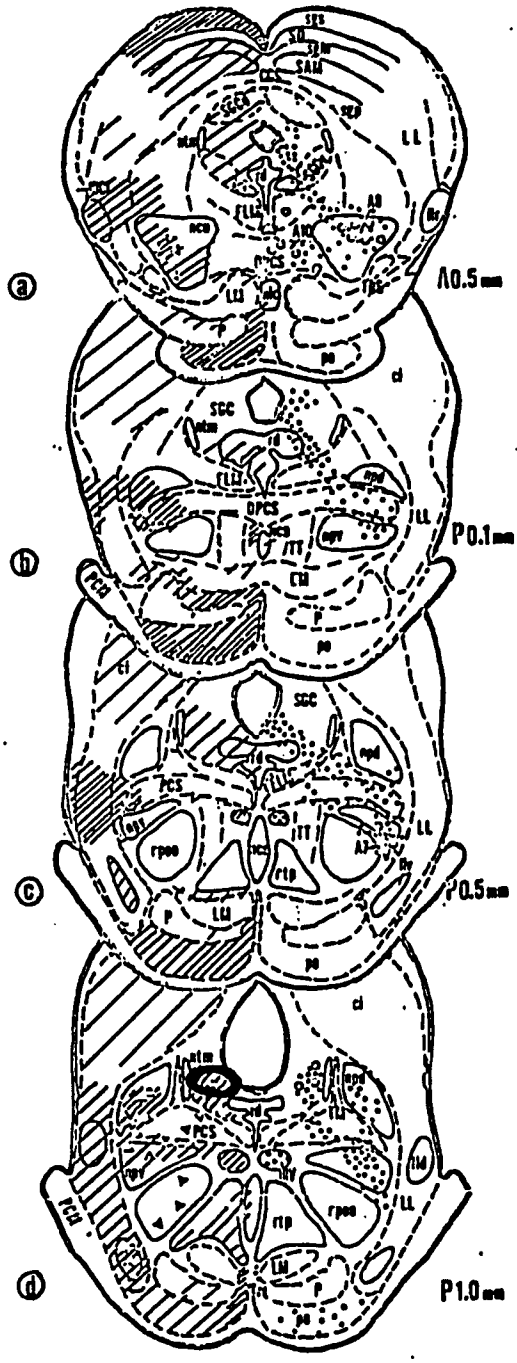


Figure 2

Figure 1

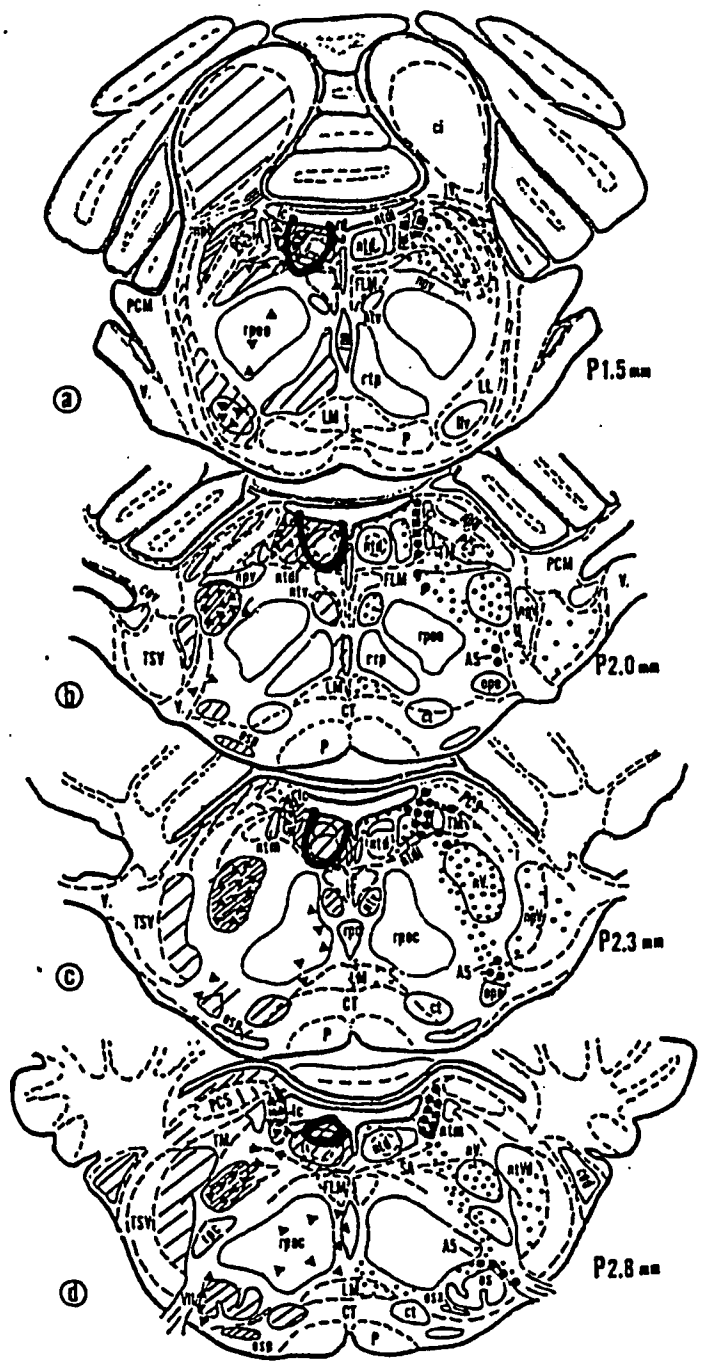


Figure 3

Figure 1

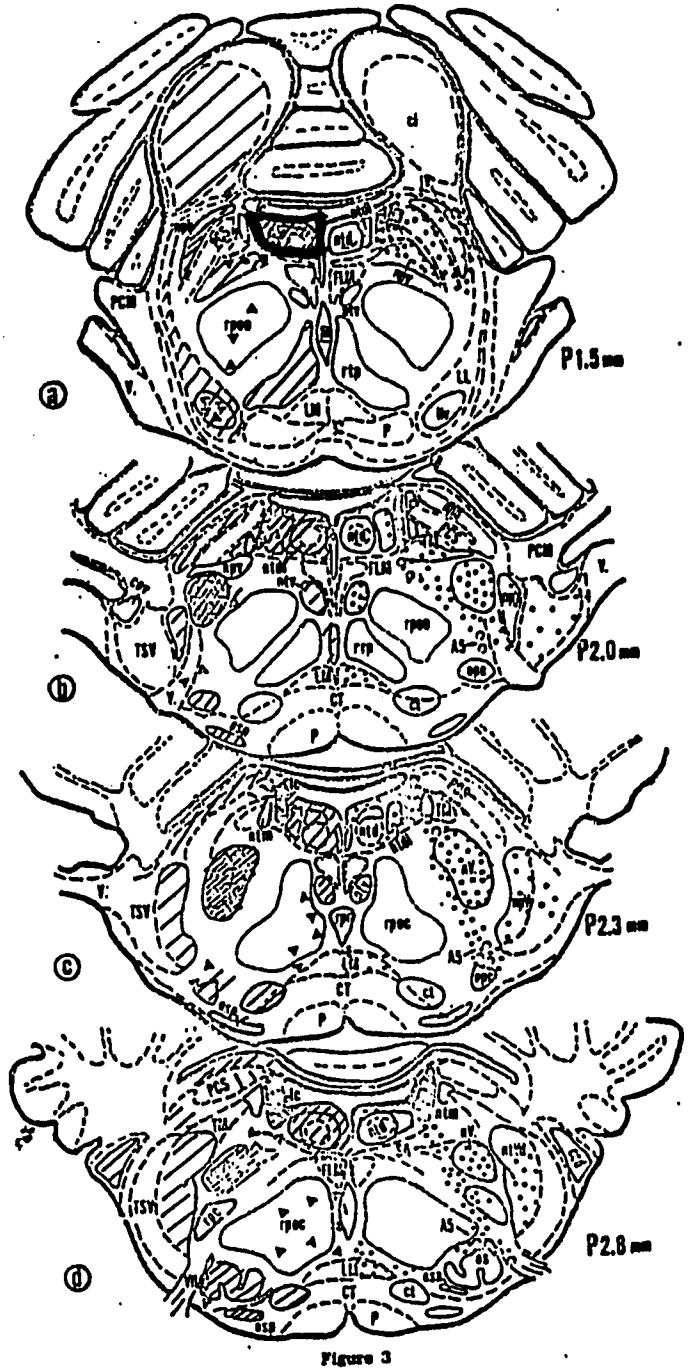


Figure 3

Figure 1

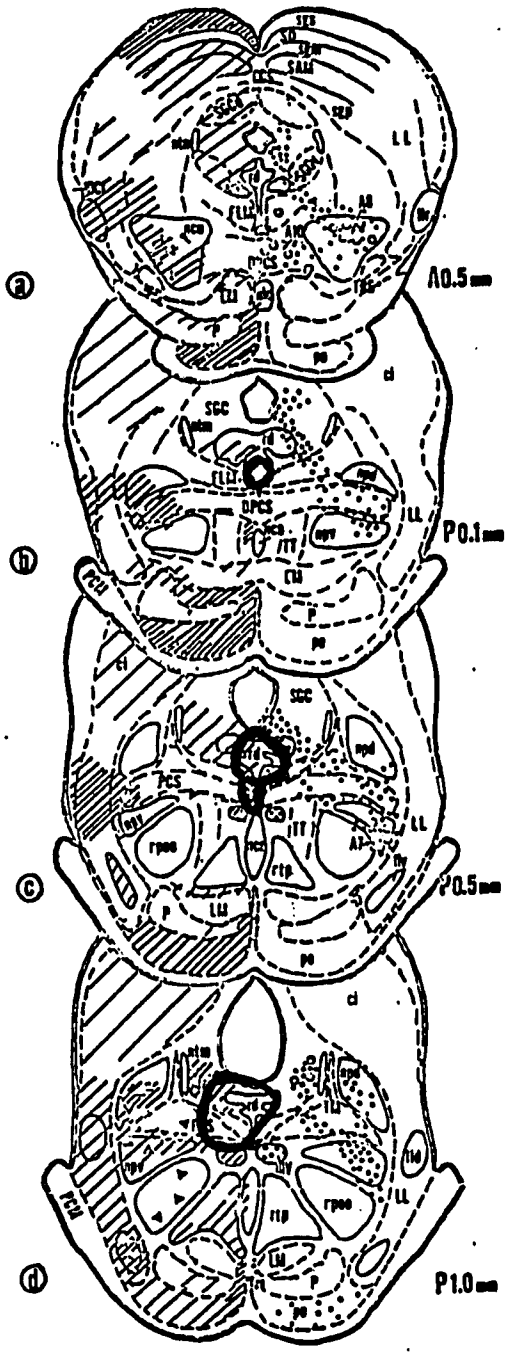


Figure 2

Figure 1

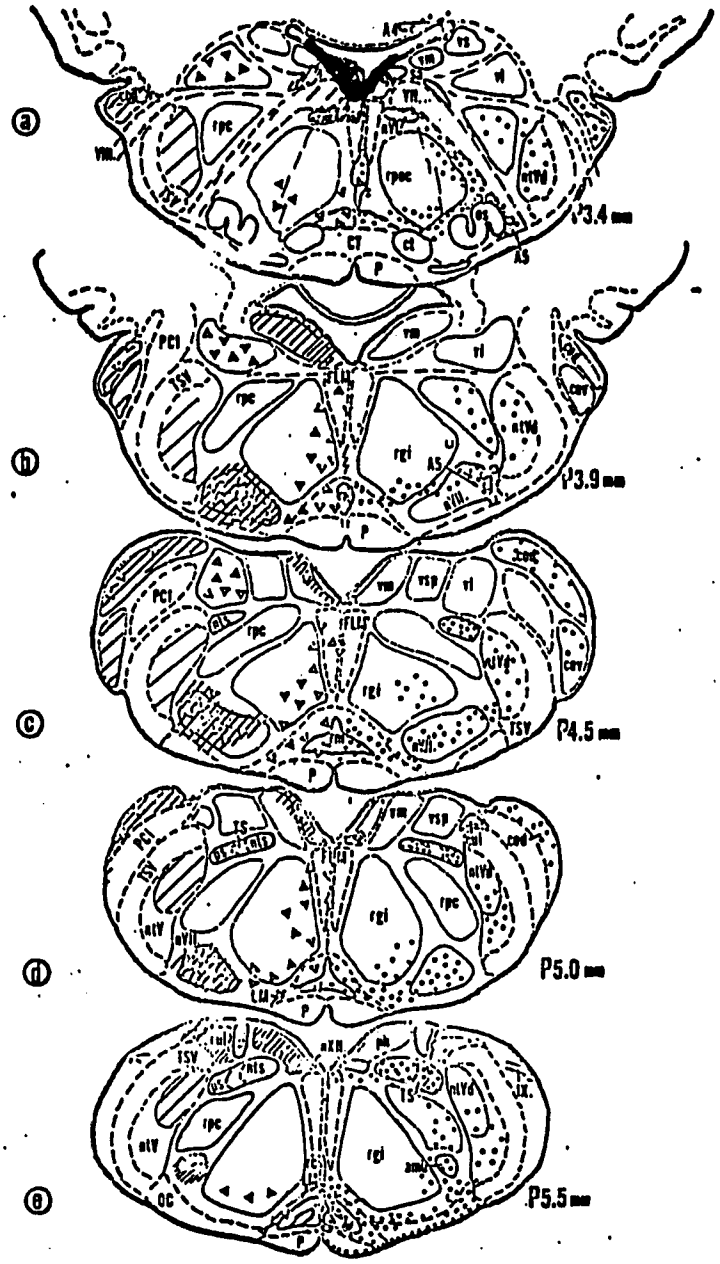


Figure 4

Figure 1

26M

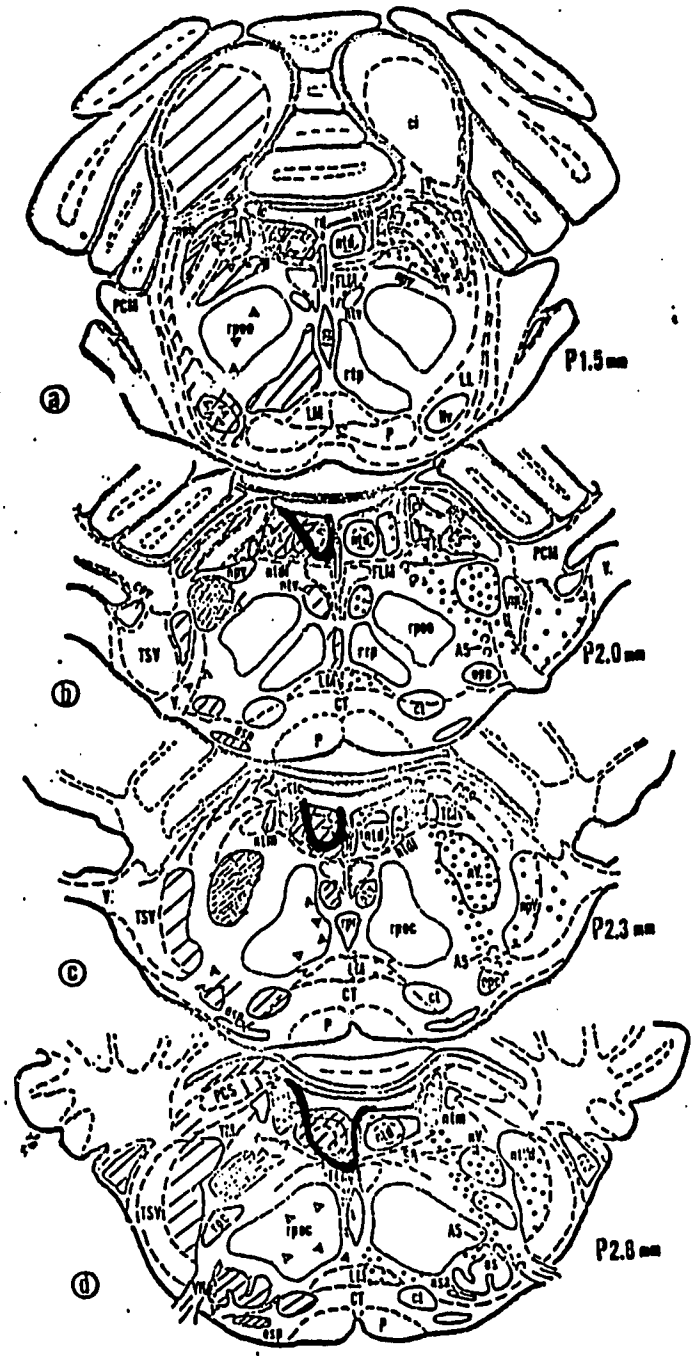


Figure 3

Figure 1

88L

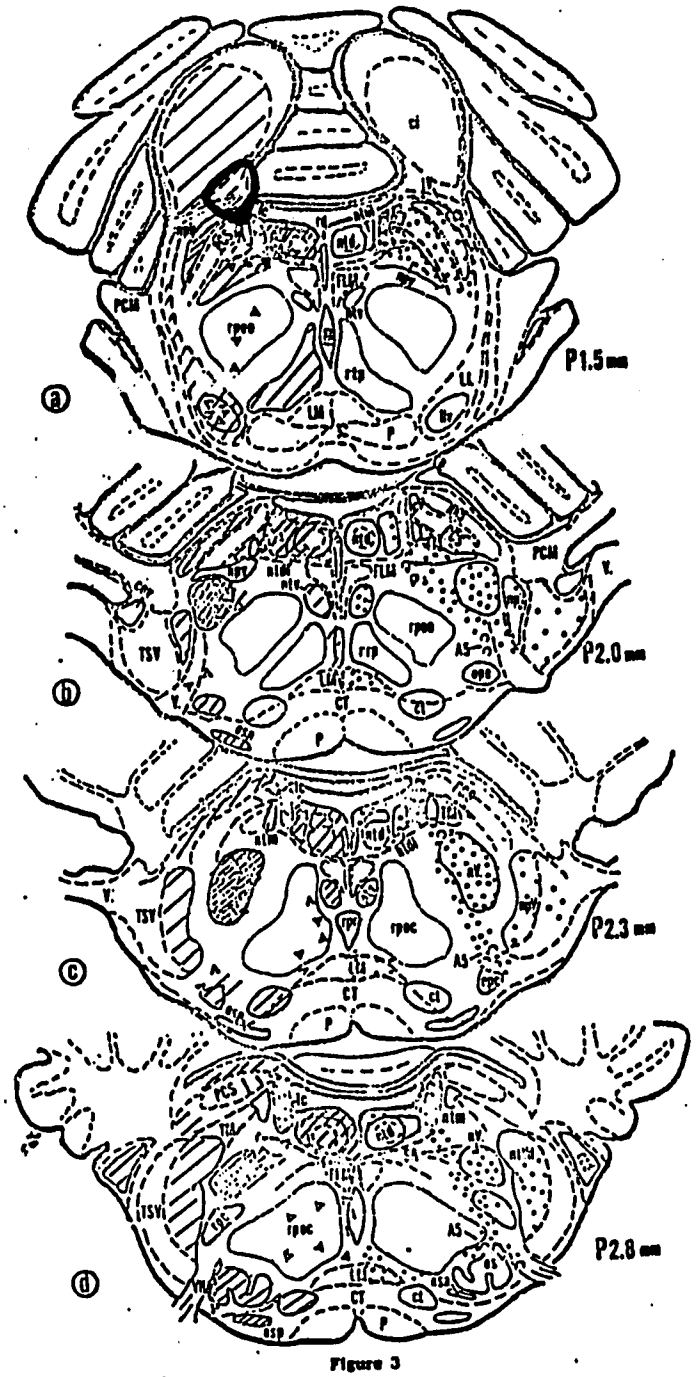


Figure 3

Figure 1

42M

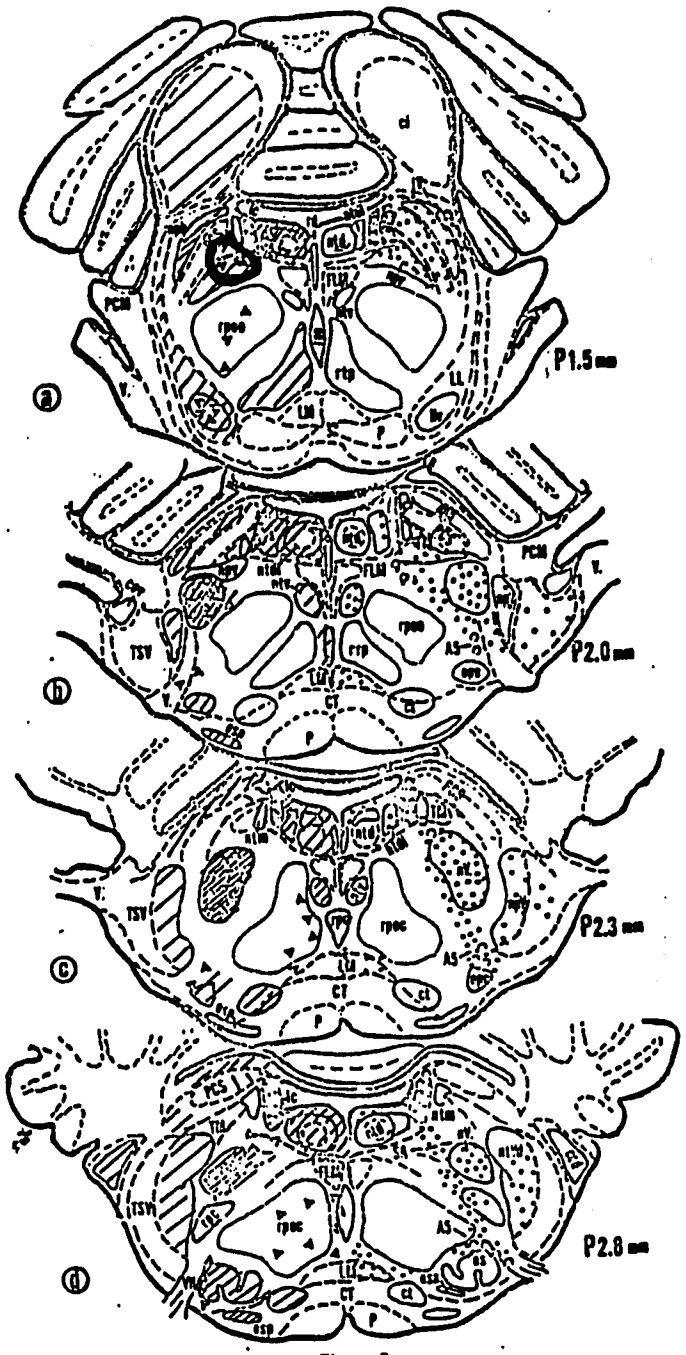


Figure 3

Figure 1

42M

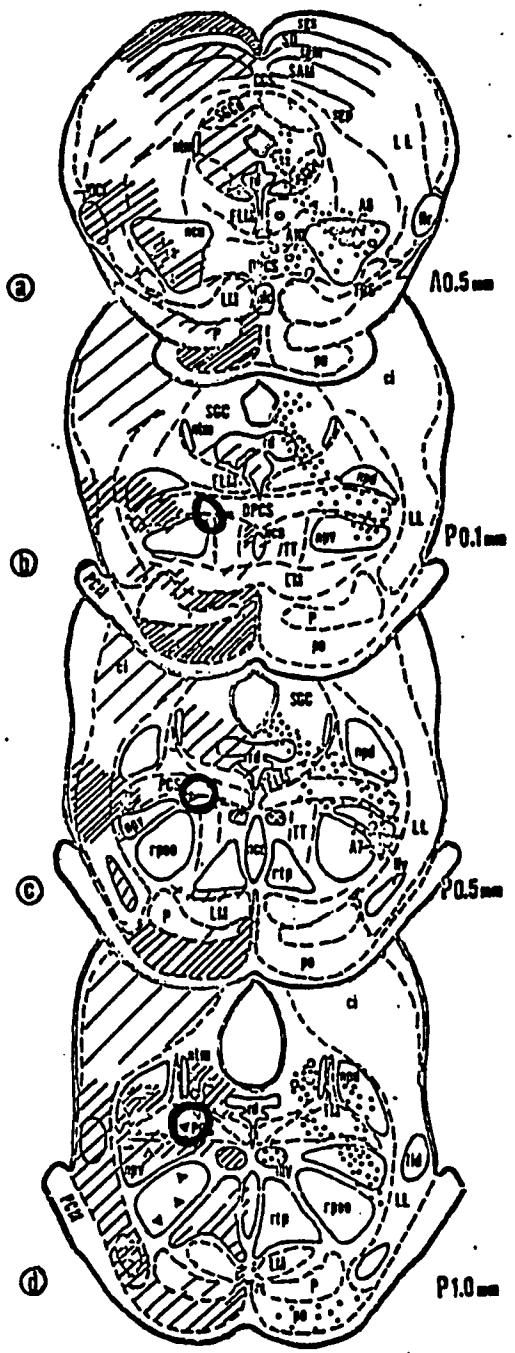


Figure 2

Figure 1

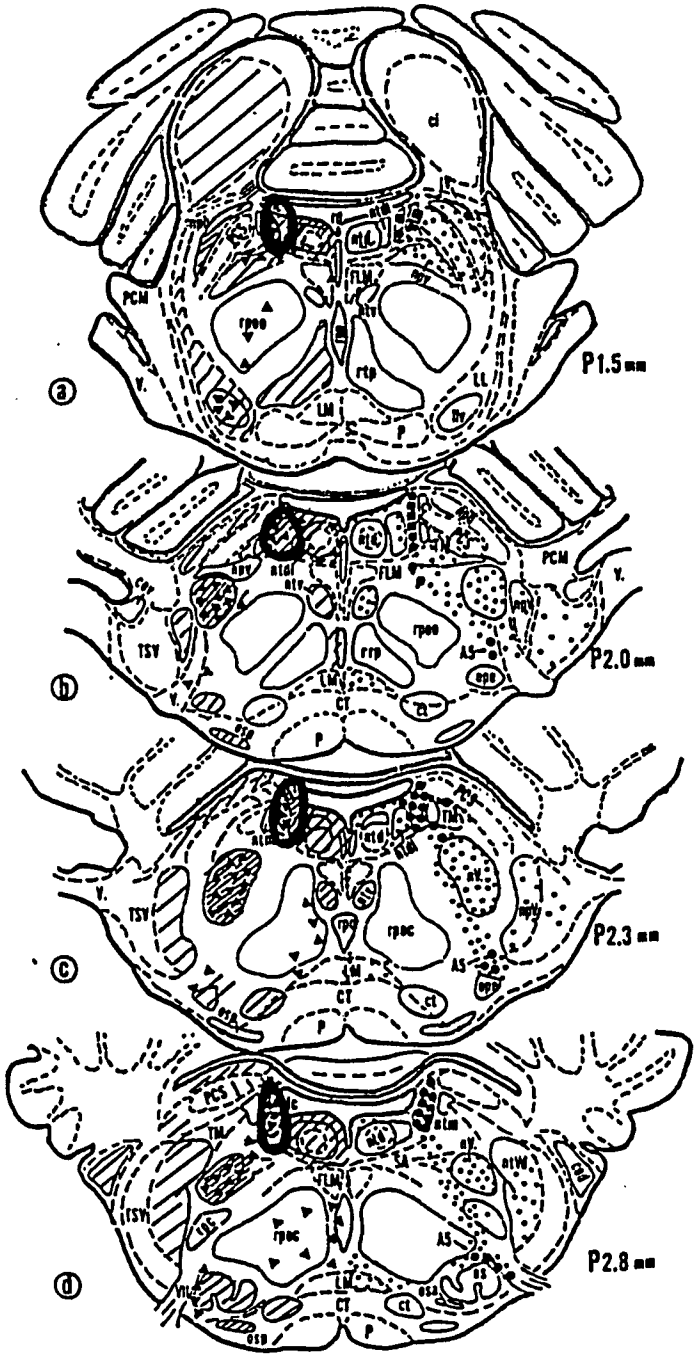


Figure 3

Figure 1

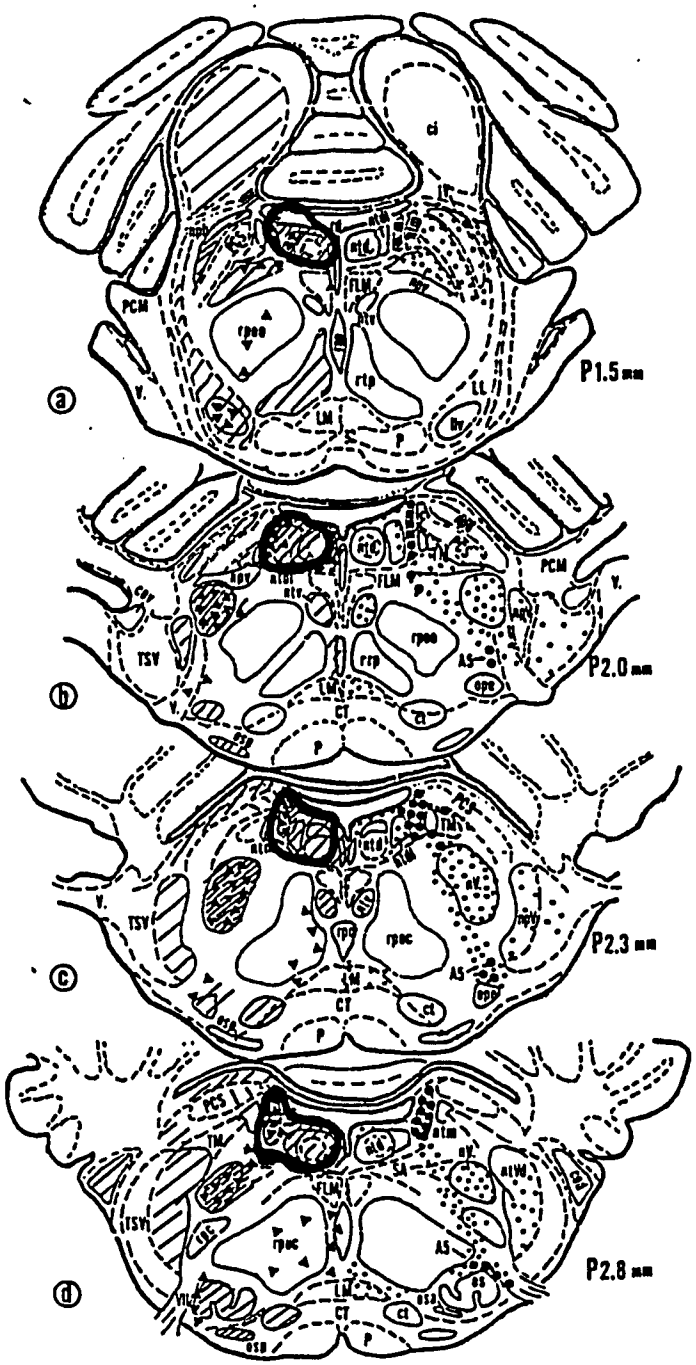


Figure 3

Figure 1

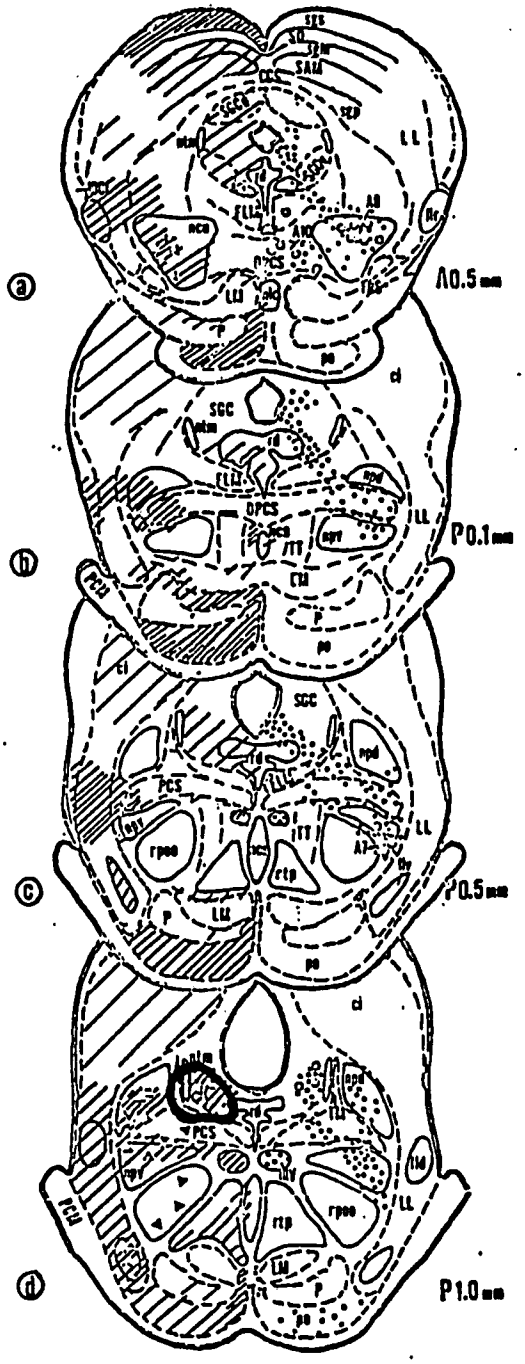


Figure 2

Figure 1

95N

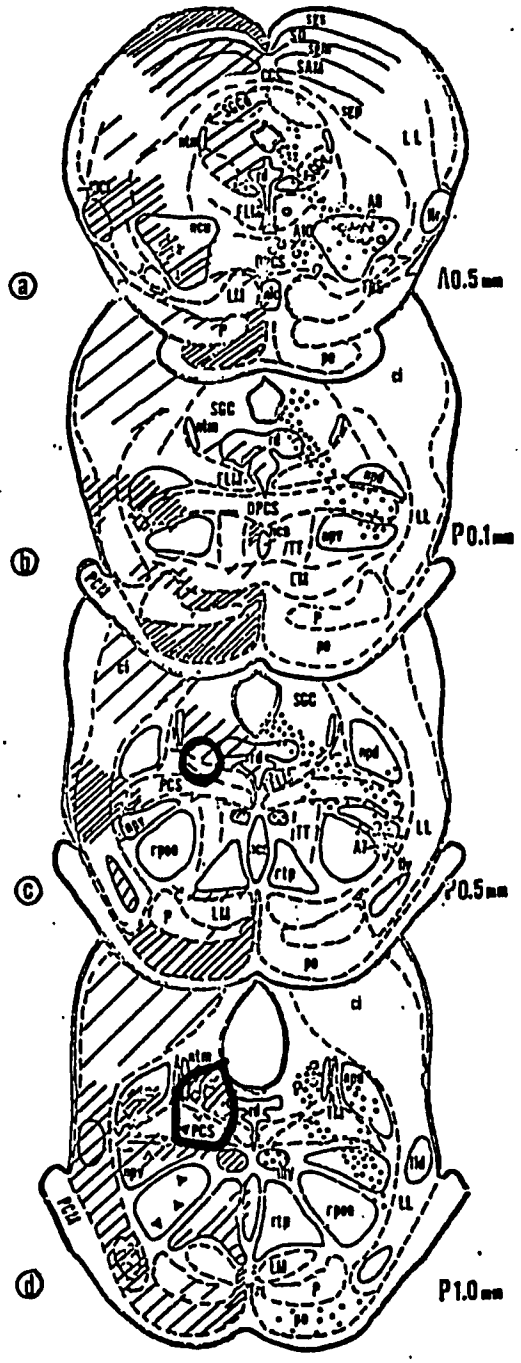


Figure 2

Figure 1

95N

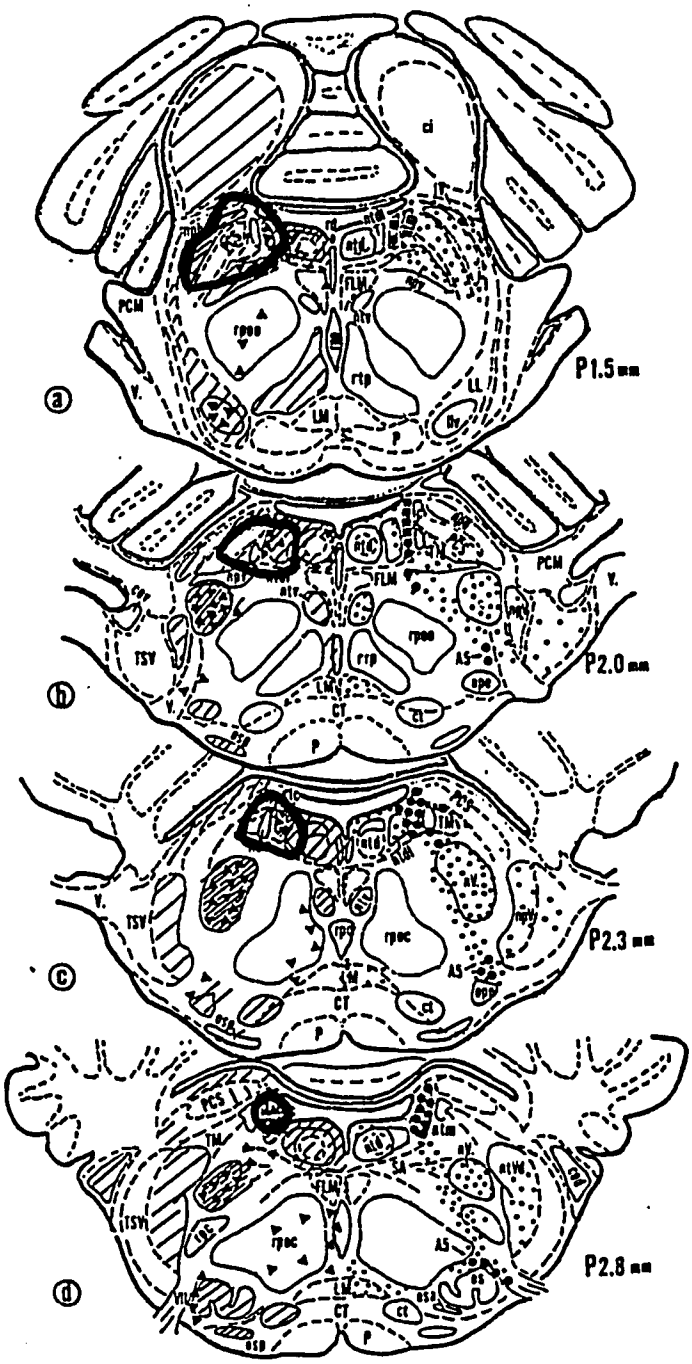


Figure 3

Figure 1

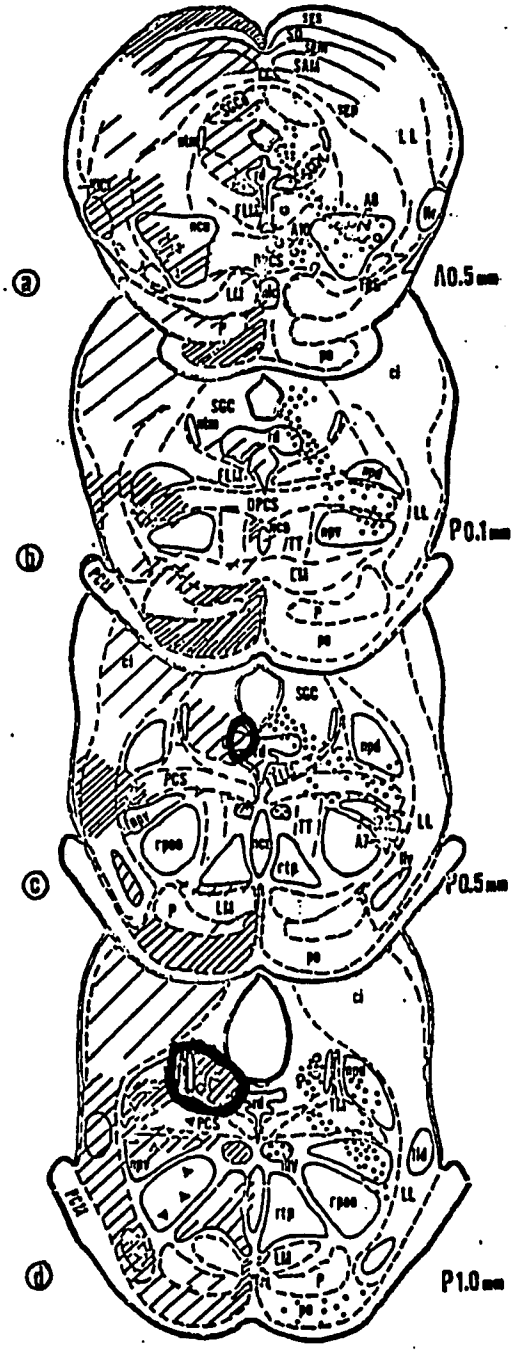


Figure 2

Figure 1

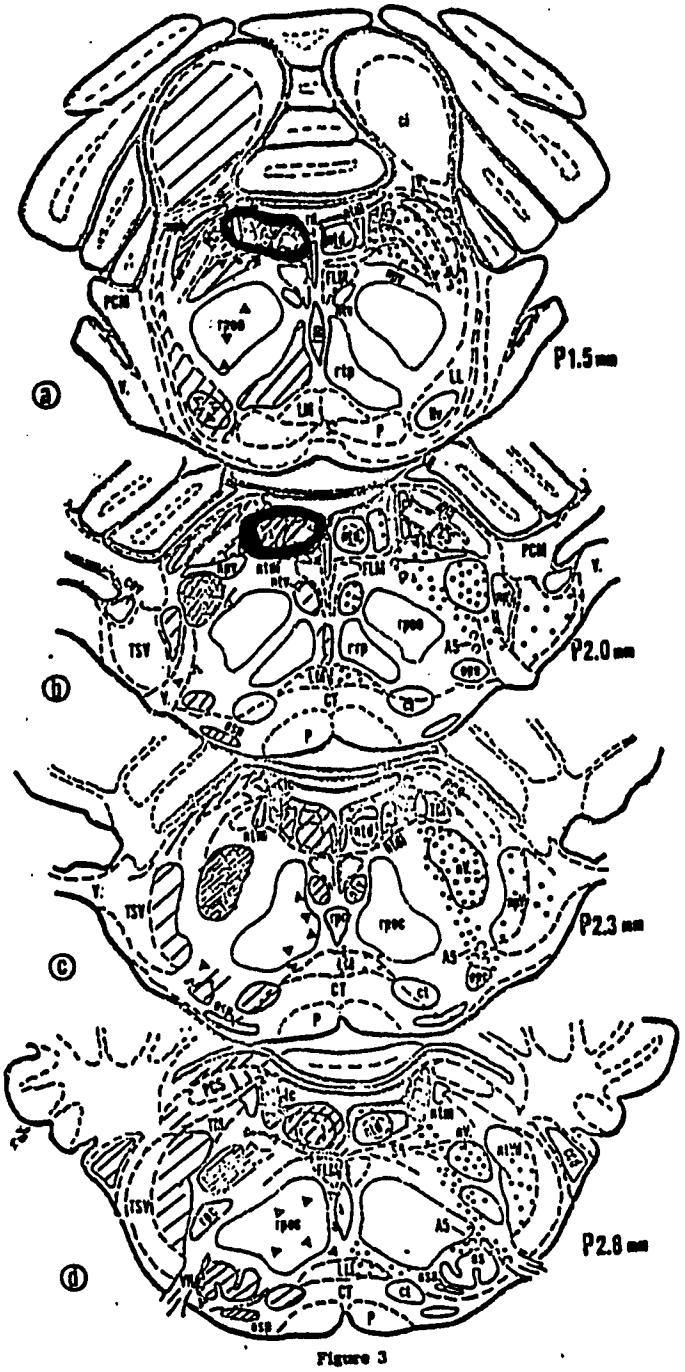


Figure 3

46M

Figure 1

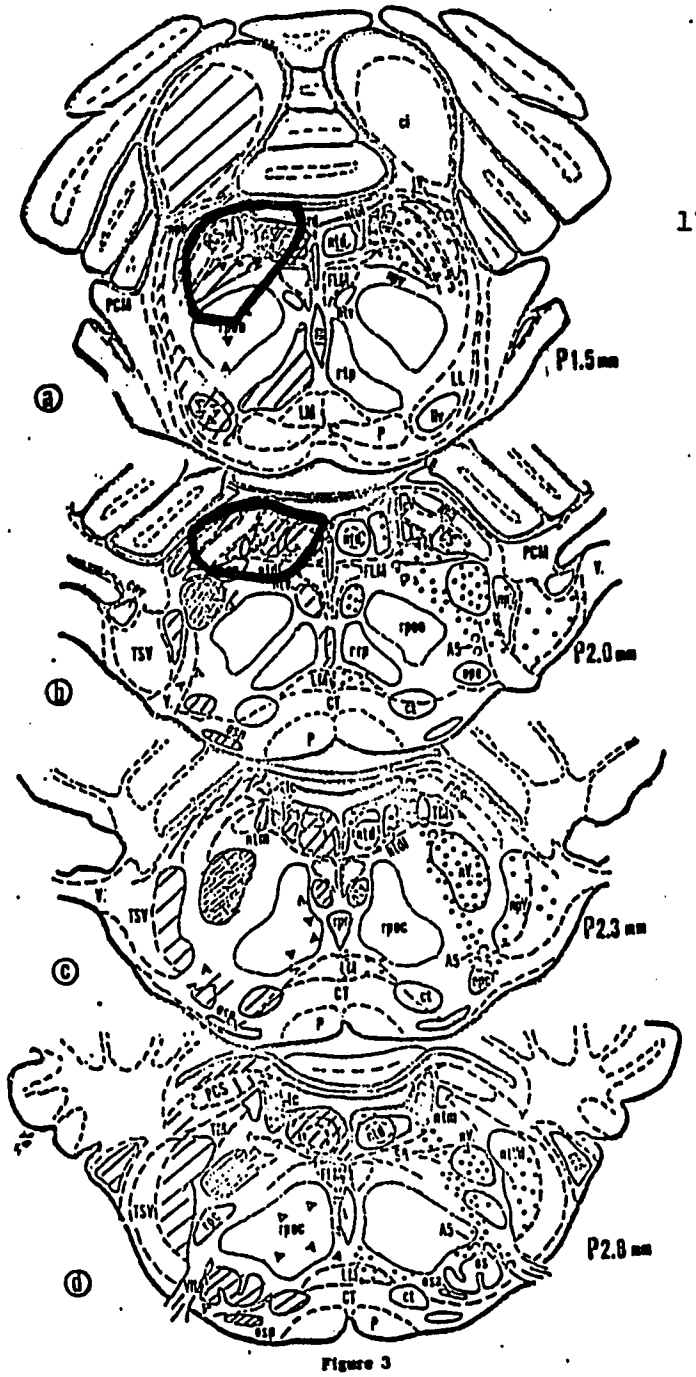


Figure 3

Figure 1

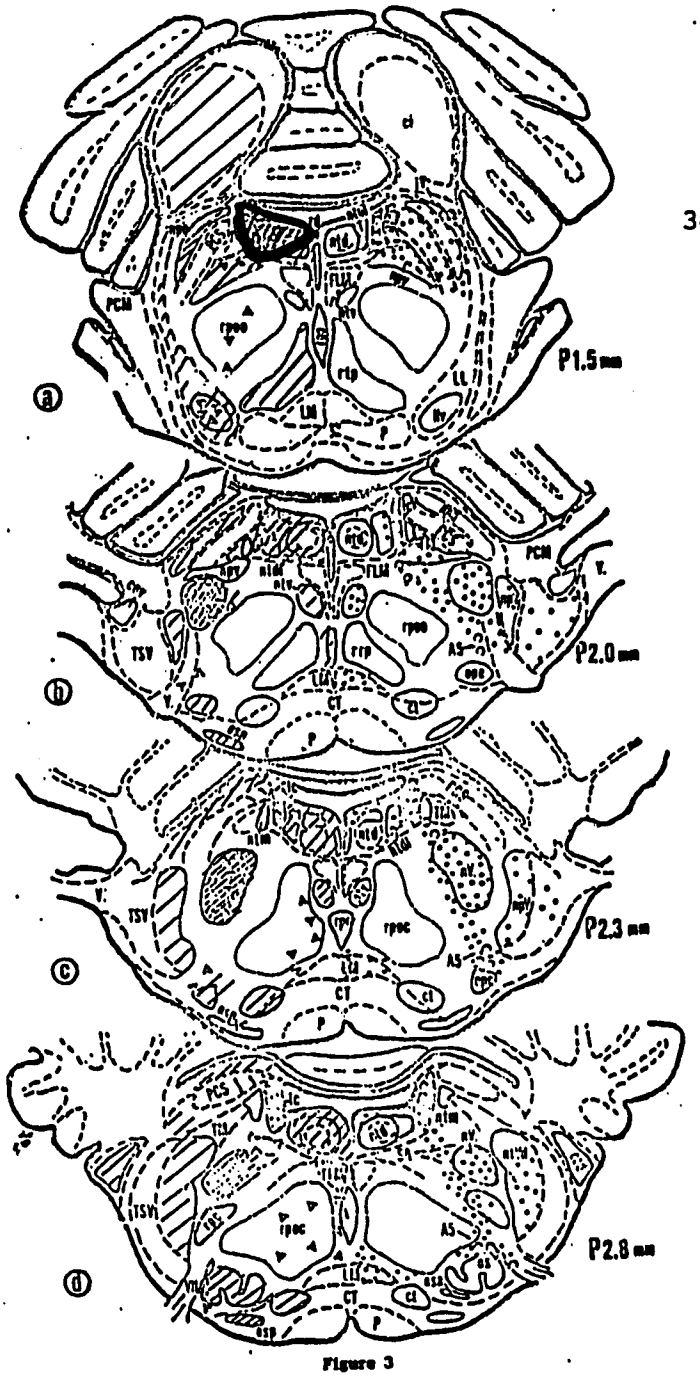


Figure 3

38M

Figure 1

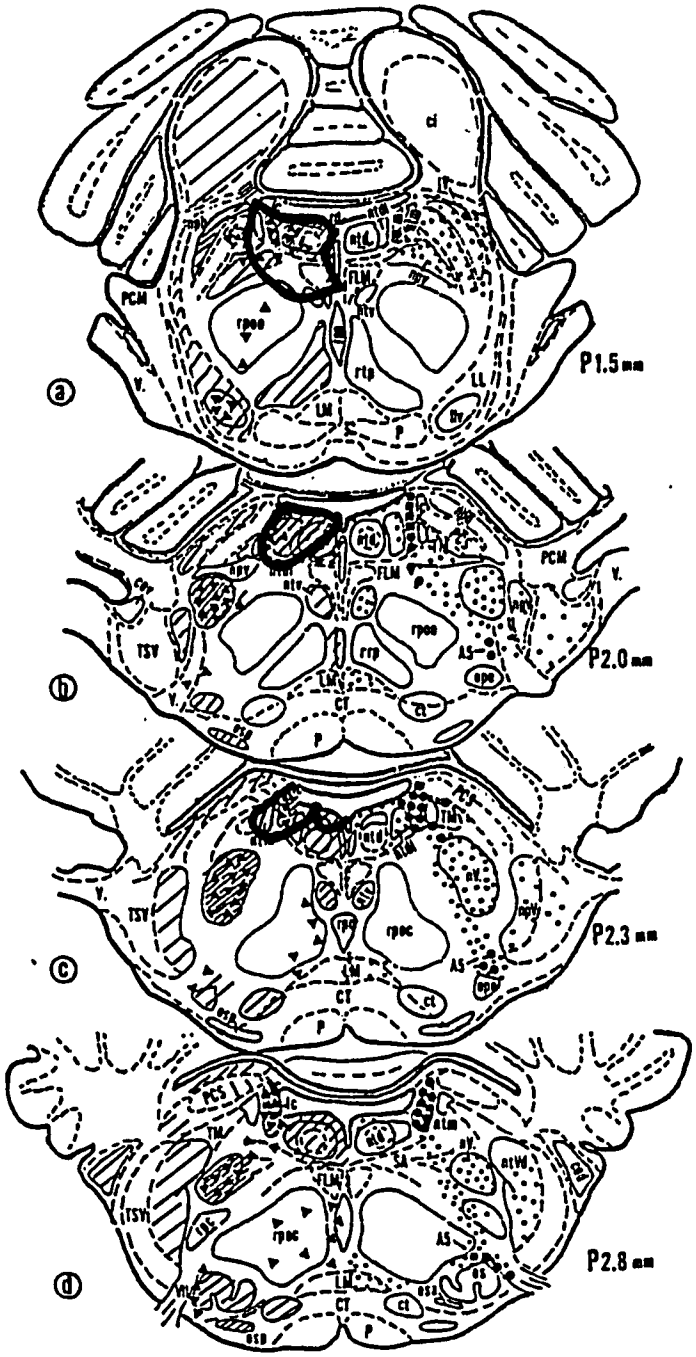


Figure 3

Figure 1

52M

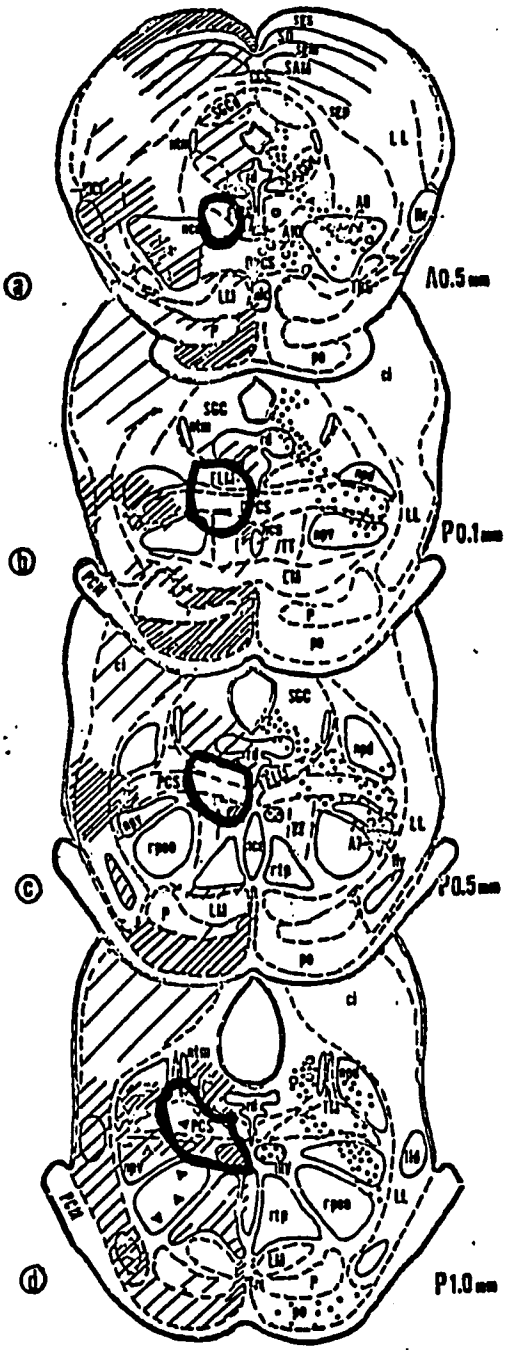


Figure 2

Figure 1

82L

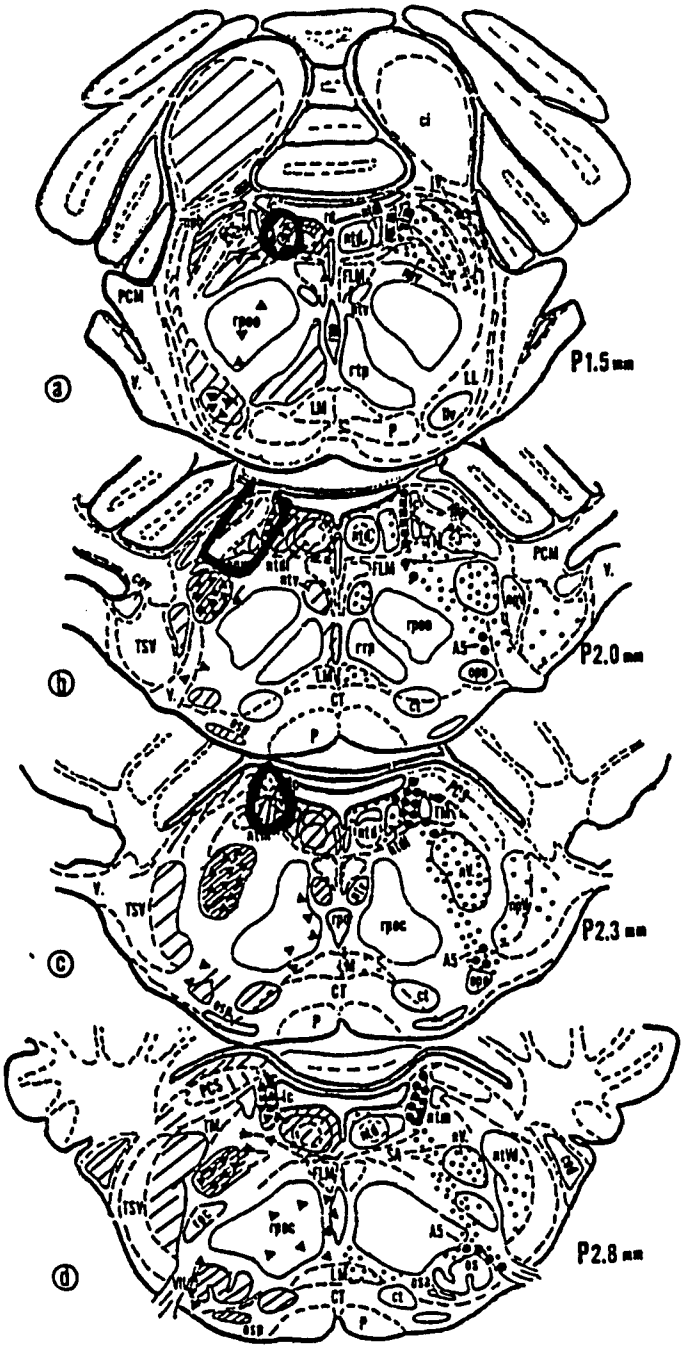


Figure 3

Figure 1

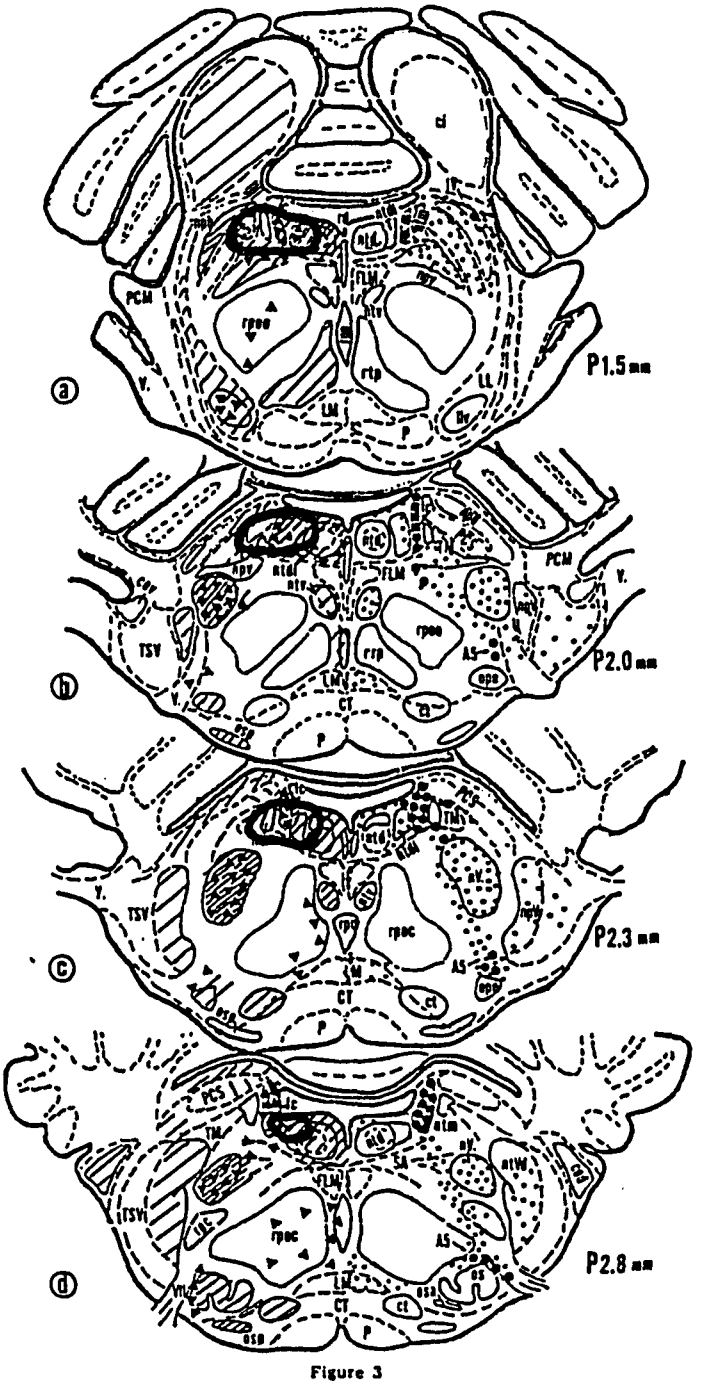


Figure 3

Figure 1

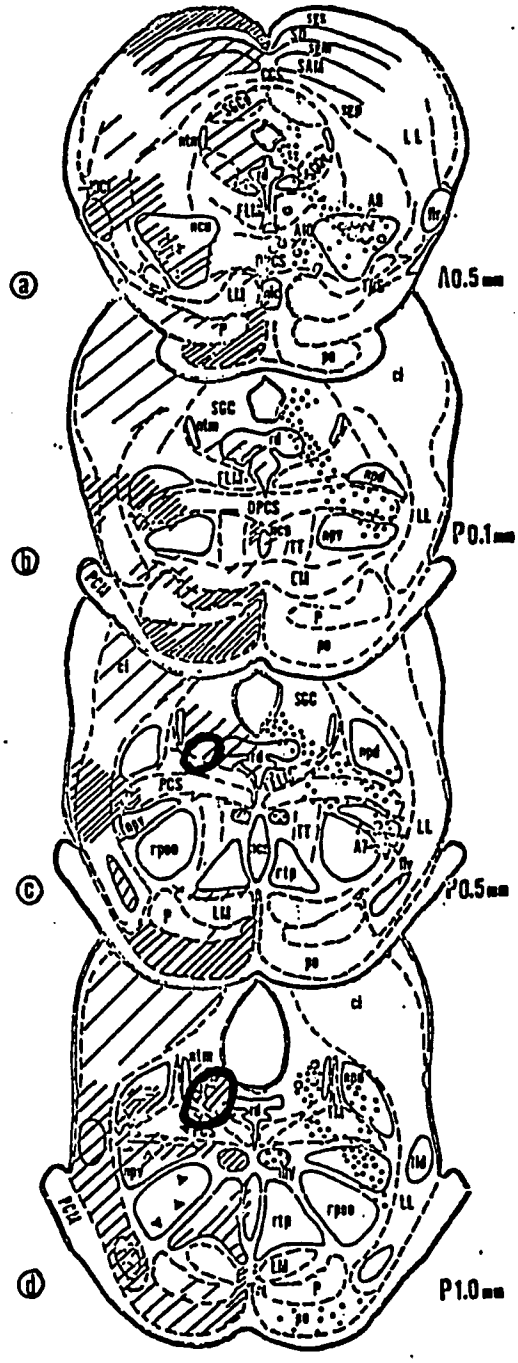


Figure 2

Figure 1

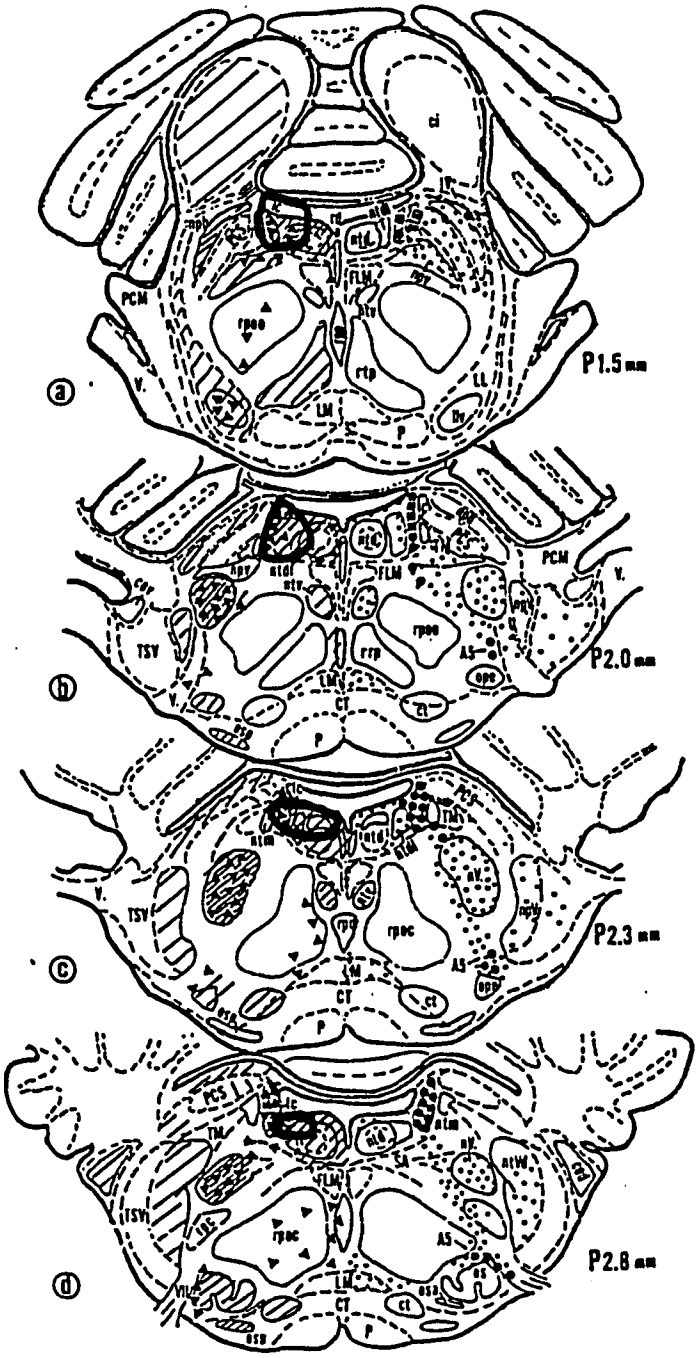


Figure 3

Figure 1

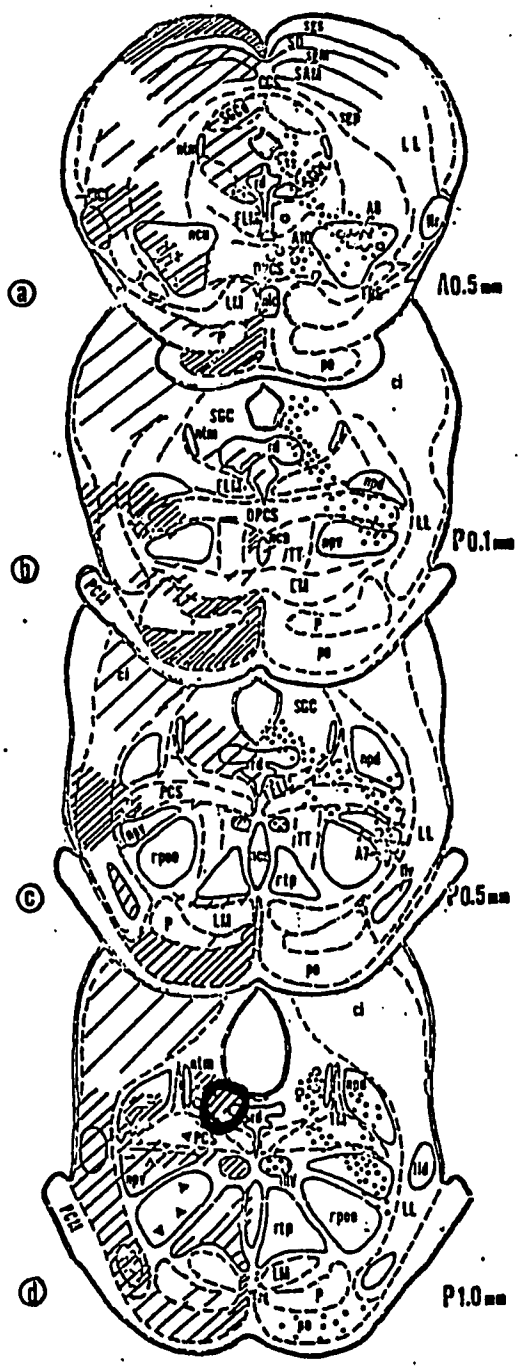
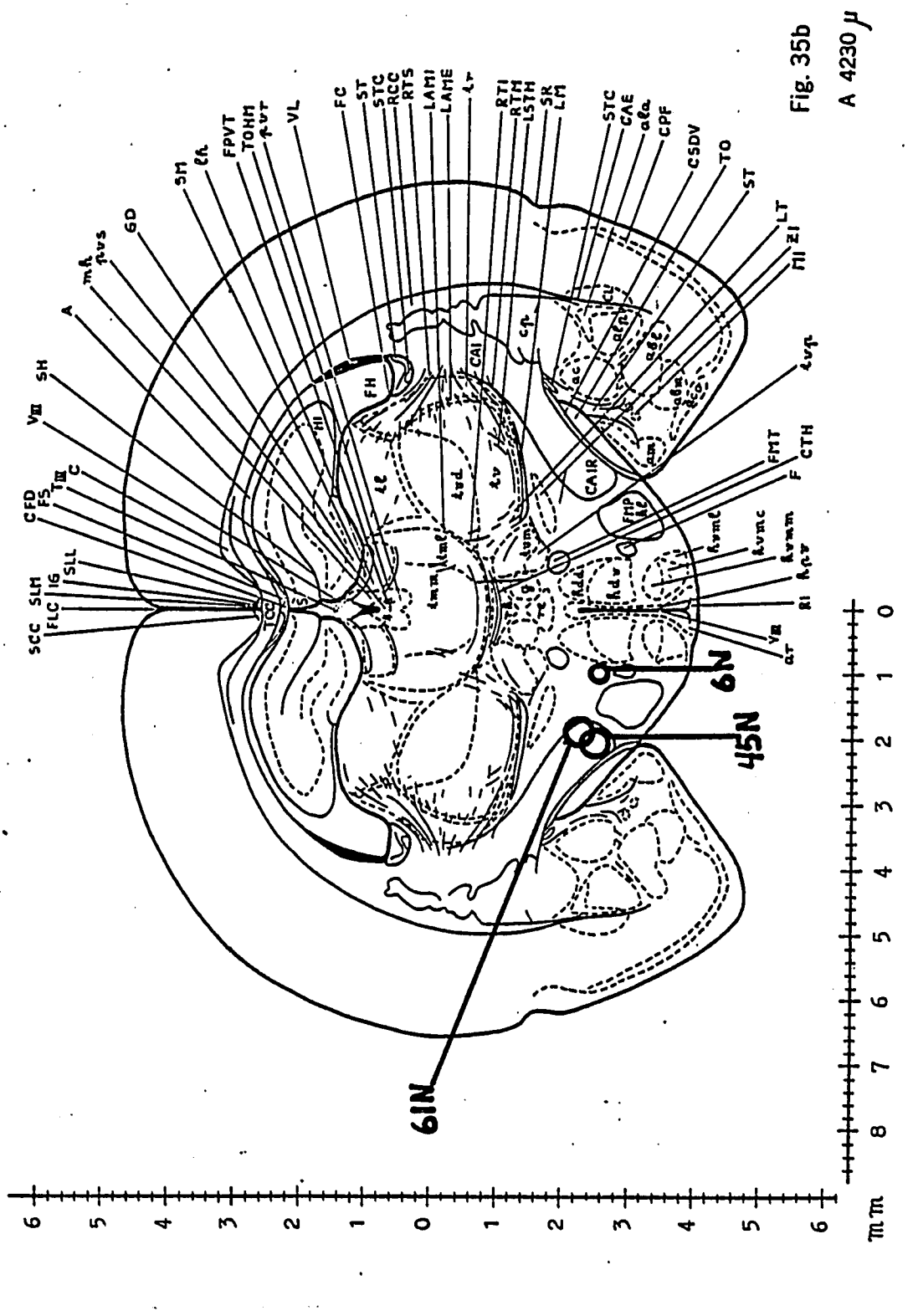


Figure 2

9N

Figure 2



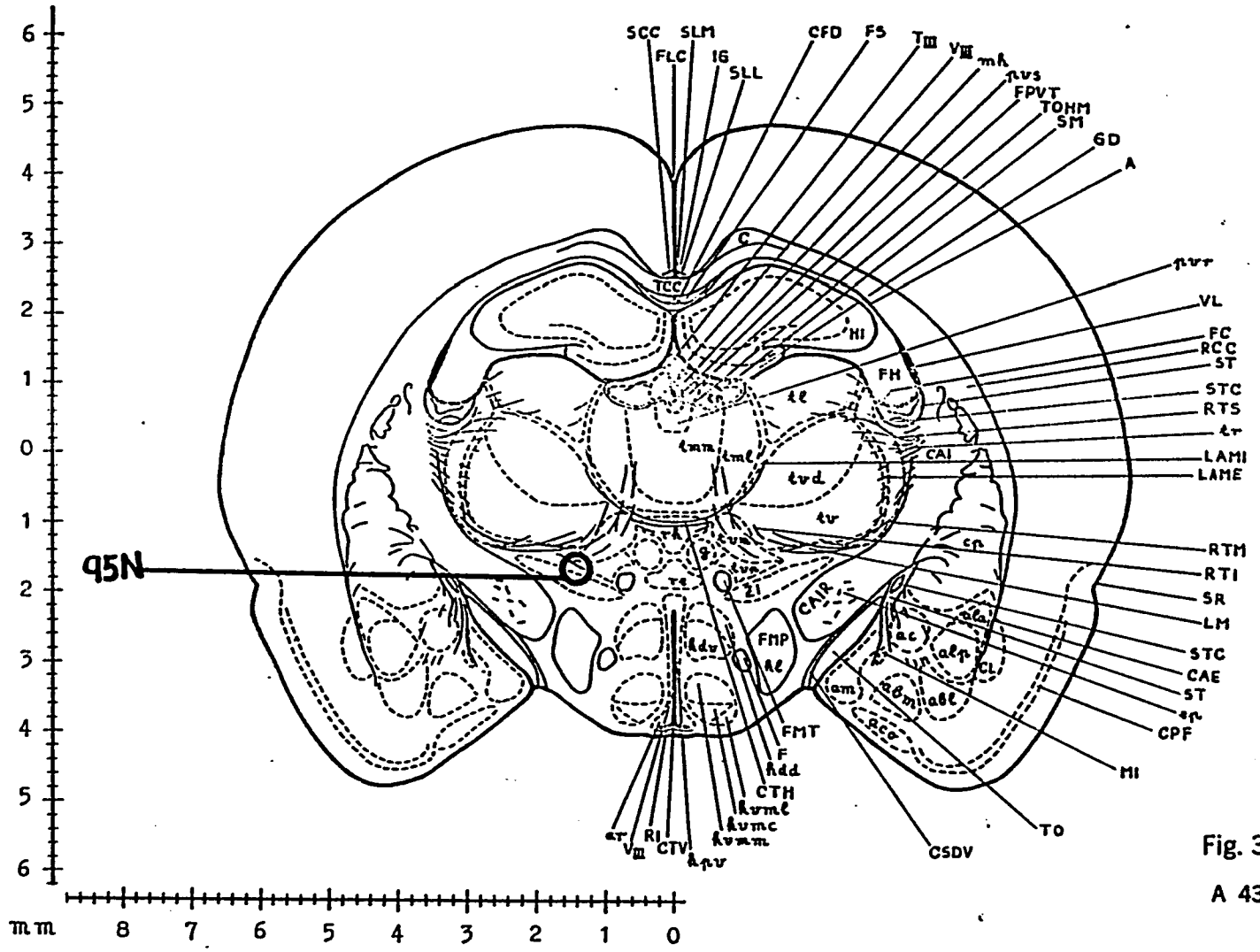


Fig. 34b

A 4380 μ

Figure 2

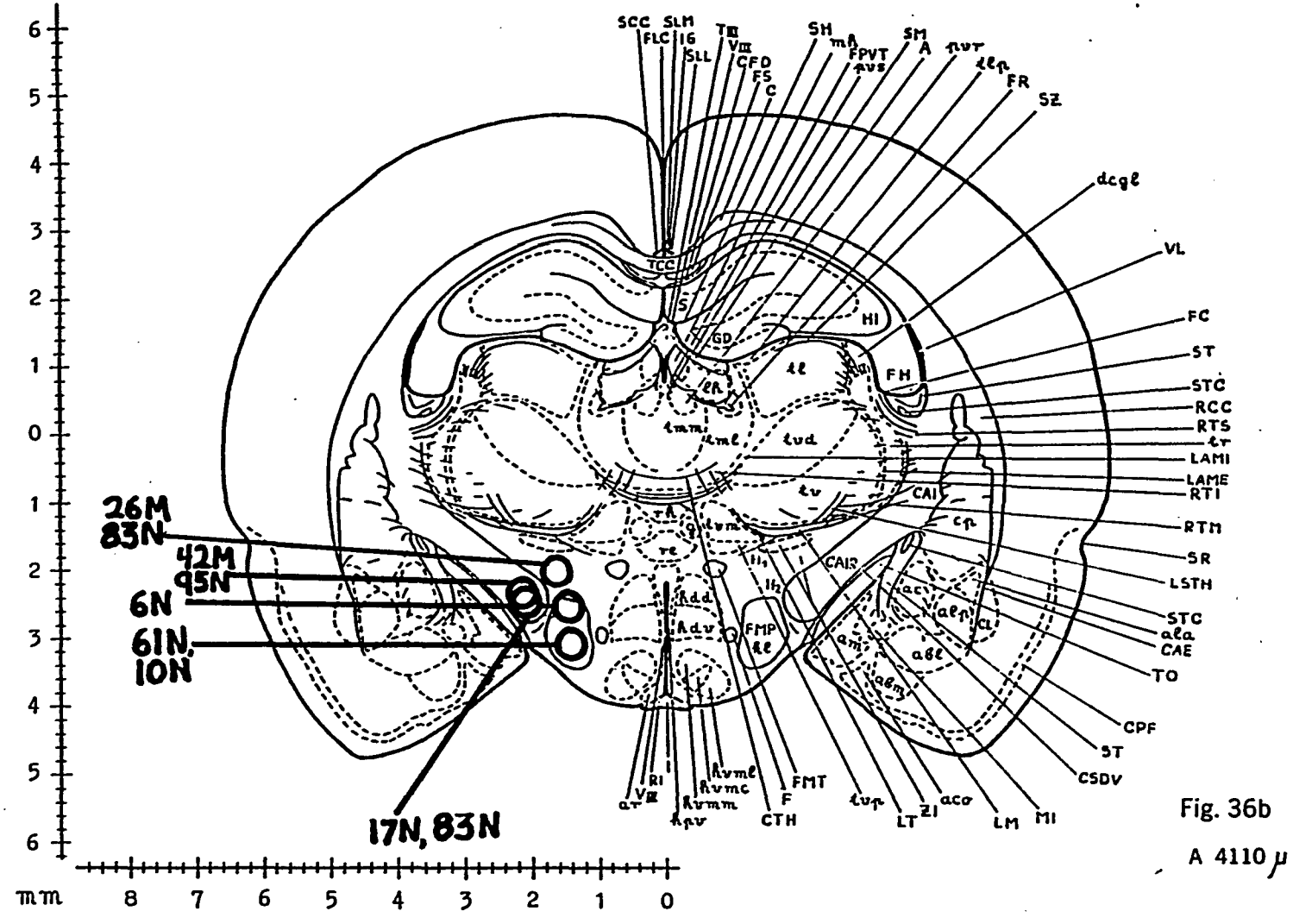


Fig. 36b

A 4110 μ

Figure 2

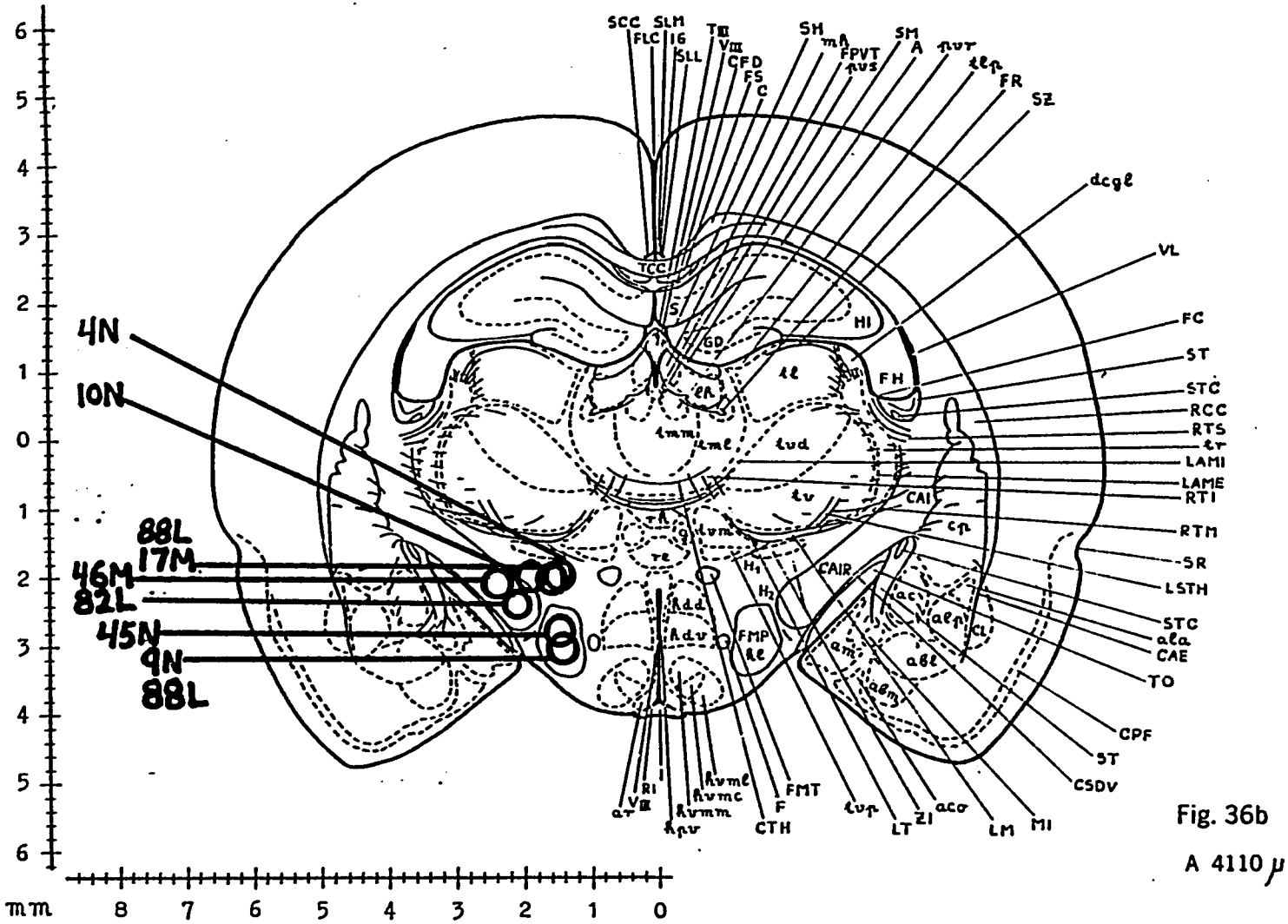


Fig. 36b

A 4110 μ

Figure 2

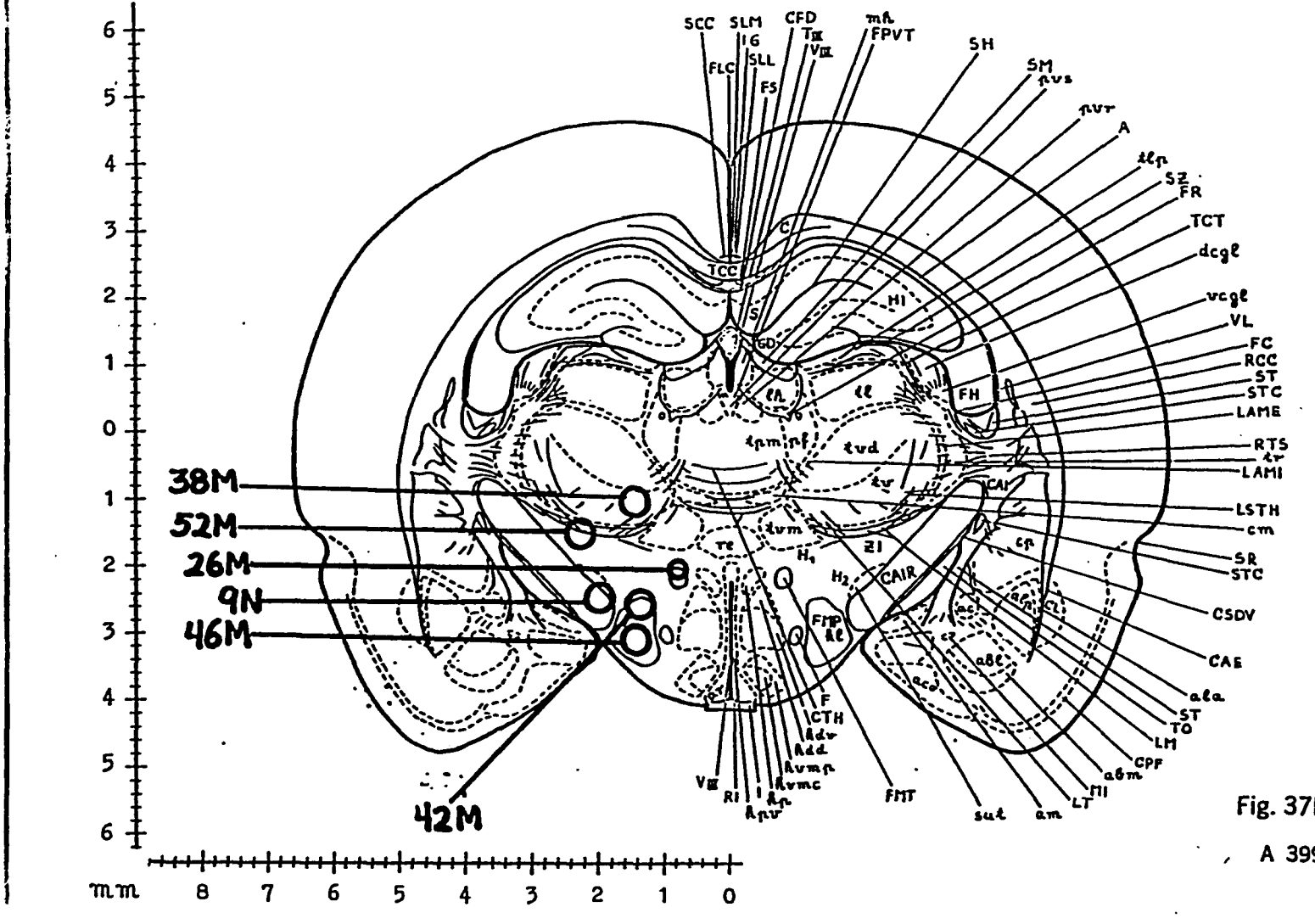


Fig. 37b

A 3990 μ

Figure 2

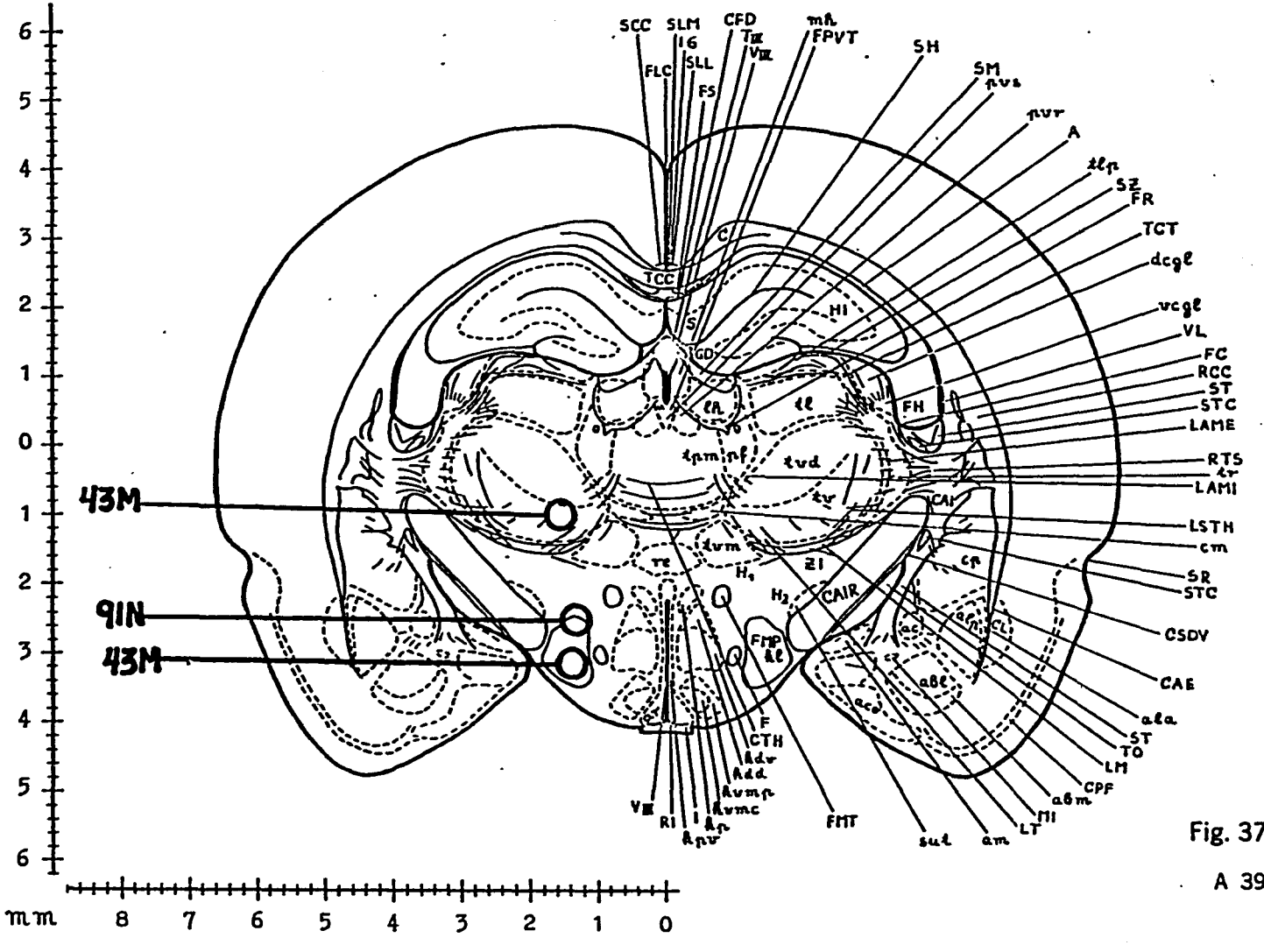


Fig. 37b

A 3990 μ

Figure 2

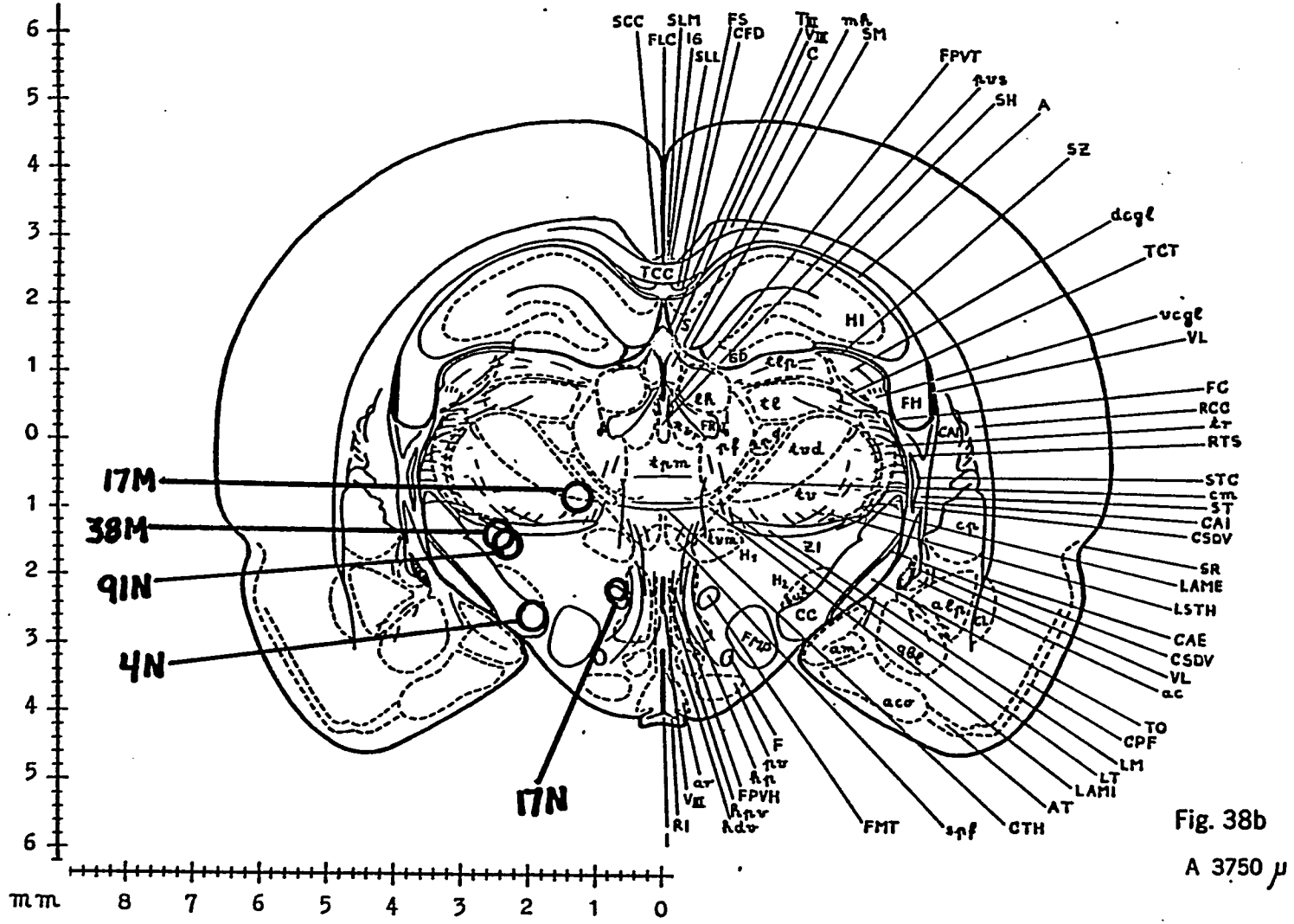


Fig. 38b

A 3750 μ

Figure 2

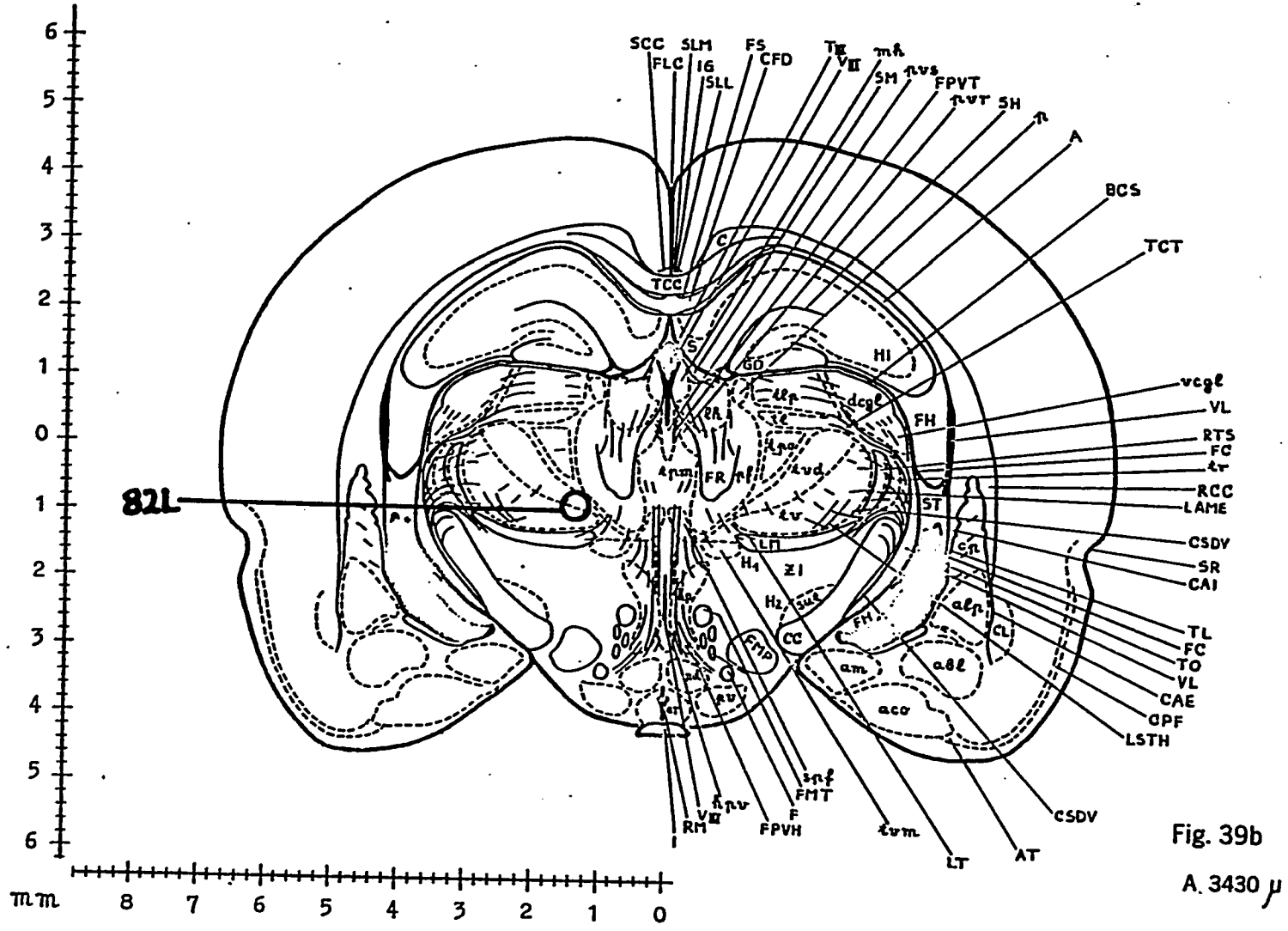


Fig. 39b

A. 3430 μ

Figure 2

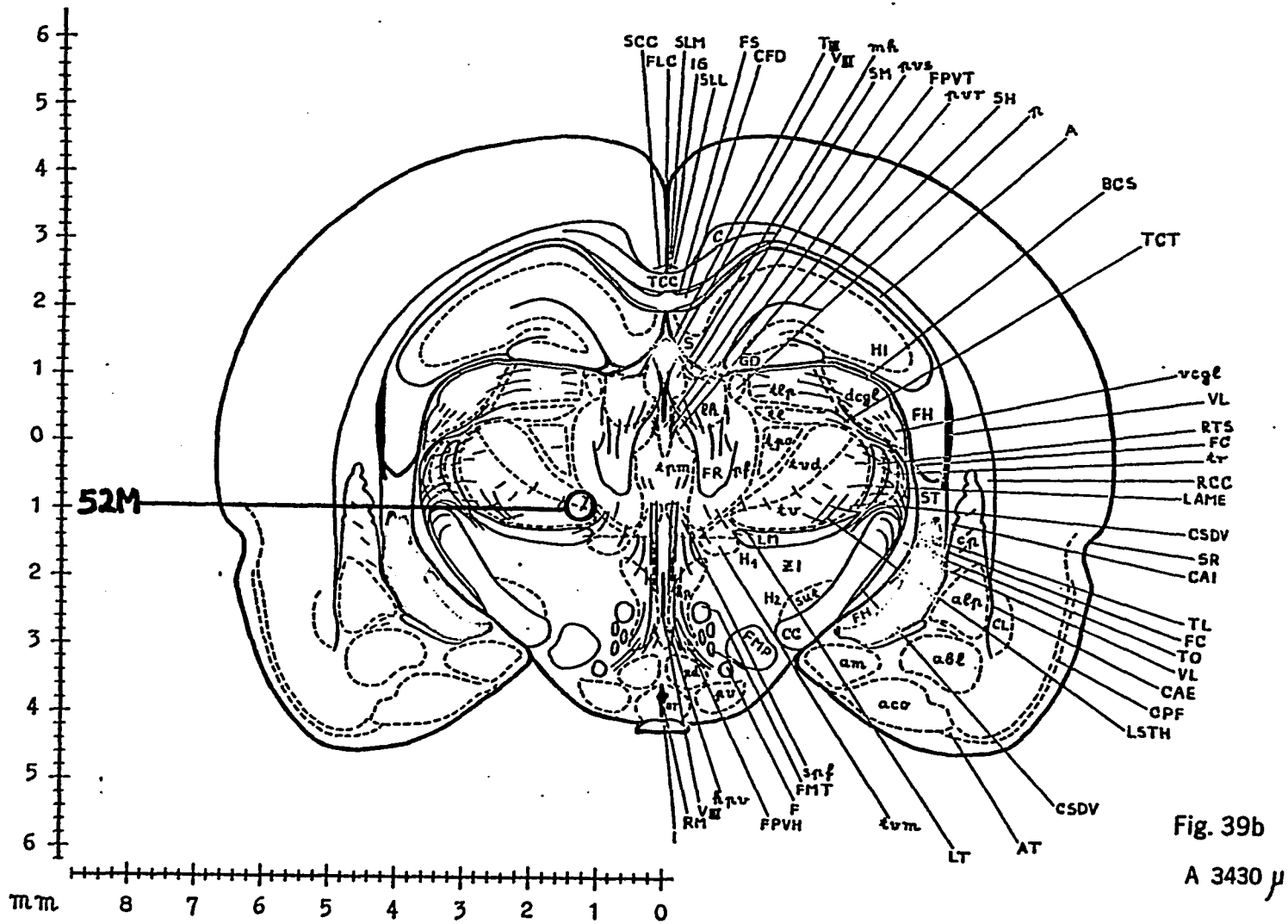


Fig. 39b

A 3430 μ

Figure 2

Figure 2

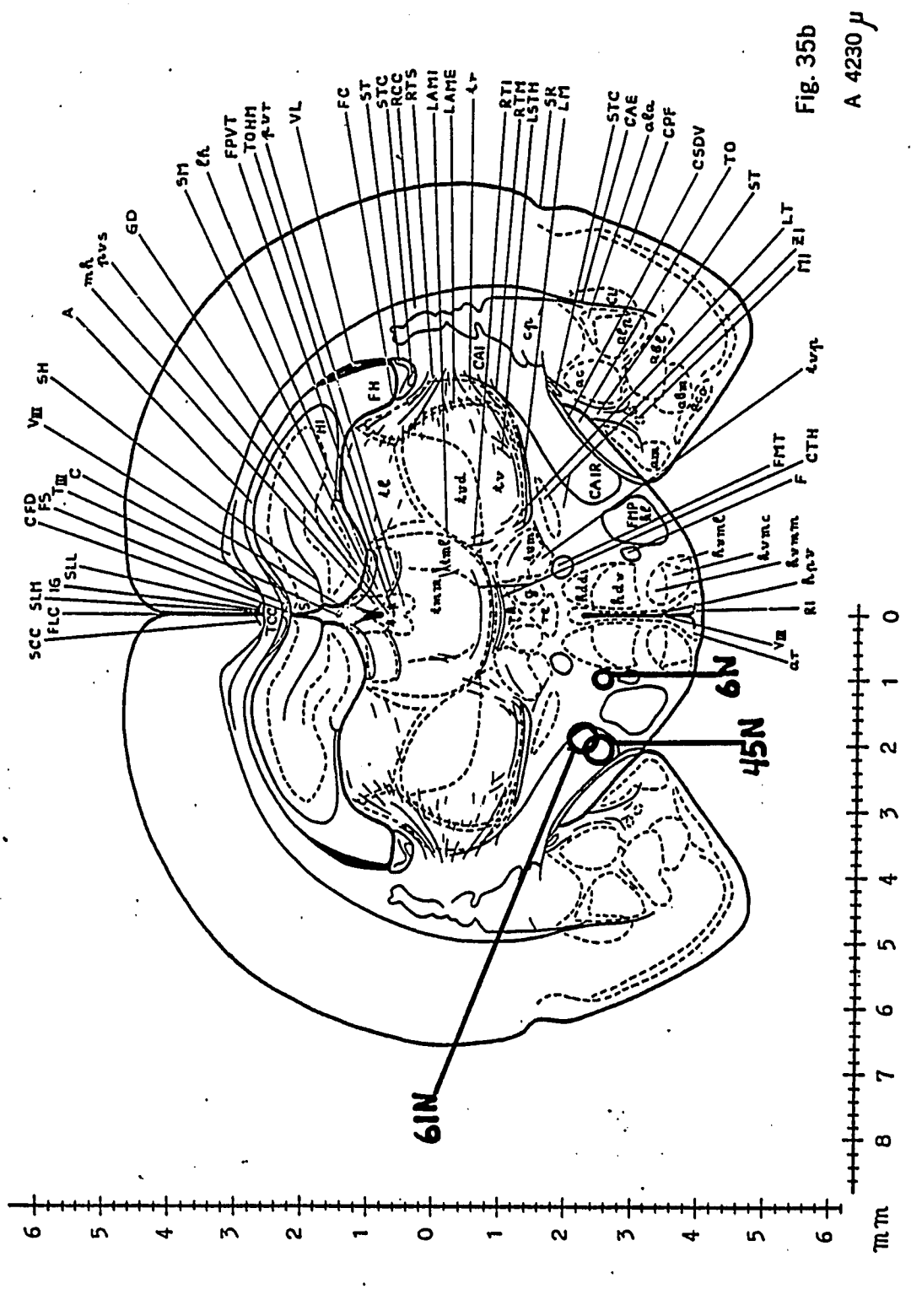


Figure 3

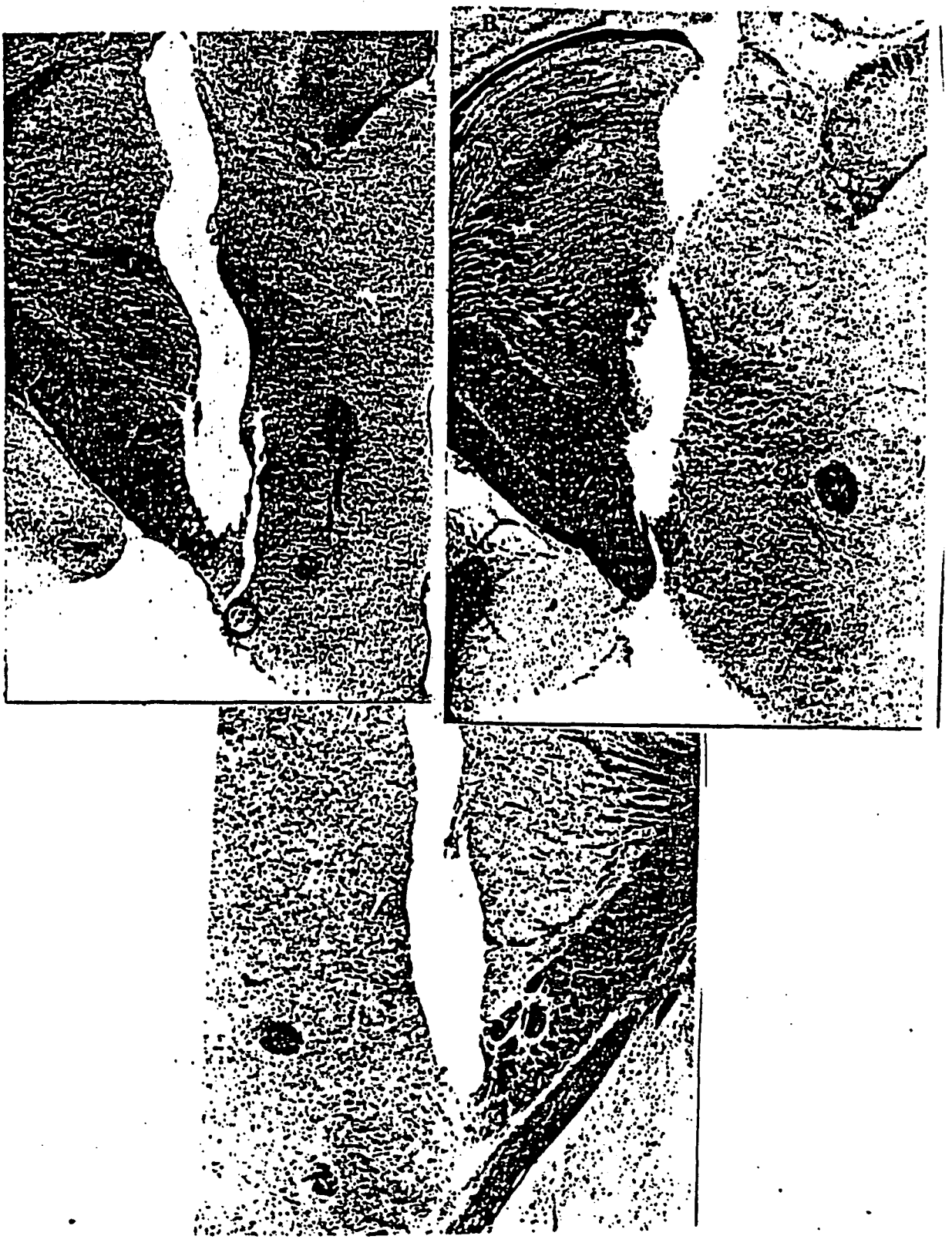


Figure 4

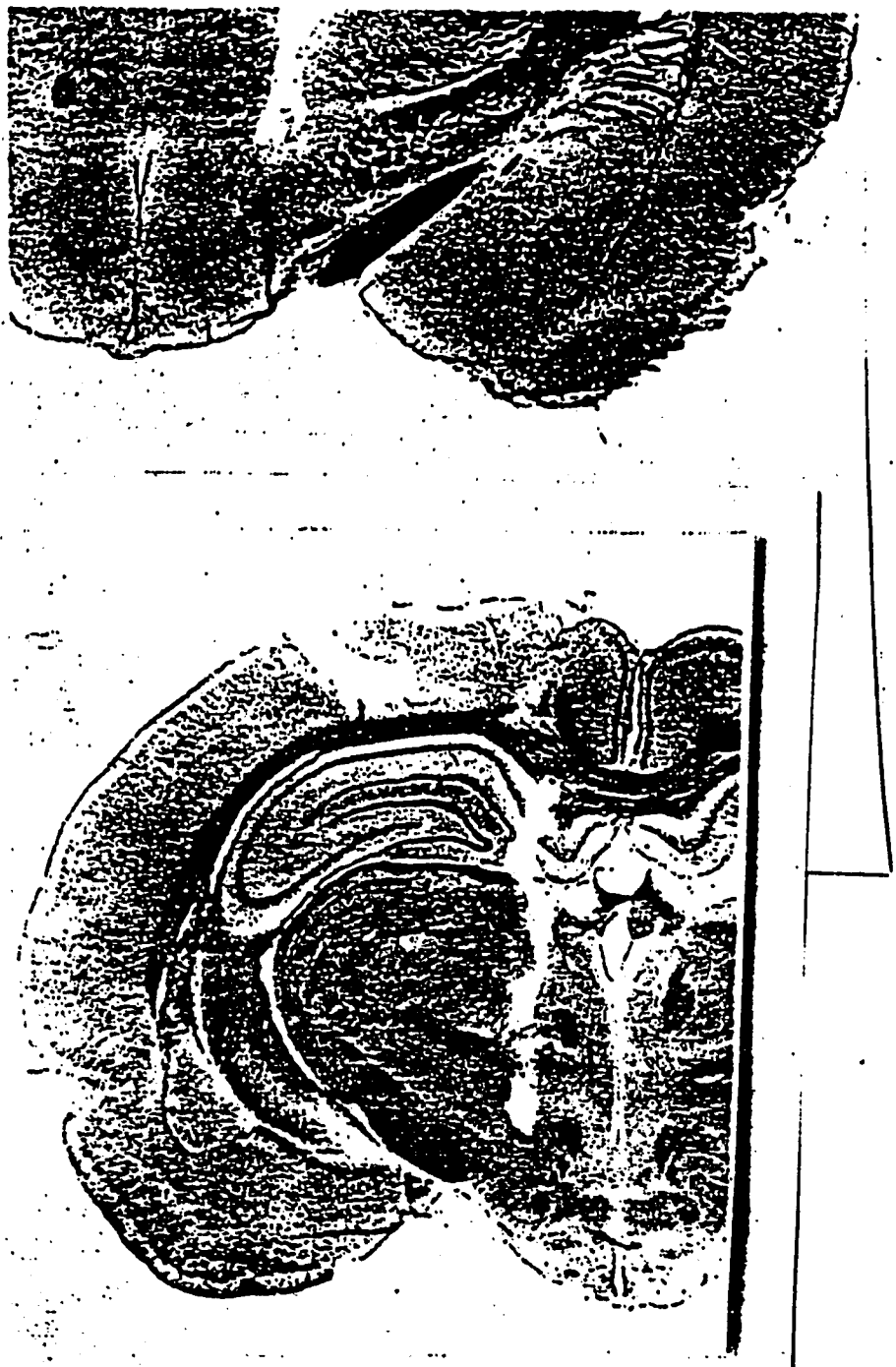


Figure 5

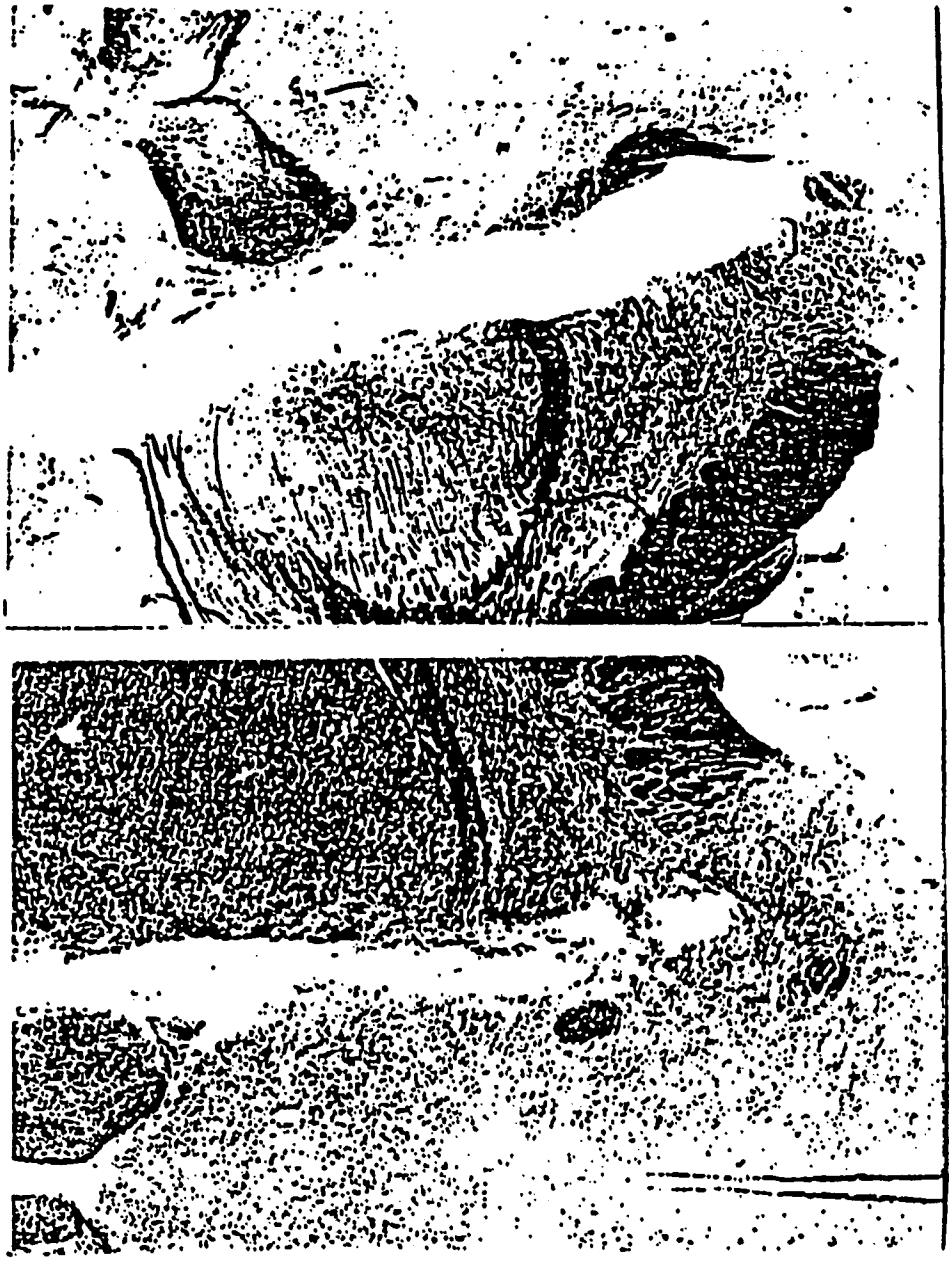
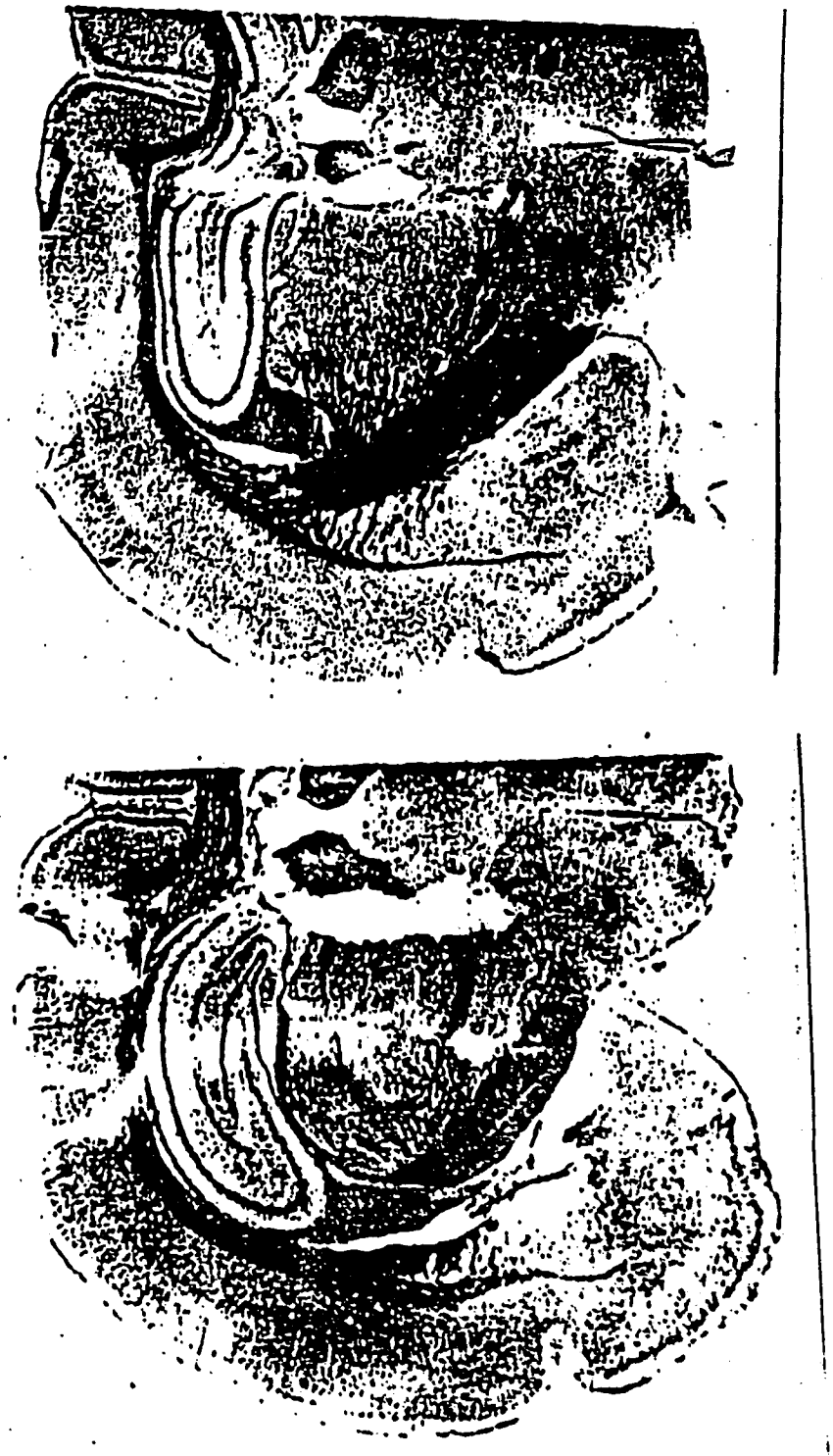


Figure 6



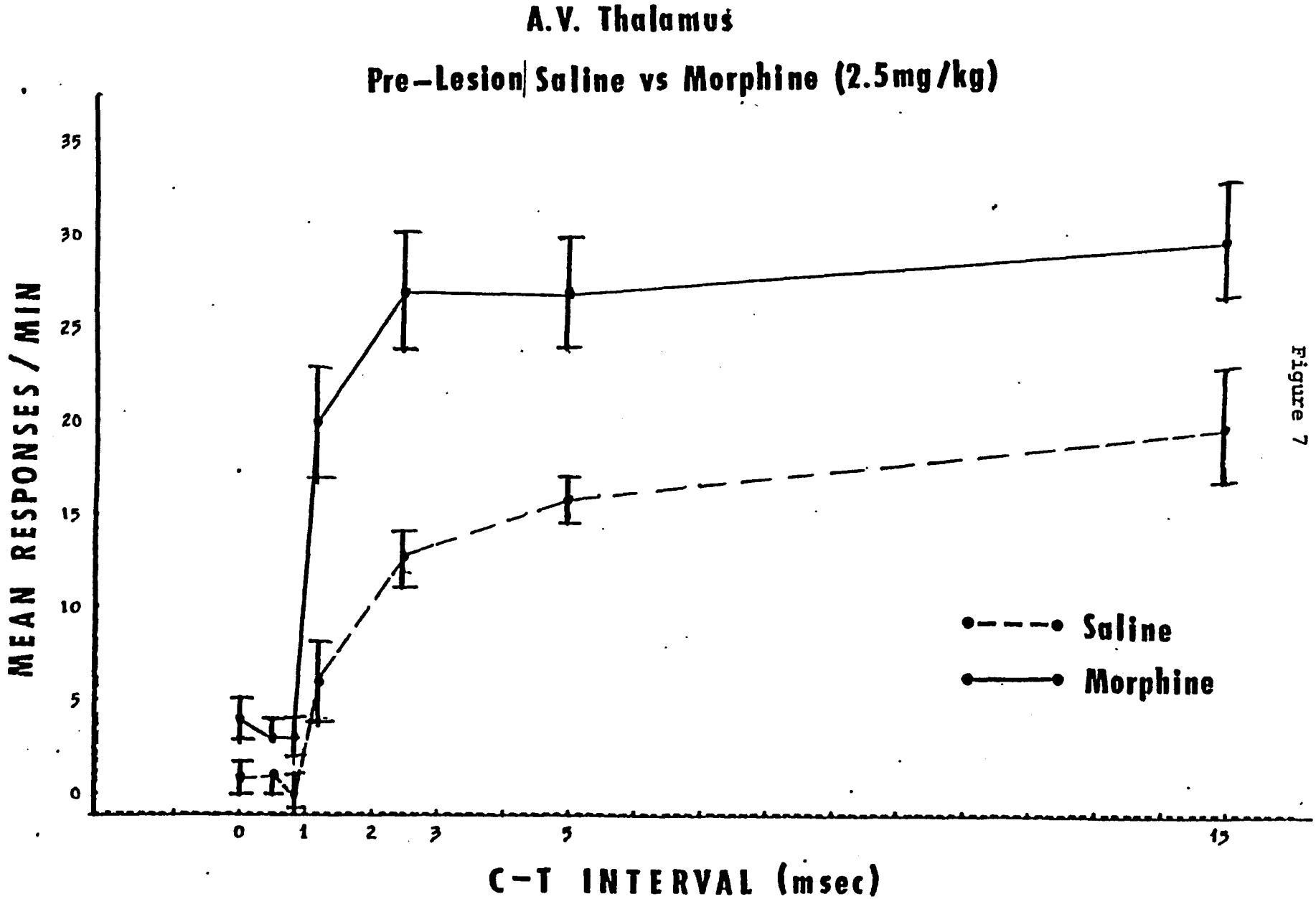

A.V. Thalamus
Pre-Lesion Saline vs Morphine (2.5mg/kg)
MEAN RESPONSES / MIN
35
30
25
20
15
10
5
0
0
1
2
3
5
15
C-T INTERVAL (msec)
Saline
Morphine

Figure 7

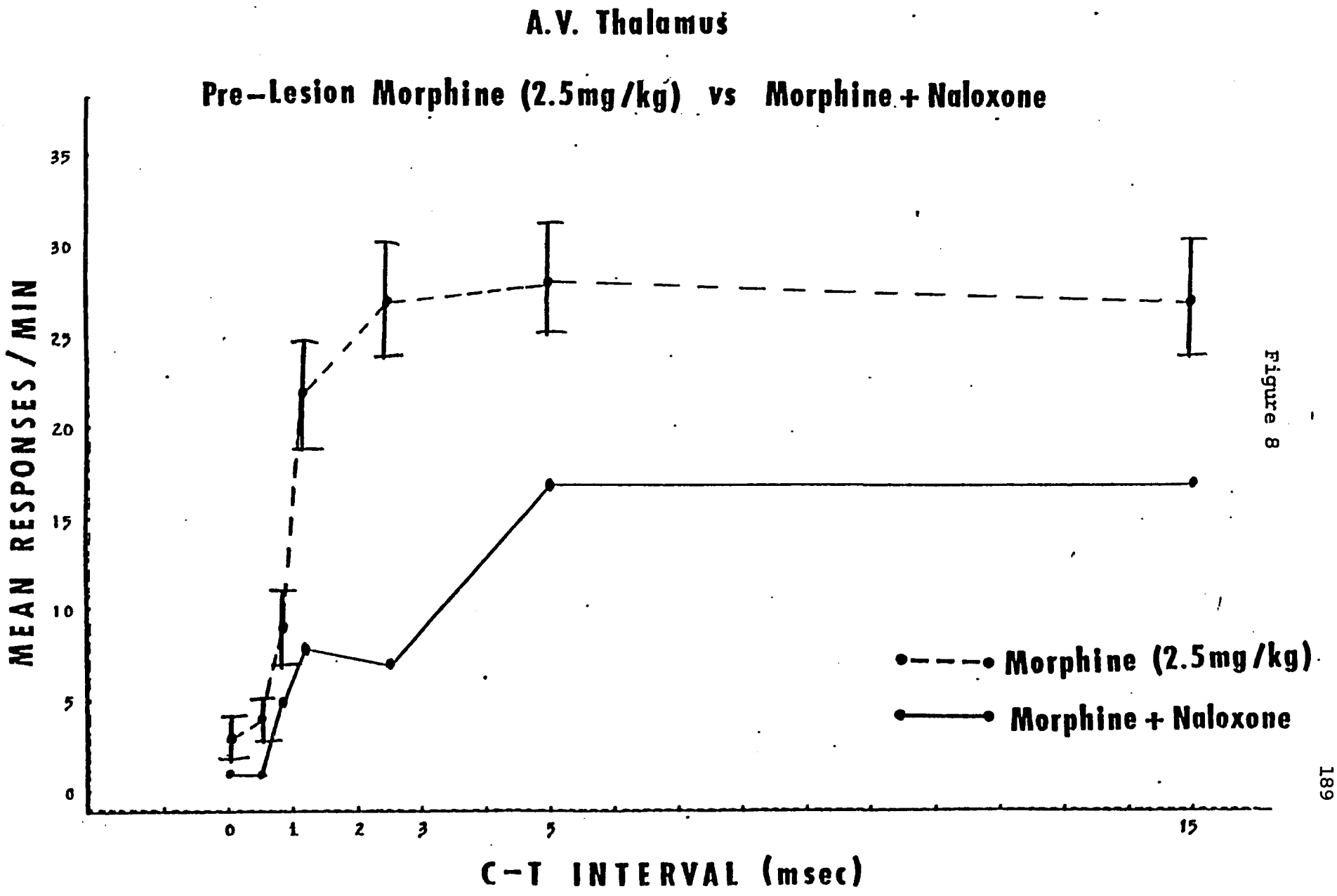

A.V. Thalamus
Pre–Lesion Morphine (2.5mg/kg) vs Morphine + Naloxone
MEAN RESPONSES / MIN
35
30
25
20
15
10
5
0
0
1
2
3
5
15
C–T INTERVAL (msec)
Morphine (2.5mg/kg)
Morphine + Naloxone

Figure 8

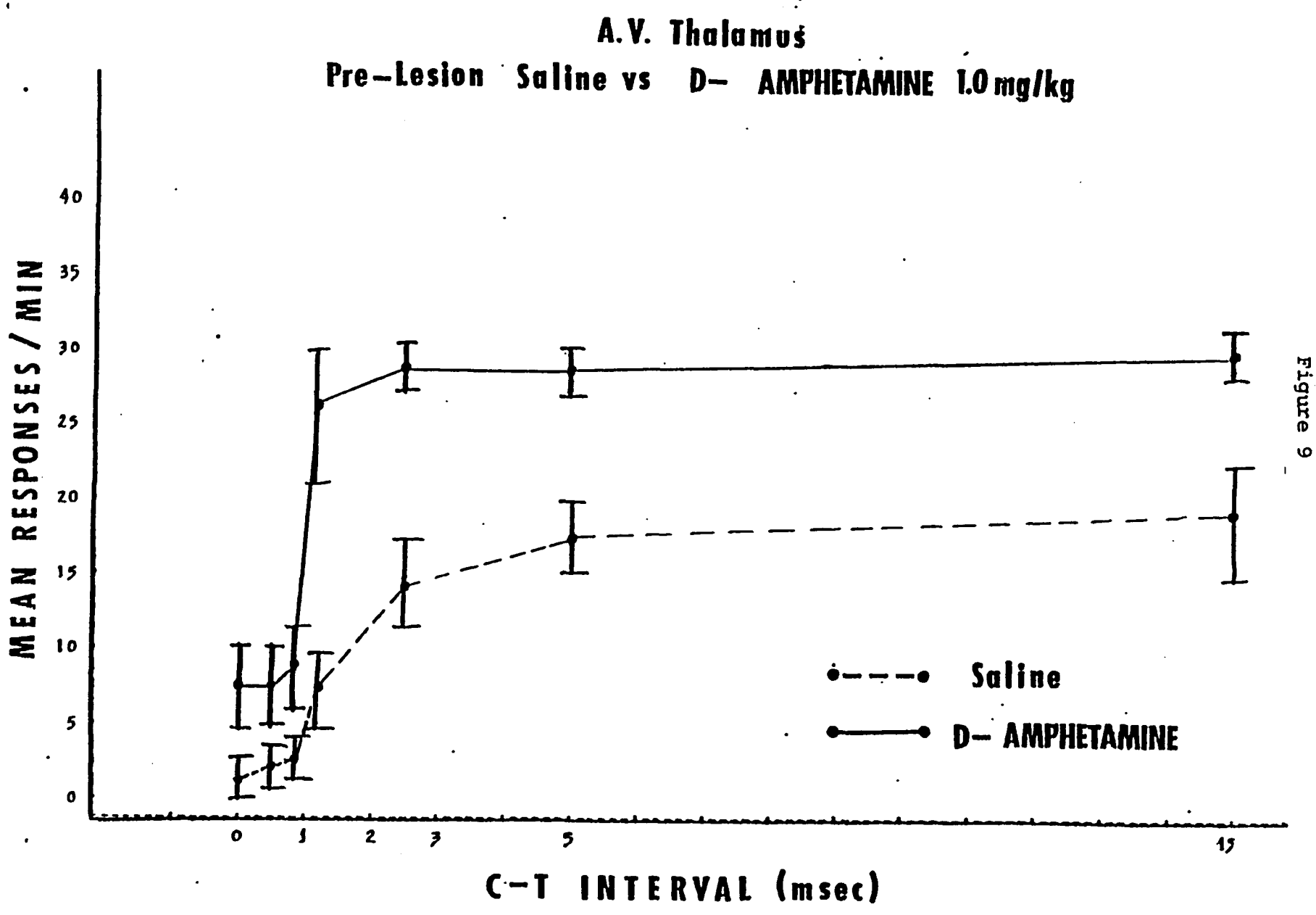

A.V. Thalamus
Pre–Lesion Saline vs D– AMPHETAMINE 1.0 mg/kg
MEAN RESPONSES / MIN
40
35
30
25
20
15
10
5
0
0
1
2
3
5
15
C–T INTERVAL (msec)
Saline
D– AMPHETAMINE

Figure 9

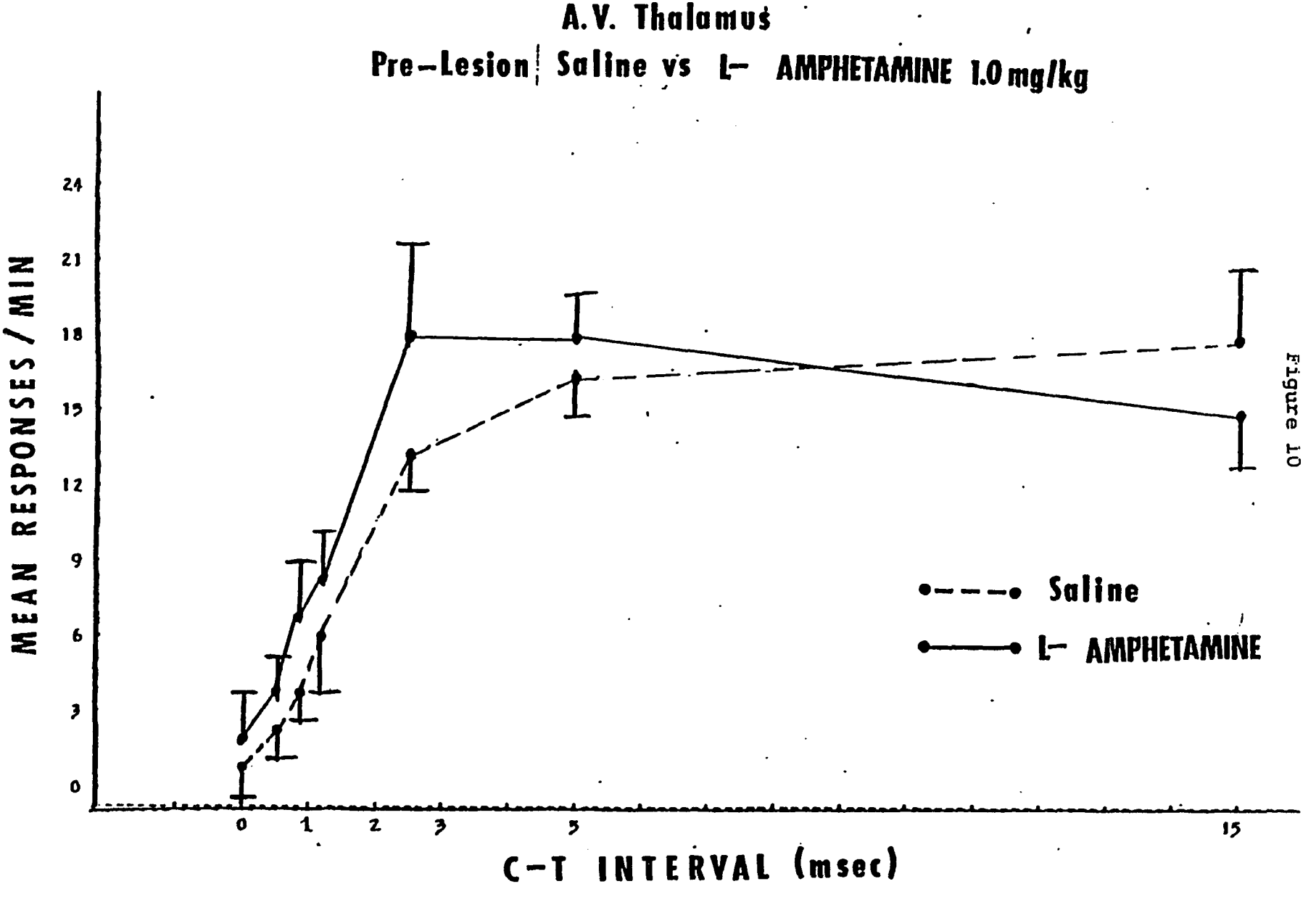

A.V. Thalamus
Pre-Lesion Saline vs L- AMPHETAMINE 1.0 mg/kg
MEAN RESPONSES / MIN
24
21
18
15
12
9
6
3
0
0
1
2
3
5
15
C-T INTERVAL (msec)
Saline
L- AMPHETAMINE

Figure 10

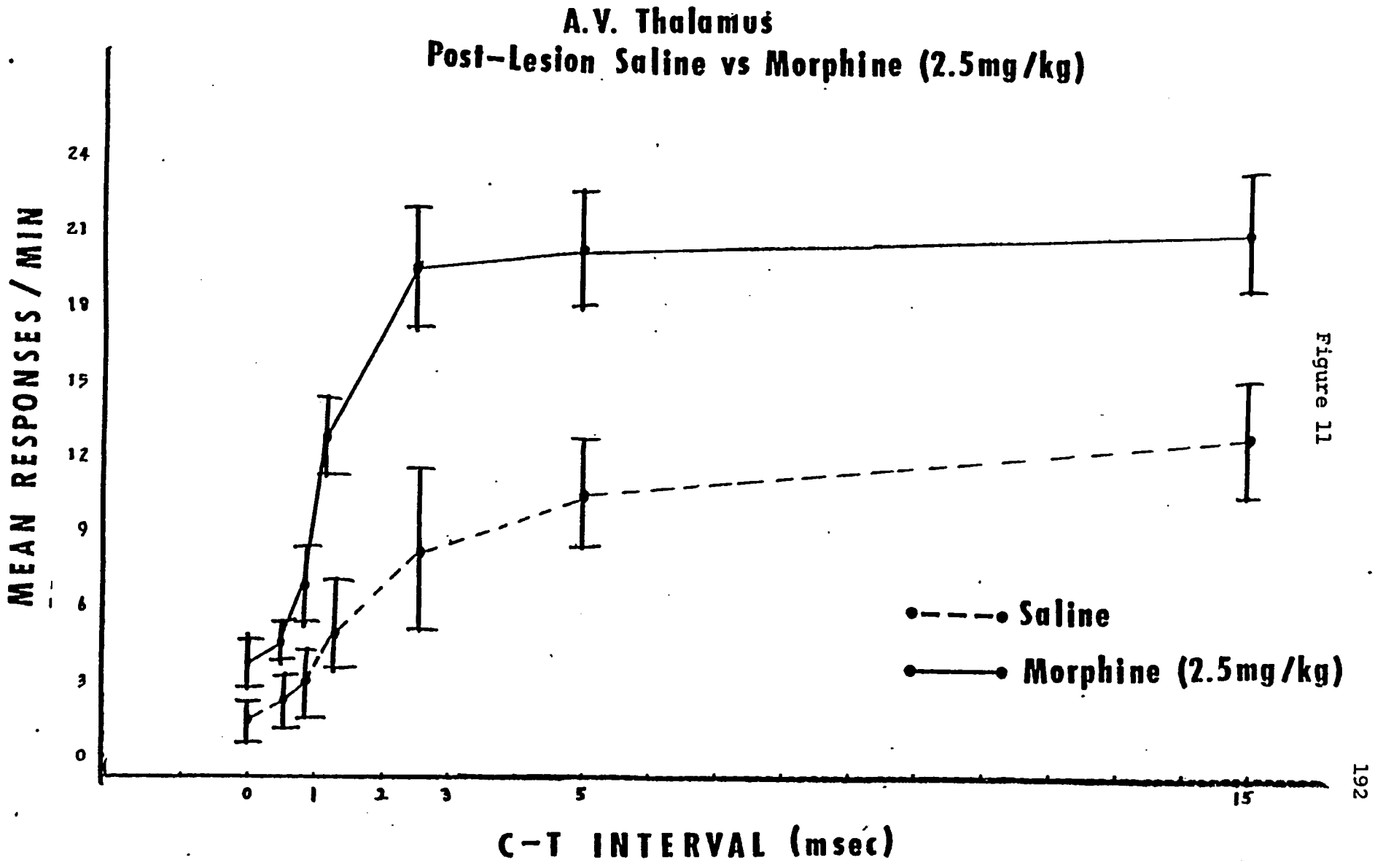

A.V. Thalamus
Post-Lesion Saline vs Morphine (2.5mg/kg)
MEAN RESPONSES / MIN
24
21
19
15
12
9
6
3
0
0
1
2
3
5
15
C-T INTERVAL (msec)
Saline
Morphine (2.5mg/kg)

Figure 11

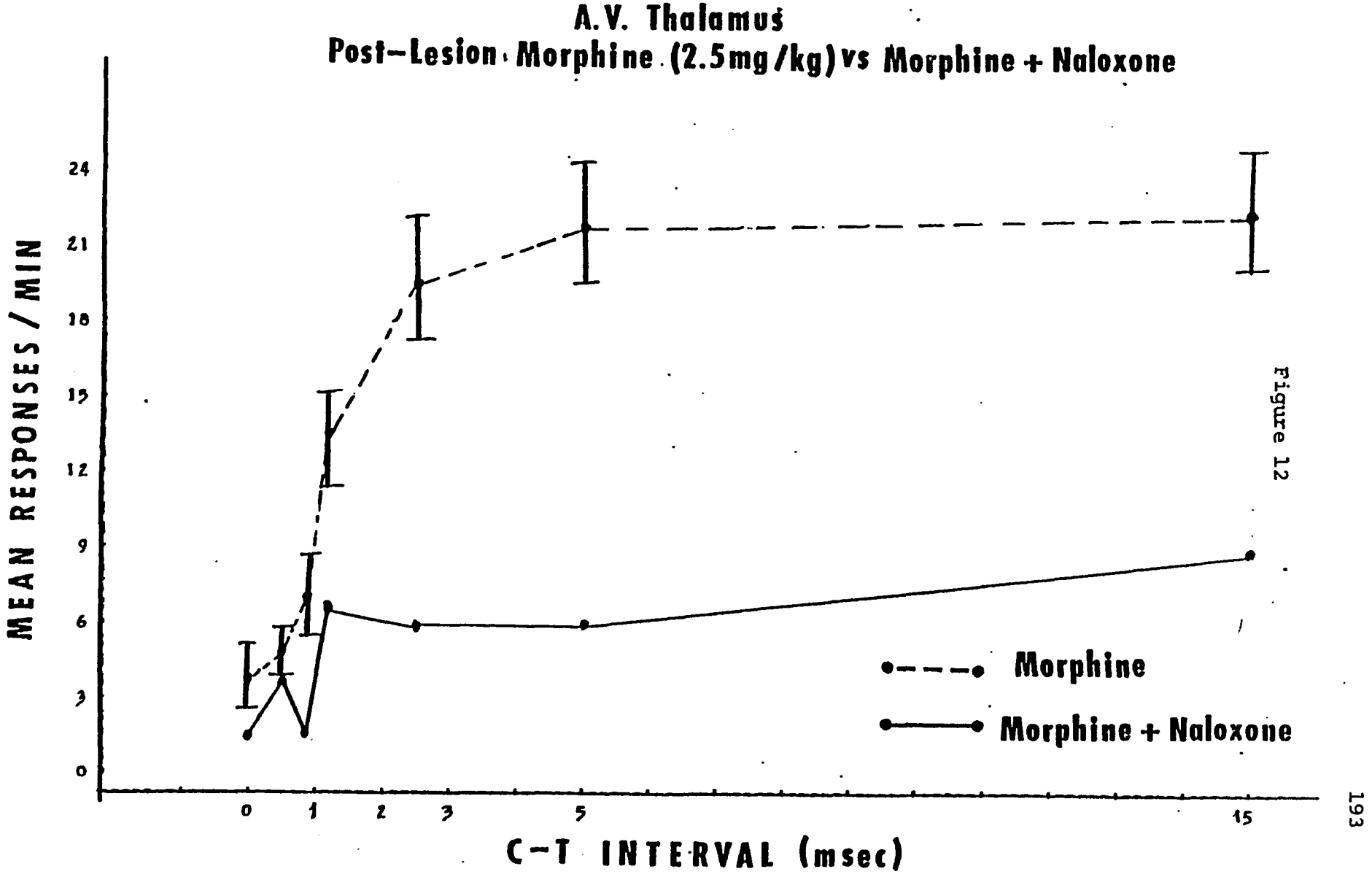

A.V. Thalamus
Post-Lesion Morphine (2.5mg/kg) vs Morphine + Naloxone
MEAN RESPONSES / MIN
24
21
18
15
12
9
6
3
0
0
1
2
3
5
15
C-T INTERVAL (msec)
Morphine
Morphine + Naloxone

Figure 12

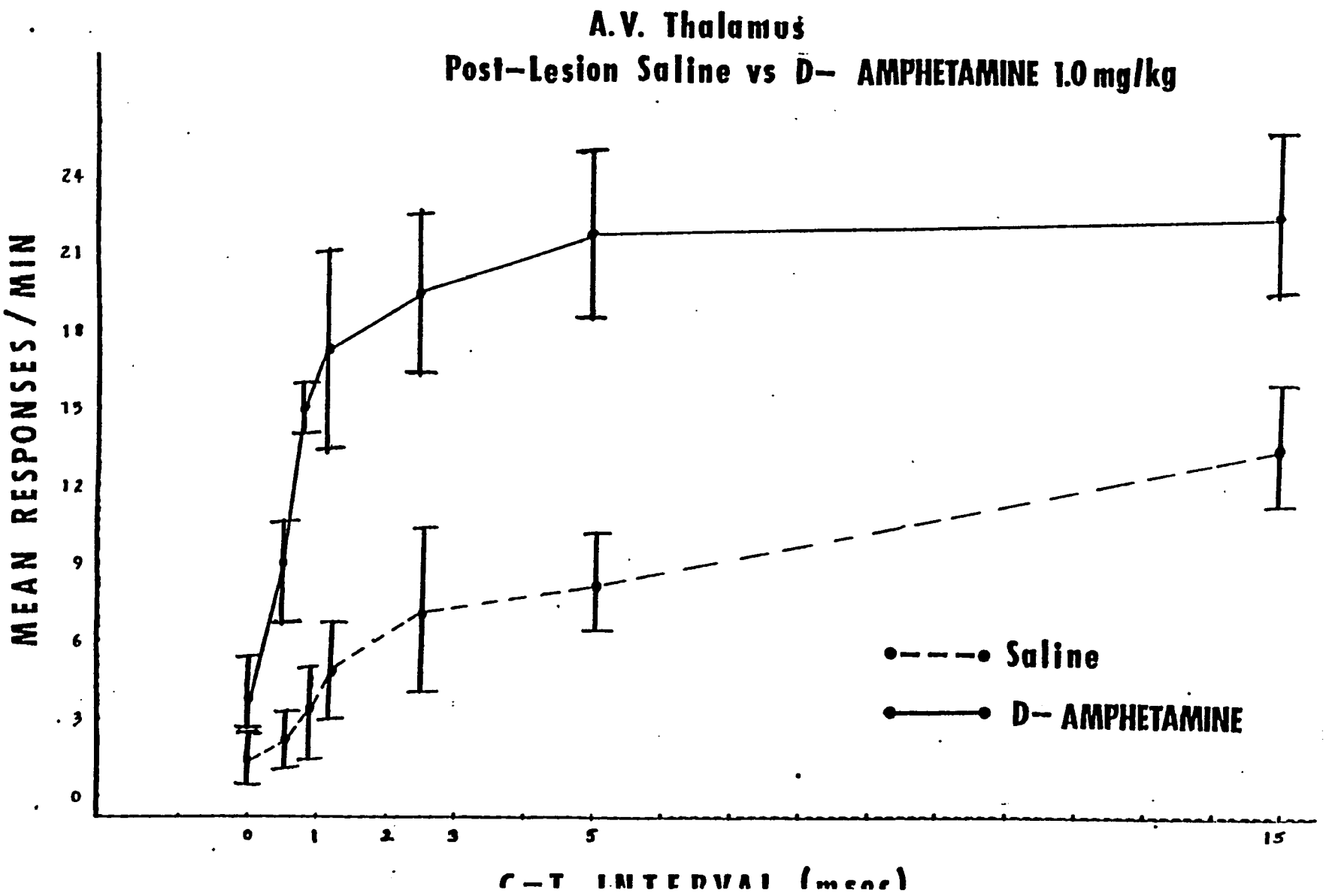

A.V. Thalamus
Post-Lesion Saline vs D- AMPHETAMINE 1.0 mg/kg
MEAN RESPONSES / MIN
24
21
18
15
12
9
6
3
0
0
1
2
3
5
15
C-T INTERVAL (msec)
Saline
D- AMPHETAMINE

Figure 13

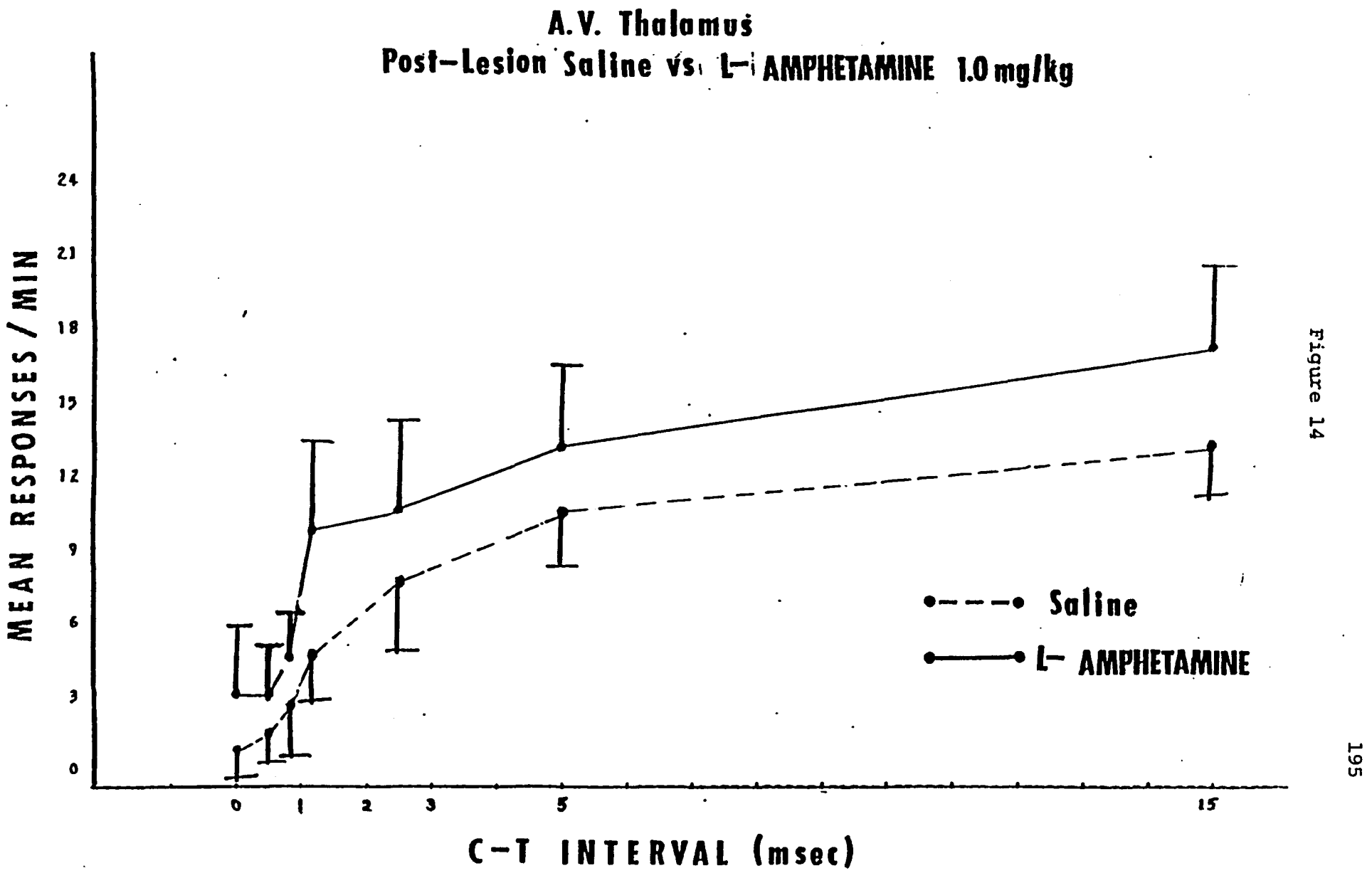

A.V. Thalamus
Post-Lesion Saline vs. L-AMPHETAMINE 1.0 mg/kg
MEAN RESPONSES / MIN
24
21
18
15
12
9
6
3
0
0
1
2
3
5
15
C-T INTERVAL (msec)
Saline
L- AMPHETAMINE

Figure 14

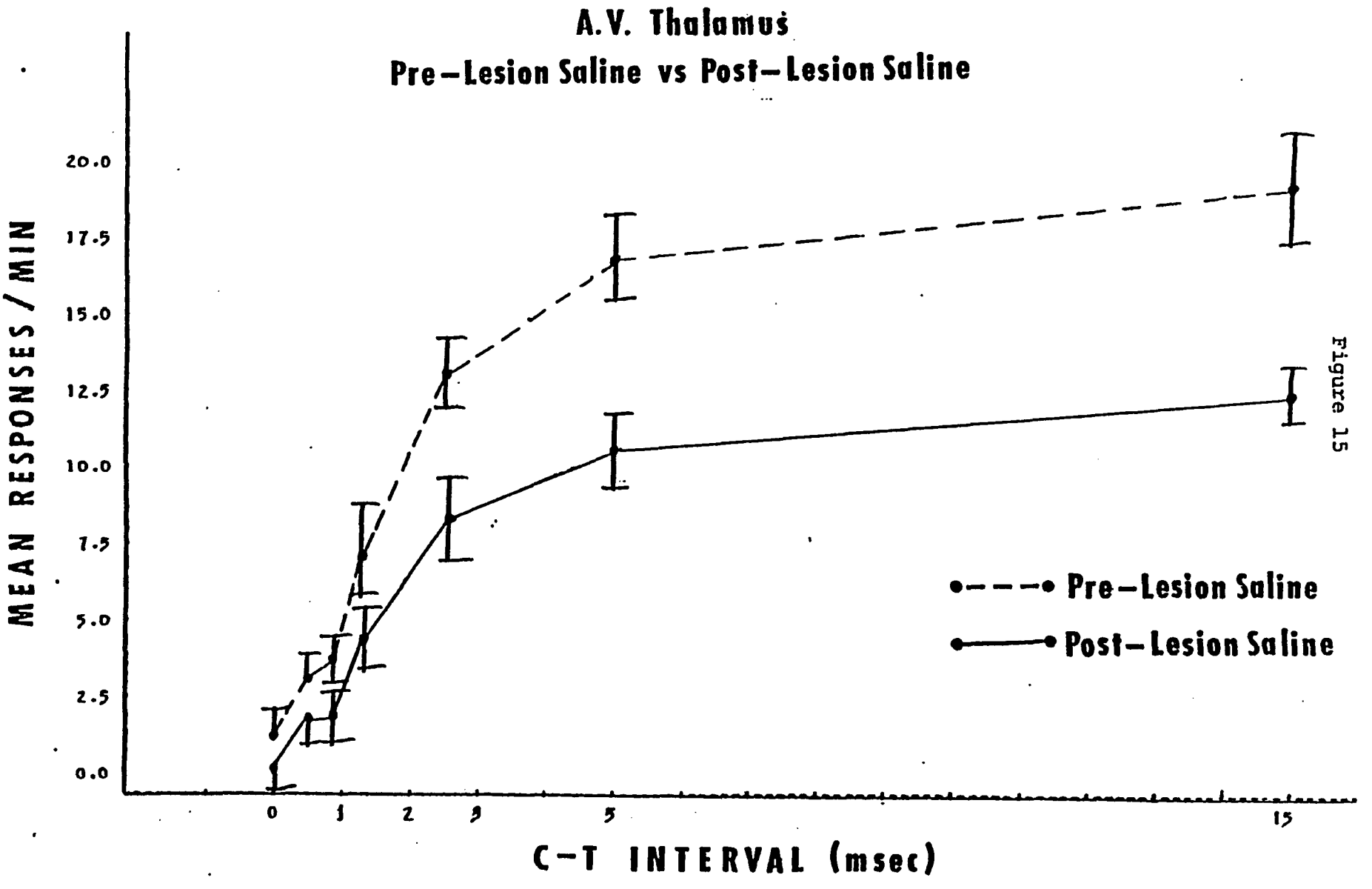

A.V. Thalamus
Pre–Lesion Saline vs Post–Lesion Saline
MEAN RESPONSES / MIN
20.0
17.5
15.0
12.5
10.0
7.5
5.0
2.5
0.0
0
1
2
3
5
15
C–T INTERVAL (msec)
Pre–Lesion Saline
Post–Lesion Saline

Figure 15

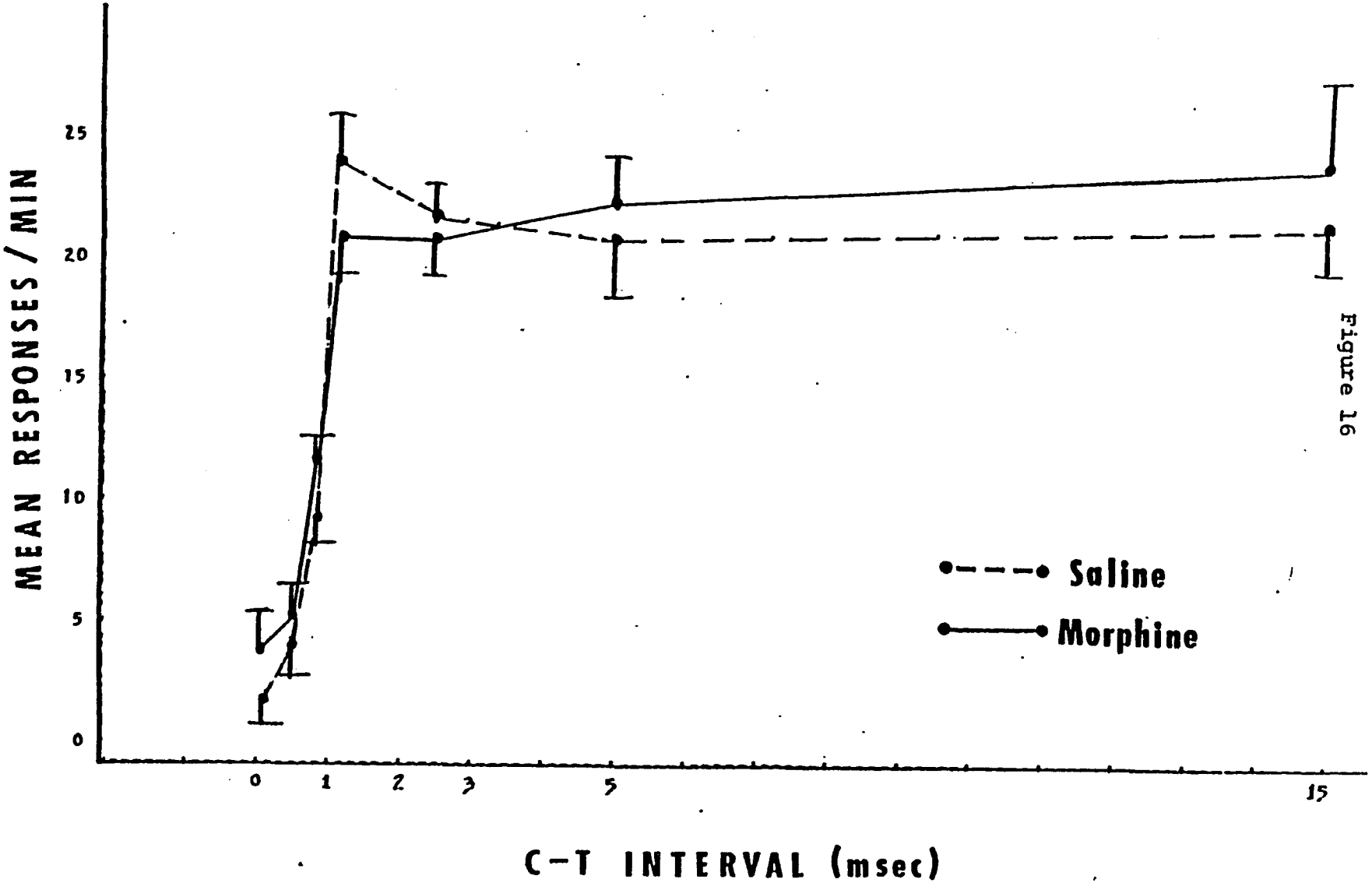

IC
Pre-Lesion Saline vs Morphine 1.25mg/kg
MEAN RESPONSES / MIN
25
20
15
10
5
0
0
1
2
3
5
15
C-T INTERVAL (msec)
Saline
Morphine

Figure 16

IC

Pre–Lesion Morphine 1.25mg/kg vs Morphine + Naloxone

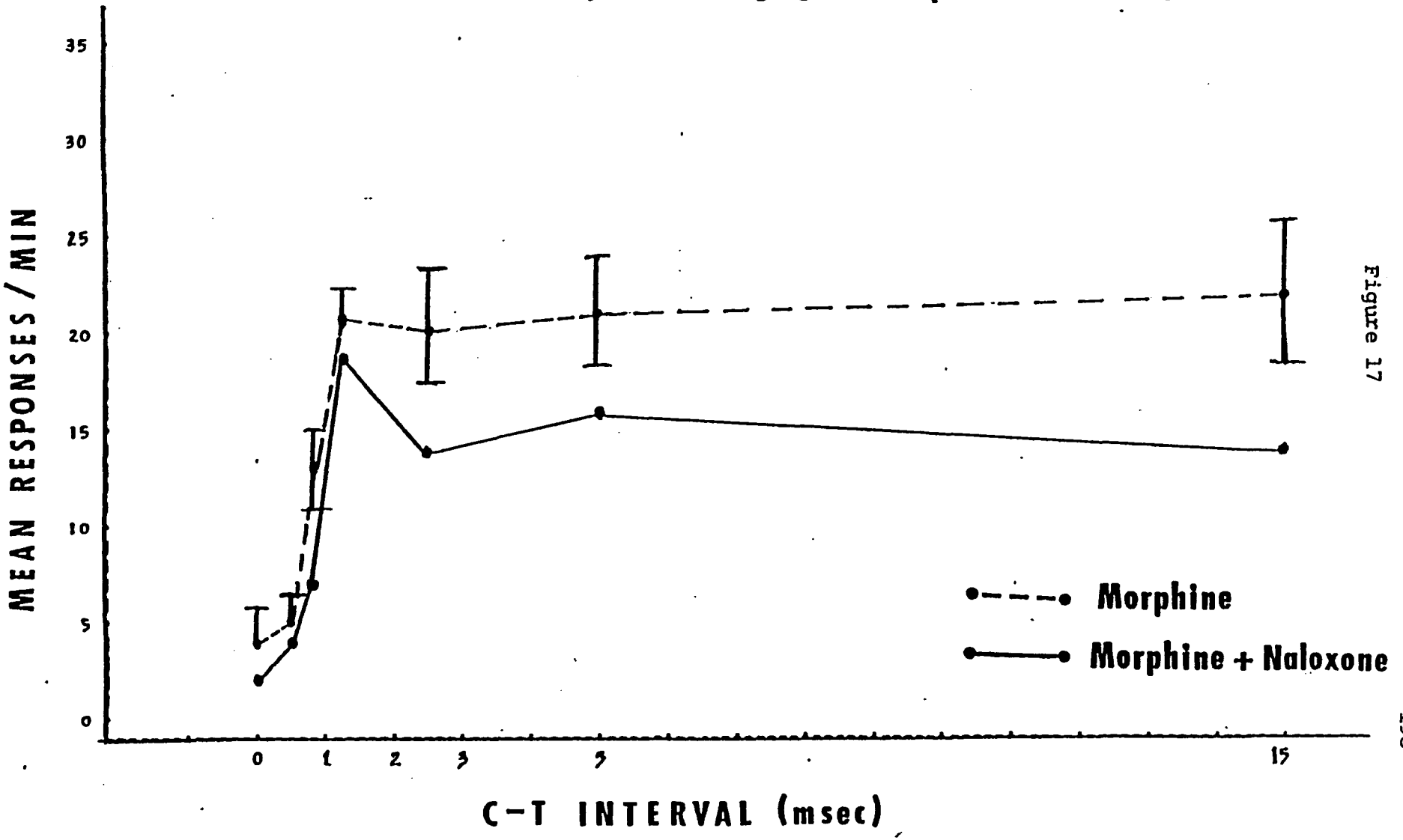


Figure 17

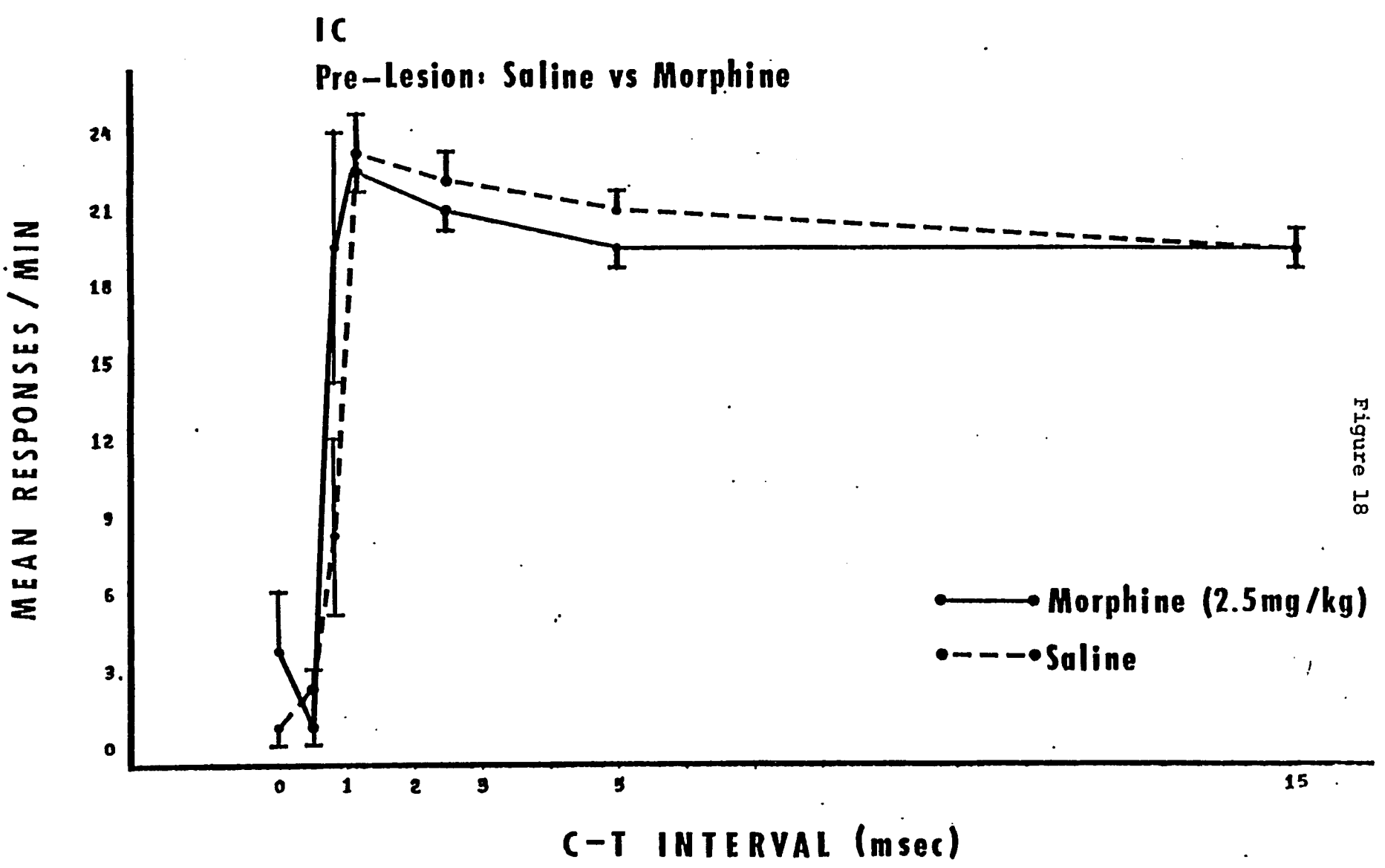

IC
Pre-Lesion: Saline vs Morphine
MEAN RESPONSES / MIN
24
21
18
15
12
9
6
3
0
0
1
2
3
5
15
C-T INTERVAL (msec)
Morphine (2.5mg/kg)
Saline

Figure 18

IC

Pre-Lesion Morphine (2.5mg/kg) vs Morphine + Naloxone

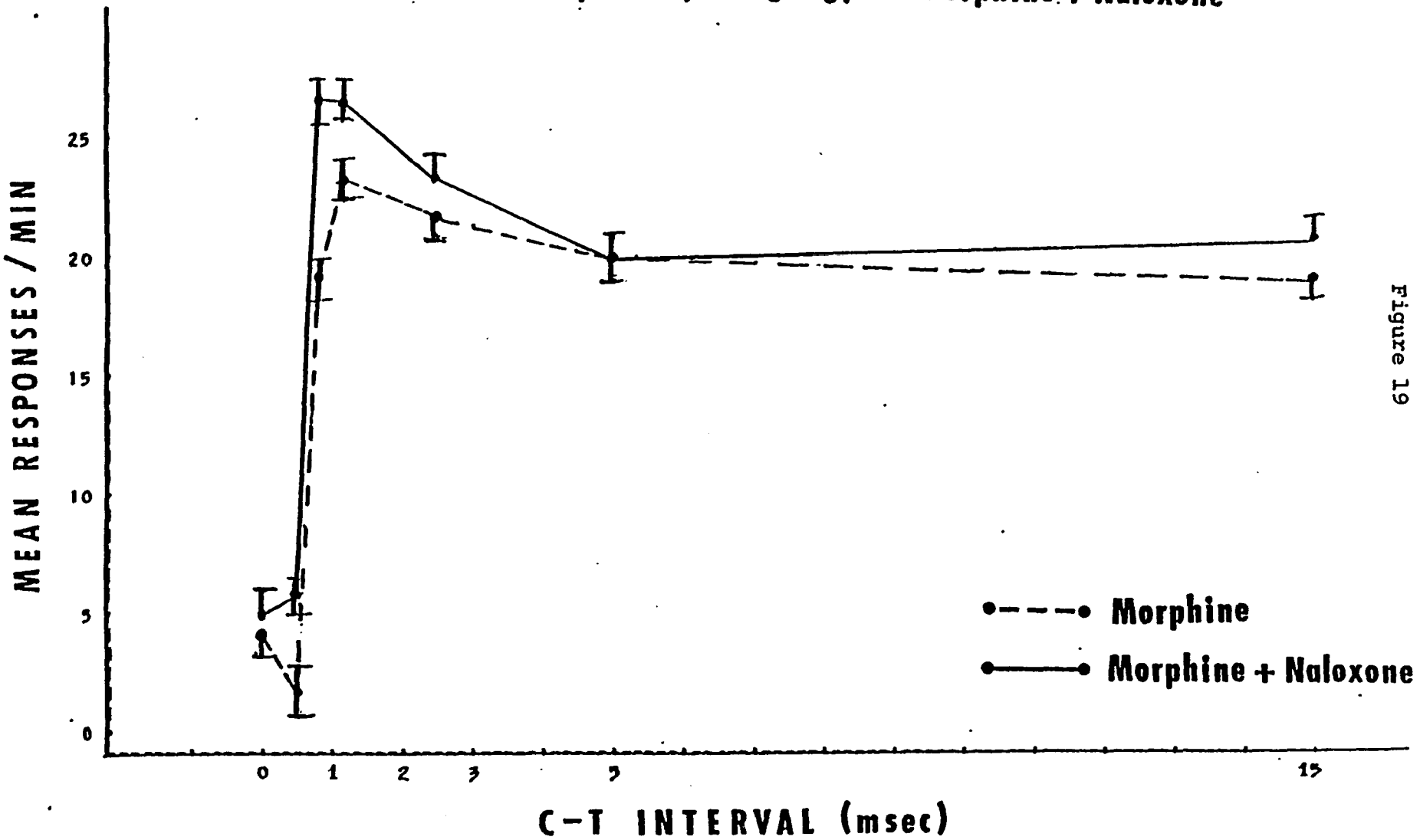


Figure 19

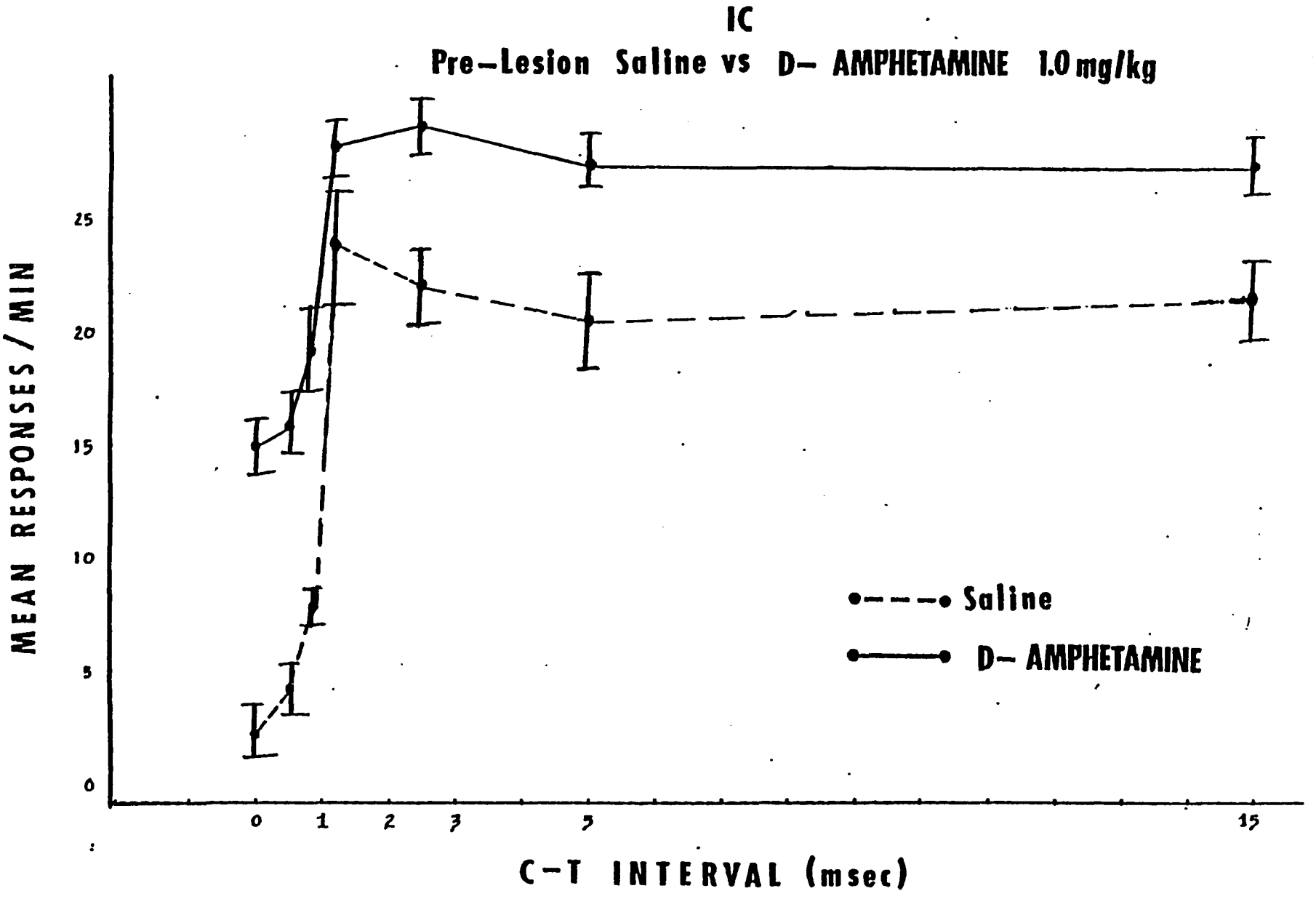

IC
Pre–Lesion Saline vs D– AMPHETAMINE 1.0 mg/kg
MEAN RESPONSES / MIN
25
20
15
10
5
0
0
1
2
3
5
15
C–T INTERVAL (msec)
Saline
D– AMPHETAMINE

Figure 20

IC

Pre–Lesion Saline vs D– AMPHETAMINE 2.0 mg/kg

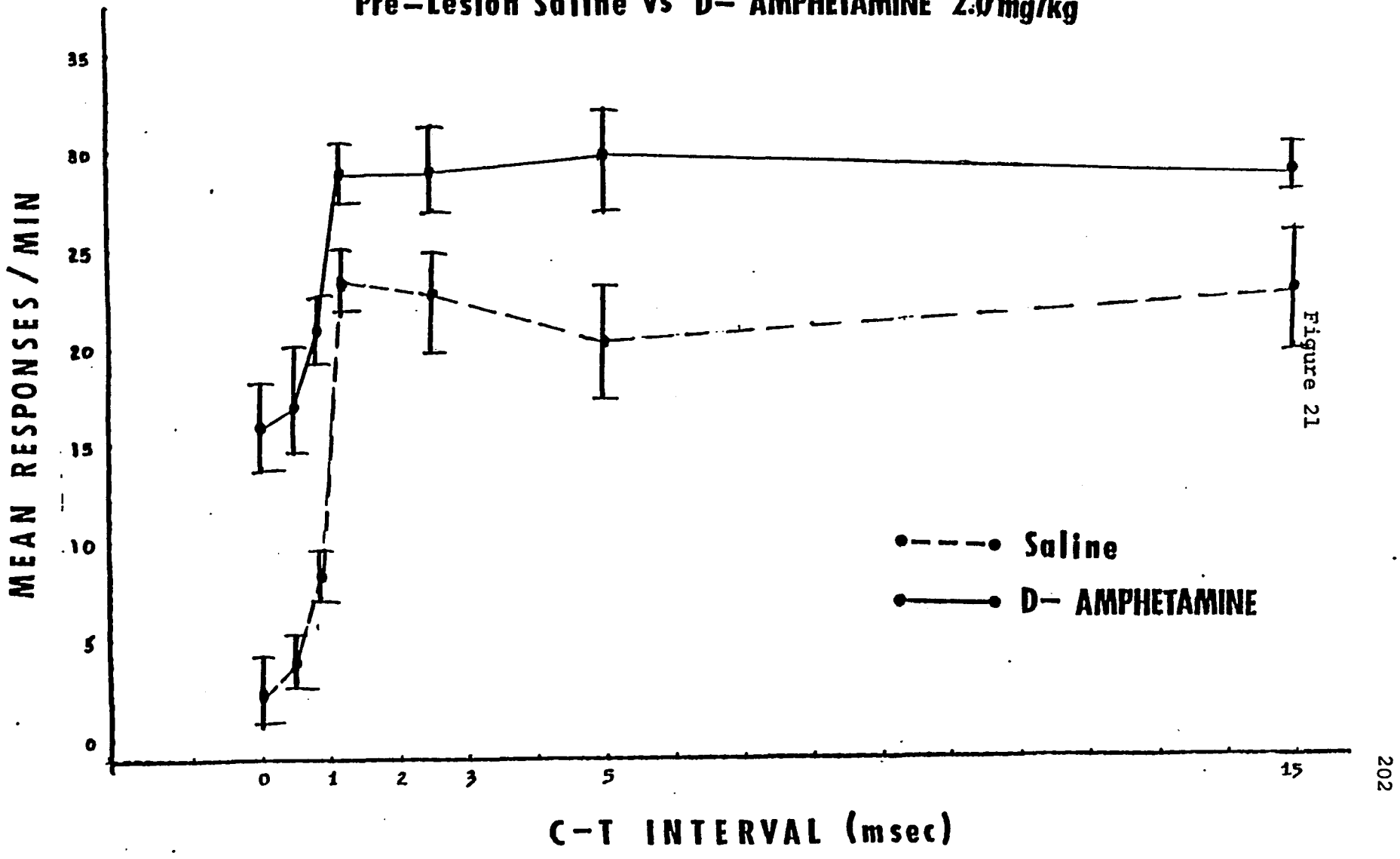


Figure 21

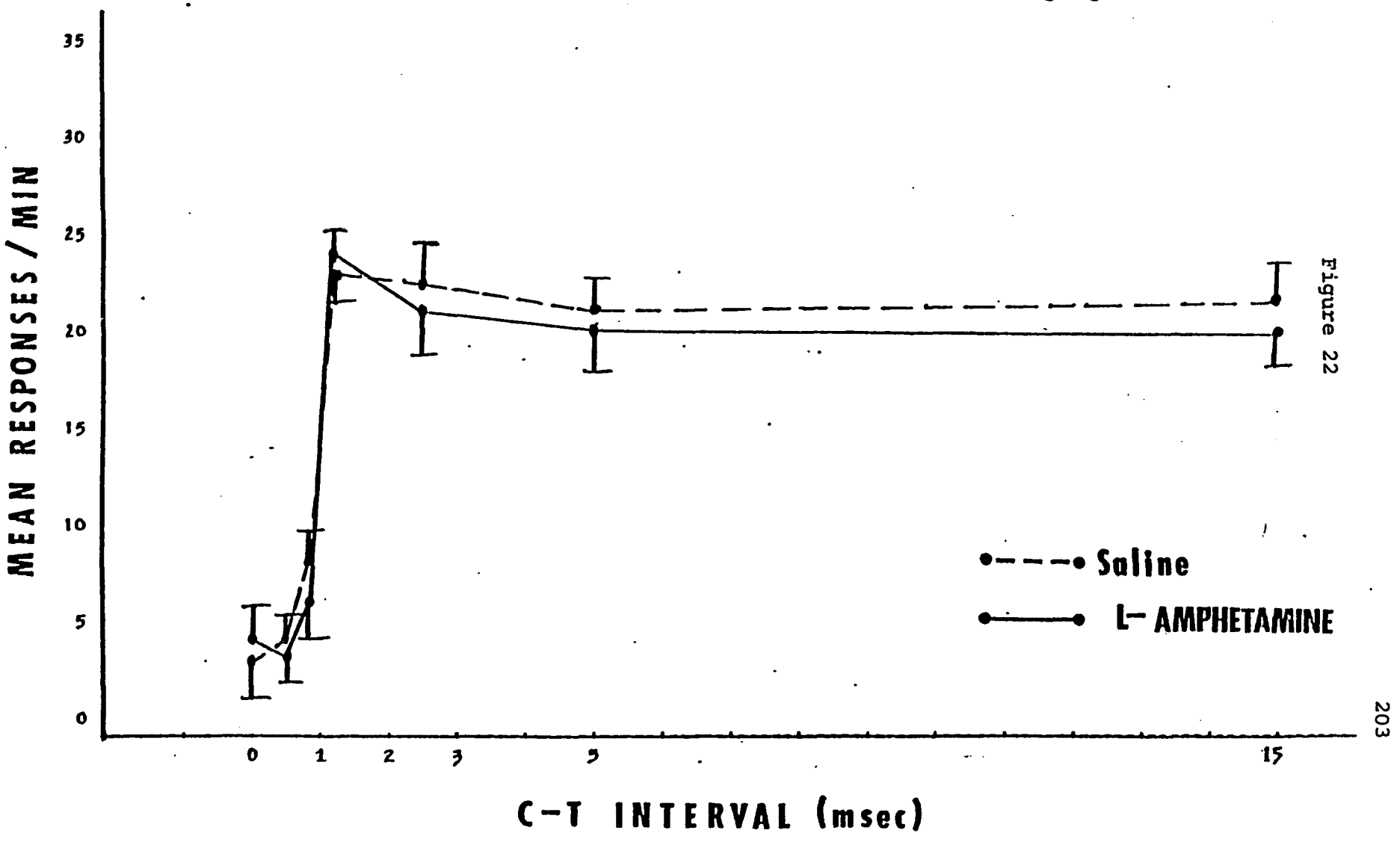

IC
Pre-Lesion Saline vs L- AMPHETAMINE 1.0 mg/kg
MEAN RESPONSES / MIN
35
30
25
20
15
10
5
0
0
1
2
3
5
15
C-T INTERVAL (msec)
Saline
L- AMPHETAMINE

Figure 22

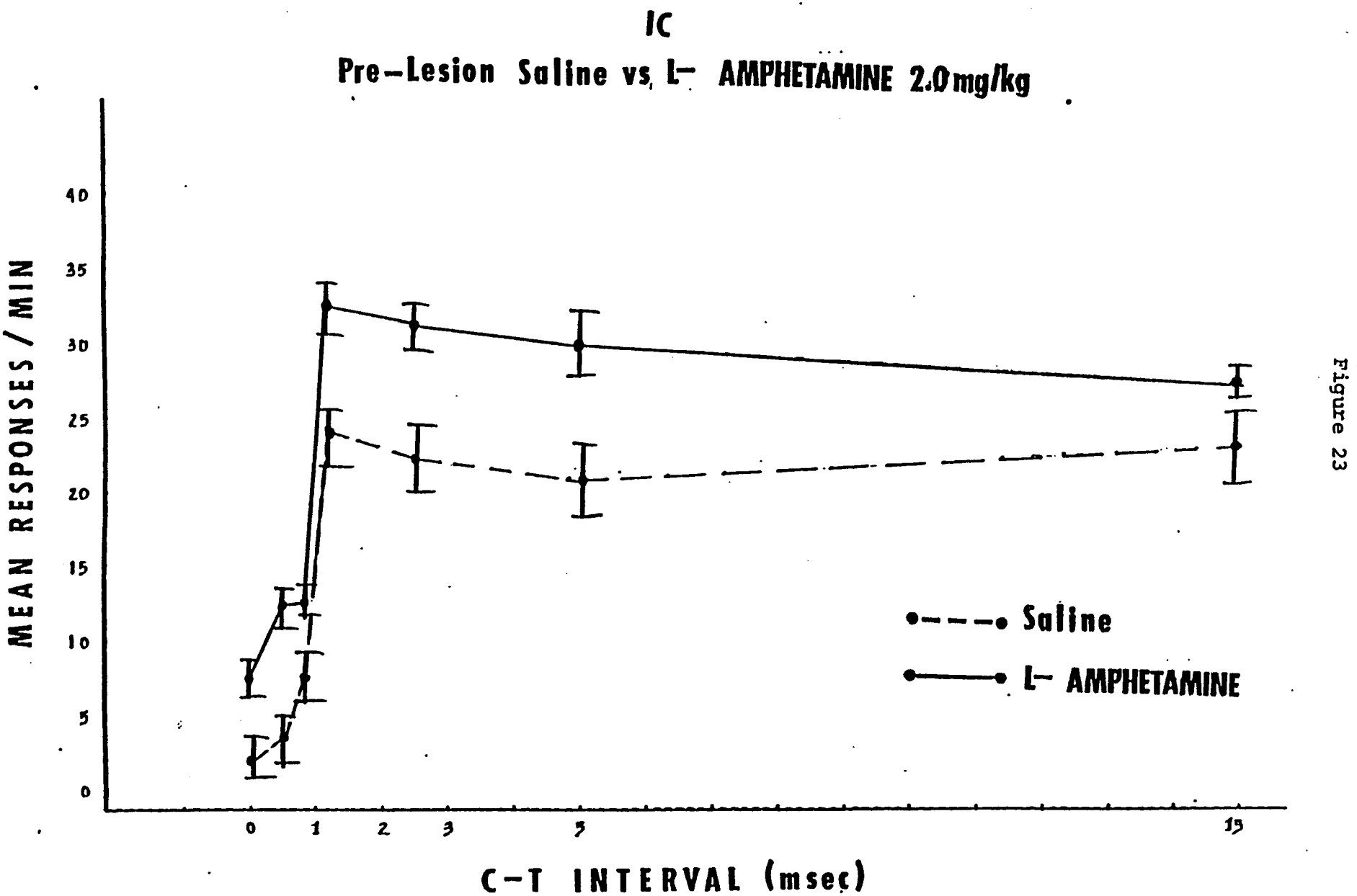

IC
Pre-Lesion Saline vs. L- AMPHETAMINE 2.0 mg/kg
MEAN RESPONSES / MIN
40
35
30
25
20
15
10
5
0
0
1
2
3
5
15
C-T INTERVAL (msec)
Saline
L- AMPHETAMINE

Figure 23

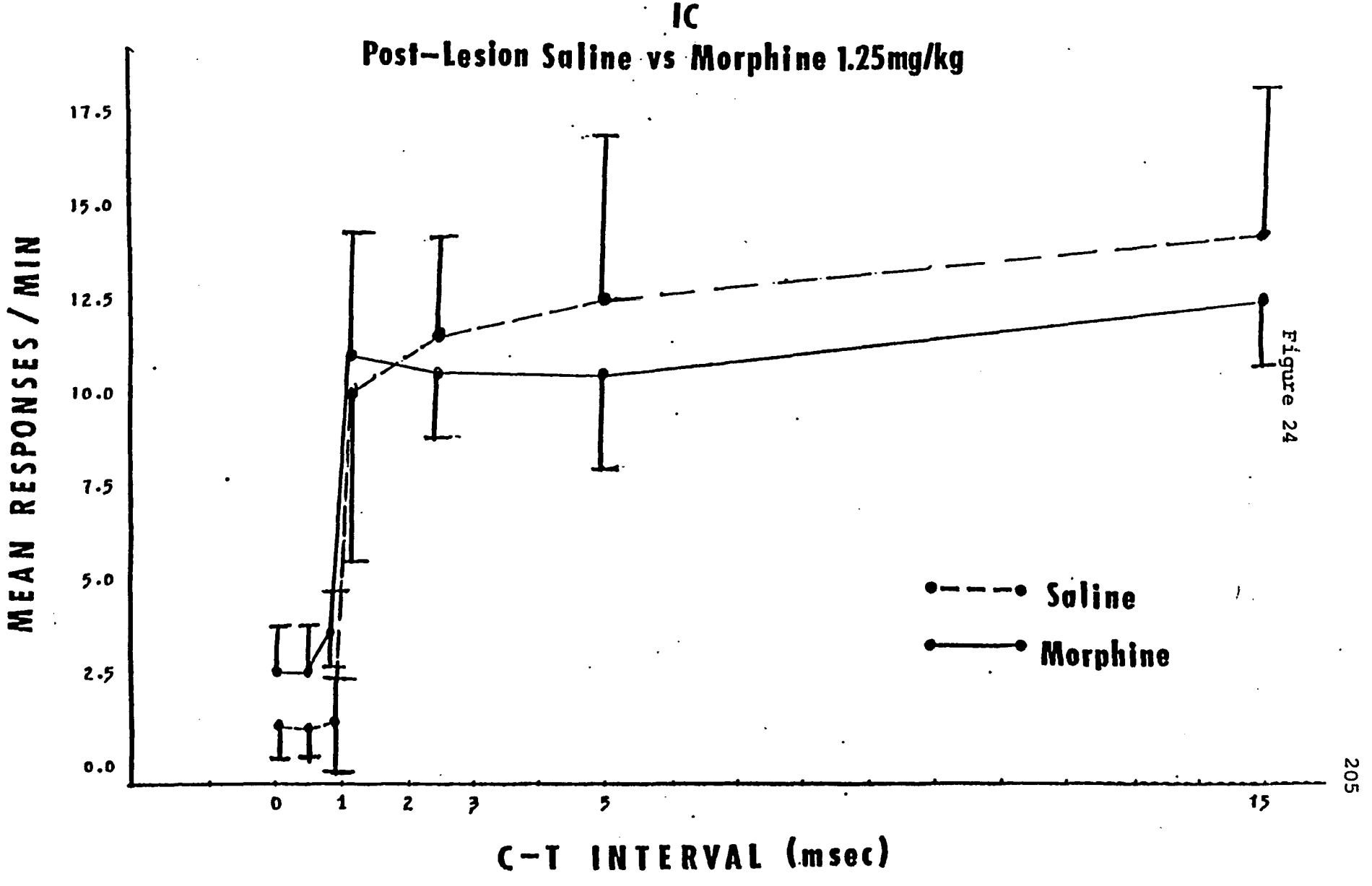

IC
Post-Lesion Saline vs Morphine 1.25mg/kg
MEAN RESPONSES / MIN
17.5
15.0
12.5
10.0
7.5
5.0
2.5
0.0
0
1
2
3
5
15
C-T INTERVAL (msec)
Saline
Morphine

Figure 24

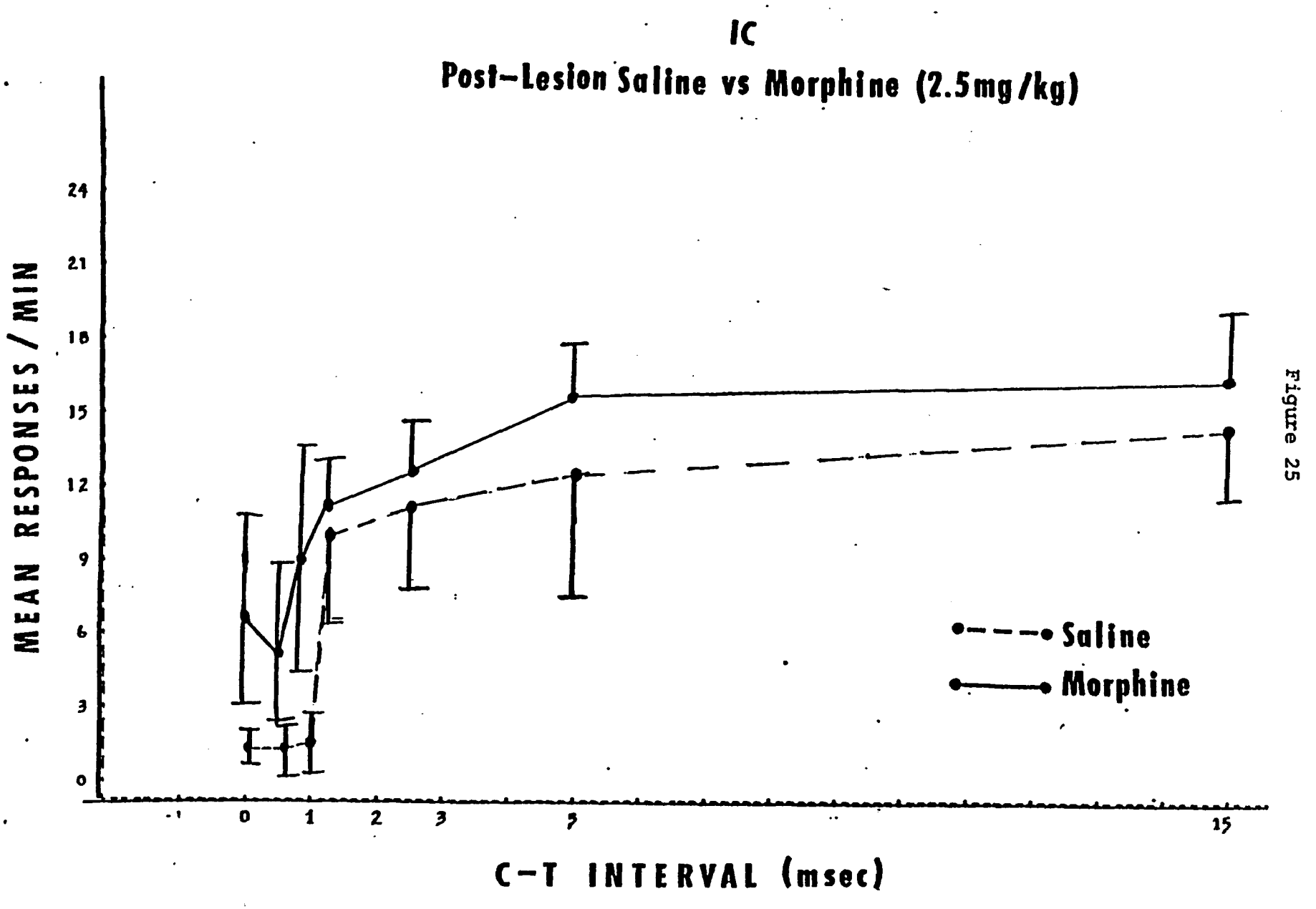

IC
Post-Lesion Saline vs Morphine (2.5mg/kg)
MEAN RESPONSES / MIN
24
21
18
15
12
9
6
3
0
-1
0
1
2
3
5
15
C-T INTERVAL (msec)
Saline
Morphine

Figure 25

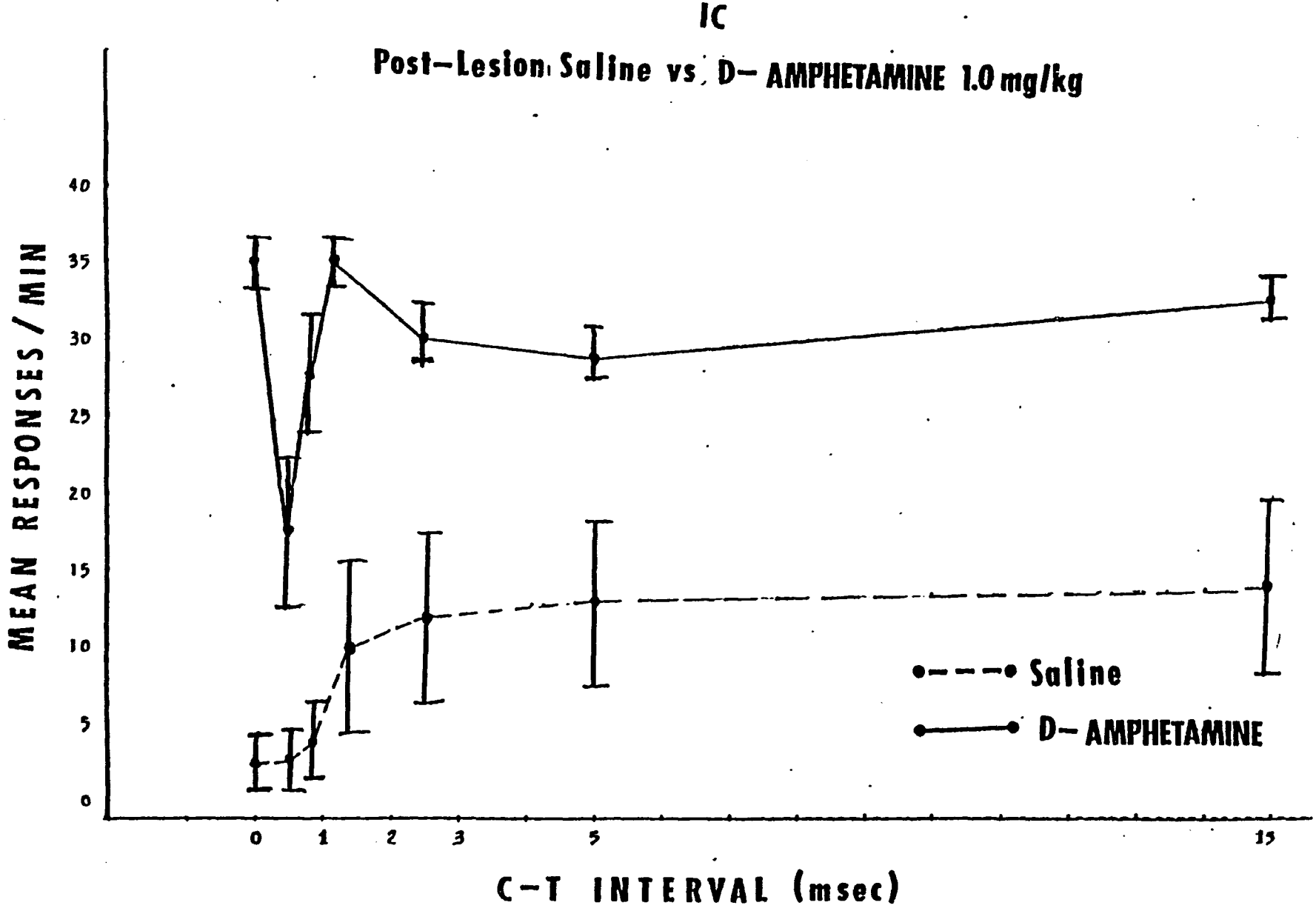

IC
Post-Lesion Saline vs D- AMPHETAMINE 1.0 mg/kg
MEAN RESPONSES / MIN
40
35
30
25
20
15
10
5
0
0
1
2
3
5
15
C-T INTERVAL (msec)
Saline
D- AMPHETAMINE

Figure 26

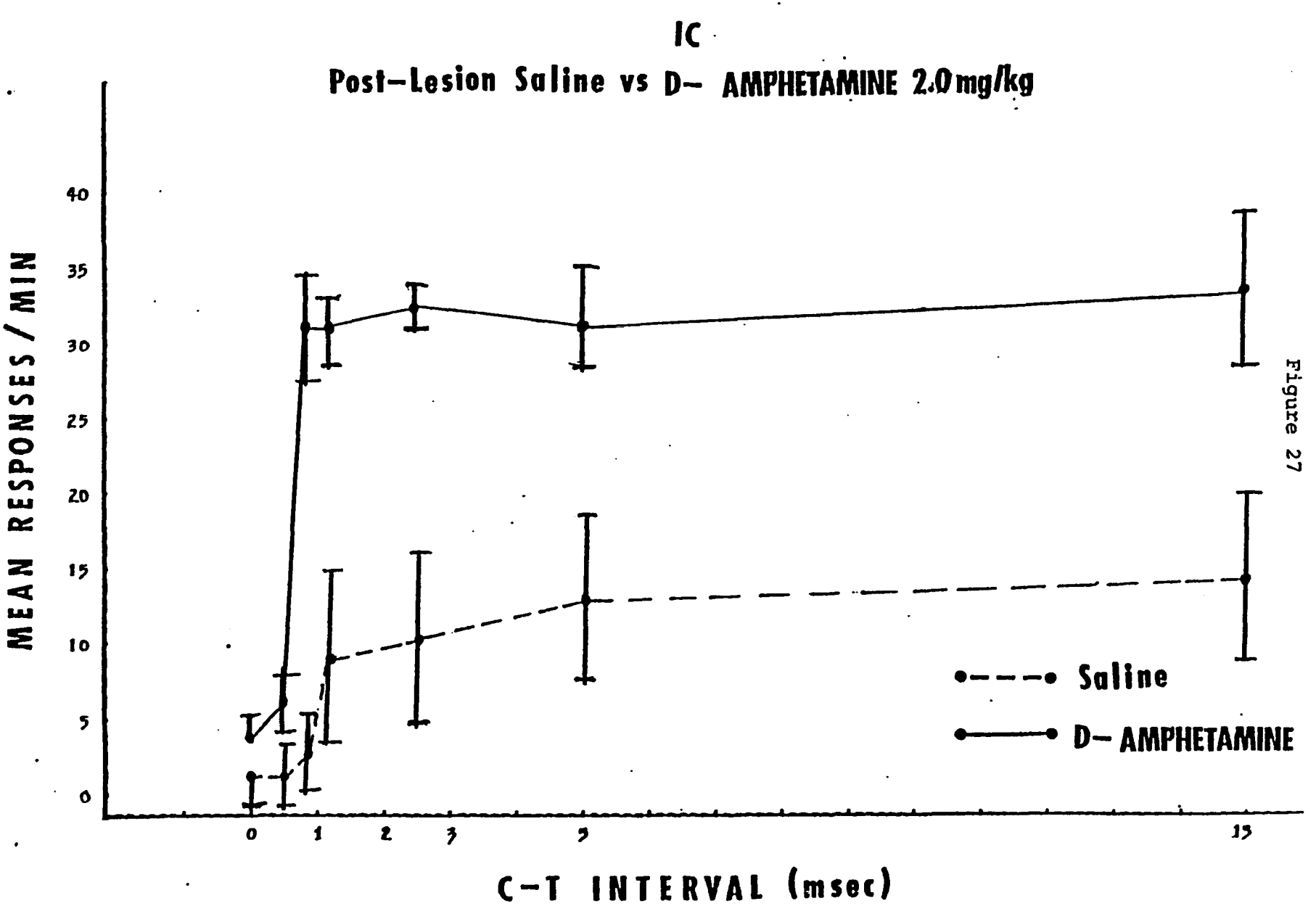

IC
Post-Lesion Saline vs D- AMPHETAMINE 2.0mg/kg
MEAN RESPONSES / MIN
40
35
30
25
20
15
10
5
0
0
1
2
3
5
15
C-T INTERVAL (msec)
Saline
D- AMPHETAMINE

Figure 27

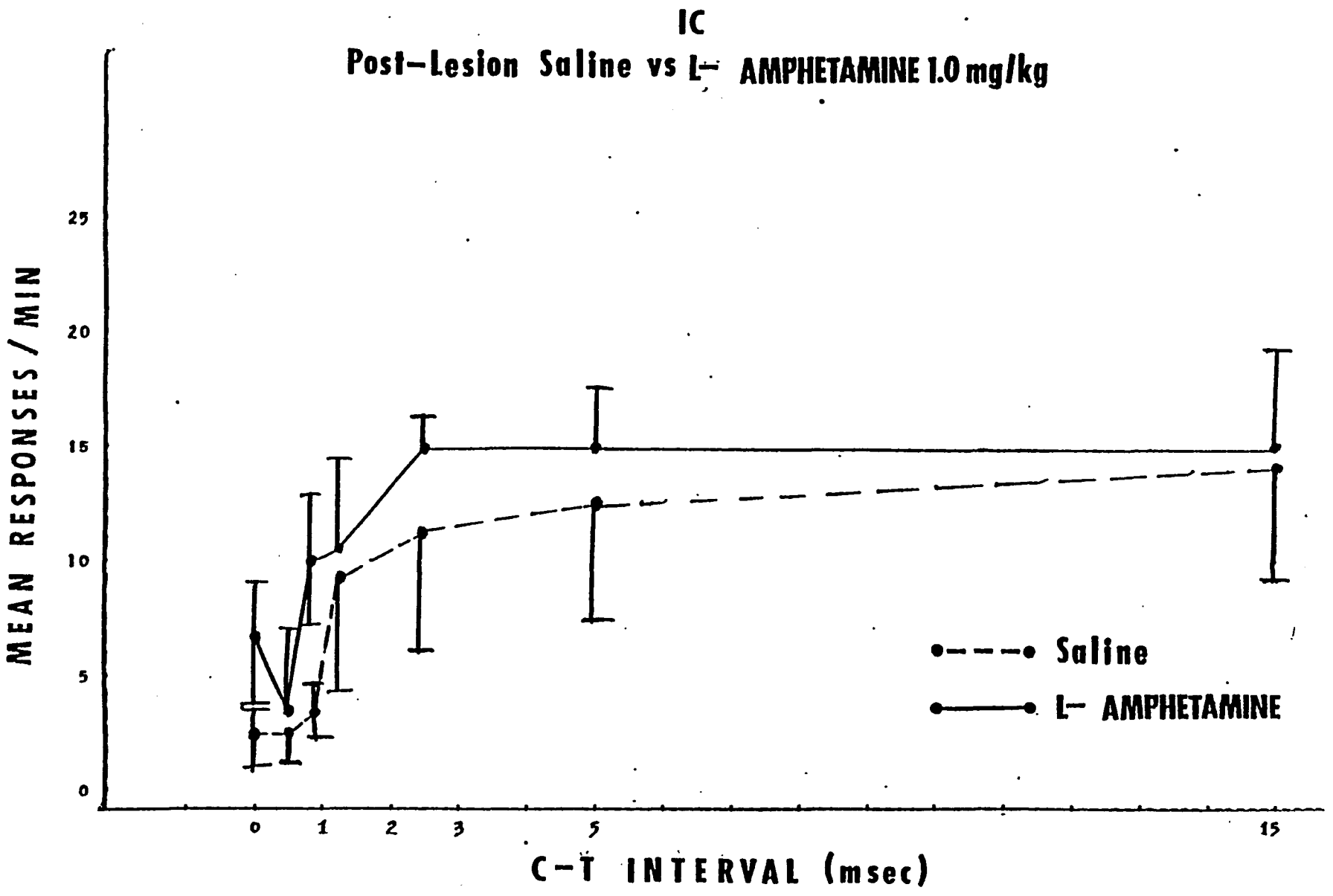

IC
Post-Lesion Saline vs L- AMPHETAMINE 1.0 mg/kg
MEAN RESPONSES / MIN
25
20
15
10
5
0
0
1
2
3
5
15
C-T INTERVAL (msec)
Saline
L- AMPHETAMINE

Figure 28

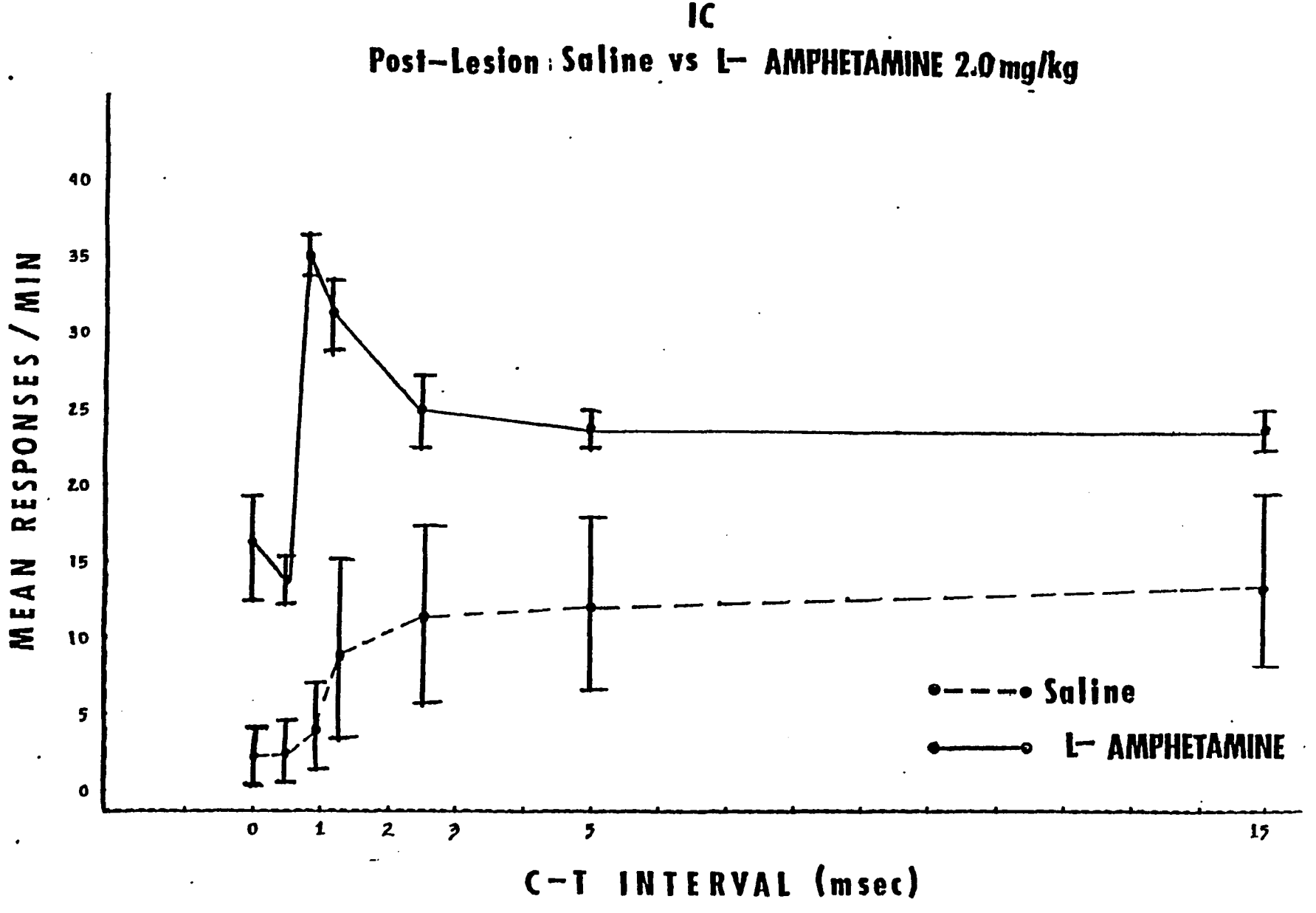

IC
Post-Lesion : Saline vs L- AMPHETAMINE 2.0 mg/kg
MEAN RESPONSES / MIN
40
35
30
25
20
15
10
5
0
0
1
2
3
5
15
C-T INTERVAL (msec)
Saline
L- AMPHETAMINE

Figure 29

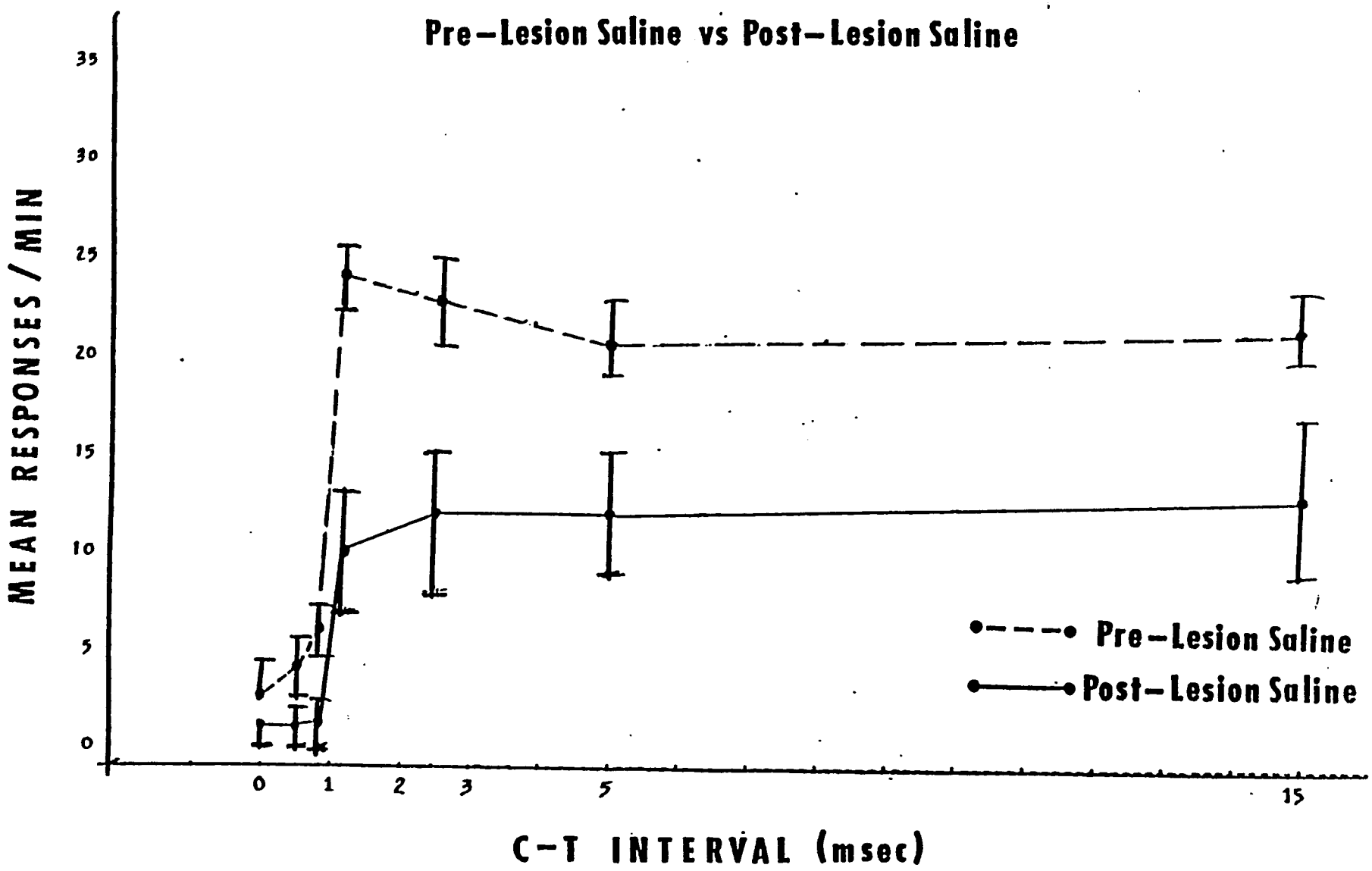

IC
Pre–Lesion Saline vs Post–Lesion Saline
MEAN RESPONSES / MIN
35
30
25
20
15
10
5
0
0
1
2
3
5
15
C–T INTERVAL (msec)
Pre–Lesion Saline
Post–Lesion Saline

Figure 30

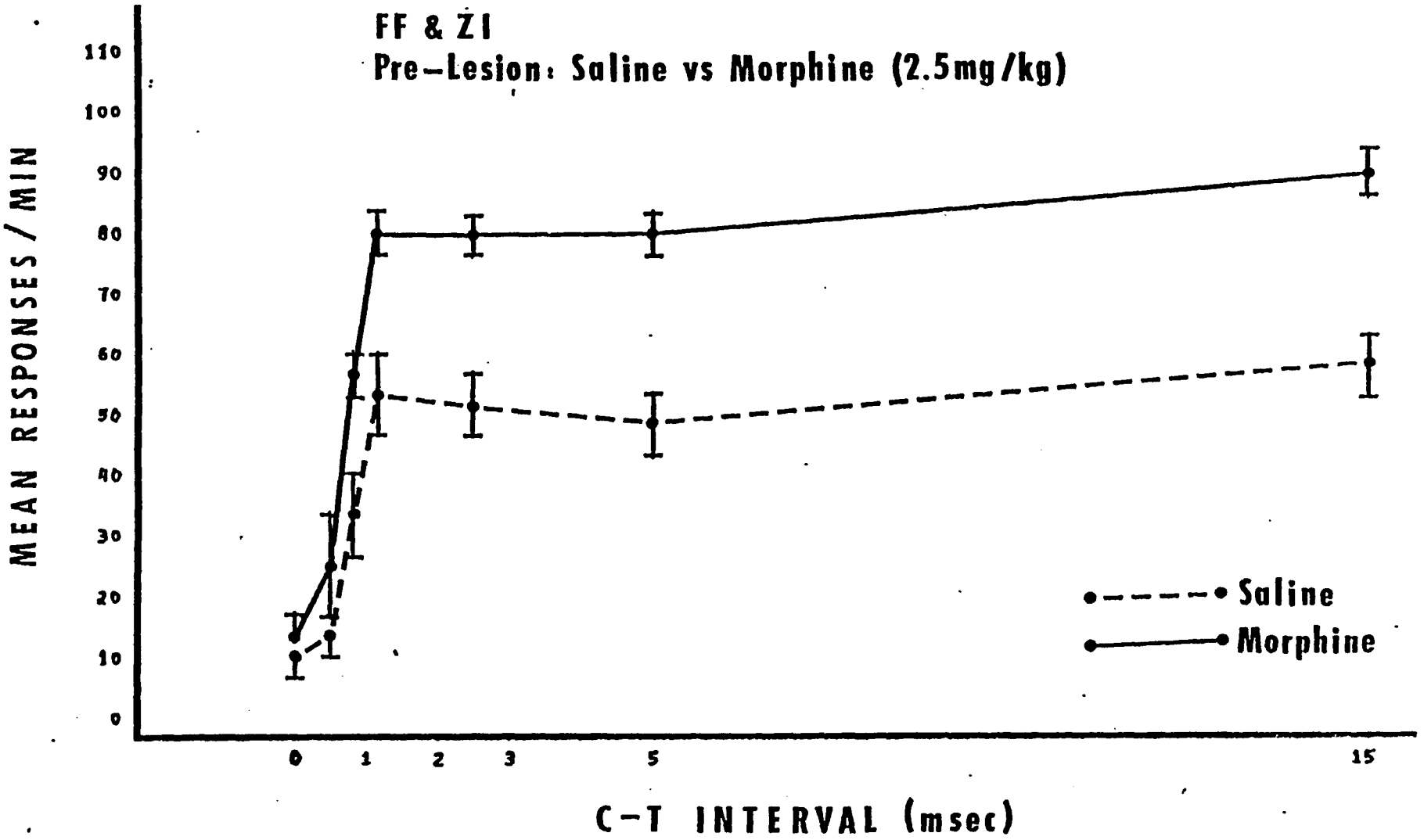

FF & ZI
Pre-Lesion: Saline vs Morphine (2.5mg/kg)
MEAN RESPONSES / MIN
110
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
5
15
C-T INTERVAL (msec)
Saline
Morphine

Figure 31

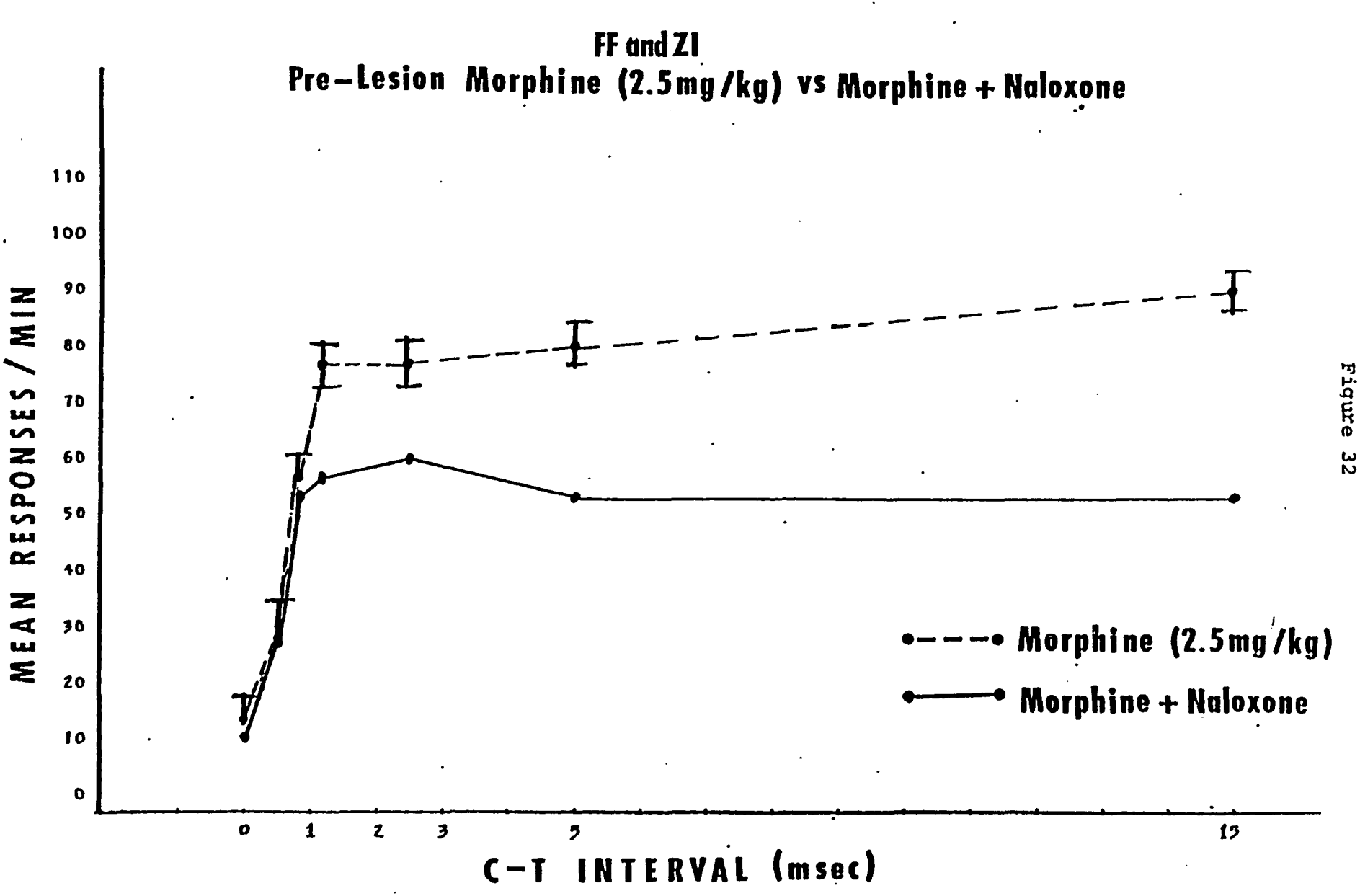

FF and ZI
Pre-Lesion Morphine (2.5mg/kg) vs Morphine + Naloxone
MEAN RESPONSES / MIN
110
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
5
15
C-T INTERVAL (msec)
Morphine (2.5mg/kg)
Morphine + Naloxone

Figure 32

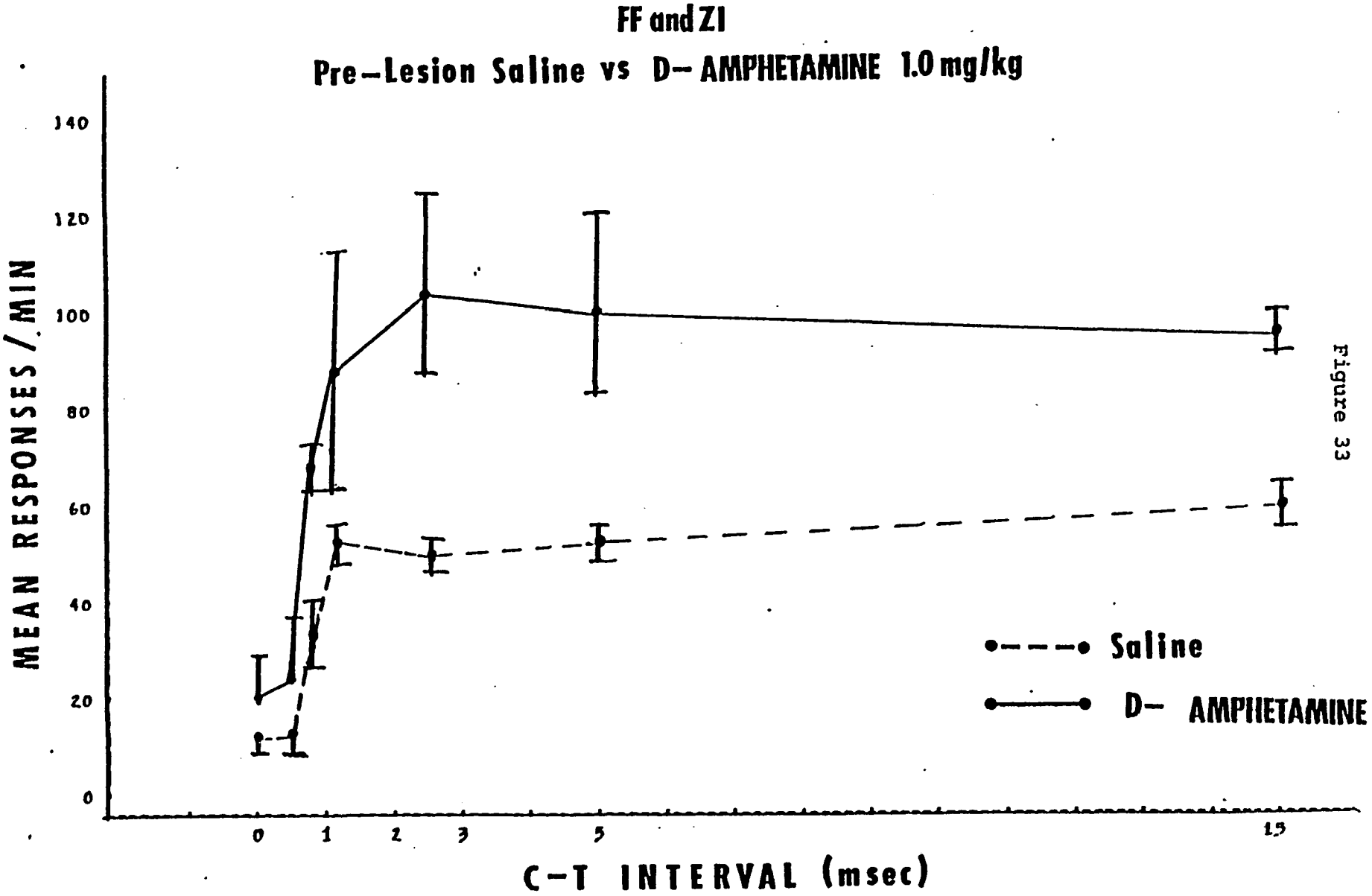

FF and ZI
Pre–Lesion Saline vs D– AMPHETAMINE 1.0 mg/kg
MEAN RESPONSES / MIN
140
120
100
80
60
40
20
0
0
1
2
3
5
15
C–T INTERVAL (msec)
Saline
D– AMPHETAMINE

Figure 33

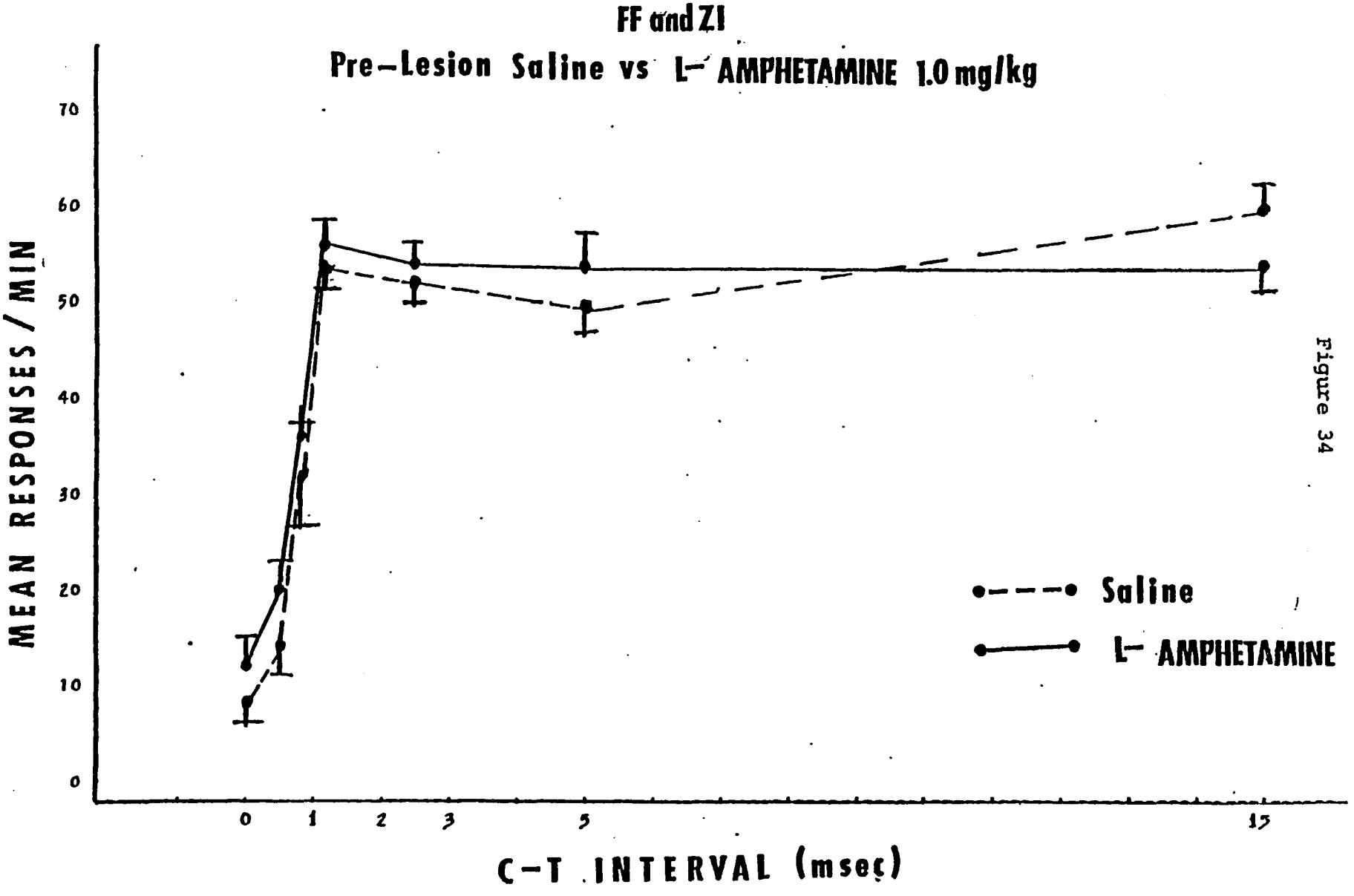

FF and ZI
Pre-Lesion Saline vs L- AMPHETAMINE 1.0 mg/kg
MEAN RESPONSES / MIN
70
60
50
40
30
20
10
0
0
1
2
3
5
15
C-T INTERVAL (msec)
Saline
L- AMPHETAMINE

Figure 34

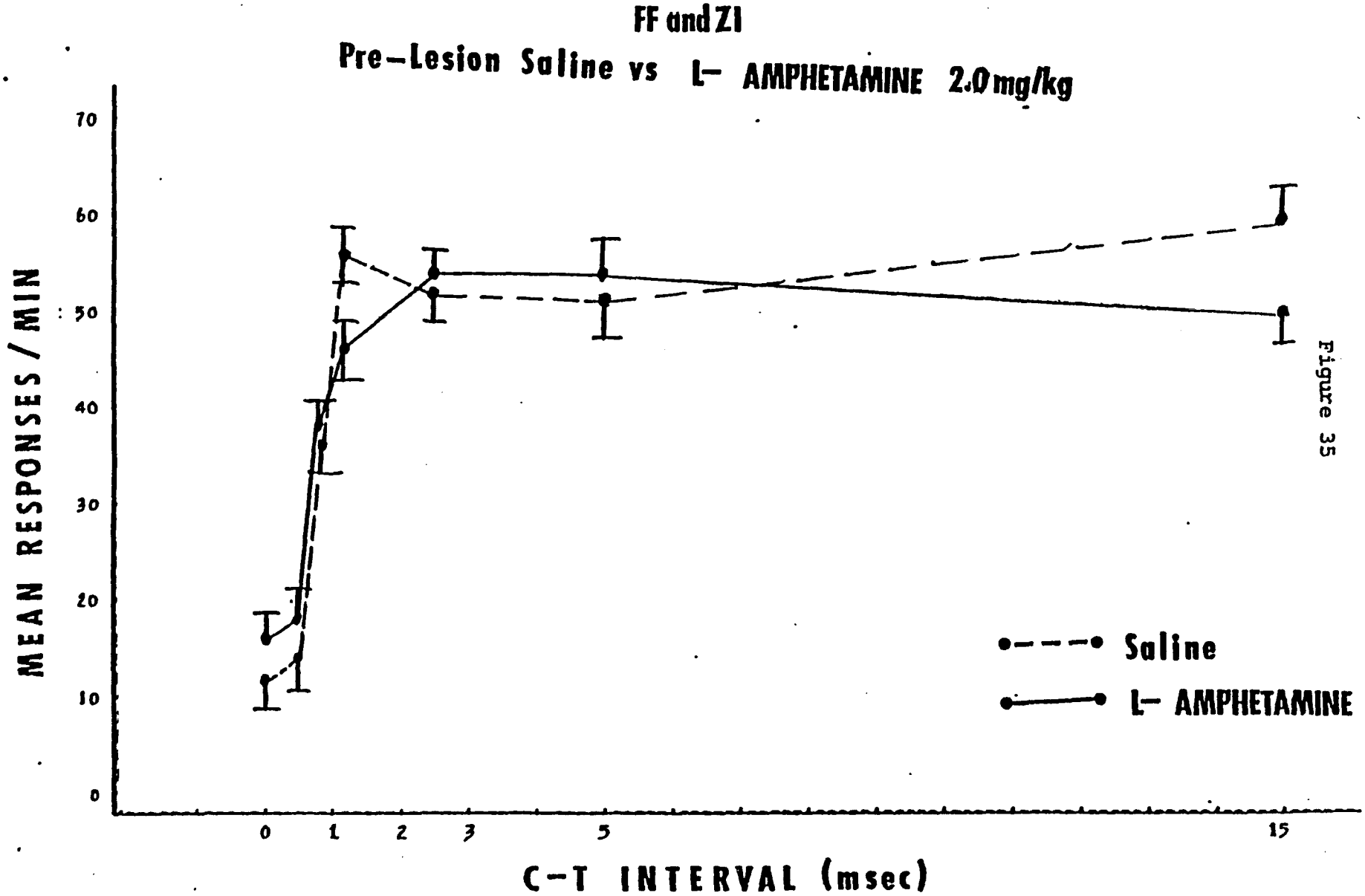

FF and ZI
Pre-Lesion Saline vs L- AMPHETAMINE 2.0 mg/kg
MEAN RESPONSES / MIN
70
60
50
40
30
20
10
0
0
1
2
3
5
15
C-T INTERVAL (msec)
Saline
L- AMPHETAMINE

Figure 35

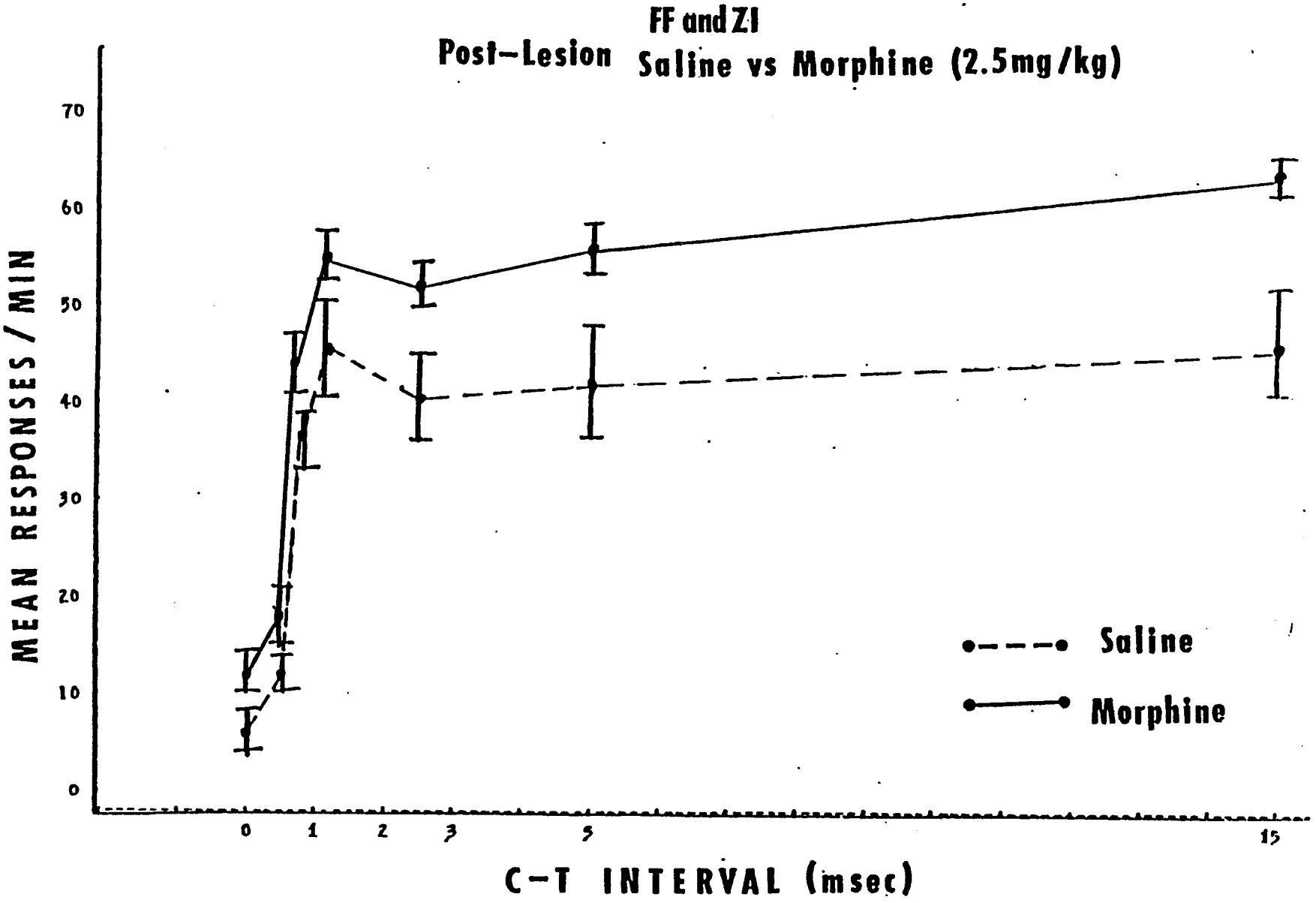

FF and ZI
Post-Lesion Saline vs Morphine (2.5mg/kg)
MEAN RESPONSES / MIN
70
60
50
40
30
20
10
0
0
1
2
3
5
15
C-T INTERVAL (msec)
Saline
Morphine

Figure 36

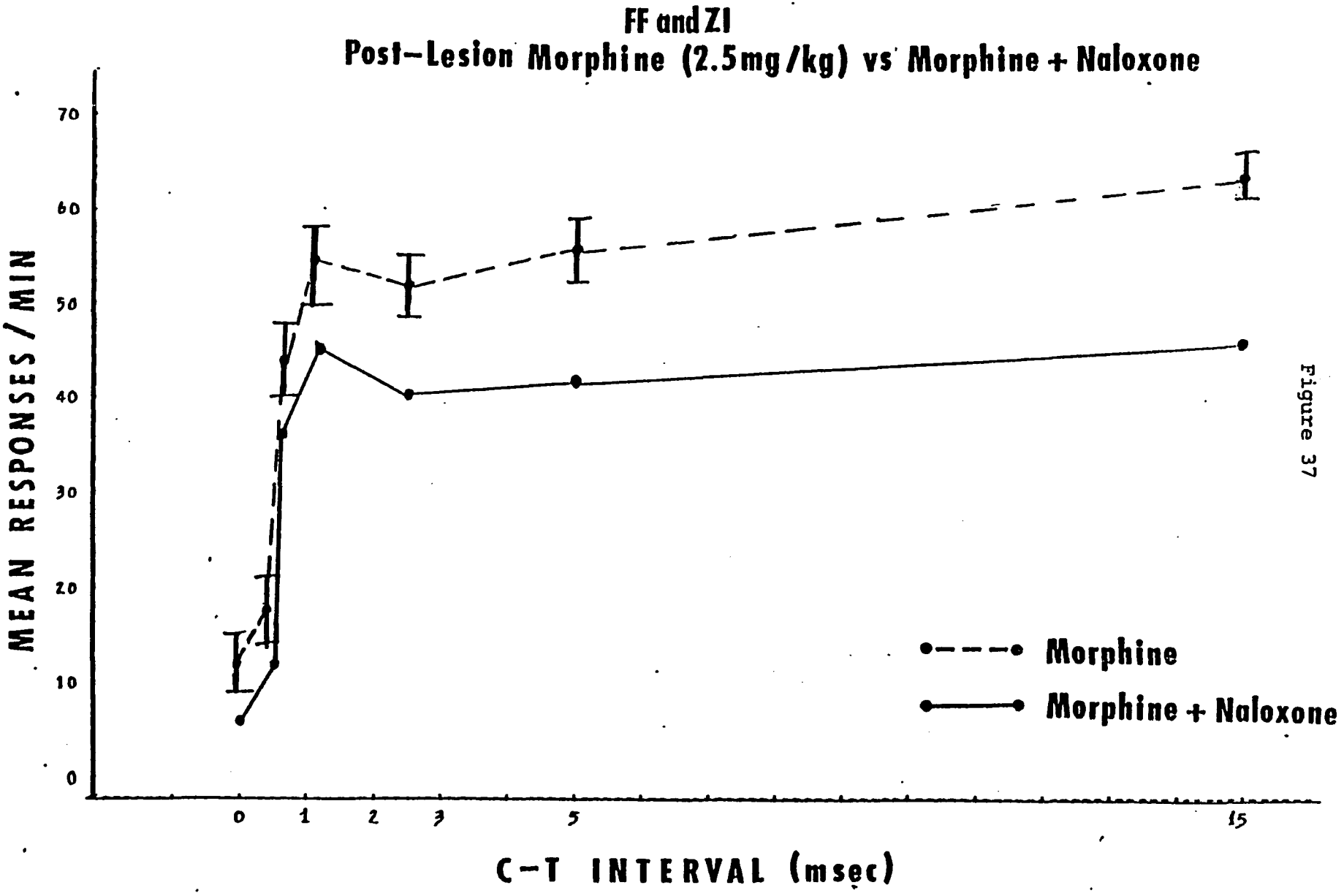

FF and ZI
Post-Lesion Morphine (2.5mg/kg) vs Morphine + Naloxone
MEAN RESPONSES / MIN
70
60
50
40
30
20
10
0
0
1
2
3
5
15
C-T INTERVAL (msec)
Morphine
Morphine + Naloxone

Figure 37

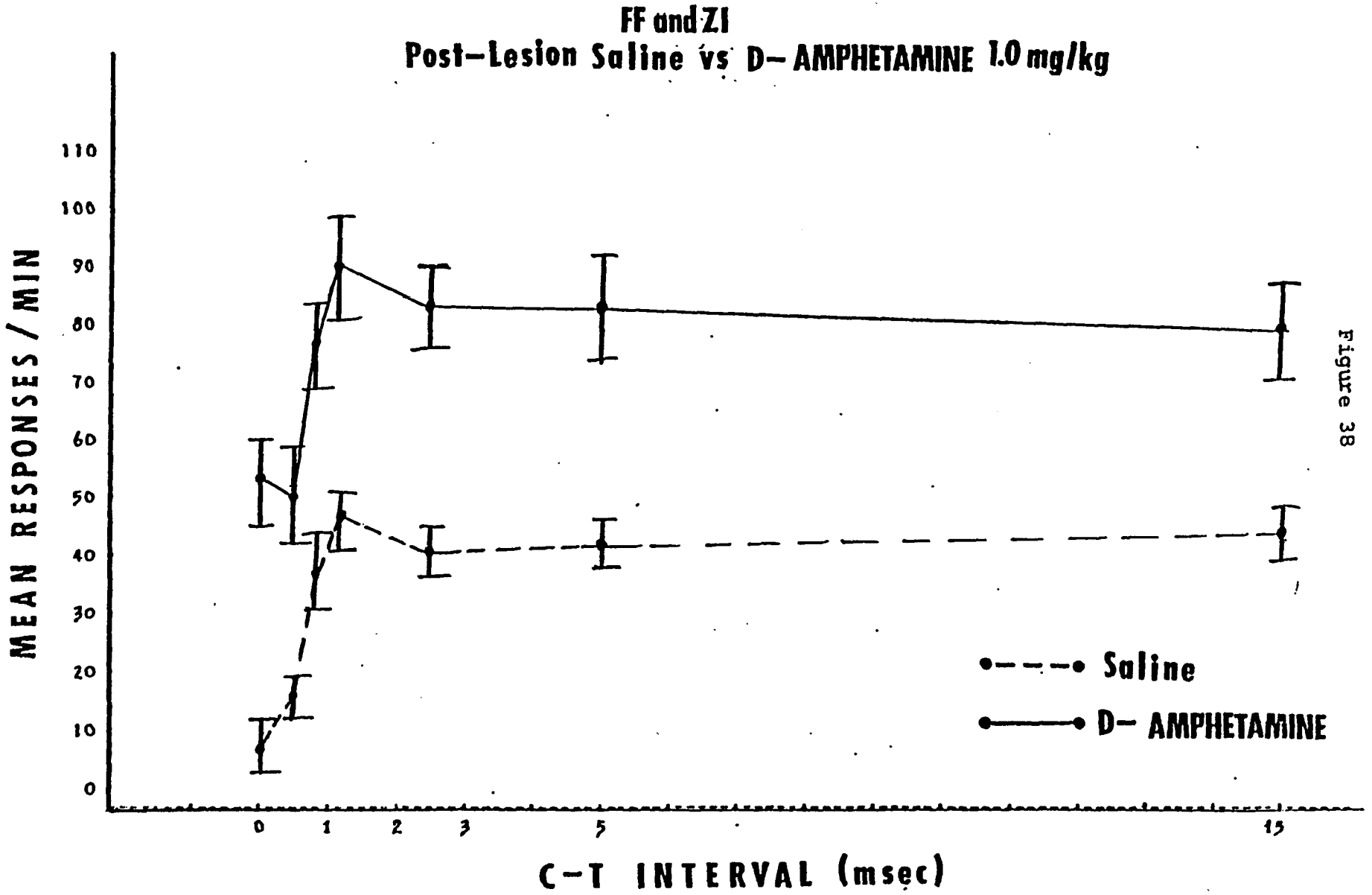

FF and ZI
Post-Lesion Saline vs D- AMPHETAMINE 1.0 mg/kg
MEAN RESPONSES / MIN
110
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
5
15
C-T INTERVAL (msec)
Saline
D- AMPHETAMINE

Figure 38

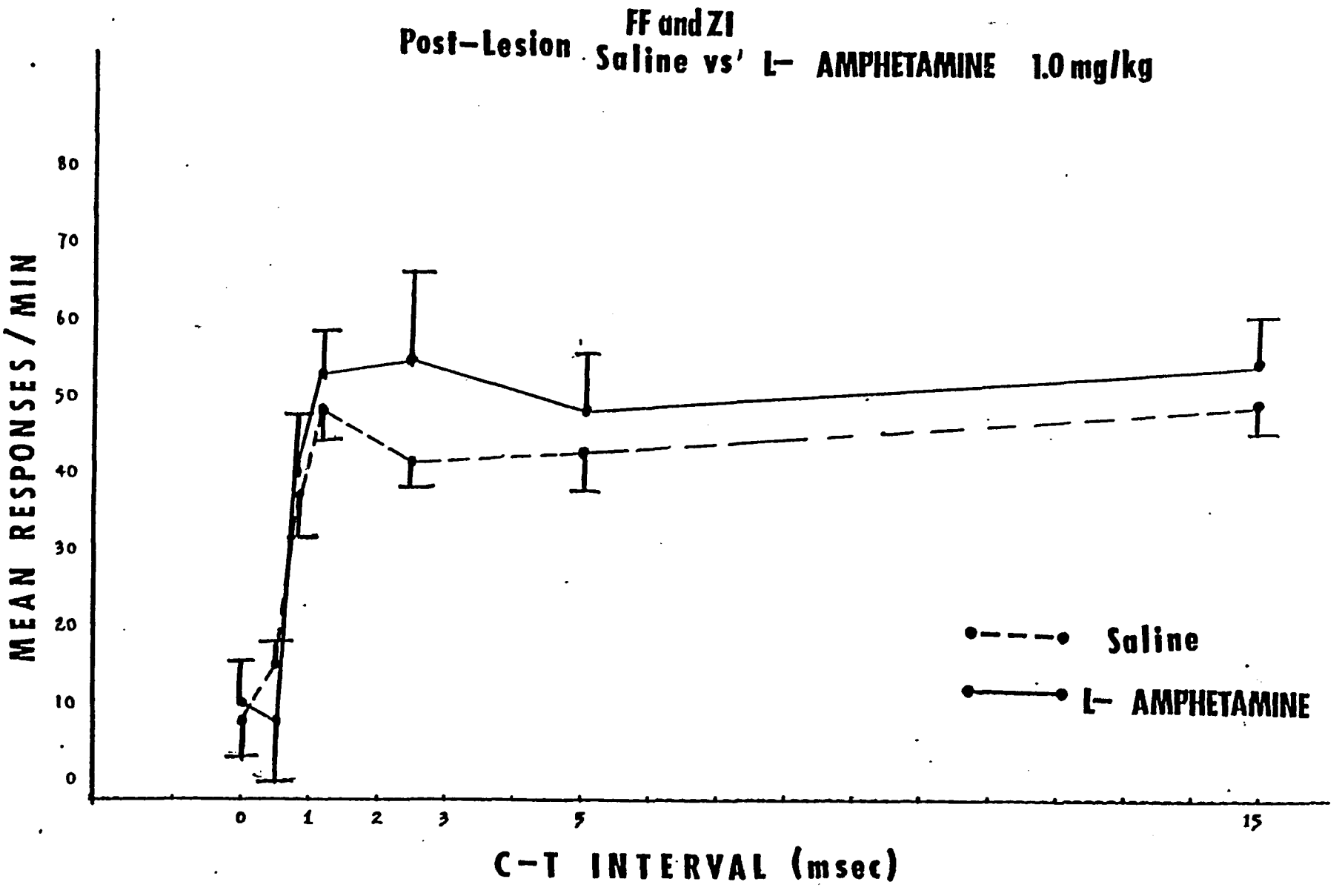

FF and ZI
Post-Lesion Saline vs' L- AMPHETAMINE 1.0 mg/kg
MEAN RESPONSES / MIN
80
70
60
50
40
30
20
10
0
0
1
2
3
5
15
C-T INTERVAL (msec)
Saline
L- AMPHETAMINE

Figure 39

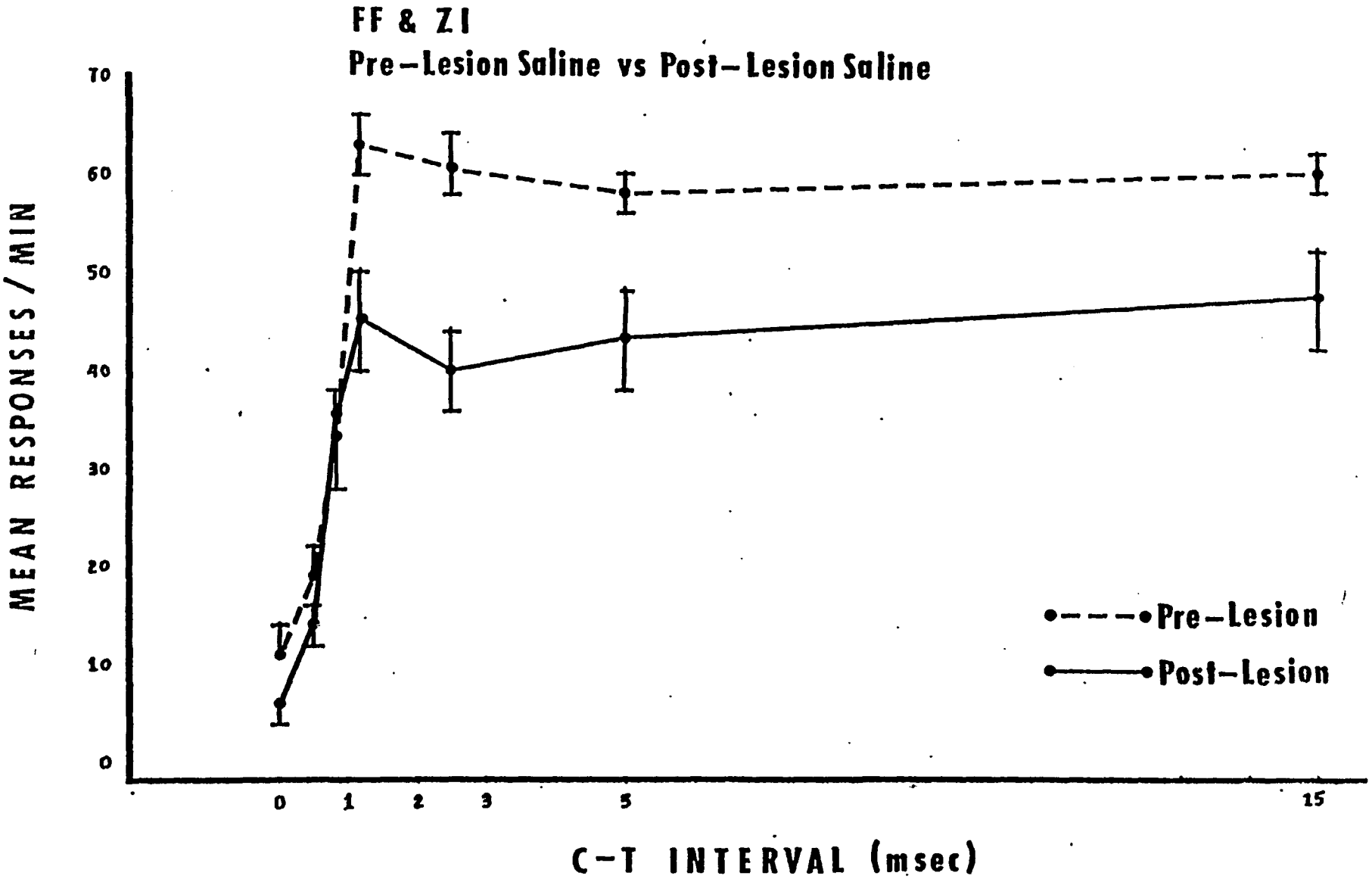

FF & ZI
Pre-Lesion Saline vs Post-Lesion Saline
MEAN RESPONSES / MIN
70
60
50
40
30
20
10
0
0
1
2
3
5
15
C-T INTERVAL (msec)
Pre-Lesion
Post-Lesion

Figure 40

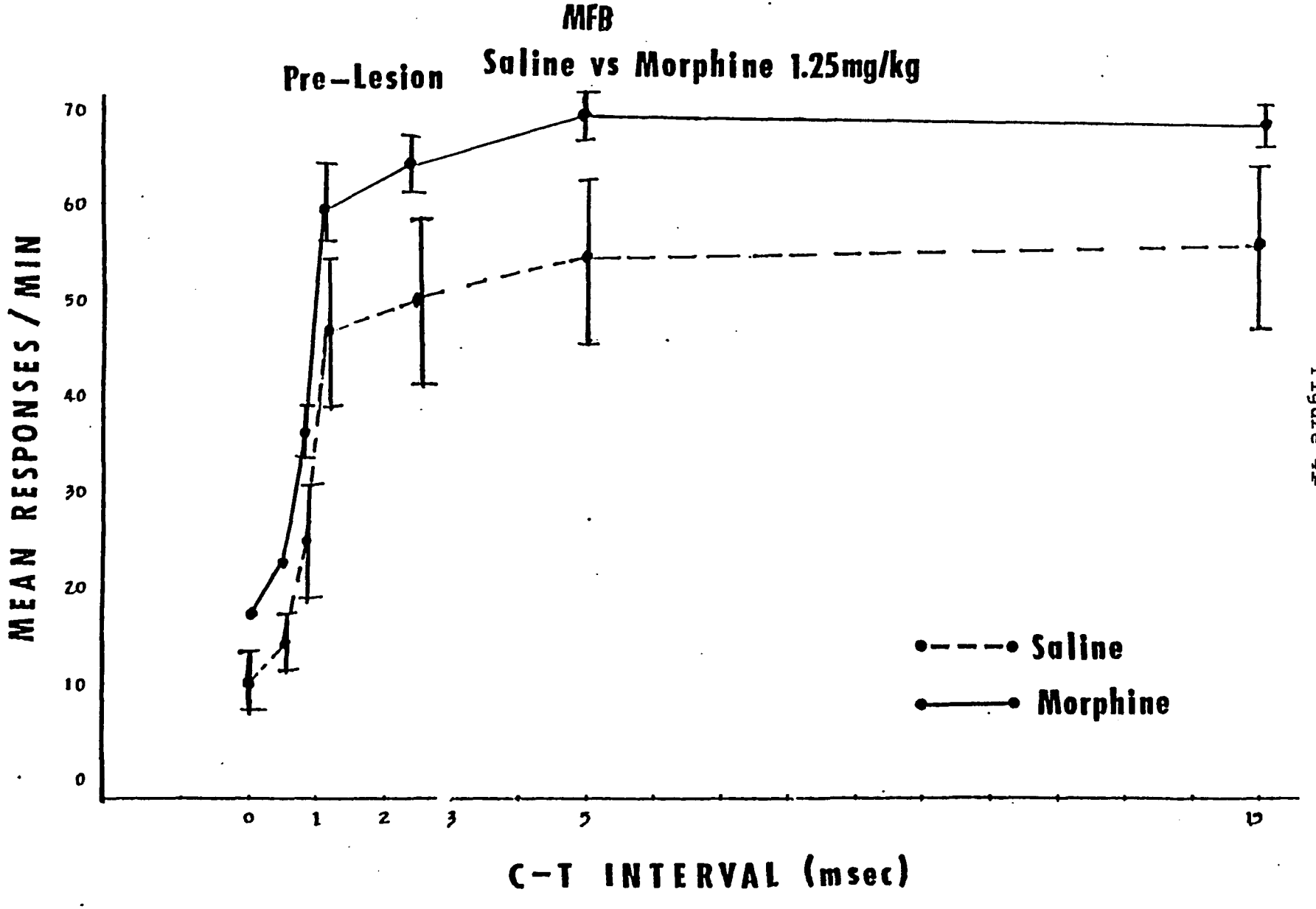

MFB
Pre-Lesion
Saline vs Morphine 1.25mg/kg
MEAN RESPONSES / MIN
70
60
50
40
30
20
10
0
0
1
2
3
5
D
C-T INTERVAL (msec)
Saline
Morphine

Figure 41

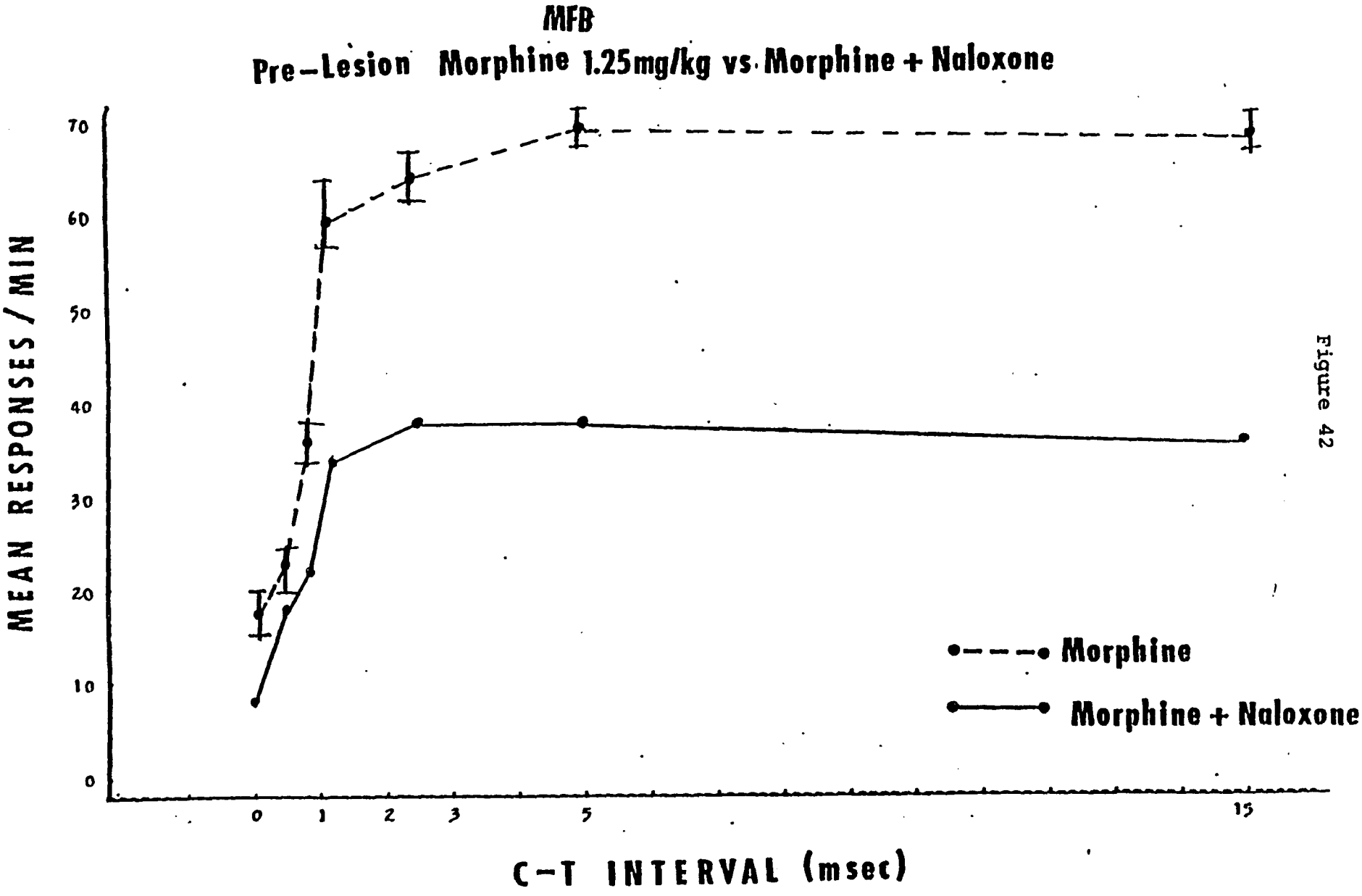

MFB
Pre-Lesion Morphine 1.25mg/kg vs Morphine + Naloxone
MEAN RESPONSES / MIN
70
60
50
40
30
20
10
0
0
1
2
3
5
15
C-T INTERVAL (msec)
Morphine
Morphine + Naloxone

Figure 42

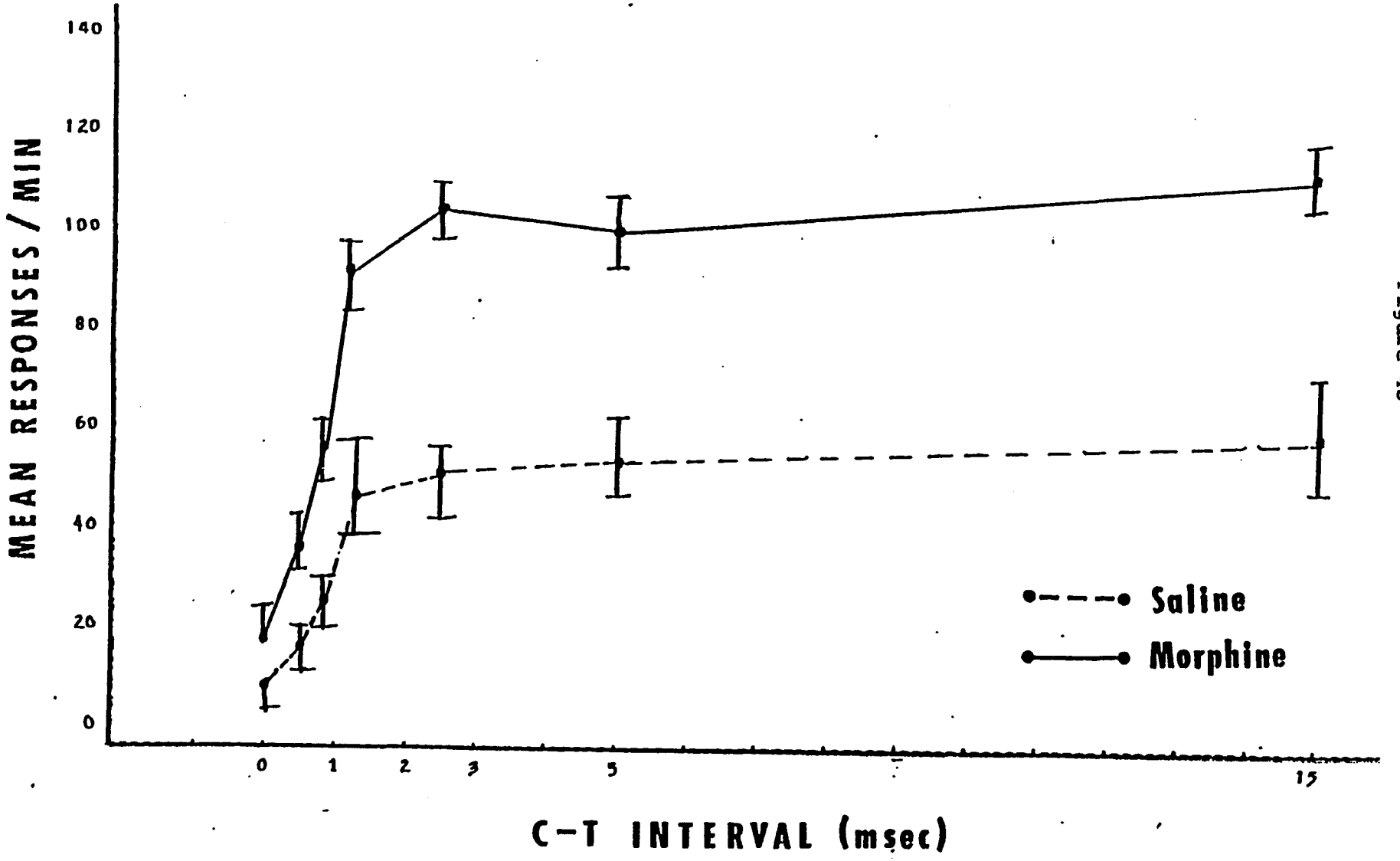

MFB
Pre–Lesion Saline vs Morphine (2.5mg/kg)
MEAN RESPONSES / MIN
140
120
100
80
60
40
20
0
0
1
2
3
5
15
C–T INTERVAL (msec)
Saline
Morphine

Figure 43

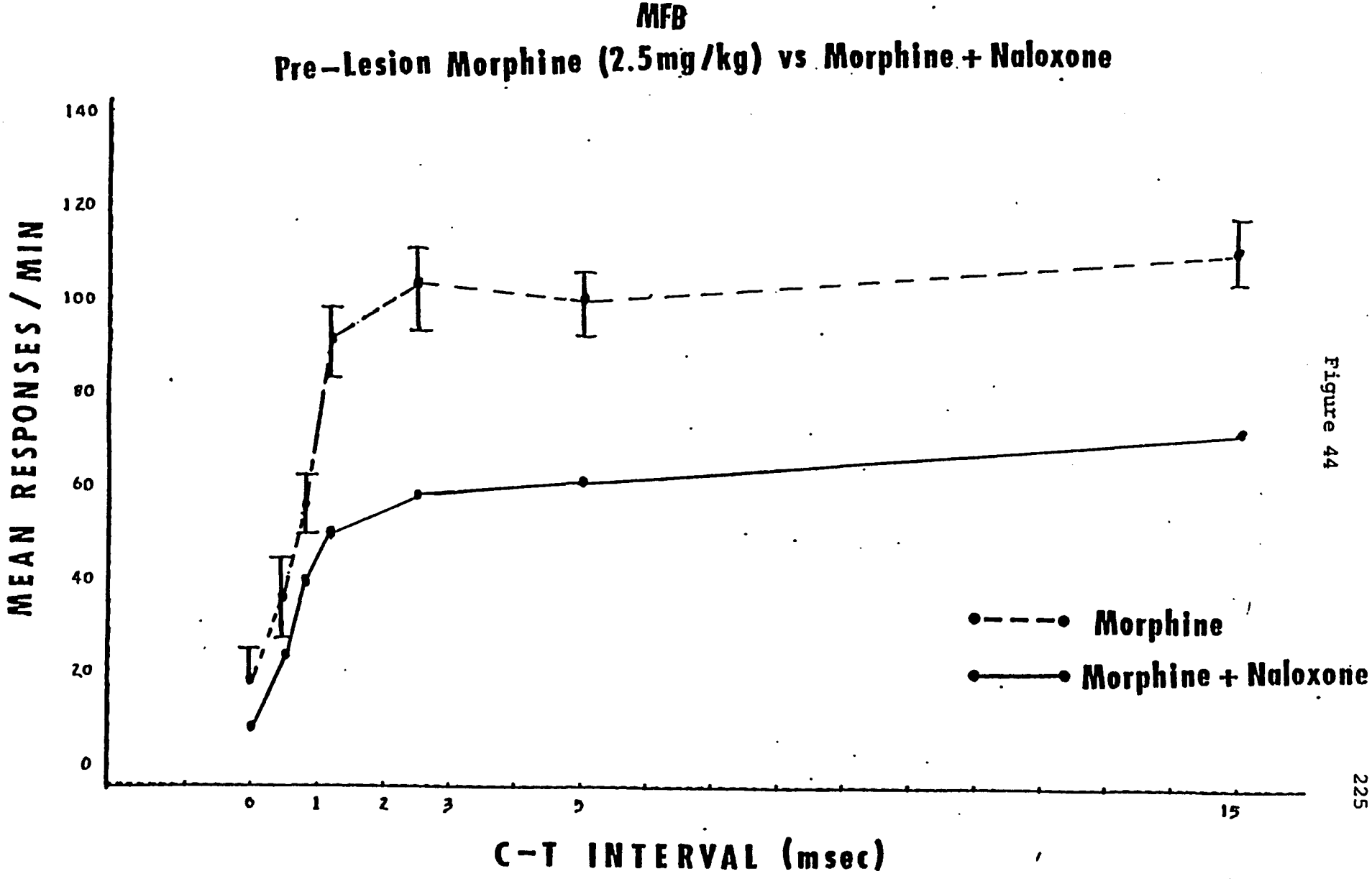

MFB
Pre-Lesion Morphine (2.5mg/kg) vs Morphine + Naloxone
MEAN RESPONSES / MIN
140
120
100
80
60
40
20
0
0
1
2
3
5
15
C-T INTERVAL (msec)
Morphine
Morphine + Naloxone

Figure 44

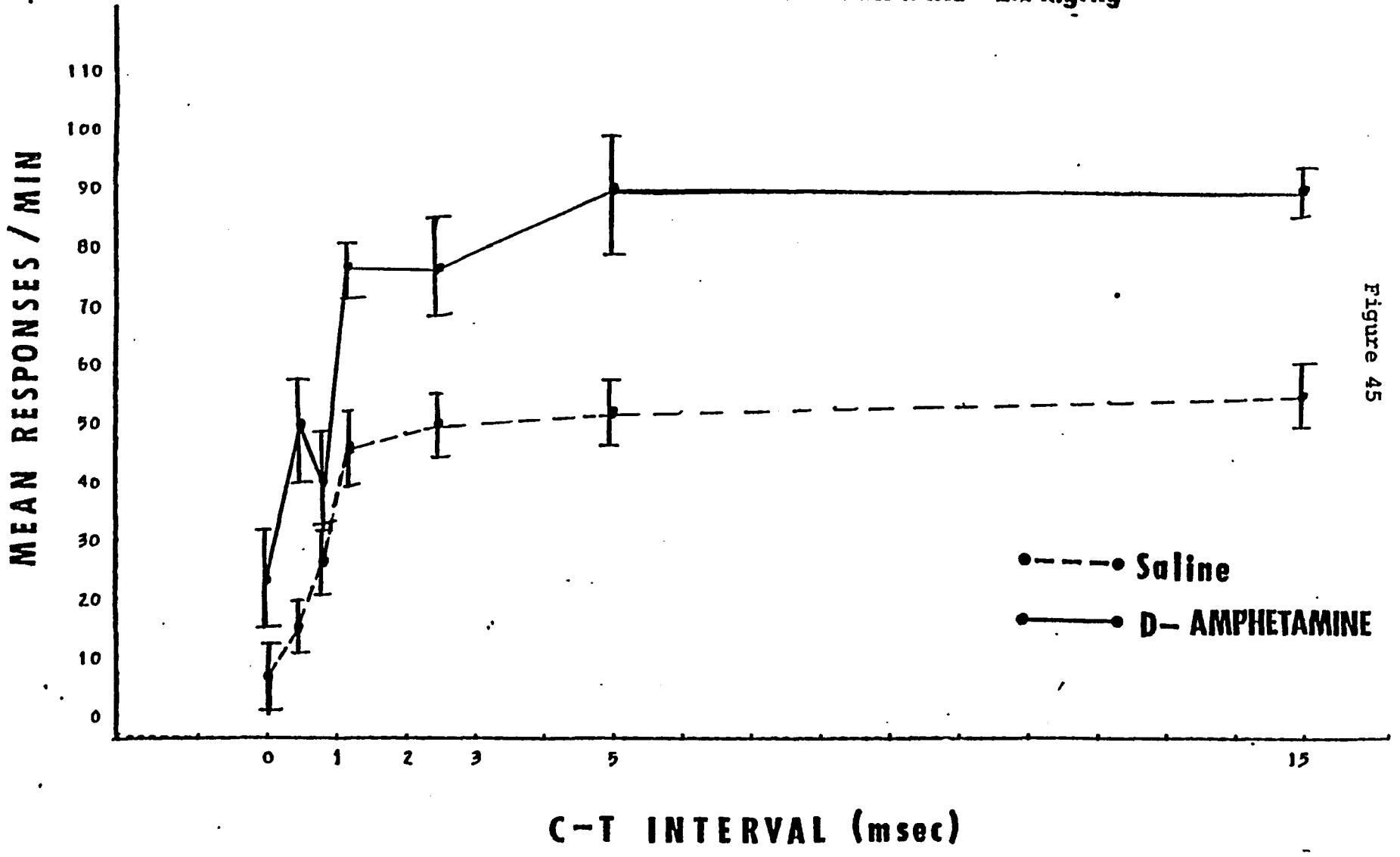

MFB
Pre–Lesion: Saline vs D– AMPHETAMINE 2.0 mg/kg
MEAN RESPONSES / MIN
110
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
5
15
C–T INTERVAL (msec)
Saline
D– AMPHETAMINE

Figure 45

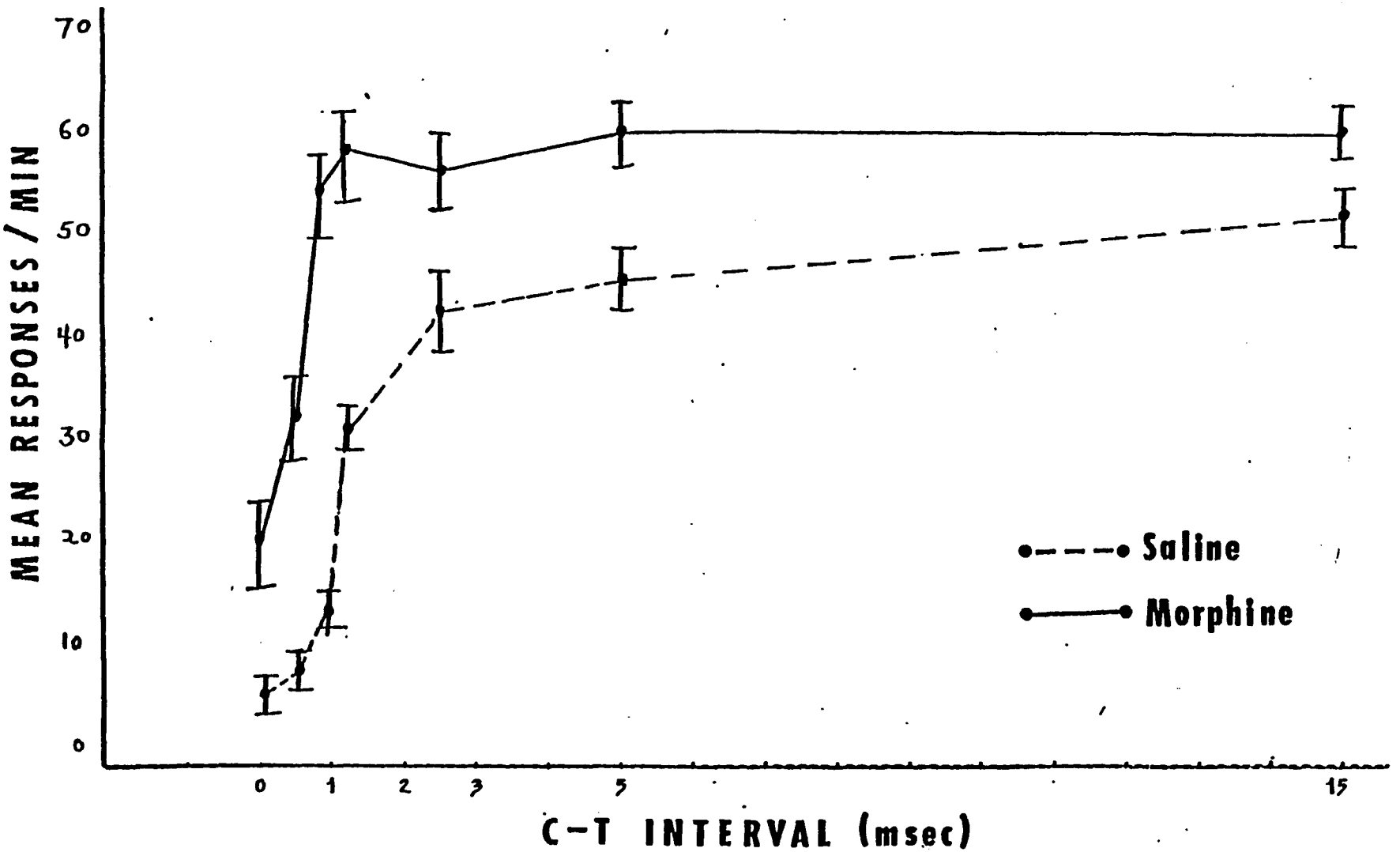

MFB
Post-Lesion Saline vs Morphine 1.25mg/kg
MEAN RESPONSES / MIN
70
60
50
40
30
20
10
0
0
1
2
3
5
15
C-T INTERVAL (msec)
Saline
Morphine

Figure 46

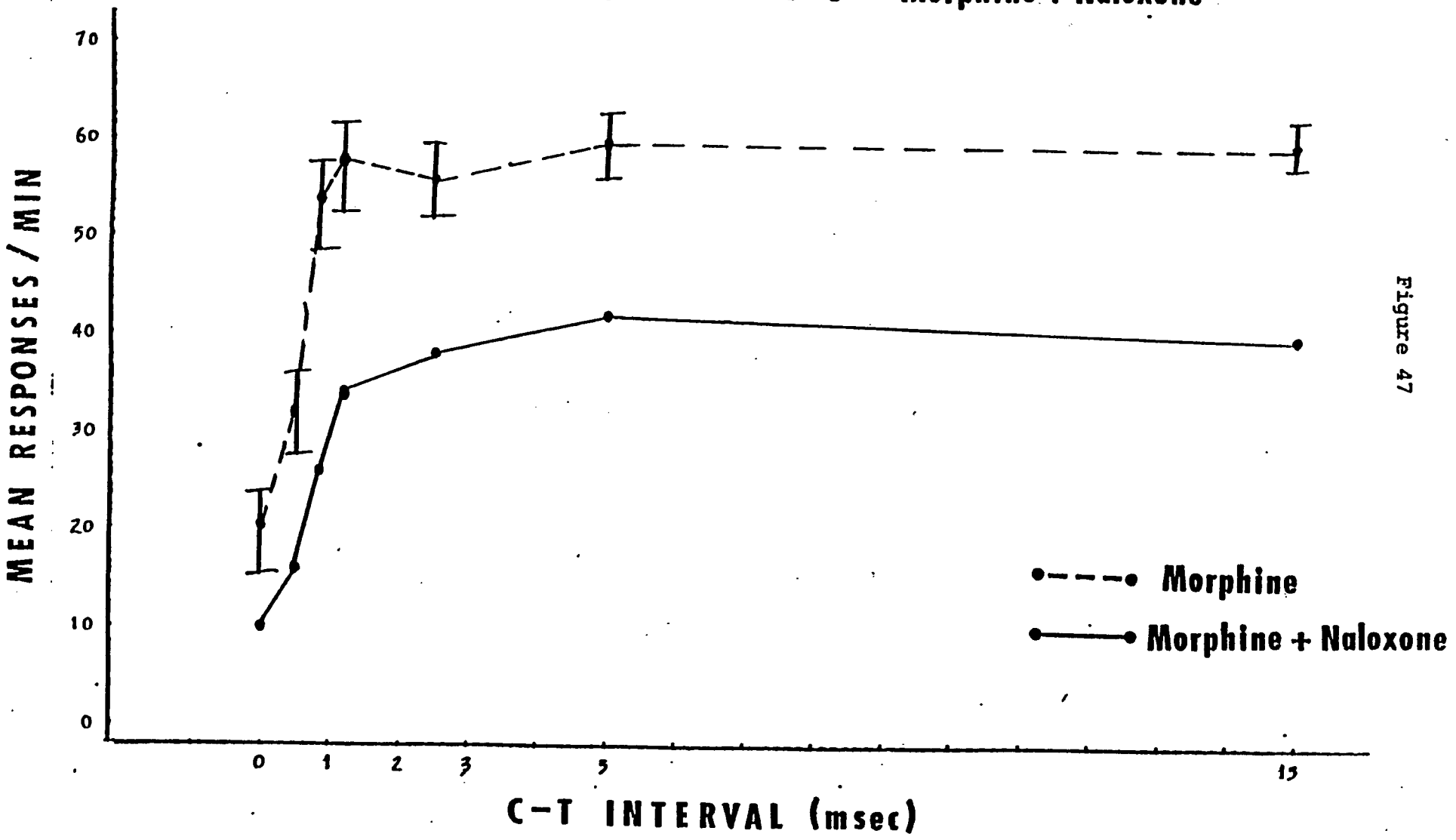

MFB
Post-Lesion Morphine 1.25mg/kg vs Morphine + Naloxone
MEAN RESPONSES / MIN
70
60
50
40
30
20
10
0
0
1
2
3
5
15
C-T INTERVAL (msec)
Morphine
Morphine + Naloxone

Figure 47

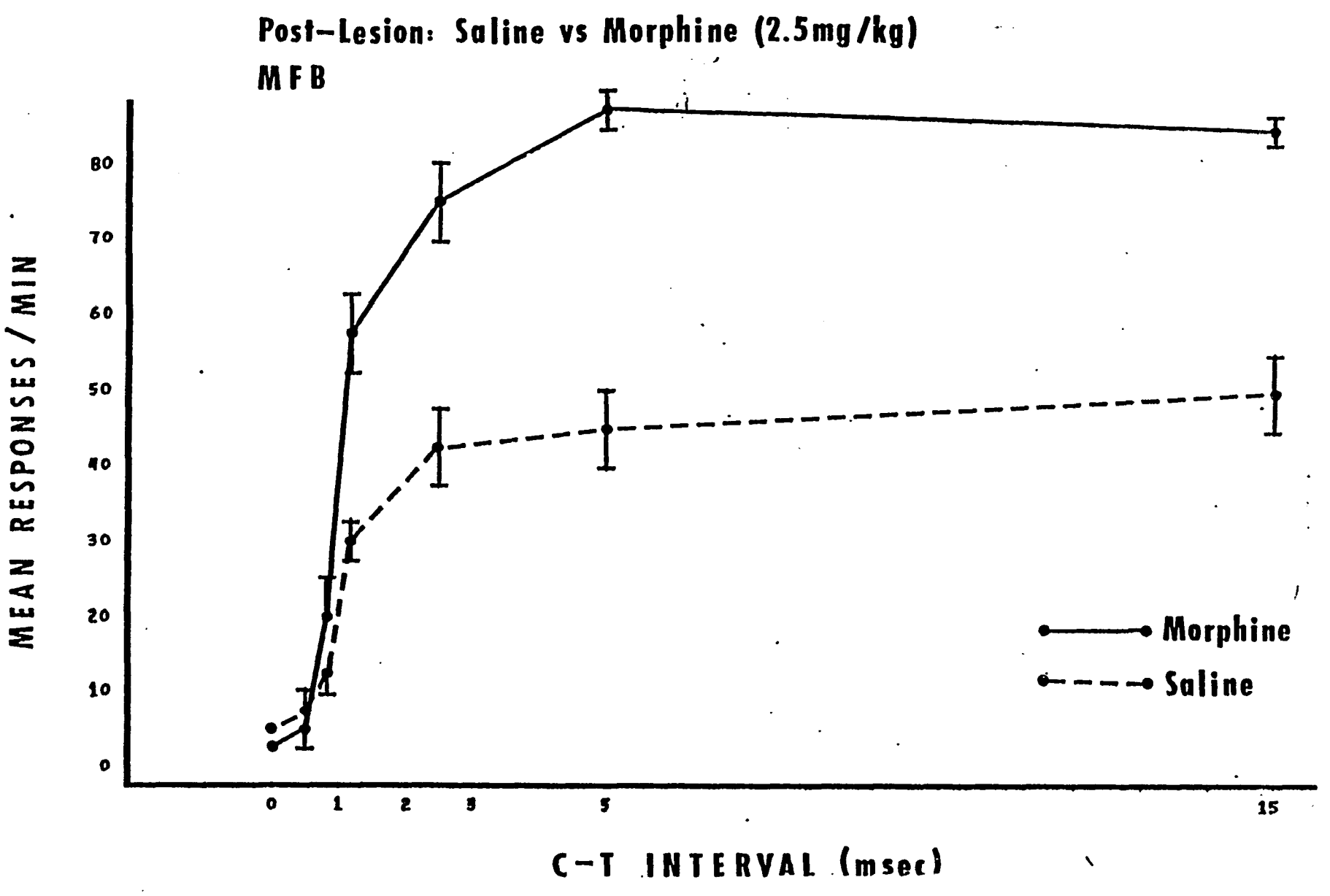

Post-Lesion: Saline vs Morphine (2.5mg/kg)
MFB
MEAN RESPONSES / MIN
0
10
20
30
40
50
60
70
80
0
1
2
3
5
15
C-T INTERVAL (msec)
Morphine
Saline

Figure 48

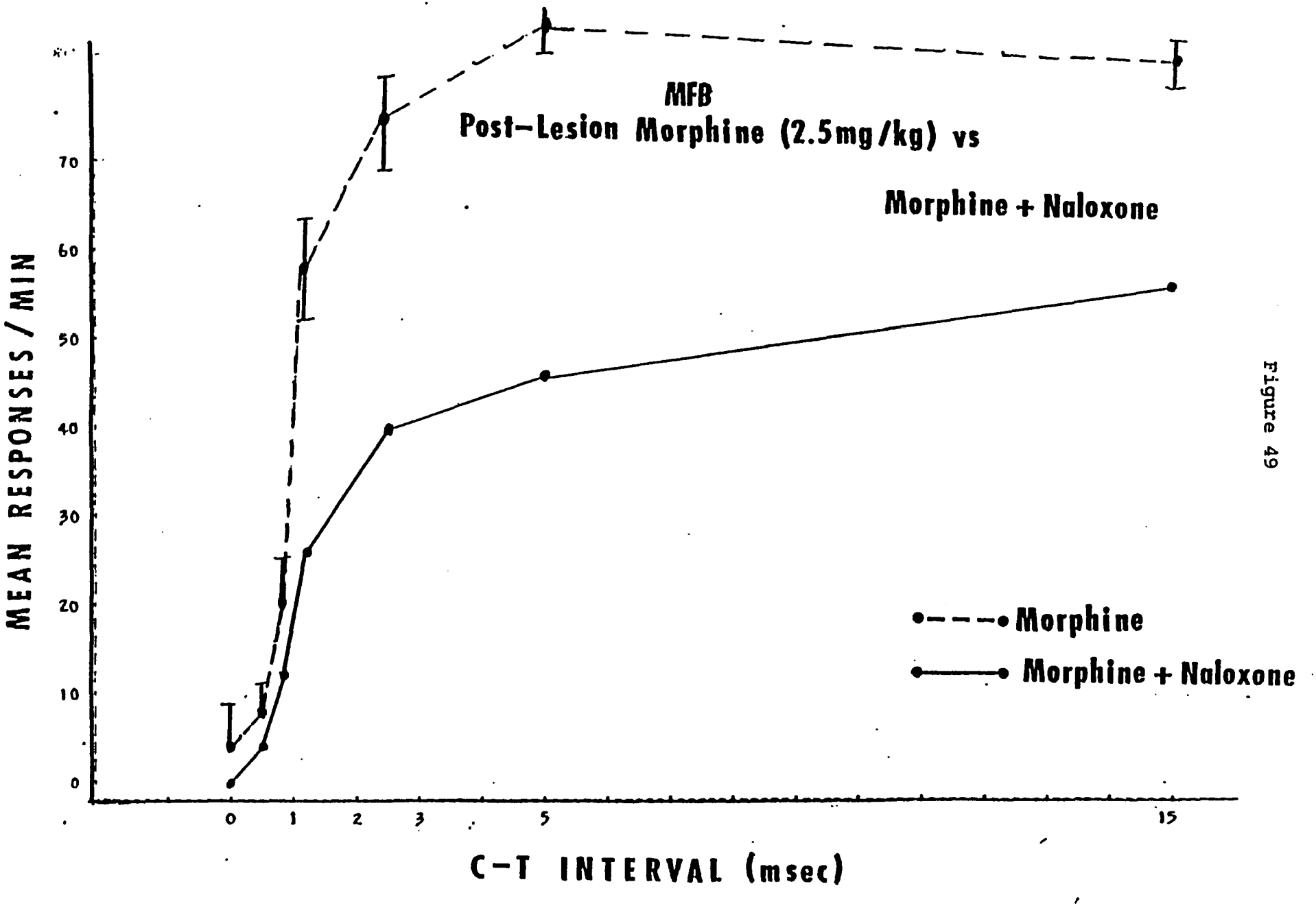

MFB
Post-Lesion Morphine (2.5mg/kg) vs
Morphine + Naloxone
MEAN RESPONSES / MIN
0
10
20
30
40
50
60
70
0
1
2
3
5
15
C-T INTERVAL (msec)
Morphine
Morphine + Naloxone

Figure 49

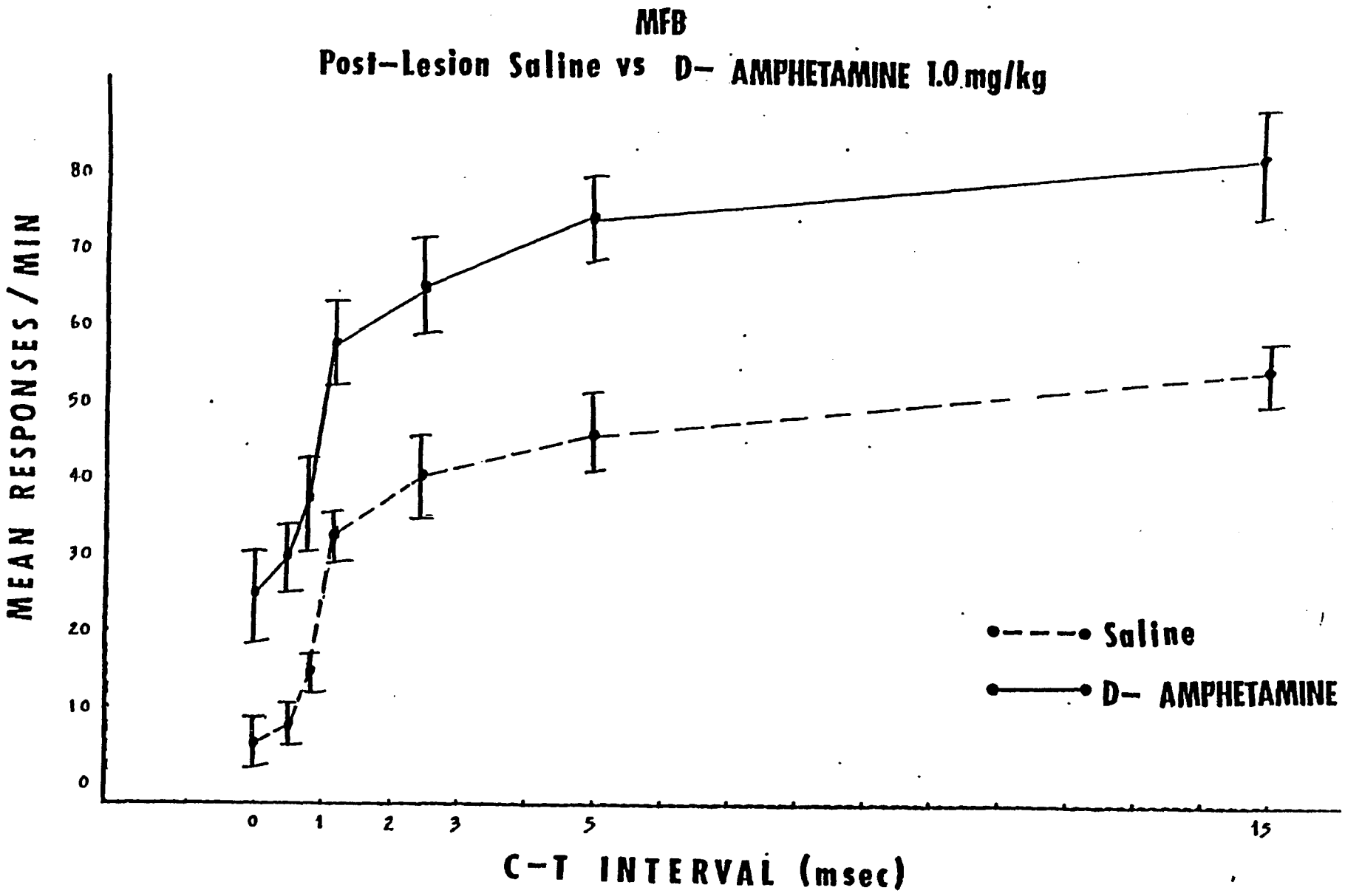

MFB
Post-Lesion Saline vs D- AMPHETAMINE 1.0 mg/kg
MEAN RESPONSES / MIN
0
10
20
30
40
50
60
70
80
0
1
2
3
5
15
C-T INTERVAL (msec)
Saline
D- AMPHETAMINE

Figure 50

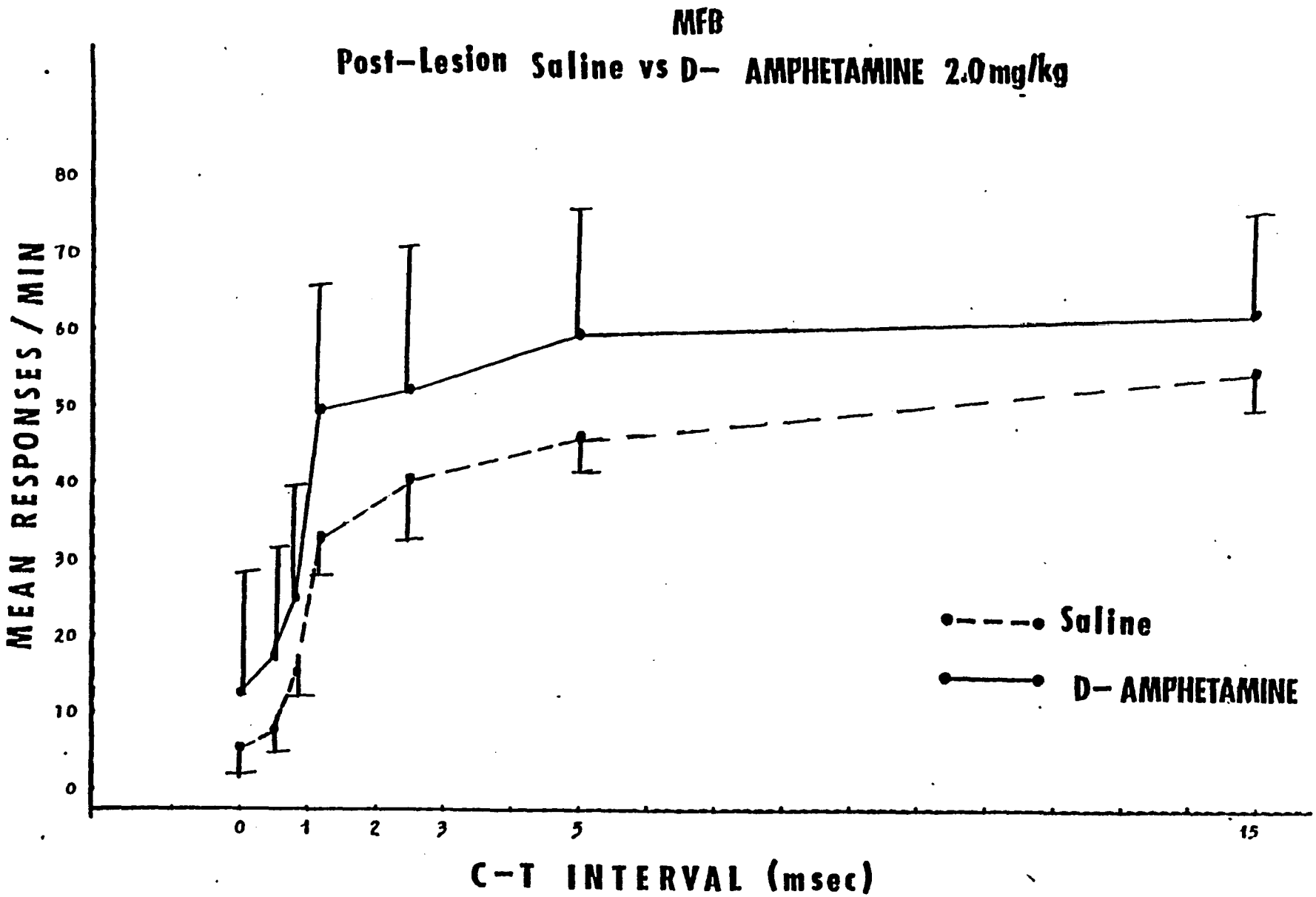

MFB
Post-Lesion Saline vs D- AMPHETAMINE 2.0mg/kg
MEAN RESPONSES / MIN
80
70
60
50
40
30
20
10
0
0
1
2
3
5
15
C-T INTERVAL (msec)
Saline
D- AMPHETAMINE

Figure 51

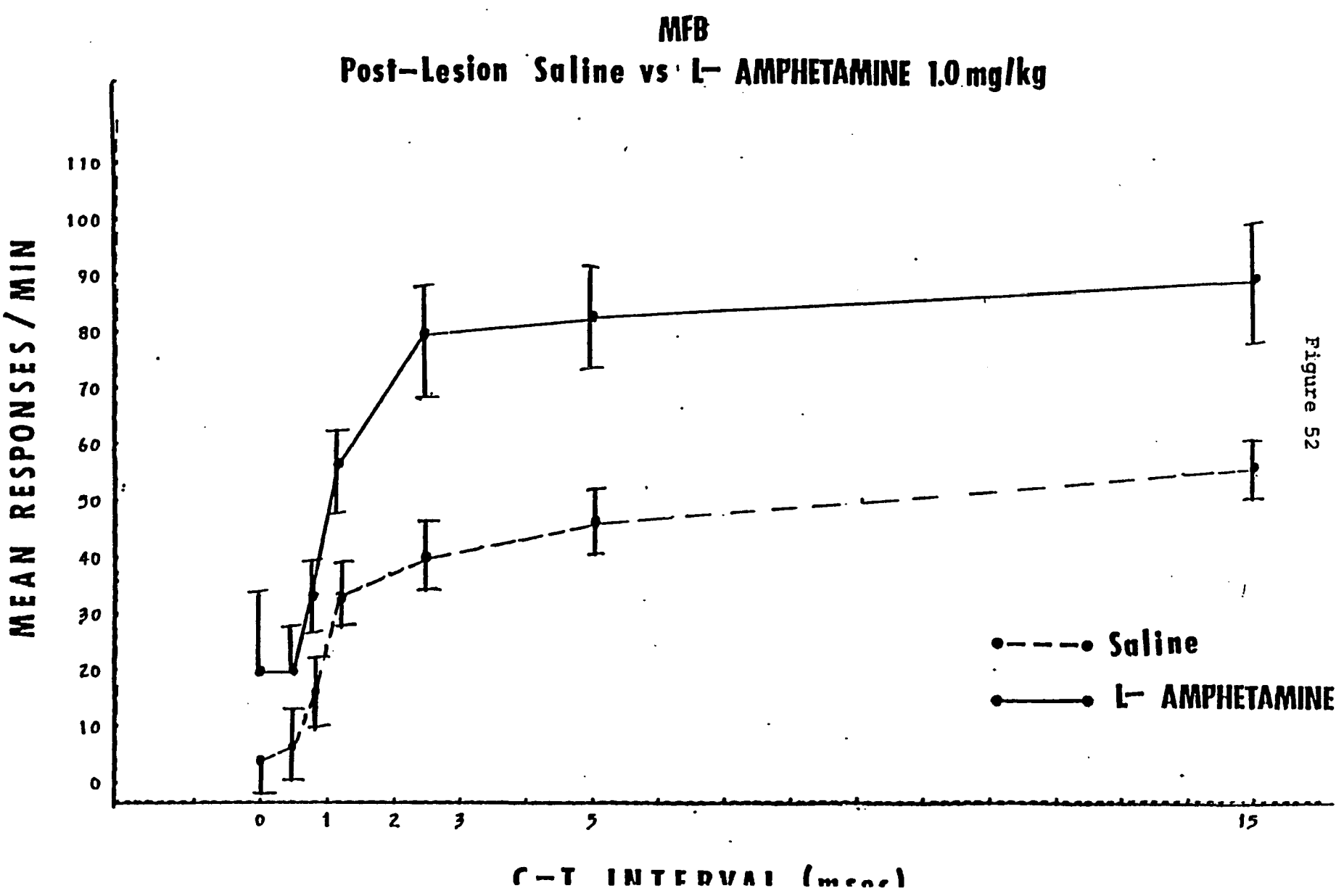

MFB
Post-Lesion Saline vs L- AMPHETAMINE 1.0 mg/kg
MEAN RESPONSES / MIN
110
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
5
15
C-T INTERVAL (msec)
Saline
L- AMPHETAMINE

Figure 52

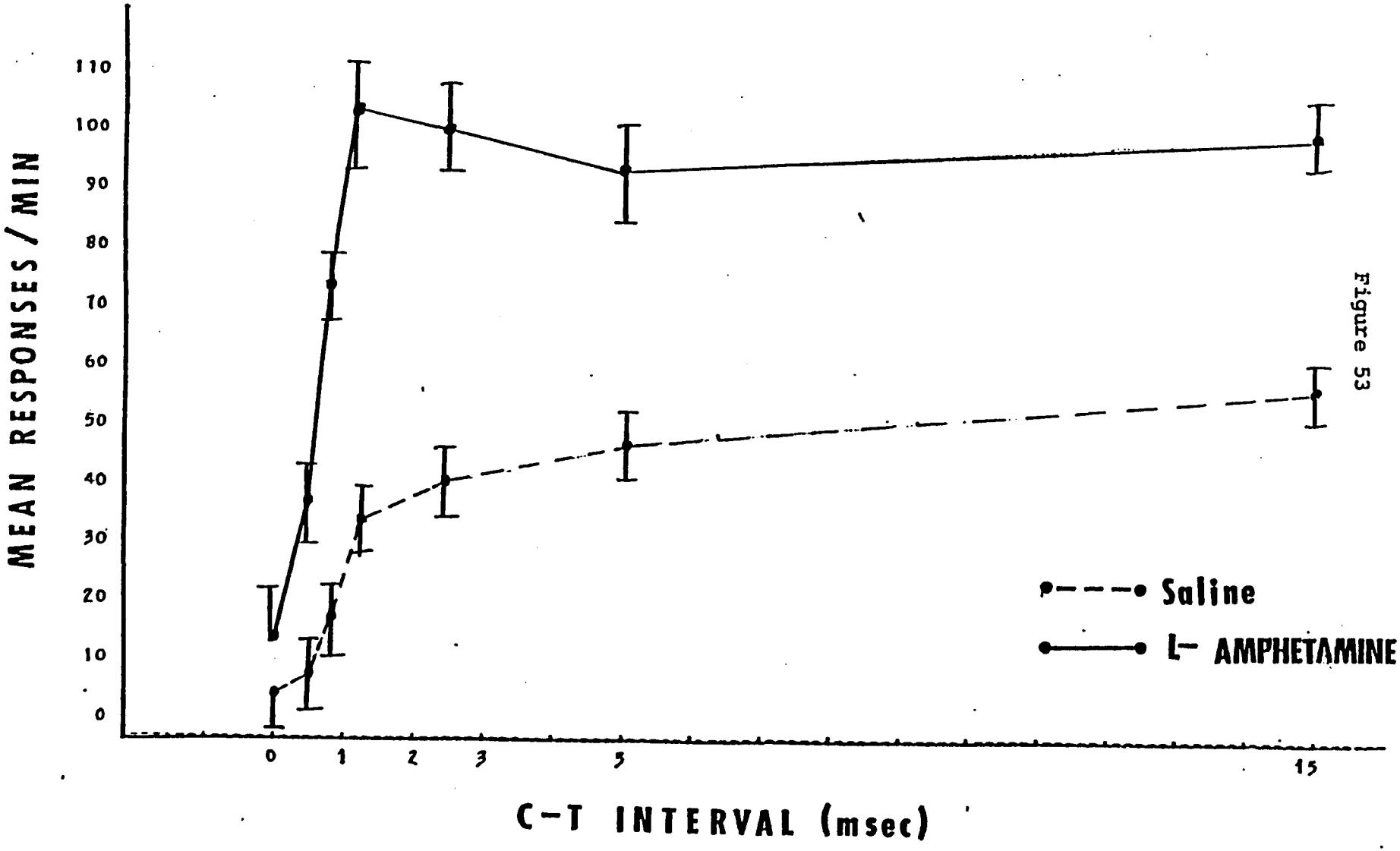

MFB
Post–Lesion Saline vs L– AMPHETAMINE 2.0 mg/kg
MEAN RESPONSES / MIN
110
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
5
15
C–T INTERVAL (msec)
Saline
L– AMPHETAMINE

Figure 53

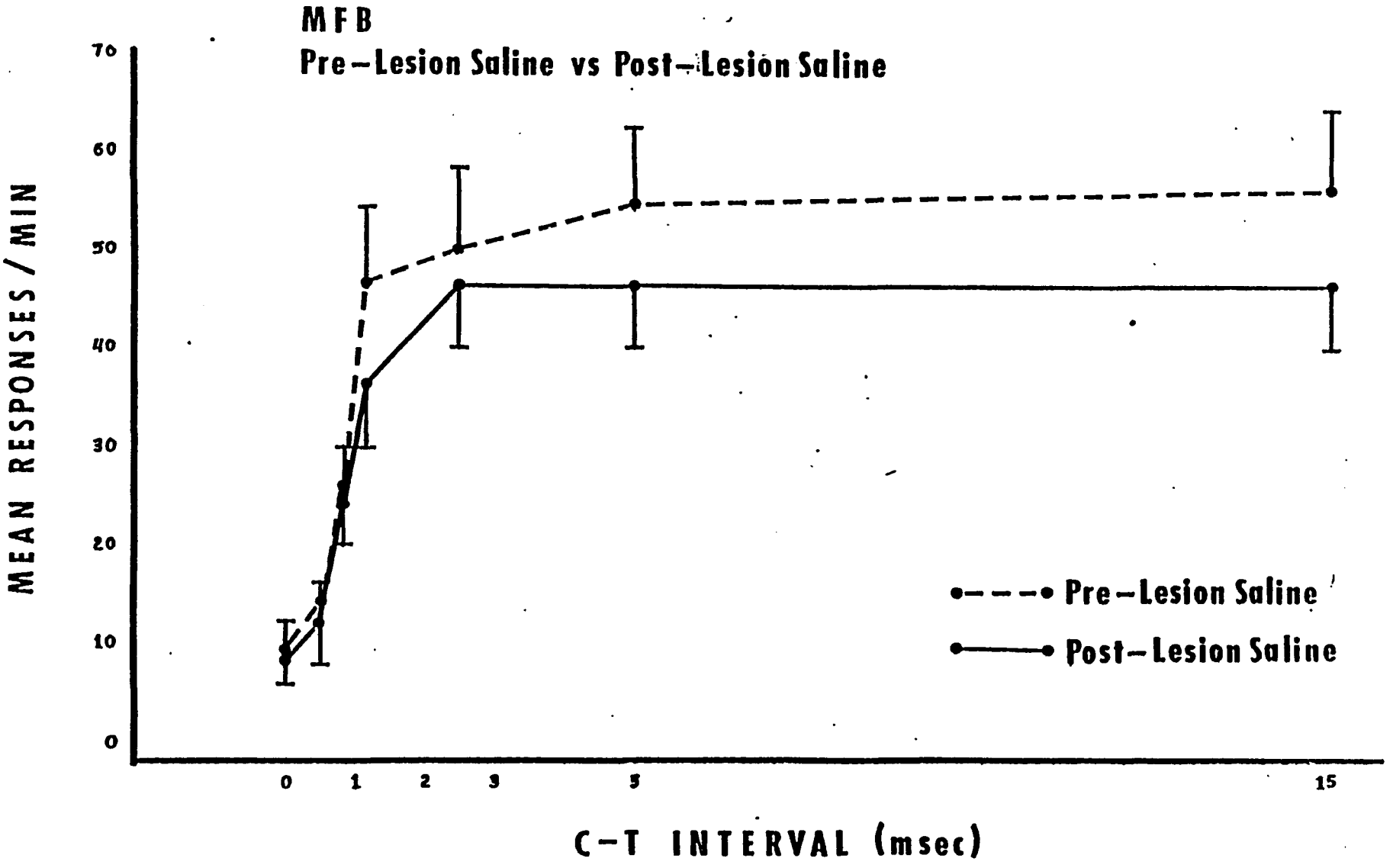

MFB
Pre-Lesion Saline vs Post-Lesion Saline
MEAN RESPONSES / MIN
70
60
50
40
30
20
10
0
0
1
2
3
5
15
C-T INTERVAL (msec)
Pre-Lesion Saline
Post-Lesion Saline

Figure 54

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