THE EFFECTS OF MORPHINE ON THE REWARDING AND AVERSIVE PROPERTIES OF HYPOTHALAMIC STIMULATION IN THE RAT

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Abstract

THE EFFECTS OF MORPHINE ON THE REWARDING AND AVERSIVE PROPERTIES OF HYPOTHALAMIC STIMULATION IN THE RAT.

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The effects of chronic morphine treatment on the initiation (self-stimulation) and termination (stimulation-escape) of lateral hypothalamic stimulation were investigated. Rats were injected with a large range of doses (20-320 mg/kg) over a period of 42 days and observed 7 hours per day every 5 days. The drug produced a pronounced attenuation of stimulation-escape, showing no indication of tolerance, in all 6 subjects. The effect on self-stimulation was typically biphasic; an initial depressive phase was followed by a facilitation. Morphine's effect on self-stimulation was less consistant than the drug's effect on stimulation escape. There were large individual animal differences. These findings add to the evidence that the positively and negatively motivating properties of lateral hypothalamic stimulation involve separate mechanisms; they suggest that both the positive and negative components of the stimulation are affected, in opposite directions, by morphine, implying a sensitivity of both neural systems to the drug. These

findings suggest an increase in the positively motivating properties and a decrease in the aversively motivating properties of lateral hypothalamic stimulation following morphine administration.

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I would also like to thank Terry Williams and Alain Coupal for their time and efforts, without which I would probably still be plugging away.

Thanks also to Jerry ... for understanding.

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In 1954, Olds and Milner made the serendipitous discovery that forebrain stimulation could serve to reinforce operant learning in rats. In that same year, Delgado, Roberts, and Miller (1954) showed that animals will also learn to escape from brain stimulation. These findings had important implications for the experimental study of brain reward and aversion mechanisms. In the two and a half decades following these intial findings, much work has been undertaken relating brain stimulation reward (self-stimulation behavior) and aversion (stimulation-escape behavior) to more conventional reinforcers (Olds, 1977; Rolls, 1975). The findings argue for the involvement of the brain loci supporting such behaviors in naturally occurring instances of positively and negatively motivated behavior.

The positively reinforcing properties of morphine have been studied extensively using self-administration paradigms. The demonstration that an animal will learn a response if that response produces access to a drug solution has led to the suggestion that drug reinforcement is a member of a larger class of other reinforcing events (presentation of food to a hungry animal, water to a thirsty animal, brain stimulation reward) (Thompson & Pickens, 1975).

Hoebel (1974) has provided evidence that changes in self-stimulation (SS) performance can reflect the reward of food to a food deprived animal or sexual behavior. As well, he has related stimulation escape (SE) to the aversion associated with food overloading or the post--ejaculatory phase. It will be suggested here that this reward-aversion system can also reflect the motivational properties involved in voluntary drug intake. As such, the study of morphine's effects on SS and SE can provide a further understanding of those neural areas subserving drug assimilation.

Simply put, the idea is that if the drug produces positive affect this should sum with the positive affect produced by rewarding brain stimulation, as reflected by a facilitatory effect on SS. Hoebel (1974) has shown a reciprocal relationship between SS and SE. A physiological manipulation which produces a facilitation in one has been shown to produce an attenuation of the other. If, then, SS is facilitated after morphine administration, then one would expect SE to be suppressed.

There are many brain areas which have been shown to support both SS and SE. A comparison of morphine's effects at these sites with known distributions of opiate receptors might allow for a generalized neural map of those areas involved in the reinforcing and motivational

components underlying opiate self-administration.

Factors Influencing SS

It has become apparent that the administration of rewarding brain stimulation and the observation of its subsequent effects on behavior does not provide a simple means of examining the brain's normal positive reinforcement mechanism. Rather, the behavior following this stimulation appears to reflect many extenuating factors in addition to the magnitude of the reinforcement. For example, a food deprived rat may increase the performance of an operant response for brain stimulation (Hoebel, 1969). Does this necessarily reflect an enhancement of the reinforcing nature of the stimulation, or could the effect be related to arousal?

It has proved extremely difficult to separate the measurement of the reward effect of brain stimulation from that of performance variables. The fact that an animal may increase responding for brain stimulation (higher response rates) does not necessarily imply that a manipulation has produced a sensitization of the "reward" system. In fact, Valenstein (1964) has challenged the use of response rates to measure reinforcement strength. For example, response rates may be lower for high intensity stimulation due to

motor artifacts which prevent a rat from responding at higher rates. However, when given a choice between this high intensity stimulation and lower intensities which support a high rate of responding, he will almost always choose the higher one (Hodos & Valenstein, 1962). Similarly, injection of methocarbamol, which acts at the spinal level to produce a flaccid paralysis (Goodman & Gilman, 1973), would certainly decrease response rates, much as would adding a 20 gram weight to the lever, however, the reward magnitude of the stimulation does not change (Edmonds & Gallistel, 1974).

Gallistel and colleagues (Edmonds, Stellar & Gallistel, 1974; Gallistel, Stellar & Bubis, 1974; Edmonds & Gallistel, 1974; Gallistel, 1969; Gallistel, 1973) have used a runway to measure the amount of reward excitation produced by brain stimulation. They have shown that the location of the rise in the function relating running speed in a runway to the number of pulses received as a reward is independent of various performance variables including motivational state, athletic skill, and state of health.

It therefore seems that although many factors may influence lever press rates for reinforcing brain stimulation, it is possible, by employing a threshold procedure, to interpret changes in SS as reflecting a

specific effect on the excitation of the reward system. Gallistel (1973) has suggested that SS behavior is a function of both "priming", the transient aftereffect of brain stimulation, and reward. However, the priming effect has been shown to include a motivational component thereby producing changes in the avidity of performance rather than changes in the reinforcing value of the stimulation (Edmonds & Gallistel, 1974).

Therefore, a paradigm less sensitive to such performance artifacts can allow for inference of changes in the rewarding properties of brain stimulation from SS behavior. A frequency threshold paradigm is designed to do just that. In essence, it allows the rat to tell us what combination of parameters make it worth his while to work for the brain stimulation. The frequency of the stimulation is varied by the experimenter and a threshold determined as the point above which the animal will perform (rewarding) and below which he will not (not rewarding). Such a paradigm may be less sensitive to performance artifacts than rate measures. For example, a change in rate per se will not seriously effect the threshold for behavior. However, a change in the reward magnitude of the stimulation will shift the curve to the right (attenuation) or left (facilitation). It therefore seems that an appropriate paradigm can allow one to

infer reinforcing properties of various drugs from their effects on SS behavior.

Escape from Prolonged Stimulation

As early as 1958, Roberts, and Bower and Miller indicated some brain regions where both approach and escape could be elicited by stimulation of the same point. They argued that initially rewarding stimulation, if continued, becomes aversive. Olds and Olds (1963) investigated this seeming paradox further and found that pure approach (positive) or withdrawal (negative) or ambivalent (mixed) behaviors could be elicited depending on the locus of the electrode.

The fact that rats will learn an arbitrary response to escape from the same stimulation they will work to self-administer has been interpreted in several ways. One possibility is that rewarding stimulation also activates an aversive system or systems and that the animal turns off the stimulation in order to escape from these aversive processes (Margules, 1966; Mendelson, 1969; Shizgal & Mathews, 1977). Another possibility is that animals terminate prolonged stimulation due to adaptation of the reward system (Deutsch & Albertson, 1974; Deutsch & Hawkins, 1972; Deutsch & Roll, 1976; Stein, 1962). That is, animals turn off the stimulation

in order to enhance the reward produced by the next "on" response.

The "aversion" hypothesis is an attractive one. Many researchers have provided evidence for distinct neural mechanisms mediating the initiation and the termination of lateral hypothalamic stimulation. Margules (1966) found placements where low current stimulation produced pure approach or withdrawal responding while higher intensity stimulation produced mixed responding. These findings suggested two partially overlapping systems; one underlying reward and the other aversion. Skelton and Shizgal (1977) found differences in the latent addition portion of the behaviorally derived excitability curves for SS and SE. These findings also suggested a direct activation of both a positive and negative system by the stimulation; directly stimulated elements of the two systems having different spatial distributions. Similarly, Shizgal and Mathews (1977) have shown that the rewarding and aversive effects of brain stimulation can be differentiated on the basis of the temporal properties of the underlying neural processes. The reward system responds quickly while the system mediating aversion is more sluggish.

Mendelson and Freed (1973) trained animals to shuttle to turn stimulation on and off. They then

measured latencies to turn stimulation off when only one train of stimulation was available per day. Learning theory would predict that if the stimulation was not aversive and the "off" response did not allow for reinstatement of the stimulation until the next day, that, over a period of time, latencies to terminate stimulation should increase. That is, animals will learn that the off response does not produce reinforcement. They found, however, that over a period of 60 days this was not the case.

As well, personal observations of unconditioned escape responses such as vocalizing and attempts to leap out of the testing chamber during prolonged stimulation, supports the conclusion that such stimulation is aversive.

Hoebel (1974) has related the escape from this aversive stimulation to naturally occurring instances of aversively motivated behavior. He has suggested that SE can reflect the negative affect of an animal following sexual behavior (Hoebel, Cardell & Coblentz, 1974) and excessive feeding (Hoebel & Thompson, 1969).

Interaction Between Positive and Negative Systems

It has been proposed that SE represents negative affect while SS represents positive affect (Hoebel, 1974). The evidence described above suggests that at least two

systems can be activated by reinforcing brain stimulation. The first, a positive system, reaches a critical level of activity soon after the onset of the stimulation. The stimulation also activates an aversive system (Shizgal & Mathews, 1977). The activity in this system will reach a critical level such that the ratio of reward: aversion will shift to a degree that the offset rather than the onset is reinforcing. These systems seem to interact in such a way that an increase in reward necessarily decreases the aversive affect produced by the stimulation and vice versa.

Following Hoebel (1974) this paper will consider SS and SE as indications of underlying reward: aversion mechanisms. An animal is assumed to increase SS and decrease SE when the excitability of the reward system is enhanced or the aversive system depressed.

Following this notion, substances which are, in themselves, reinforcing, may sum with reinforcing brain stimulation to produce an enhancement of the positive value of the stimulation. On the basis of this reasoning, it is possible that common mechanisms underlie the rewarding and aversive effects of brain stimulation and self-administered drugs.

Morphine Self-administration

Animals will self-administer opiates, such as morphine, orally (Wikler, Martin, Pescor & Eades, 1963) intravenously (Deneau, Yanagita & Seevers, 1969; Weeks, 1962) and intraventricularly (Amit, Brown & Sklar, 1976). The motivation to self-administer morphine may be mediated by two distinct mechanisms;

(1) Drug taking might postpone aversive withdrawal symptoms

(2) The drug itself might function as a positive reinforcer (Dews, 1973).

Deneau et al. (1969) found that monkeys would self--administer morphine and other psychoactive substances the first time they were given the opportunity to do so. Since no abstinance syndrome existed at the beginning of the experiment, an explanation of physical dependence as the sole motivational component of opiate self--administration is unsubstantiated. Rather, these data suggest that the initiation or morphine self--administration is more probably due to the positively reinforcing properties of the drug, while a secondary motivation for continued drug use may develop from the discomfort caused by abstinance. Stolerman and Kumar (1970) found no difference between animals chronically treated with morphine and uninjected rats with respect

to the amount of morphine solution drunk. As well, Pickens (1968) has demonstrated self-administration of cocaine, a drug which does not produce physical withdrawal symptoms. It therefore seems that relief from withdrawal symptoms cannot solely account for the acquisition of a preference for self-administered drugs.

Morphine appears to produce a positive affective state. In one study (Rossi & Reid, 1976), rats were placed in one compartment of an alley for 30 minutes either 4.5 or 7 hours after an injection of morphine (10 mg/kg) or saline for three days. Rats that had been placed in the box 4.5 hours after the morphine injection showed a marked preference for the place where they had experienced morphine, suggesting that the drug had produced a positive affective state which was positively reinforcing.

Neurochemical Basis of Positive Reinforcement

A number of investigations have pointed to a catecholamine (CA) involvement in the self-administration of morphine. Systemic administration of the drug produces increased dopamine (DA) turnover in rat striata (Clouet & Ratner, 1970). Alpha-methyl-para-tyrosine (a-mpt), a drug which blocks the synthesis of CA's, effectively decreases morphine self-administration in

drug naive (Kerr & Pozuelo, 1972; Davis & Smith, 1972) as well as morphine dependent (Lewis & Margules, 1975) rats. Similarly, 6-hydroxydopamine (6-OHDA), which destroys CA cells, has been shown to attenuate morphine self-administration (Meade & Amit, 1974).

The CA's have also been implicated in the pharmacological effects of SS. A-mpt (Edmonds & Gallistel, 1977; Poschel & Ninteman, 1966), 6-OHDA (Breese, Howard & Leahy, 1970), reserpine (Franklin & Herberg, 1974) and chlorpromazine (Olds, Killam & Buch y Rita, 1956) all decrease SS. Disruption of SS by catecholamine receptor blockade could reflect either a reward deficit or a performance deficit. While serious performance deficits have been demonstrated after dopamine receptor blockade, paradigms less sensitive to these deficits have indicated decreased reward value of stimulation rather than decreased performance capacity of the animal following pimozide treatment (Fouriezos & Wise, 1976) and A-mpt (Edmonds & Gallistel, 1974). As well, drugs which enhance the release of CA's into the synaptic cleft (amphetamine, for example) increase SS behavior (see Wise, 1978; German & Bowden, 1974; for reviews).

It therefore seems that CA's are involved in drug self-administration as well as in SS, two behaviors which are maintained by positive reinforcement. While the

extent of this involvement is unknown, there appears to be similarities between the central effects produced by self-administered drugs and SS.

If the positive effects produced by morphine and those produced by rewarding brain stimulation are mediated by a common mechanism, then morphine might be expected to cause an enhancement of SS behavior.

Effects of Morphine on SS

Olds and Travis (1960) first studied the effects of morphine on press rates for various current intensities of lateral hypothalamic stimulation. They found a general inhibition of SS immediately following morphine injections. This was neither terribly exciting nor surprising since Tatum, Seevers and Collins (1929) had previously described in great detail the initially depressive effects of morphine on both central and behavioral systems. It was not until the early 1970's that studies examining the effects of morphine on brain stimulation reward were again undertaken.

Adams, Lorens and Mitchell (1972) tested rats over a period of six hours per day for 5 days with daily injections of morphine (10 mg/kg). They confirmed the depressive effects observed by Olds and Travis and observed an increase in response rates 5-6 hours after

injection. Tolerance was found to occur to the depressive effect while the facilitatory phase continued to grow in magnitude and occurred earlier in time after repeated injections. In a follow-up study, Lorens and Mitchell (1973) found that the duration of the depressant effect and the temporal appearance of the excitatory effect were dose dependent. Small doses (5-10 mg/kg) produced an initial inhibition of SS, followed 2-3 hours later by facilitation. The largest dose of the drug (20 mg/kg) produced a long-lasting depression (3 hours post-injection) followed 5-6 hours post-injection by a facilitatory effect. Bush, Bush, Miller and Reid (1976) tested bar pressing rates 1, 4, and 23 hours after 5, 10, or 15 mg/kg of morphine for a period of 20 days. They again observed a dose-dependent depression of SS at hour 1 followed by a facilitatory effect at hour 4. Response rates returned to pre-drug baseline levels by the 23rd hour post--injection. The facilitatory effect did not tolerate across 20 days of injection.

These and other studies have confirmed that the effects of morphine on SS can be described as a complex interaction of dose X days X hours since injection. Morphine injections initially depress SS (Adams, Lorens & Mitchell, 1972; Bush et al., 1976) followed 4-6 hours later by facilitation (Lorens & Mitchell, 1973; Glick &

Rappaport, 1974). Tolerance develops to the depressive effect (Ornstein & Huston, 1977; Pert, 1975; Reid, Bozarth & Gorman, 1977) while the facilitatory effect grows in magnitude with repeated injection of the drug (Reid et al., 1977; Lorens & Mitchell, 1973) or does not change (Esposito & Kornetsky, 1977), showing no indication of tolerance.

This biphasic pattern has also been observed in tests of motor activity following various doses of morphine (Tatum et al., 1929; Holtzman, 1976). Wauquier and Niemegeers (1976) have attributed the initial depression of SS to motoric disruption (for example, the catatonia and muscular rigidity observed after injection of the drug). However, a number of independent investigations have suggested that a facilitation of motor activity is not related to facilitatory changes in SS observed following morphine injections. Bellisle, Winer and Shizgal (Note 1) have observed that the time course of the facilitatory effect on SS does not follow that of the facilitation of spontaneous motor activity produced by the drug suggesting that this effect is temporally dissociable from a more general arousal or hyperactivity. Heroin does not produce systematic increases in the performance of operant responses for food at doses that facilitate SS (Koob, Spector &

Meyeroff, 1975). It therefore seems that opiates generally have relatively specific facilitatory effects on SS.

The most parsimonious interpretation of these findings is that the opiate-induced facilitation of SS reflects a change in the motivational valence of brain stimulation (M.E. Olds, 1976; Esposito & Kornetsky, 1978; Reid et al., 1977), and that this change reflects the positively reinforcing properties of the drug. It follows therefore that the more positively reinforcing the drug, the greater one would expect the facilitation of SS to be. Bozarth and Reid (1978) tested this hypothesis by administering equianalgesic (implying equipotent) doses of a variety of drugs rated from low to high on a preference scale by humans. It was found that nalorphine and pentazocine, drugs which produce no known positive affects, produced negligible facilitation of SS rates as compared to codeine, methadone, morphine and levorphanol (drugs with high addiction liability). These findings strengthen the notion that the self-administration of various drugs is mediated by the positively reinforcing properties of these drugs, which in turn may be mediated by the same neural substrate mediating SS.

Alternatively, the facilitation of SS produced by morphine may be at least partially due to a drug-induced desensitization of the neural system mediating the

aversive component of the stimulation.

Effects of Morphine on Escape from Aversive Stimulation

The effects of morphine on escape from aversive stimulation have been less well documented than its effects on brain stimulation reward.

Marcus and Kornetsky (1974) used the response of turning a wheel manipulandum to assess morphine's effects on the positive (lateral hypothalamus) and negative (reticular formation) consequences of brain stimulation. They found that 30 minutes post-injection, morphine (4 and 12 mg/kg) produced a dose related increase in current intensity thresholds to escape stimulation. As well, a dose of 4 mg/kg (but not 8 or 12 mg/kg) produced a significant decrease in intensity threshold to self-stimulate. The SS threshold changes were attributed to the drug's reinforcing properties while the SE data seemed to be related to morphine's analgesic properties.

In a series of studies examining changes in aversive stimulation thresholds following morphine administration, Rosenfeld and co-workers (Rosenfeld & Holzman, 1978; Rosenfeld & Holzman, 1977; Rosenfeld & Vickery, 1976) found elevated intensity thresholds for escape from aversive electrical stimulation of the spinal trigeminal tract and for medial thalamic stimulation. In contrast,

morphine did not alter thresholds at a number of aversive sites including the dorsal midbrain central gray and the pontine nucleus subcoeruleus. It was concluded from this series of studies that certain systems (those intimately involved with descending pain systems) are inhibited by morphine, while others are not. This again implied that morphine's depressive effects on aversive consequences of central stimulation were related to its analgesic properties.

Pert (1975) also examined morphine's modulation of aversive affects associated with electrical stimulation of the central gray matter. A shuttle box paradigm allowed rats to terminate the aversive stimulation by running from one side of the shuttle box to the other. Morphine (15 mg/kg) was found to increase response latencies with tolerance developing to that effect.

It can therefore be seen that morphine has the ability to decrease the aversion produced by electrical brain stimulation. This effect may be related to the analgesic properties of the drug. It is therefore possible that the facilitation of SS following morphine administration is related to its analgesic properties. That is, morphine's analgesic action might block the aversive consequences which accompany SS, thus producing an enhancement of the rewarding properties of the

stimulation. Farber and Reid (1976) tested this hypothesis by using combinations of positive (lateral hypothalamus) and negative (reticular formation) stimulation. If the facilitation of SS was related to a decreased aversion or analgesia, then animals would be expected to press more for combinations of positive and negative stimulation after morphine than for positive stimulation alone. Animals were tested 4 hours after injection of morphine (15 mg/kg), the time corresponding to the maximum facilitation of SS. Press rates were not significantly different for the two stimulation conditions. This is not terribly surprising since Marcus and Kornetsky, Pert, and Rosenfeld had shown that the attenuation of the aversive consequences of the stimulation occurred within the first few hours after drug administration. In addition to the temporal differences between morphine's modulation of aversive and appetitive brain stimulation, there is evidence suggestive of dissimilar properties of the aversion presumed to be present in each train of stimulation in a SS paradigm and that produced by reticular formation stimulation.

Kestenbaum, Deutsch and Coons (1973) found that adaptation occurred in midbrain pain systems. That is, the animals would initially show overt signs of aversion

such as squealing and trying to leap out of the testing chamber. However, as the stimulating train continued, these responses disappeared and the animal appeared to become comfortable again. In contrast, the aversion produced by hypothalamic stimulation summates during a train (Shizgal & Mathews, 1977). As well, the aversive and appetitive systems seem to interact (Hoebel, 1974). The consequences of the activation of the aversive fibers may be dependent on the initial level of activity existing in the reward system.

Therefore, inferences concerning the sensitivity of the aversive component involved in lateral hypothalamic stimulation to morphine made on the basis of a comparison with effects on the reticular formation pain system must be made tentatively, if at all.

Levitt and co-workers (Baltzer, Levitt & Furby, 1977; Levitt, Baltzer, Evers, Stilwell & Furby, 1977) have more adequately tested the hypothesis that the morphine-induced facilitation of SS is related to a drug-induced inhibition of the aversive component of such stimulation. Rats were trained to shuttle in order to initiate and terminate lateral hypothalamic stimulation. Mean "on" time and mean "off" time per crossing were recorded as the number of crossings per time unit. Morphine and etorphine, a more potent narcotic analgesic, both increased mean on time

per crossing while having little effect on mean "off" time. These findings were interpreted as both an inhibition of the aversive component of the stimulation in one paper (Baltzer et al., 1977) and to a direct facilitation of reward processes in another (Levitt et al., 1977). These ambiguities may be attributed to the paradigm which makes it difficult to unambiguously assess changes in the aversive component of the stimulation. Each behavior is measured against a shifting baseline which is dependent on the amount of time the stimulation is left on and off. It therefore seems that the effect of morphine on escape from aversive lateral hypothalamic stimulation must still be clarified.

The present study was undertaken to more accurately describe the chronological evolution of morphine's effects on SS and SE. Separate paradigms were used to assess aversively and positively motivated behaviors. Due to the interaction of dose X days X hours after injection, the design of the experiment was such that a large range of doses (20-320 mg/kg) was tested over a period of 6 hours per day for 40 days. Tolerance and withdrawal effects were assessed. Concurrent observations were made in a SS paradigm as well as a SE paradigm. It was hoped that the specificity of morphine's motivational and reinforcing properties could be determined.

Methodological Considerations

Earlier in the chapter, the difficulties of differentiating rewards vs. performance effects due to pharmacological manipulations were presented. In view of the arguments presented by Valenstein (1964) and Gallistel (1973; Gallistel et al., 1974) a means of assessing changes in the reward value of stimulation was sought that was less ambiguous than the rate or shuttle box measures.

The most typical measure of reinforcement strength is response rate. Many authors have realized the problems with using such measures (Levitt et al., 1977; Marcus & Kornetsky, 1974). To date, however, few paradigms have been used which are rate-independent. Both the Gallistel runway and a threshold procedure developed by Fouriezos and Wise (1976) claim to be able to differentiate reward from performance. The tasks allow for interpretable distinctions between changes in the magnitude of reinforcement and changes due to performance artifacts.

In light of the motoric disruption caused by morphine (Tatum et al., 1929; Bellisle et al., 1977), as well as the importance of keeping the stimulation field (the current intensity) constant, a frequency threshold procedure was chosen. In this paradigm, the animal is asked to respond for stimulation which is positively reinforcing and to extinguish when it is not.

As an indication of non-specific arousal, drug induced catatonia, or changes in behavior due to stereotypy, a combination of changes in asymptotic rate of responding as well as the more "conventional" rate measure, supra-threshold rate, along with the frequency threshold changes may give a more interpretable indication of morphine's effects on SS behavior.

The frequency threshold measure can also assess effects on SE. A comparison of differences in the two paradigms can provide, in addition to changes in the excitation of each system, an indication of non-specific performance effects.

Method

Subjects

Male Sprague-Dawley rats (Canadian Breeding Farms, St. Constant, Quebec) weighing approximately 350 grams at the time of surgery, were housed individually and maintained on ad lib food and water throughout the experiment. Under sodium pentobarbitol anesthesia (60 mg/kg, i.p.), monopolar electrodes were stereotaxically aimed at the lateral hypothalamus (AP, -0.4 mm; LAT, -1.7 mm; 8.0 mm below the dura; incisor bar at +5 mm). Electrodes were 00 stainless steel insect pins insulted

with Formvar to within 0.5 mm of the tip. Six stainless steel jeweller's screws served as current return. The electrode shaft was fixed to the skull with dental acrylic.

Stabilization

Self-stimulation: After at least five days recovery from surgery, the rats were trained by successive approximation to self-stimulate in a wooden box (25 cm x 28 cm x 82 cm) equipped with two rodent levers (Lehigh Valley Electronics, 121-05). In the left rear corner, one lever was attached approximately 2 inches above the wire mesh floor. Depression of this lever initiated a 500 msec. train of rectangular, cathodal pulses, .1 msec. in duration. During stabilization, the stimulation period (S.P.) (the period is the reciprocal of the frequency) was kept constant at 10 msec. and the current intensity was manipulated until a high rate of responding was attained. A Tektronix D61A oscilloscope was used to monitor the stimulation trains as well as to set the SPs and current intensity. The electrode was connected to the stimulator through a mercury commutator (Leslie Manufacturing Corp.).

Stimulation-escape: After successful training in the SS paradigm, animals were trained to escape a ten second train of stimulation. Depression of a lever in

the diagonally opposite corner from the SS lever (right front) terminated the stimulation. When the animal moved to a neutral corner, the stimulation was again initiated and this procedure repeated until the rat was shaped to the lever. Animals showing severe motor artifacts resulting in the inability to adequately press the lever, were discarded from the study.

Once the shaping procedure was completed, the "on" time of the stimulating train was fixed at 10 seconds and the "off" time at 1 second. Therefore, at the start of each session, the stimulation was automatically delivered; a lever depression produced a 1 second break in the staimulation. If the rat failed to respond, the stimulation was automatically terminated after 10 seconds and reinstated 1 second later.

For each animal, the current intensity that produced optimal SS and SE was determined and used for the remainder of the experiment. The intensities ranged from 300-700 μamps.

After successful training with a fixed period of 10 msec., the training sessions were modified such that the SP was increased every 2.5 minutes in 0.1 $\log_{10}$ steps until the subject stopped responding. Rats were run alternately in the SS and SE paradigm on the hour and on the half hour respectively over a period of 7 hours

per day. In the SS paradigm, 10 priming trains were delivered at the beginning of each 2.5 minute step.

Thresholds at each hourly interval were determined as the SP at which the animal responded at ½ of his maximum rate at that hour. Training was continued until stabilization of thresholds was achieved over a 7 hour period on two consecutive testing days. The criterion for stabilization was a difference of not more than 0.1 $\log_{10}$ units between any two hourly thresholds.

Procedure

After stabilization of SS and SE, Ringer's solution (1 ml/kg) was administered to each animal and hourly thresholds were determined. The average threshold for two Ringer's days was determined for each behavior in each subject and a six week series of tests was begun. Each subject was tested every 5 days. Morphine HCl was administered daily. Injections were always administered at the same hour either in the experimental room (on test days) or in the animal colony.

The testing procedure consisted of seven identical one hour cycles, a ½ hour test of SS followed by a ½ hour test of SE. A 1 hour break separated the first and second cycles; cycles two to seven were contiguous. Drugs were administered on the hour between the first and

second hourly tests. A ten minute "warm-up" period during which time no data was collected, preceded each daily test session. The current intensity was held constant across behaviors and within animals. This procedure was used in an attempt to hold constant the size of the stimulation field. SPs were presented in an ascending series of 0.1 $\log_{10}$ steps with response rates recorded every 2.5 minutes. If the rat did not respond at a criterion level during the first 2.5 minutes, the SP was decreased until vigorous behavior was reinstated. The ascending series began thereafter.

Drug Solution

Morphine hydrochloride was dissolved in injectable Ringer's solution. The dosages used ranged from 20-320 mg/kg. The initial concentration was 20 mg/ml. At the higher doses (above 80 mg/kg) the concentration was increased to 40 mg/ml. After five days of injections at a dose of 20 mg/kg (i.p.) the dose was incremented in .05 log steps until a dose of 80 mg/kg was achieved. After five days of injection at this dose, the dose was again increased in .05 log steps until a dose of 320 mg/kg was achieved. Animals were maintained at this dose for an additional nine days.

Withdrawal

After the final injection of morphine, the entire procedure was repeated for an additional five days substituting Ringer's solution for the drug. Threshold changes were determined at 23, 27, 46, 50, 53, 69, 73, 76, 119, 122, and 125 hours abstinance.

Animals were then perfused through the heart with .9% saline solution followed by 10% formalin. After a minimum of five days, the brains were sectioned at 40 µm and stained with thionin for histological verification of electrode placements.

Results

Figure 1 shows reconstructions of the electrode placements for five of the six subjects. No histology was available for rat 34. All electrode tips were located in the lateral hypothalamus, according to the atlas of Pellegrino and Cushman (1967).

Figure 2 shows the mean changes in SS and SE SP thresholds as a function of time since drug administration. (The SP is the reciprocal of the frequency). An increase in SP threshold reflects a decrease in the number of pulses necessary to maintain the behavior (i.e., a facilitatory effect). All thresholds are expressed as

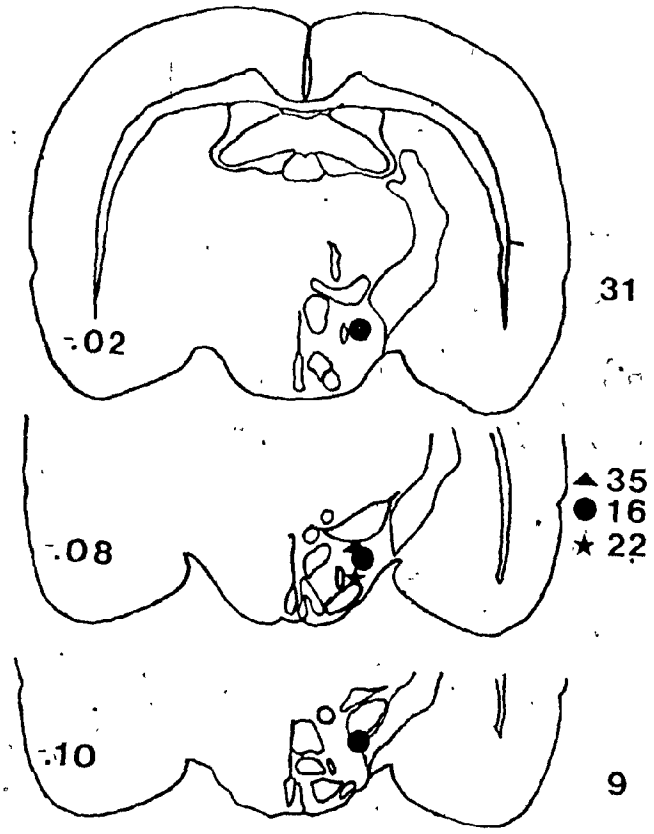
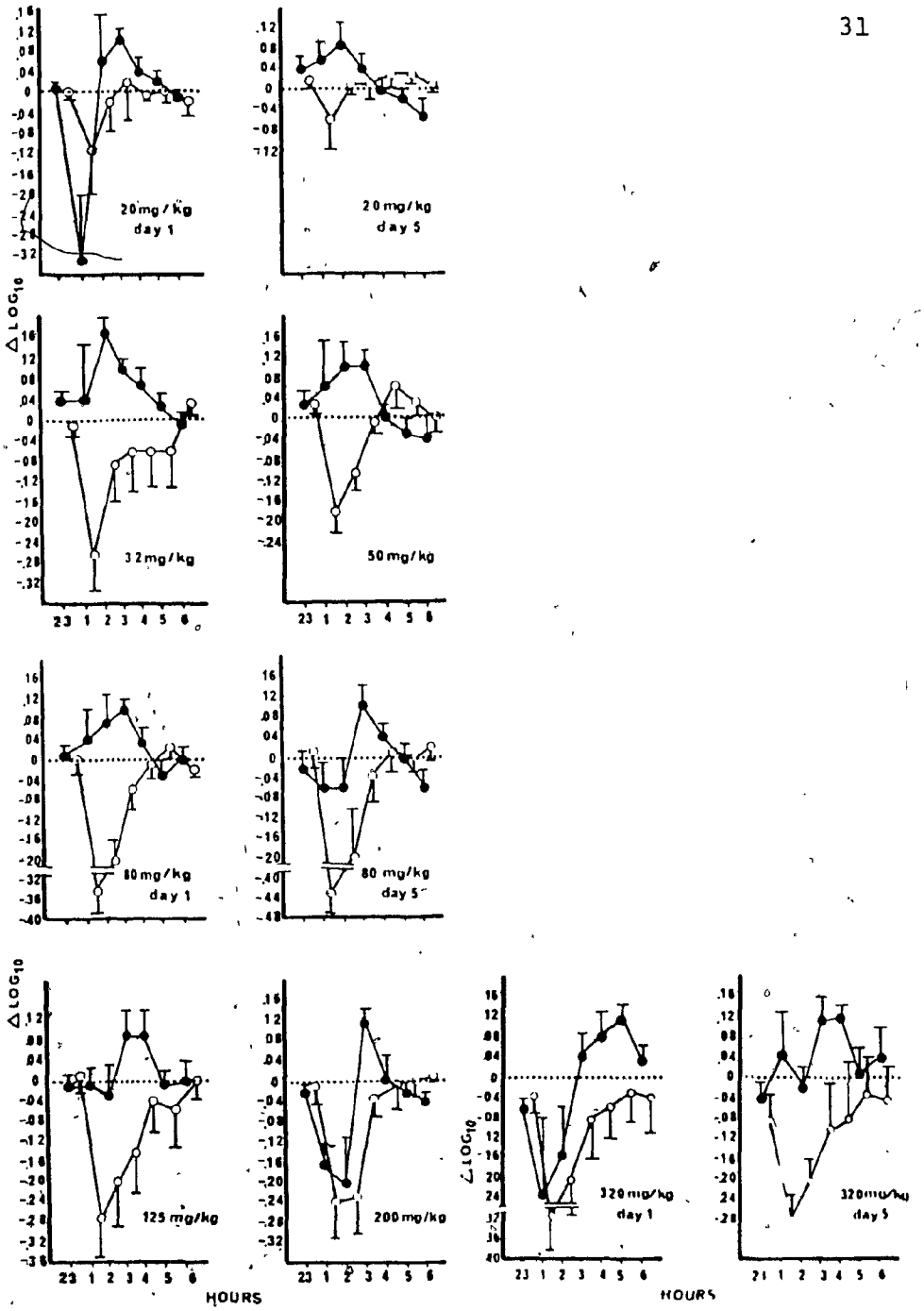


Figure 1. Reconstructions of electrode placements. The numbers accompanying each section refer to the atlas of Pellegrino and Cushman 1967. Histology was not available for animal #34.

Figure 2. Mean changes ± S.E.M. in period threshold for all doses of the drug as a function of hours since drug administration and dose tested.

= self-stimulation

= stimulation-escape

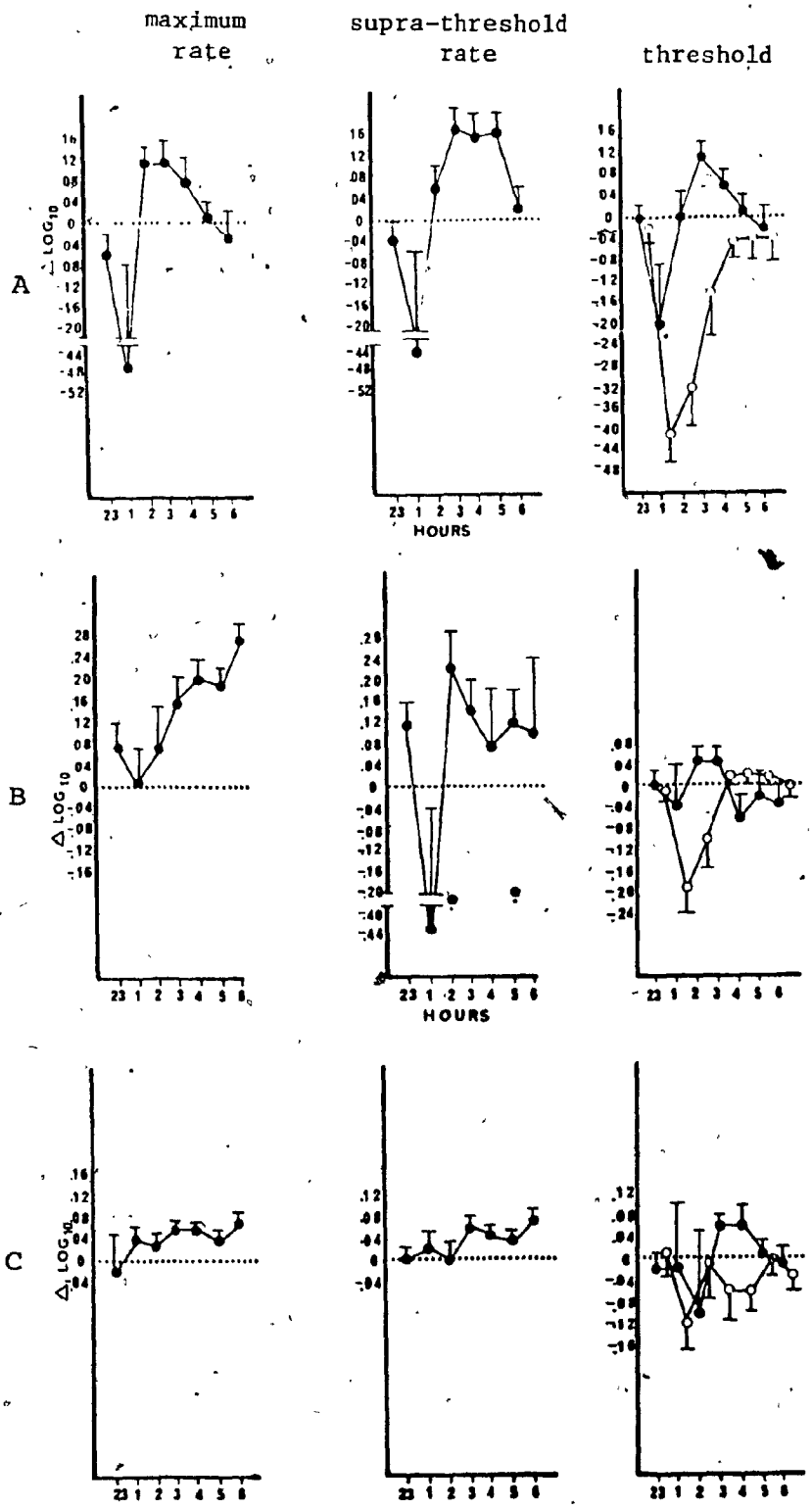

20mg/kg day 1
20mg/kg day 5
32mg/kg
50mg/kg
80mg/kg day 1
80mg/kg day 5
125mg/kg
200mg/kg
320mg/kg day 1
320mg/kg day 5
ΔLOG10
HOURS

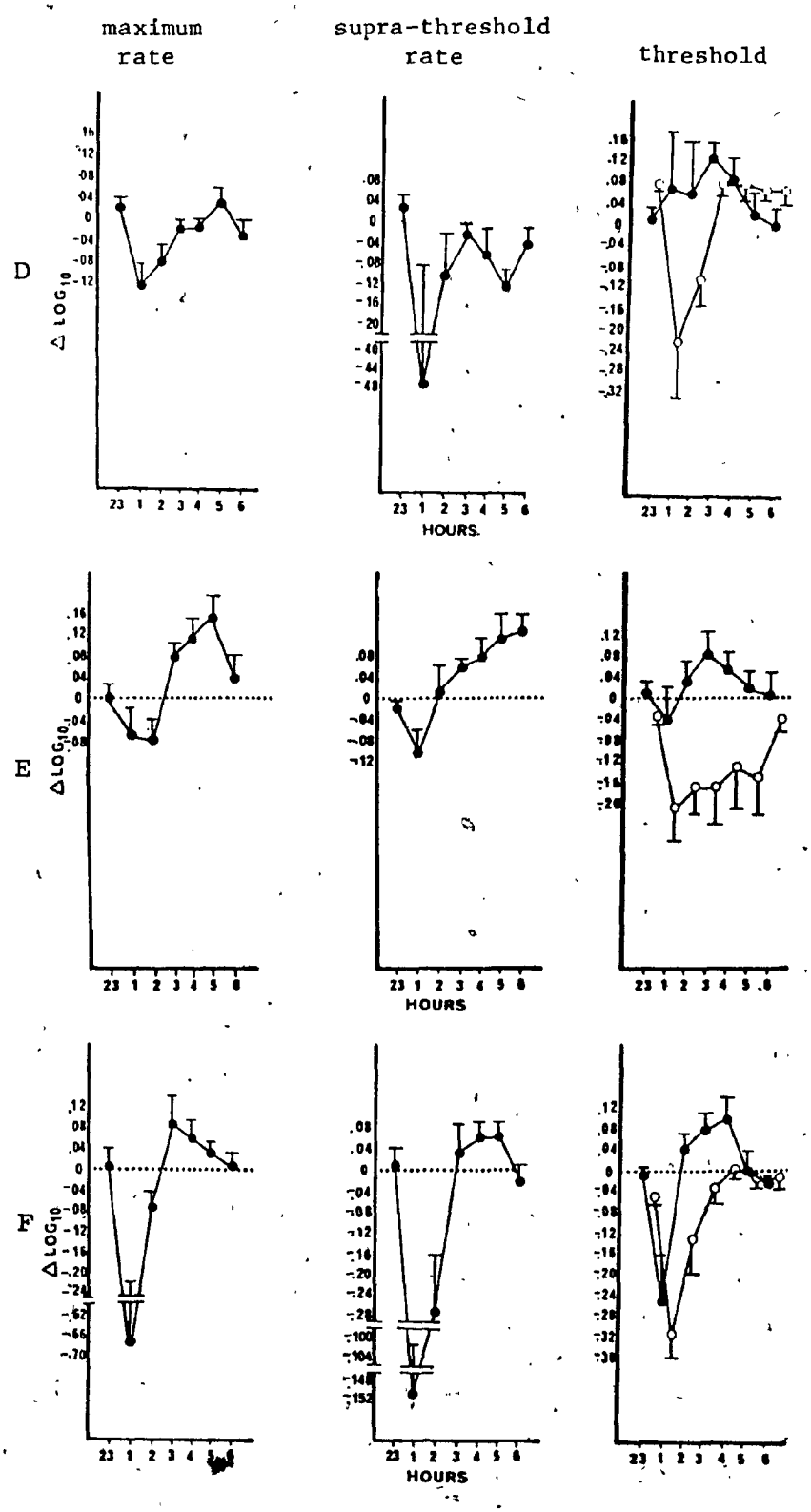
differences from the mean threshold on Ringer's injection days for each animal. An analysis of variance for repeated measures (Dose X Hours) revealed a highly significant effect of hour for SS ($F(6,30)=5.29$, $p<.001$) and SE ($F(6,30)=15.29$, $p<.001$), as well as a significant interaction of dose X hours for SS ($F(36,180)=2.89$, $p<.001$). Tukey post-hoc comparisons confirmed the significant facilitatory effects observed in SS following 32, 200, and 320 mg/kg of morphine. Significant depressive effects on SE were found at all doses.

The effect of dose was not significant for SS or SE. Therefore, data for doses of 20 mg/kg to 125 mg/kg were pooled yielding mean rate changes for each animal. Due to stereotypic responding as indicated by non-reinforced responding at the highest doses of the drug as well as obvious motoric disruption, these doses were not included in this analysis. All dose effect were pooled (20-320 mg/kg) yielding average threshold changes for each animals. Changes in asymptotic rate of responding and supra--threshold rate of responding for SS and threshold changes for SS and SE as a function of time since drug administration are shown in Figure 3. Tukey post-hoc tests confirmed the highly significant decrease in period threshold at 1 hour post-injection for SE in all animals. The effects of morphine on SS threshold changes in less

Figure 3. Changes in maximum rate (left panel) and supra-threshold rate (center panel) of responding for self-stimulation as well as threshold changes (right panel) for S.S. (●—●) and S.E. (○—○) in each animal collapsed across dose.

Asterisks in center panel 'B' indicate averages of all 6 points. Due to obvious motoric disruption, the highest dose was dropped from the analysis for this subject. Graphed data points above those with asterisks are therefore an average of 5 points.


maximum rate
supra-threshold rate
threshold
A
B
C
Δ LOG10
HOURS


maximum rate
supra-threshold rate
threshold
D
E
F
Δ LOG10
HOURS.
HOURS
HOURS

consistant than that on SE. Figures 3c and 3d represent the classic biphasic effect of morphine on SS. The other four animals show negligible depressive effects and facilitatory effects of varying magnitude. Similar inconsistancies are observed in the rate transformations.

Supra-Threshold Rate

Nearly all doses of the drug produced the typical biphasic effect; a depressive phase lasting for 1-2 hours post-injection with the facilitatory phase lasting from the third to fifth hour post-injection. The average curves collapsed across dose for each animal are shown in the center panels of Figure 3. As can be seen, large individual differences exist between animals.

Asymptotic Rate Changes

The average changes in maximum rate of responding for each animal, collapsed across dose, is shown in the left hand panels of Figure 3. Figures 3b, 3c and 3d show curves which exhibit the biphasic effect; the initial depression lasting up to 2 hours with a facilitatory effect following thereafter. The other three animals show varying degrees of maximum rate changes.

Tolerance

Tolerance effects are shown in Figure 4 for three doses employed to assess these effects; 20, 80, and 320 mg/kg. The depression seen in SS at hour 1 on the first test day at 20 mg/kg is seen to tolerate five days later on the second test of 20 mg/kg. The depression of SE shows no such tolerance effects. No other tolerance effects can be seen.

Withdrawal

Threshold changes as a function of hours abstinance are shown in Figure 5. No significiant differences were found between the thresholds on Ringer's injections days and those thresholds obtained during abstinance. The SS data did however, show a main effect of hour ($F(12,60) = 4.33$, $p<.01$). Tukey post-hocs revealed a threshold increase between the 23rd hour since the last morphine injection and the last test at the 125th hour. The SE data showed no significant effect of withdrawal of the drug.

Discussion

This study permitted a series of comparisons between morphine's effects on SS and SE. While the effects of this drug on SS have been well described (Esposito & Kornetsky, 1978) the effect on escape from prolonged lateral hypothalamic stimulation as well as the interaction of the drug's effects on SS and SE had not adequately been delineated.

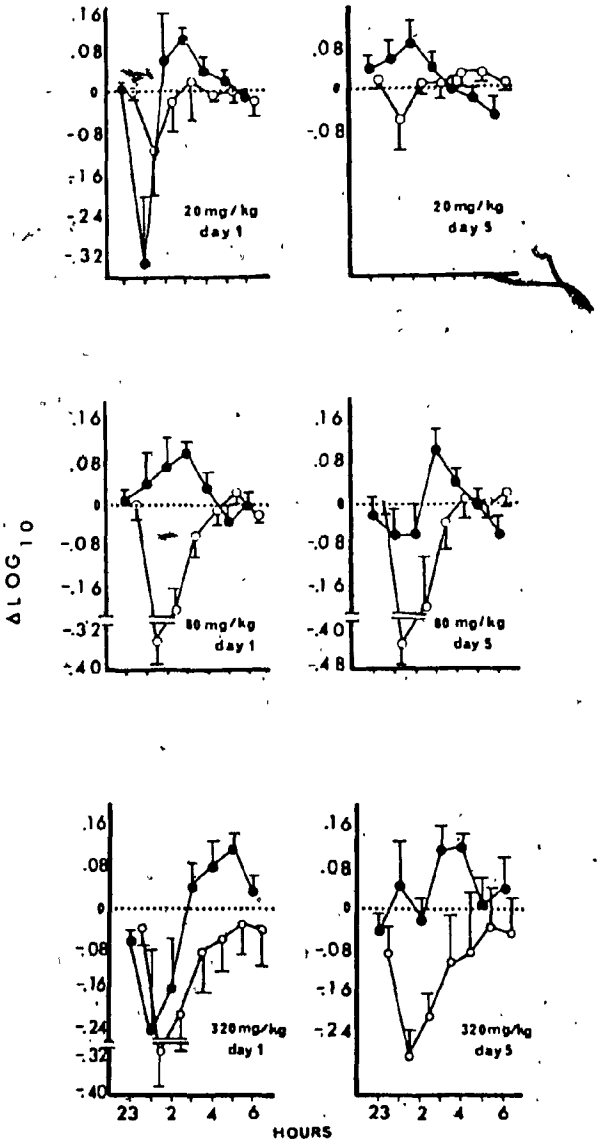
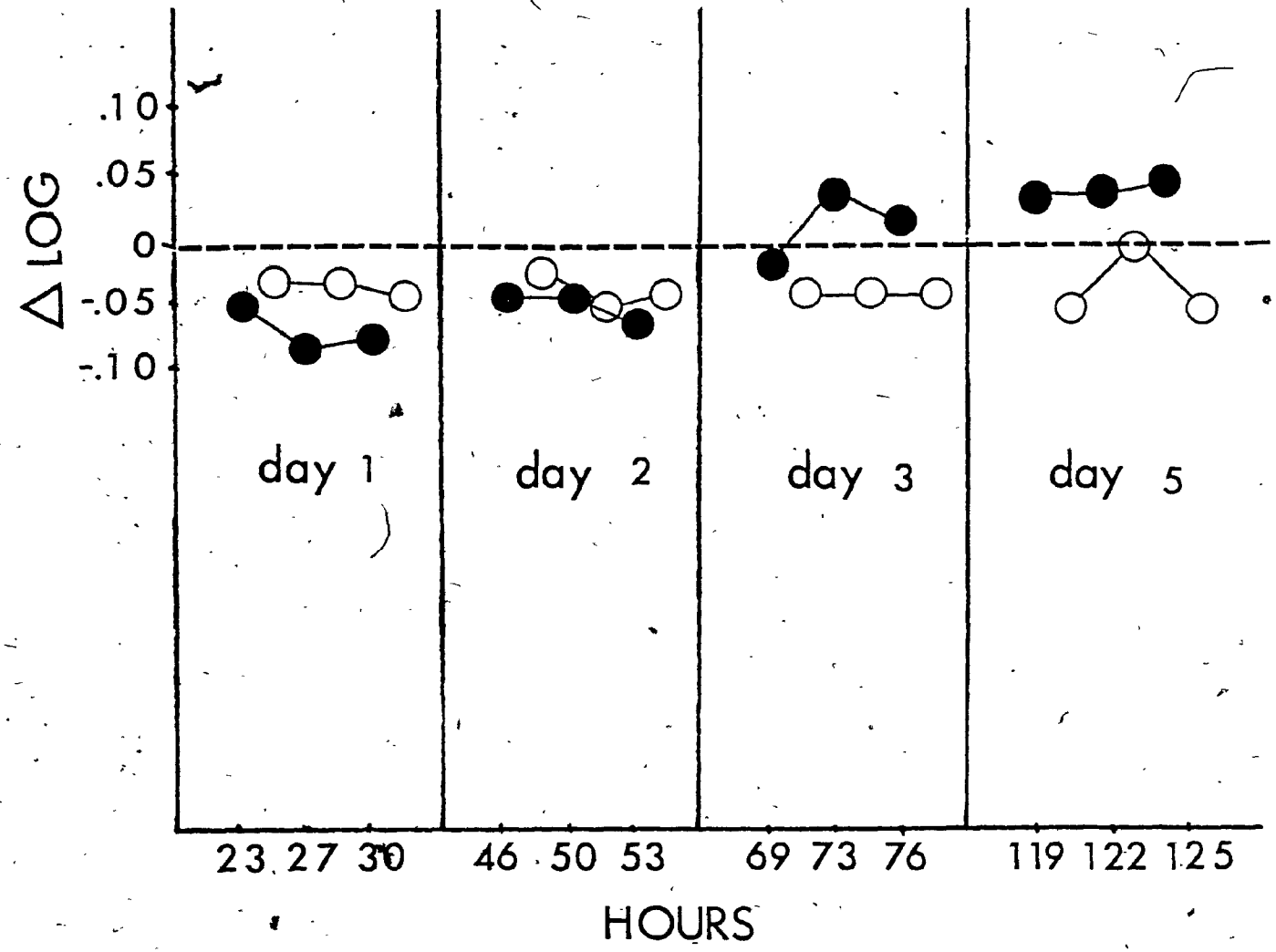


Figure 4. Tolerance effects for S.S. (●—●) and S.E. (○—○) at the three doses employed to assess these effects.

Figure 5. Mean a threshold changes for S.S. (●—●) and S.E. (○—○) as a function of hours abstinance.


Δ LOG
.10
.05
0
-.05
-.10
day 1
day 2
day 3
day 5
23 27 30
46 50 53
69 73 76
119 122 125
HOURS

Stimulation-Escape

A significant attenuation of SE was found at all doses tested (Fig. 2) for each animal. This was in accordance with the findings of Marcus and Kornetsky (1974), Levitt et al. (1977) and Baltzer et al. (1977). The lack of tolerance to this depressive effect (Fig. 4) at a time where depressive effects on SS had tolerated, suggested that this effect of morphine was not due to motoric disruption, but rather, was due to a desensitization of the neural substrate mediating the aversive consequences of brain stimulation. As well, the individual animal threshold changes (Fig. 3) demonstrated that at the times when SE was depressed, SS generally showed no change or a slight facilitation, again suggesting that morphine produces a change in the affective consequences of the stimulation.

The lack of tolerance to the attenuation of SE is contradictory to Pert's (1975) findings. These differences can probably be attributed to the differences in the stimulation site. Pert used the superior colliculus as the negative stimulation site. Kestenbaum et al. (1974) have shown that there is behavioral adaptation to the aversion produced by stimulation of some midbrain sites. In contrast, Shizgal and Mathews (1977) have demonstrated a summation of the aversive effects of lateral hypothalamic

stimulation. It seems that in addition to these differences, the aversion produced by stimulation of these two areas can be dissociated in terms of their sensitivity to morphine. The effects at Pert's placements (unlike this one) would appear to be related to morphine's analgesic properties. Morphine's attenuation of the aversive properties of lateral hypothalamic stimulation would appear to be due to a modulation of the motivational component involved in SE.

This finding casts some doubt on the relevance of Farber and Reid's (1976) study. Since midbrain and lateral hypothalamic stimulation seem to be qualitatively different, it is not clear that one can equate the aversion of midbrain stimulation with the aversive effects associated with lateral hypothalamic stimulation.

Self-Stimulation

The effect of morphine on SS was less consistant than the drug's effect on SE; so much the case that it necessitated looking at the data from individual animals. The reasons for such individual differences are unclear.

A measure of relative "positiveness" of the stimulation was derived from a ratio of the SS : SE thresholds. A ratio greater than 1 would imply a more positive placement than one at which the ratio was less

than 1. In this situation an animal is self-stimulating at a period where it is no longer escaping. When the ratio is less than 1, the opposite is true. While differences in these ratios were substantial, it does not seem that these were responsible for or could totally account for the varying degree of facilitation of SS induced by morphine. In one study (L. Reid, Note 2) it was found that the morphine-induced facilitation of SS did not correlate with electrode placement. Since a similar degree of variability has been demonstrated in the self-administration paradigm as well as in the conditioned taste aversion paradigm (Z. Amit, Note 3), which also measure affective states associated with drug administration, these differences may be due to the different susceptibility to the drug's reinforcing effects of the individual subjects.

As can be seen in Figure 3, both rate measures tended to be more susceptible to the motoric disruption caused by morphine than did the threshold measure. For example, rat 9 (Fig. 3a) showed very large depressions of rate, suggesting some motor incapacitation, although the SS threshold changes did not show similar depressions. Rather, the threshold for this animal increased slightly at a time when rates were significantly decreased. At

the other extreme, rat 35 (Fig. 3f) showed quite large increments in rate with negligible changes in SS thresholds. This would seem to imply that non-specific arousal affected the rate measure while not affecting thresholds.

Withdrawal

During the withdrawal phase of the experiment, SE was quite stable across all test sessions (Fig. 4). SS however, showed significant differences between the first test during abstinance and the last test, five days later. One explanation for this finding is that SS thresholds are decreased due to the negative affective state induced by the discomfort of withdrawal. That is, more pulses are required in order to maintain behavior. The reason for the lack of a significant effect of abstinance on SE is unclear. Hoebel (1974) would have predicted that if one induces a negative affective state in an animal, much like overloading it with food, reciprocal shifts in SS and SE would result. SE, however, in this test did not change. It would therefore seem that the state of withdrawal is one instance where this relationship does not hold.

Interaction Between SS And SE

The next question was addressed towards a possible

relationship between the effect of morphine on SS and SE. More specifically, is the facilitation of SS due, at least in part, to a decrease in the aversiveness of the stimulation?

The data suggest that both the positive and negative components of the stimulation are affected, in opposite directions, by morphine. However, the time course for the attenuation of SE and the facilitation of SS were not congruous. The depression of SE occurred sooner in time (1-2 hours post-injection), and the behavior, in most cases, began to return to baseline levels at a time when SS thresholds were facilitated (3-4 hours post-injection). It is possible that the depressive effects produced by morphine on SS mask a potential facilitation which has been shown to occur with smaller doses of the drug (Reid et al., 1978). However, even after five days of injections at three separate doses, neither a consistant nor significant correlation between the maximum facilitation of SS and the maximum depression of SE was found.

Hoebel (1974) has described the relationship between the rewarding and aversive systems as reciprocal. Manipulations that produce an enhancement of SS have been shown to attenuate SE. This suggests an interaction between these two neural systems. In order to demonstrate

this supposed relationship, it would be necessary to have electrode placements that are more negative than those used in this study. In such a case, at the period threshold for SS, there is a fair amount of aversion in each train of stimulation. If one then induces a desensitization of this aversive system, one might expect an enhancement of SS. A positive correlation between the maximal effects on SS and SE would then lend support to the notion that the facilitation of SS is related to the attenuation of SE.

In this study, the most "negative" placement was of with a ratio of .97 for SS:SE thresholds. Since this is still not an aversive placement per se, the data cannot support or reject the proposed hypothesis. Further experimentation with more aversive placements is necessary to fully elucidate what these relationships are.

In summary, the findings of this study have confirmed those of others; morphine induces a facilitation of SS. This facilitation does not appear to be due to increased arousal or hyperactivity, but can be attributed to a direct action of the drug on the neural substrate underlying brain stimulation reward.

As well, morphine produces an attenuation of SE. This effect does not seem to be a result of motoric disruption nor does it seem to be related to analgesia.

The data imply that morphine produces a desensitization of the neural substrate mediating aversively motivated behaviors.

It seems that the systems underlying the appetitive and aversive properties of lateral hypothalamic stimulation are both sensitive to morphine. It is, at this point, unclear as to the interaction between morphine's modulation of SS and SE. However, in terms of Hoebel's (1974) hypothesis concerning the reward: aversion relationship, it may be that, at some electrode placements, an attenuation of SE contributes to the enhanced positive affect of SS produced by morphine.

Both the SS and SE paradigms allow one to infer the specificity of morphine's reinforcing effects as well as the drug's motivational influences on behavior. Future studies comparing morphine's effects at sites that contain high concentrations of opiate receptors or that are connected to such sites may lead to a further understanding of the neural areas involved in the reinforcing and motivational processes underlying opiate self-administration.

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2. L. Reid, personal communication

3. Z. Amit, personal communication

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