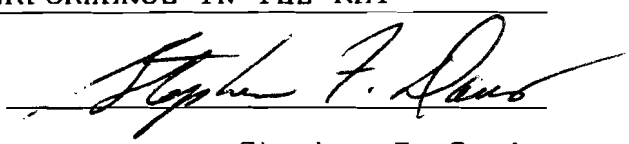
AN ABSTRACT FOR THE THESIS OF

John Colladay Syler for the Master of Science in Psychology presented on December 1991 Title: THE EFFECTS OF POST-TRAINING NALOXONE ADMINISTRATION UPON SHUTTLE AVOIDANCE PERFORMANCE IN THE RAT

Abstract approved: 

Stephen F. Davis

Endogenous opioid substances have been demonstrated to have a profound affect on memory and learning alike. In the present study, naloxone hydrochloride was administered to rats intraperitoneally in one of two doses. The subjects received post-training doses of either 2.5 mg/kg or 10.0 mg/kg of naloxone and were tested for avoidance response retention in a shuttle paradigm. All animals receiving naloxone were compared to saline controls. The animals were tested for retention 24 hours following training as well as at one week and two weeks respectively. Results indicated that all animals remembered at the 24 hour retention trial. The

groups did however differ from each other at one week post-training. Only the low dosage naloxone (2.5 mg/kg) group differed significantly from the other two groups. The low dosage naloxone group had significantly faster approach latencies than either the high dosage naloxone group or the saline group. The results are discussed in terms of behavioral evidence supporting the theory of multiple opiate receptors and in terms of long-term memory consolidation processes.

THE EFFECTS OF POST-TRAINING NALOXONE ADMINISTRATION UPON SHUTTLE AVOIDANCE PERFORMANCE IN THE RAT

A Thesis

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by

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CHAPTER 1

INTRODUCTION

The juice of the opium poppy, especially when processed into morphine and heroin, is a powerful painkiller. In 1973, scientists at the Johns Hopkins University discovered that opium binds to specific sites, known as opiate receptors, located on neurons in the brain and spinal cord of many animals. Once locked in, the drug slows the rate at which the cell fires. As fewer signals pass along the nerves, the brain senses less pain.

Why does the central nervous system possess specific receptors for the juice of a particular flower? The answer came in 1975 with the isolation of a brain chemical called enkephalin. When a pain impulse enters the spinal cord, selected neurons release enkephalin. In turn, enkephalin attaches to the opiate receptors and inhibits the release of the neurotransmitters that would propagate the pain signal. Opium's painkilling action, it has turned out, is just a coincidence (Clark, 1989).

Endomorphine, endorphine and enkephalin are names given to the group of endogenous (made in the organism) opiates which will occupy the opiate receptors in the brain. Morphine and other opiate drugs are exogenous

(made outside of the orgamism) compounds that are structurally similar to these endogenous opiates. The endogenous opiate substances are far more potent than the exogenous opiates derived from the poppy (Leventhal, 1988).

During periods of extreme stress, both humans and animals can exhibit a remarkable insensitivity to pain. For example, soldiers who lose a limb in battle sometimes do not feel the pain for many hours. The anterior pituitary, a brain structure, is known to secrete a form of endogenous opiate during stressful periods. By diffusing through specific regions of the central nervous system, these peptides inhibit neurons associated with pain impulses (Darnell, Lodish & Baltimore, 1986).

Those animals that developed an endogenous opiate system may have established an evolutionary advantage over animals that failed to develop such a system. In the past most organisms encountered a hostile environment, fearing attack from natural predators. If the organism was attacked and injured, one possible defense mechanism would be to escape further visual detection by freezing. Beyond this simple defensive posture, something else also would be happening that could prove extremely advantageous for survival of the

organism--temporary analgesia due to the endogenous opiate system. It stands to reason that pain ordinarily results in the display of behaviors that hurt the organism's chances for survival. For example, if the organism licks a wounded paw, a predator will notice the movement. Also, an organism that moves slowly due to pain is less likely to escape. If the organism is to have any chance of survival, an injury would best be ignored. Hence, there would be a very powerful evolutionary advantage for a species to have developed a degree of analgesia in times of such stress (Leventhal, 1988, p.113).

One of the criteria used to test for the effects of both exogenous and endogenous opiates is to inhibit their effects. Naloxone, the chemical antagonist of morphine, frequently is employed for this purpose. Naloxone is known to be metabolized in a matter of just a few minutes (Goldstein, 1976). Naloxone easily crosses the blood-brain barrier; most of its behavioral effects are probably due to the limited access of opioids to their receptor cites in the brain and spinal cord (Leventhal, 1988, pp. 79-80).

Any action of naloxone on behavior, for example, learning, may be taken as presumptive evidence that opioid systems are involved at some level in mediating

the behavior. Naloxone has been reported to affect learning and memory in a number of conditioning situations when the drug is injected systemically (into the blood stream) either before or after training. For example, Messing et al. (1979) and Gallagher (1982) reported that naloxone enhanced retention of a passive avoidance response in rats.

It is believed by experts in the field that naloxone's effect is exerted primarily upon a specific form of endogenous opiate known as Beta (or B)-endorphine (Izquierdo, Dalmaz, Dias & Godoy, 1988). Naloxone is believed to antagonize the effect of endogenously released brain B-endorphin for several reasons. First, the tasks in which memory is enhanced by posttraining naloxone administration are accompanied by a transient depletion of B-endorphin activity in the hypothalamus, but not a depletion of other endogenous opioids. Second, the B-endorphin depletion cannot be explained by synthesis inhibition, destruction, or the release of different metabolites of B-endorphin. Third, the tasks that are followed by a depletion of brain B-endorphin, but not of other central or peripheral opioids, are followed by a naloxone reversible analgesia. Therefore, by exclusion, the depletion of brain B-endorphin reactivity due to training procedures

can be explained as being caused by a release and then by subsequent destruction of the peptide (Izquierdo, Dalmaz, Dias & Godby, 1988).

Opiates are well-documented modulators of memory for a variety of tasks (Gallagher, Rapp & Fanelli, 1985). There is anatomical evidence indicating that opiate-containing terminals synapse upon dendrites of brain stem neurons. In complementary electrophysiological studies, the application of opiates and opioid peptides decreases the firing of neurons in specific areas of the brain. Taken together, these data suggest that endogenous opiates may provide inhibitory influence on certain brain stem neurons that have widespread projections ascending throughout the brain. These neurons project directly into the areas of the brain specifically responsible for learning and memory (Bennett & Hock, 1990).

A number of experiments have shown that opioid-antagonists can influence learning processes. In general, memory improvement is seen following post-training administration of opioid-antagonists. These effects have been seen in a variety of experimental conditions including the one-trial inhibitory avoidance paradigm, maze learning, discrimination learning, and brightness discrimination

(Castellano, Ines, Pavone & McGaugh, 1989). Post-training naloxone administration has been shown to facilitate memory in all of the tasks in which it has been studied (Izquierdo, Dalmaz, Dias & Godoy, 1988). It is much more difficult to make generalized statements concerning research which utilizes opiate injections. For example, in one study, researchers found that one type of enkephalin, Leu-enkephalin, impaired Y-maze discrimination in mice, while another type, Met-enkephalin, enhanced the discrimination (Martinez, Olson & Hilston, 1984b). These results suggest the possibility that these two similar opiates may have different physiological effects. Naloxone (1.0 and 10.0 mg/kg) also blocked the enhanced actions of the Leu-enkephalin. The results of this work suggest that neither naloxone nor the enkephalins influence locomotor activity, shock-induced behavior was not affected by either chemical. The effect(s) of these compounds, therefore, would not appear to be on motor neurons. So, by implication, sensory neurons are affected.

The effects of the administration of Leu-enkephalin on the retention of active avoidance behavior were recently studied in mice (Dana & Martinez, 1986). Mice received 4 training trials on Day 1, 24 trials on Day 2, and 10 test trials on Day 5. Leu-enkephalin impaired

the acquisition of avoidance behavior when administered prior to testing on Day 2. Impairment of retention was demonstrated on Day 2 and Day 5 when Leu-enkephalin was administered immediately after training on Day 1. The results of this study indicate a long-term nature of the enkephalin effect. The impairing effect was attenuated but not blocked by naloxone. The pattern of the results from the different tests conducted supports the hypothesis that the endogenous opiate Leu-enkephalin impairs both acquisition of learning and memory consolidation in animals. This impairment is suggested to be naloxone-reversible.

The effect of opiate antagonists on other types of memory, e.g., spatial memory, remains unclear. One method of opiate antagonist administration is referred to as pre-training whereby the drug is administered before the training. The other method is referred to as post-training administration where the drug is administered after treatment. Gallagher, Bostock, and King (1985) found that post-training opiate-antagonist treatment enhances the rate at which rats previously trained on an eight-arm radial maze attain criterion performance when the maze is placed in a novel spatial environment. These results suggest that endogenous opioid peptides are involved in the acquisition of

spatial information. Gallagher and her colleagues, however, did not find a significant effect of post-training administration of an opiate antagonist on initial acquisition of the eight-arm radial maze.

Izquierdo and Netto (1990) have shown that naloxone administered at a dose of 0.2 mg/kg immediately following training antagonized the deleterious effect of post-training endorphin administration and prevented the enhancing effect of pretest endorphin administration on retention of a step-down inhibitory avoidance task in rats. Results of this work indicated that post-training naloxone has two different effects, or sets of effects, each with a different dose threshold, an interference with endorphin-induced state dependency and a true modulatory effect. State dependency refers to the fact that learning and memory depend on the relationship between the endogenous state that develops after training and the one that develops during retention testing. The effects of post-training treatments on later retention performance is refered to as memory modulation.

Results also indicate that the immediate post-training administration of naloxone is a viable option for blocking endogenous opiates as compared to pre-training administration which has recently been

discovered to affect behavior in a confounding manner. More specifically, it has been shown that an injection of saline or naloxone five minutes before behavioral testing can increase the rate of autoshaping compared to injections 30 minutes before (Messing & Sparber, 1983).

The effects of immediate post-training subcutaneous (under the skin) administration of naloxone (0.25, 1 or 5 mg/kg) on retention behavior of rats trained in an inhibitory avoidance task have been investigated (Del Cerro & Borrell, 1985). Naloxone did not significantly modify retention latencies of rats that had been familiarized with the apparatus prior to training with weak footshock. However, administration of naloxone facilitated retention behavior of non-familiarized rats who experienced the same weak footshock during training. A facilitory effect of the drug also was observed when strong footshock was paired with a familiar situation. These data indicate that naloxone influences retention behavior depending upon the degree of novelty of the training situation and strength of the shock.

The effects of naloxone on visual recognition were evaluated in a study using monkeys. In 80% of the animals, naloxone yielded an inverted U-shaped dose-effect curve. For each of these animals at least one dose produced an increase in the number of objects

correctly recognized. Lower doses had little effect (0.3 mg/kg), while higher doses (10.0 mg/kg and above) tended to disrupt motor behavior (Mishkin & Aigner, 1988).

Researchers have known for years that rats exposed to inescapable shocks subsequently exhibited deficiencies to escapable shock in a novel situation 24 hours later. This effect has been termed learned helplessness (Overmier & Seilgman, 1967). Naloxone blocks the learned helplessness effect, allowing efficient escape performance on the subsequent test. In contrast, naloxone impaired the performace of rats pretrained with escapable shocks and animals with no previous exposure to shock. These effects occurred at lower doses and increased substantially with higher doses. These results suggest a significant role for endogenous opiates in the induction of learned helplessness as well as in the acquisition of efficient escape behavior (Whitehouse, Walker, Margules & Bersh, 1983). The results of this research further imply that the endogenous opiate systems are involved in simple learning processes, especially ones utilizing fear and pain.

As one can see, there is considerable interest in the role that the endogenous opiate system plays in the

modulation of learning and memory. The general finding appears to be that opiate agonists tend to inhibit learning or cause amnesia and opiate antagonists tend to facilitate the learning/memory processes. However, the specific paradigm in which these drugs are tested influences the outcome.

Memory has been tested in a radial maze, with shock avoidance or food receipt serving as a reinforcer. For example, in a conditioned emotional response (CER) paradigm, mice were shocked in one maze arm with a tone present and later tested with the tone to determine the number of entries into each maze arm. Pre-test administration of B-endorphin enhanced the CER performance as reflected by a reduced number of entries. However, when the task was learned in a new spatial environment, post-training injections of B-endorphin into the medial septal area of the brain impaired acquisition (G. A. Olson, R. D. Olson & Kastin, 1989).

Possible task-specific results also have been found in studies utilizing discrimination learning paradigms (G. A. Olson, R. D. Olson & Kastin, 1989). In a two-choice, discrete-trial procedure utilizing monkeys, morphine was found to disrupt the discrimination, and naloxone was shown to have no effect alone, although it inhibited the action of morphine. Naloxone, however,

facilitated retention of a Y-maze discrimination when injected alone immediately after training.

These results, in conjunction with the inverted U-shaped function relating naloxone dose and visual recognition in monkeys (Mishkin & Aigner, 1988), indicate that the drawing of general conclusions about the effects of endogenous opiates on discrimination learning would be tenuous at best. Clearly, additional research is needed in this area.

The data considered thus far have dealt with direct modulation of learning by facilitating or inhibiting acquisition of memory. It is conceivable that endogenous opiates may exert an indirect effect upon learning and/or memory. Indirect modulation might be accomplished by altering the reward or cue properties of the variables being studied. For example, Kirkham and Blundell (1987) discovered that naloxone administration reduces food intake in rats by promoting satiation and prolonging satiety. Hence, a motivational state, not learning, has been changed.

In order to avoid the possible satiation confounds inherent in the appetitive learning situation, the present study proposed to investigate the effects of naloxone on passive avoidance behavior (Martinez, Vasquez, et al., 1980). In passive avoidance learning, an animal

is placed in the lighted side of a two-chamber shuttle box facing away from the dark compartment. It is well known (Whitehouse, Walker, Margules & Bersh, 1983) that rodents will automatically leave the light compartment and enter the dark compartment when the door separating the two chambers is opened. The animal is then given a shock and can be injected with any one of several neuromodulating chemicals. After some period of time, the animals' latency to reenter the dark compartment is measured.

It follows that if the neuromodulating chemical does not have any interference effect upon learning, the animal will "passively" avoid reentering the dark chamber as this side of the shuttle box has become associated with shock. Conversely, it follows that if the neuromodulating chemical interferes with learning, then the animals will not be hesitant to reenter the dark (shock) side of the shuttle box.

Recent research has indicated that injections of opiate antagonists, agonists or control vehicles prior to behavioral testing also may cause confounding. More specifically, it has been shown that an injection of saline administered 5 minutes before behavioral testing increased the rate of autoshaping compared to injections administered 30 minutes before the experimental session

(Messing & Sparber, 1983). As saline is the typical carrier for opiates and naloxone, such effects are not desirable. In order to avoid such confounds in the present study, naloxone was administered after the avoidance training trial (see Izquierdo & Netto, 1990).

Size of dose was another manipulation employed in the present experiment, small and large doses of naloxone, were administered to separate groups respectively. Previous research has shown that intraperitoneal (ip) administration of naloxone results in a dose-related impairment of avoidance response acquisition (Aigner & Mishkin, 1988). It is generally accepted that doses below 2.5 mg/kg are considered to be small, while 10.0 mg/kg is generally considered a rather large dose (Turnbull, Hill, Miller, McElroy & Feldman, 1982). Thus, an associated goal of this project was to evaluate the effect(s) of dose size on post-trial administration of naloxone. All naloxone-treated animals were compared to controls (saline-injected) animals.

CHAPTER 2

Method

Subjects.

Thirty naive male Holtzman rats served as subjects. Each animal was individually housed in a wire-mesh cage with water and food available on an *ad libitum* basis. The animals were maintained on a 16:8 hour day/night cycle. The subjects were approximately 180 days old at the inception of the experiment.

Apparatus.

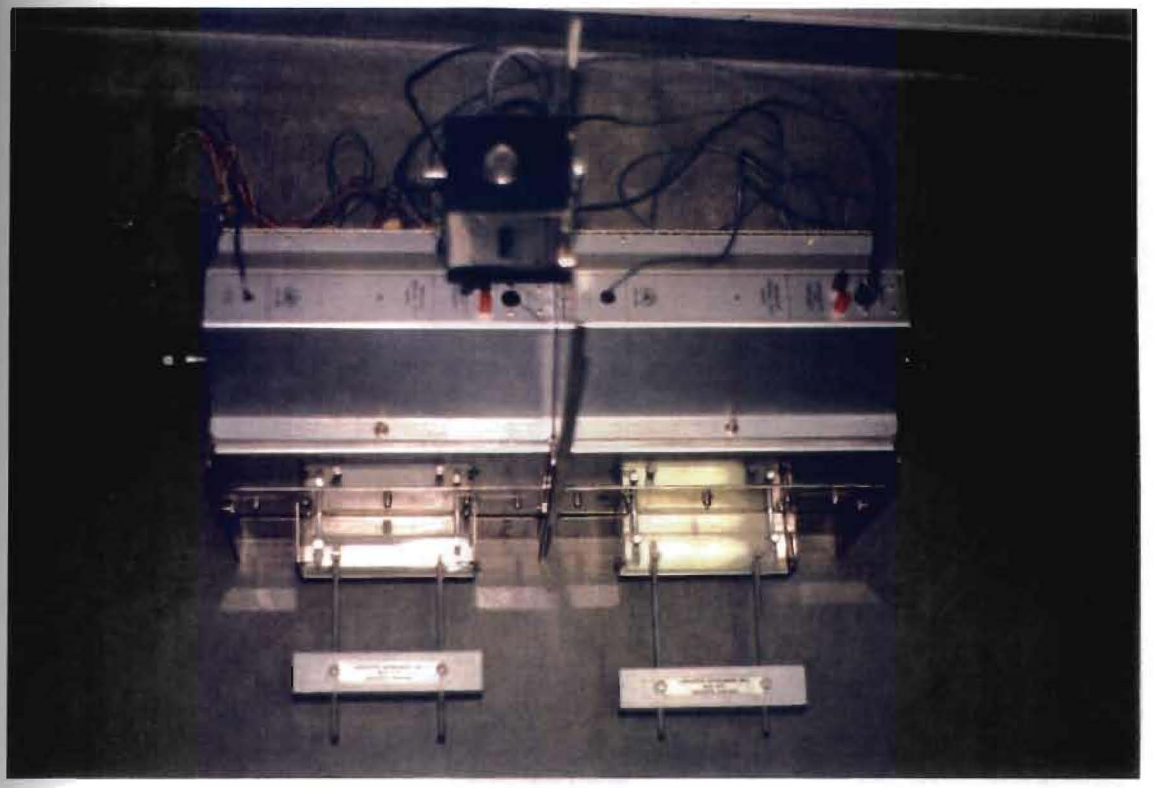
A two-chamber Lafayette Modular Testing Unit (Model 85000) served as the experimental apparatus. The grid floor of one of the two chambers of the shuttle-avoidance apparatus was attached to a shock producing unit (Lafayette Model 81335). One chamber was designated as the introduction chamber, while the shock-producing side was designated the aversion chamber. The guillotine door separating the two chambers was operated manually. Placing an animal on the pressure-sensitive floor of the introduction chamber, in conjuction with a series of electromechanical relays, activated a digital timer (Lafayette Model 54030). Breaking a photoelectric beam located 13 cm beyond the door to the aversion chamber

stopped the timer, thus yielding a latency (seconds) to enter the aversion chamber. A 12-watt lamp positioned 24 cm above the grid floor and concealed by a piece of translucent plexiglass was used to illuminate the first (introduction) chamber. There was no ambient illumination in the room. Figures 1 through 4 illustrate the shuttle box.

Procedure

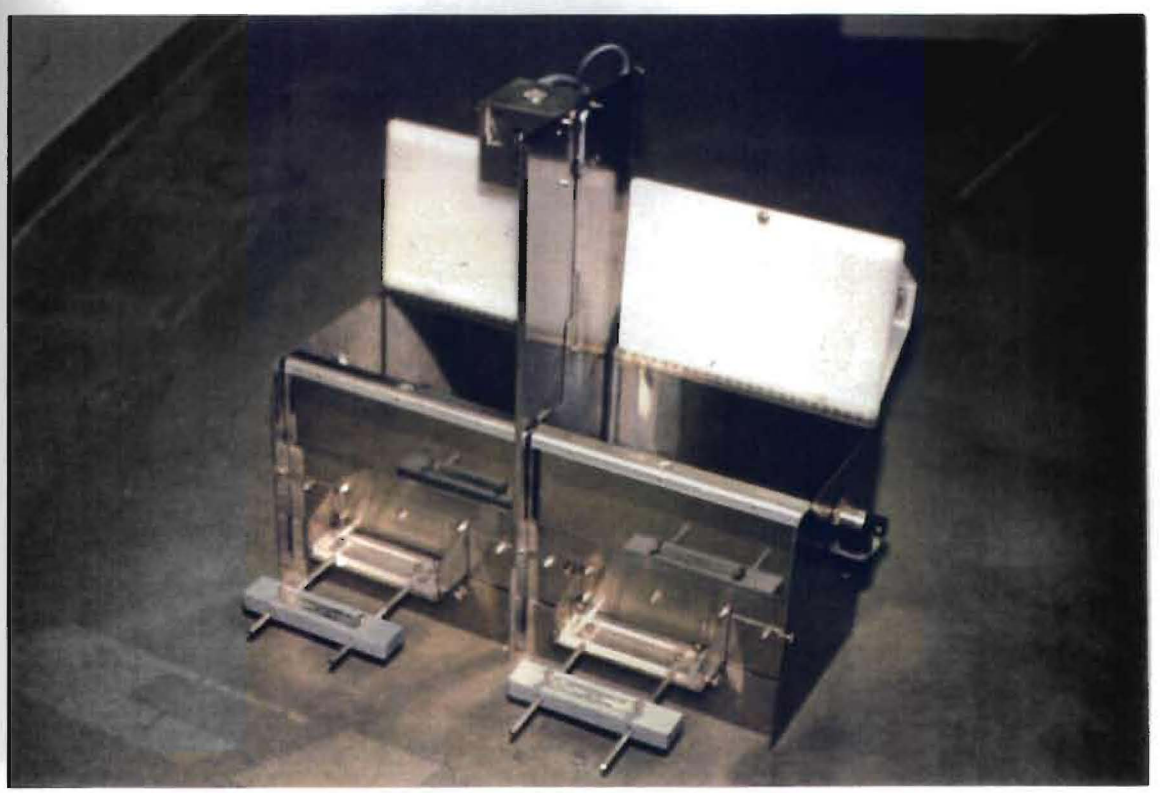
Upon arrival from the supplier, all subjects were given a 150-day rest period. During the last 10-days of the rest period, each animal was removed from its home cage and handled for approximately 5 minutes per day. On the final day of this 10-day period, each animal was weighed following handling. Drug doses were calculated from the body weights recorded following handling on the final day of this period.

The animals then were assigned randomly to one of three treatment conditions: Control (n=10), Low Dose (n=10), and High Dose (n=10). Control subjects received an interperitoneal (ip) injection of 1.0 ml of .09% saline. Subjects in the Low Dose group received an ip injection of Naloxone Hydrochloride (2.5 mg/kg); subjects in the High Dose group also received an ip injection of Naloxone Hydrochloride (10 mg/kg). Sufficient saline was added to the naloxone for the Low



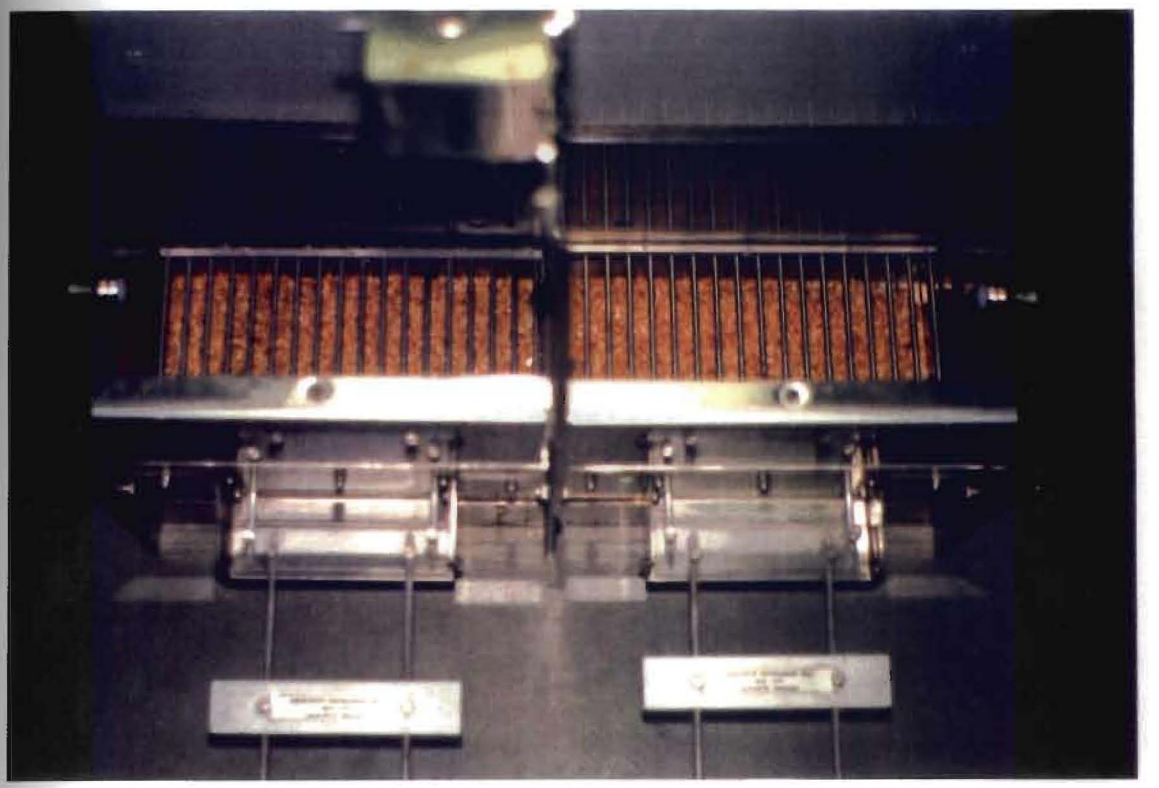
Shuttle box as viewed from above (doors closed)

FIGURE: 1



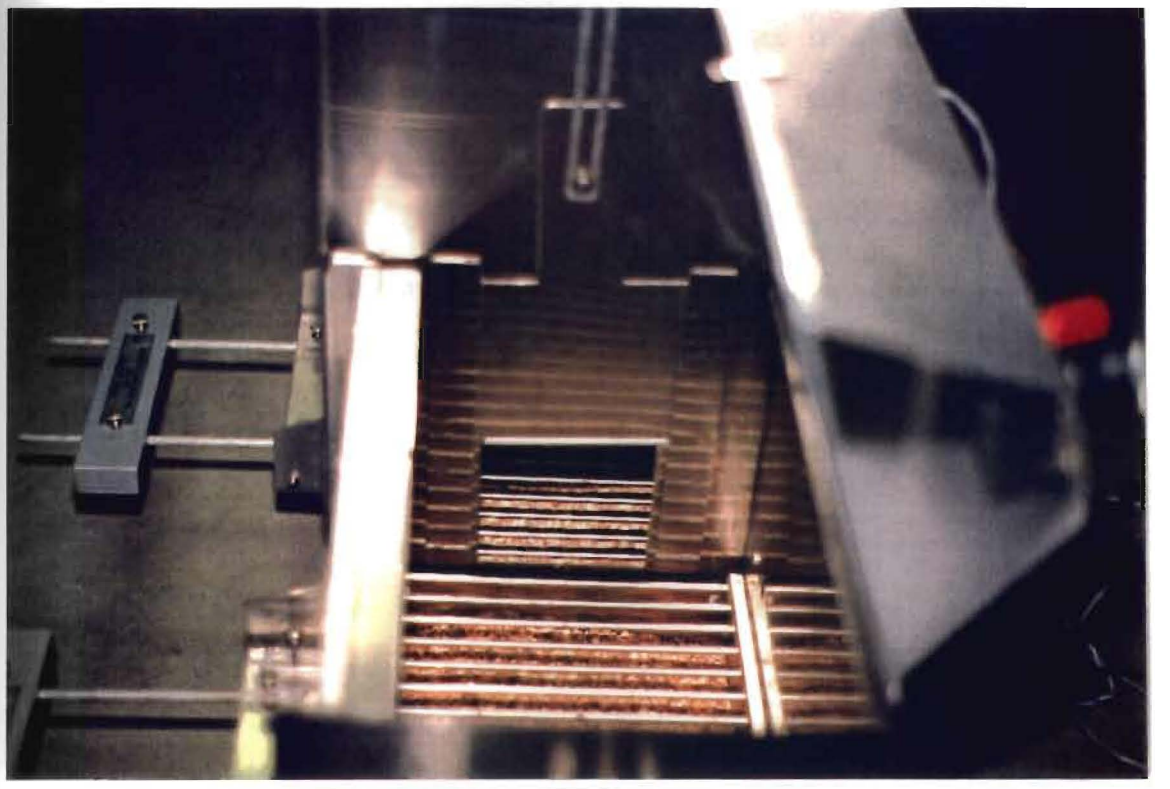
Shuttle box as viewed from above (doors open)

FIGURE: 2



Shuttle box as viewed from above (note two chambers)

FIGURE: 3



tle box as viewed from side (note guillotine door in open position)

FIGURE: 4

Dose and High Dose animals to result in a total injection volume of 1.0 ml for all subjects. All solutions were administered immediately following the training trial. All trials were conducted between 16:00 and 20:00 hours.

The training trial consisted of placing the designated animal in the illuminated introduction chamber facing away from the guillotine door. The lid was then closed. After 5 seconds, the guillotine door separating the two compartments was opened and the animal was allowed to step through to the dark aversion compartment. If the animal did not step through after 600 seconds (10 minutes), it was to be removed from the apparatus and dropped from the experiment.

The guillotine door was closed as soon as the photoelectric beam was broken. Three seconds later the animal received an inescapable foot-shock (100mA, 3.0 Second, 28 VDC). Following shock application, the animal was immediately removed from the chamber, injected with the appropriate drug, and then returned to its home cage.

A series of retention tests took place 24 hours, 1 week, and 2 weeks following training. The retention task was exactly like the training task with the exception that the animals received neither shock nor

drug. If an animal failed to enter the dark compartment within 600 seconds (10 minutes), it was removed from the apparatus and received a score of 600.

CHAPTER 3

RESULTS

Results

Analysis of variance (ANOVA) of the step-through latencies for the training day failed to yield statistically reliable effects, $F(2, 27) = .184$, $p > .05$. Thus, the groups were deemed equivalent on the day of training.

An ANOVA conducted on the latencies obtained on training and the three subsequent retention days yielded significance for the days, $F(3, 119) = 347.88$, $p < .001$, effect. Subsequent Newman-Keuls tests indicated the training latencies were significantly ($p < .001$) shorter than those of the three retention days which did not differ reliably. These results are presented graphically in Figure 5.

In order to ascertain any differential retention effects, a separate ANOVA was performed on the latencies from the retention days. This analysis yielded significance for the days, $F(2, 54) = 5.32$, $p < .007$, and group X days, $F(4, 54) = 2.64$, $p < .042$, effects. Subsequent Newman-Keuls tests, used to probe the significance, indicated that the Day 1 latencies were significantly ($p < .05$) longer than those on Days 2 and 3, which did not differ. Moreover, the low dosage

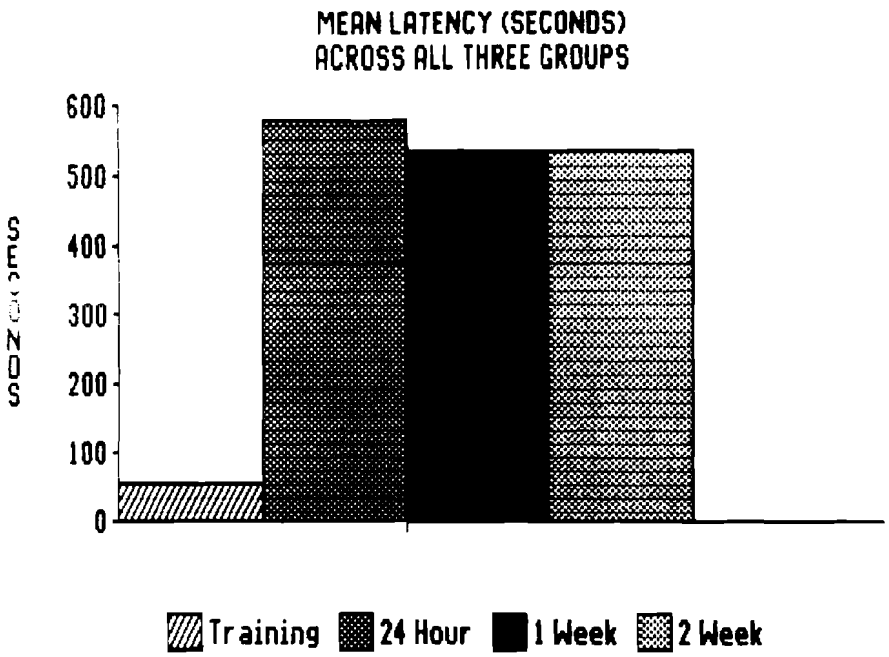


FIGURE 5: Mean latency in seconds across all three groups. Training = the training day, 24 Hour = the first retention day 24 hours following training, 1 Week = the second retention day one week following training, 2 Weeks = the third retention day two weeks following training.

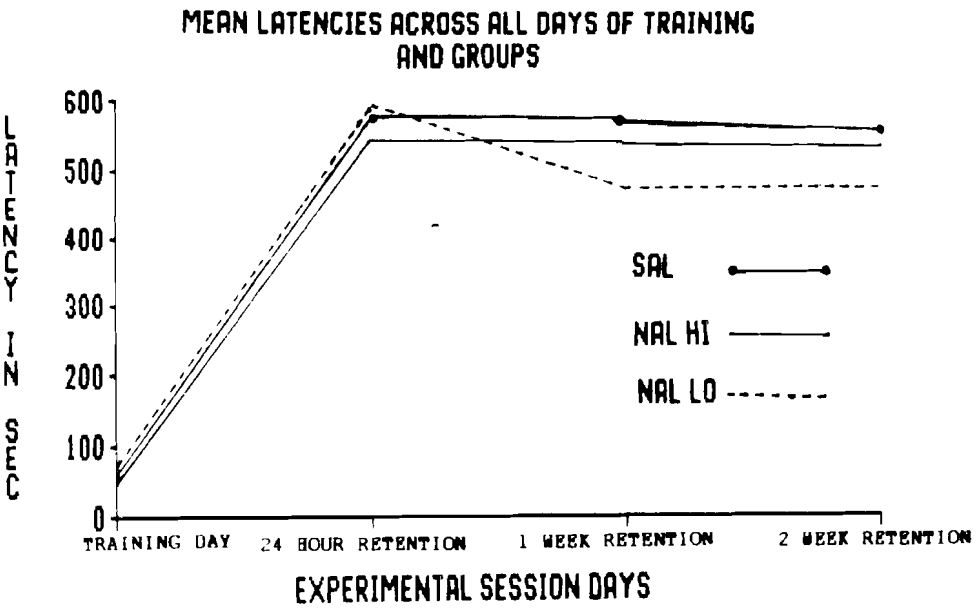


FIGURE 6: The mean latencies for all four days of the experiment across all groups. SAL = Saline 1.0 mg, NAL HI = Naloxone high dose 10.0 mg/kg, NAL LO = Naloxone low dosage 2.5 mg/kg.

Naloxone group (2.5 mg/kg) designated NAL LO had significantly faster latencies ($p < .05$) than the other two groups (Saline group SAL and high dose Naloxone 10.0 mg/kg designated NAL HI) on the retention days one week and two weeks following training. This pattern is illustrated in Figure 6. Figures 7 and 8 illustrate the percentage of animals which achieved ceiling effects 24 hours and 1 week following training.

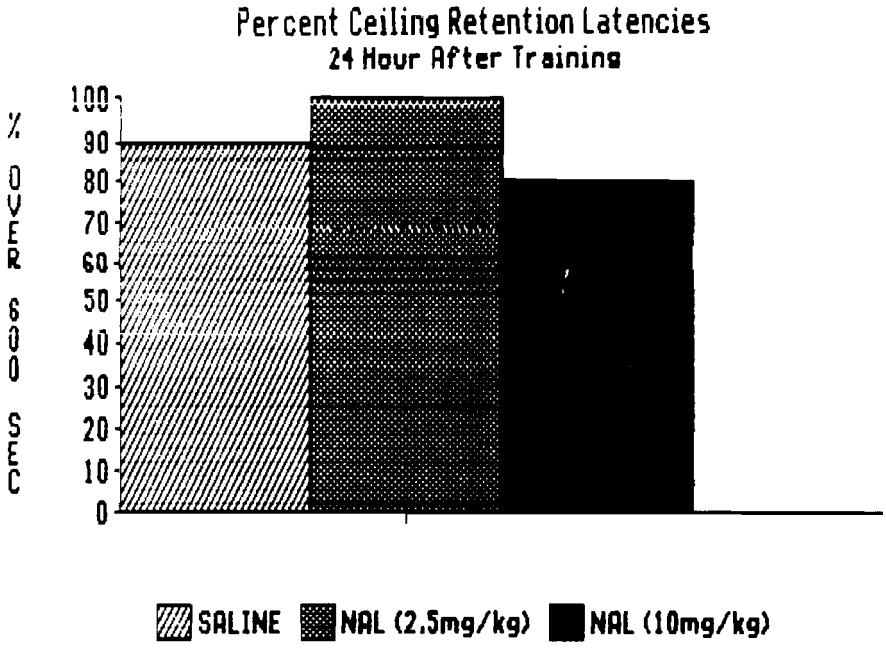


FIGURE 7: The percent of retention latencies achieving ceiling effect 24 hours following training. The ceiling effect is achieved when the latency was above 600 seconds. Saline = saline treated animals, NAL (2.5 mg/kg) = low dosage of naloxone treated animals, NAL (10 mg/kg) = high dosage of naloxone treated animals.

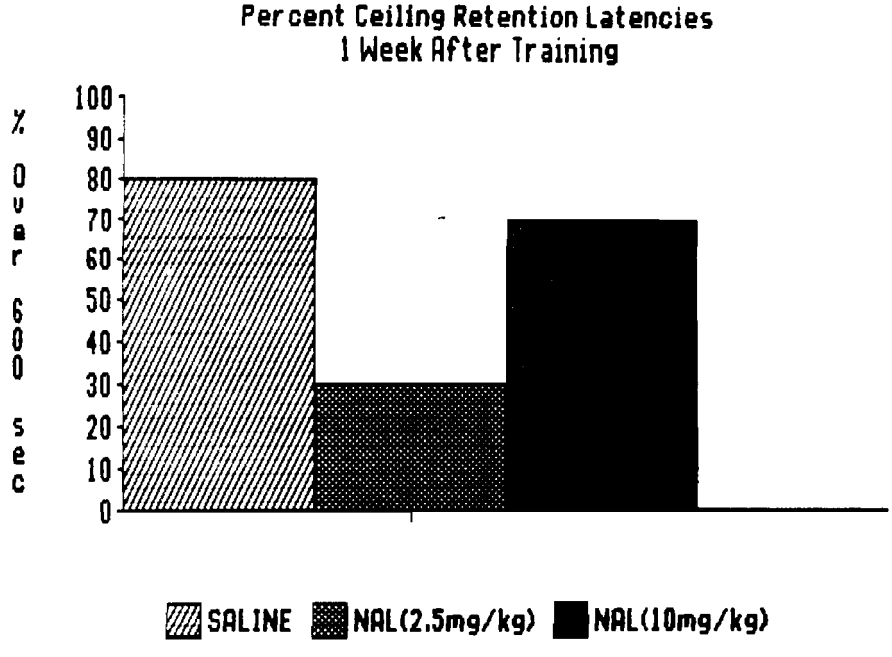


FIGURE 8: The percent of retention latencies achieving ceiling effect one week following training. The ceiling effect is achieved when the latency was above 600 seconds. Saline = saline treated animals, NAL (2.5 mg/kg) = low dosage of naloxone treated animals, NAL (10 mg/kg) = high dosage of naloxone treated animals.

CHAPTER 4

DISCUSSION

Clearly, it is evident that the paradigm of passive avoidance acquisition is a viable method of testing memory in animals. The significant increase in latency to enter the dark compartment following the training trial indicates that the animals did indeed learn that is was aversive to cross to the preferred (dark) side of the shuttle box.

Any definitive conclusions about the role of endogenous opiates in the present learning paradigm are difficult to ascertain. It was apparent that all groups of animals remembered the aversive incident quite well after 24 hours. In fact, only the low dosage naloxone animals demonstrated any deterioration in memory 2 weeks later.

Previous research by others has indicated that in this paradigm, most animals can be assessed for the memory effects of neuromodulating chemicals after only 24 hours (Martinez, Vasquez, et al. 1980). It is interesting that such a high number of animals "remembered" the training day and thus did not cross over to the dark chamber on the 24-hour-retention test. In fact, almost 90% of all animals tested achieved the

600-second ceiling score. More intriguing are the results obtained 1 week following training. At 1 week, only 30% of the animals in the low dose naloxone group achieved the ceiling latency effect. This percentage is to be compared to 80% of the subjects in the saline group and 80% of subjects in the high dosage naloxone group. The low dosage naloxone group clearly did not seem to remember the aversion learning as well as the other 2 groups.

It is possible that the effects obtained 24 hours following training were due to the amount of shock delivered on the training trial. It is well known that the shock used in the present study (100 milliamps) represents a rather intense application (Martinez, Vasquez, et al. 1980). It is also known that levels of released endogenous opioids change as the time after stress is varied. There is an accumulation of evidence which suggests that endogenous opioid peptides are released after stressful experiences, including electric foot-shock (Bodnar, Kelly, Brutus & Glusman, 1980) and that these endogenous peptides bind to opiate receptors. Because of the high intensity of shock used in the present study, it is possible that the subjects experienced an endogenous opiate release which interfered with the expected naloxone effect. The

ceiling effect seen 24 hours following training thus may be a function of a very large endorphin release at training which tended to confound the 24 hour retention testing.

It is difficult to explain the differences between the low (2.5 mg/kg) and high (10 mg/kg) dosage naloxone groups. A falling off in the response of an organism to a high dose of a narcotic agonist or antagonist drug is most easily explained by receptor fatigue (Kosterlitz, Lord, Paterson & Waterfield, 1980). However, such an explanation is inadequate in this case, because naloxone is a relatively "pure" antagonist, the dose of naloxone and morphine that have memory modulatory effects are relatively low, and the effective dose range is narrow. A more plausible explanation concerns the concept of multiple types of opiate receptors. At low concentrations (2.5 mg/kg) naloxone is presumed to interact primarily with one type of receptor, whereas, at higher concentrations (10mg/kg), it has its effects upon other receptor types. At high doses, when other types of drug-receptor interactions occur, the memory effects of the drug may be masked. It is interesting, in this context, that others have also found that dose-response curves for naloxone are sometimes U-shaped (Jacob & Ramabadran, 1978).

While this U-shaped relationship was not clear at the 24-hour-retention test, it was clearly discernable at the 1 and 2 week retention tests. Again, this may be due to a function of the amount of shock delivered at the training trial, making the training more salient after only 24 hours.

It is conceivable that the relationship existed 24 hours following training; however, was not clearly visible because of the small number of subjects and a related problem the large amount of within-groups variance. For example, most researchers investigating the effects of opioids upon memory have used very large groups of subjects. Whitehouse, Walker, Margules, and Bersh (1983) used 84 animals, while Dana and Martinez (1986) used 202 animal subjects in their work with naloxone. Thus, because of the relatively small group of subjects utilized in the present study it is possible that actual relationships did not become clear, especially at the retention test 24 hours following training.

Another possible explanation for the results obtained in the current study concern the possibility that the endogenous opioids were indeed not responsible for the effects witnessed. It is entirely possible that endogenous opiates are not responsible for long-term

memory consolidation. It is conceivable that the naloxone blocked some other group or groups of an unknown memory influencing neuropeptide. Possibly this peptide is responsible for the long term memory assessments made at the one and two week retention tests.

Previous results have suggested that there is an analogy of sorts between the present findings with naloxone and previous data from other laboratories on the effects of post-training adrenocorticotropic hormone (ACTH) and epinephrine administration. These two hormones cause memory facilitation at low doses; at high doses or when given to animals that presumably release them in large amounts, ACTH and epinephrine cause instead a naloxone-reversible amnesia that is attributable to a release of brain endorphin (Izquierdo, Dalmaz, Dias & Godoy, 1989). Thus, like ACTH and epinephrine, naloxone appears to present different types of post-training effects on memory dependent upon the dose.

Memories are, no doubt, based upon changes in certain neurons excited by experiences. An experience, in this case a conscious perception or apprehension excites not only "memory cells" but, as well, other brain and hormonal systems. There is increasing

evidence that the cellular storage processes are influenced by activity in these other systems (McGaugh, 1983). Although the details of classical theories of learning have differed, the theories have had a common interest in providing an explanation of the role of motivation and reward in learning. It now seems possible that motivation and reward may influence learning perhaps largely or only in part through the influences of endogenous opiates and other hormones released by experience. Endogenous opiates may act to strengthen William James's habits (1890), Thorndike's connections (1949), and even (or especially) Tolmans's cognitions (1951). Understanding the ways in which endogenous opiates interact with brain systems to modulate memory storage is essential for understanding the physiology of memory.

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