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Substance P Enhancement of Passive and Active Avoidance Conditioning in Mice[1]

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SCHLESINGER, K., D. U. LIPSITZ, P. L. PECK, M. A. PELLEYMOUNTER, J. M. STEWART AND T. N. CHASE. *Substance P enhancement of passive and active avoidance conditioning in mice.* PHARMACOL BIOCHEM BEHAV **19**(4) 655–661, 1983.—In a series of seven experiments we explored the effects of peripherally administered substance P on passive and active avoidance conditioning in mice of two genotypes. The peripheral post-trial administration of substance P significantly enhanced the retention of a single-trial passive avoidance task. This effect was dose dependent; 1 ng/g of substance P enhanced the retention of this habit, whereas higher and lower doses were either less effective or ineffective. In heterogeneous strain (HS) mice, substance P administered before training on an active avoidance task did not alter the rate at which these animals learned this habit. However, animals that had been trained with substance P were significantly more resistant to extinction than were animals that had been injected with vehicle. Similarly, C57Bl/6J mice that had been treated with substance P immediately after active avoidance training were more resistant to extinction than were mice that had been given control injections. The enhancement of retention of the passive avoidance habit with substance P was reversed in animals that had been pretreated with naltrexone. Substance P enhancement of the retention of the passive avoidance habit, and its reversal with naltrexone, was observed in both sham operated and adrenalectomized mice.

Substance P Active and passive avoidance learning

OVER the past decade, evidence has accumulated indicating that both the central and peripheral administration of many hypothalamic and pituitary hormones are capable of modifying the performance of experimental subjects on a wide range of behavioral tasks. Many of these findings have been discussed and summarized in a series of recent reviews [4, 17, 28]. Within the context of the findings we will report below, it is especially interesting to note that certain neuroactive peptides, and some of their analogs and fragments, are capable of changing the performance of animals in learning and memory tasks [21]. Some of the peptides that have been found to influence adaptive behavior include the enkephalins, ACTH, MSH, TRH and vasopressin [3, 5, 7, 19, 20, 21, 25]. The effects of certain endogenous peptides have been shown to be dose dependent, to occur following their central or peripheral administration and, in some cases, to be independent of their "classical" endocrine effects. Such results have led some investigators to postulate that many peptides may have multiple functions, a phenomenon that some have speculated to be efficient in an evolutionary sense [17].

Substance P (SP) has also been implicated in mediating a number of behaviors. For example, intraventricular, intracerebral and intraperitoneal administration of SP has been reported to (a) produce analgesia [6,33], (b) decrease spontaneous locomotor activity and counteract amphetamine-induced hyperactivity following peripheral administration of the peptide [30], (c) to result in site-dependent circling behavior following injection of SP into the substantia nigra [29], and (d) to produce caudally directed biting and scratching, following intrathecal injection [14].

One group of investigators has reported that central administration of SP can modify memory storage in rats, an effect that depends on the site of administration of SP within the central nervous system [12, 13, 31, 32]. These investigators report that administration of SP into the substantia nigra or the amygdala impairs memory for a passive avoidance habit, whereas injections of SP into the lateral hypothalamus or the medial nucleus of the septum facilitates the retention of this habit. As these authors point out, these data indicate that central administration of SP mimics results obtained when the brain is stimulated directly. Electrical stimulation of the septum and the lateral hypothalamus facilitates learning and memory processes, while stimulation of the amygdala and the caudate, a treatment that activates the substantia nigra, has deleterious effects on the retention of learned habits.

Our search of the experimental literature indicates that

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there is only one published paper on the effects of peripheral administration of SP on learning and memory [11]. In this experiment the intraperitoneal administration of 250 and 500 μg/kg of SP disrupted active avoidance learning. Unfortunately, SP was given before training and it is therefore difficult to conclude that SP had its influence on learning and memory processes directly. Instead, these results could also be due to SP's effect on nonspecific performance variables.

Here, we report that the peripheral post-trial administration of SP (a) facilitates the retention of a single-trial passive avoidance habit, (b) does not affect the acquisition of an active avoidance habit, but does delay its extinction, (c) that the facilitation of the retention of the single-trial passive avoidance habit with SP can be reversed in animals pretreated with naltrexone, and (d) that the facilitation of the retention of the passive avoidance habit with SP, and its reversal with naltrexone, are results obtained in adrenalectomized animals and in sham-operated controls.

METHOD

Animals

Mice of two genotypes, heterogeneous strain (HS) and inbred C57Bl/6J animals, were used in all experiments. The HS animals, derived from breeding together animals from eight different inbred strains [24], were produced from stocks obtained from the Institute for Behavioral Genetics, University of Colorado. The C57Bl/6J mice, the degree of inbreeding of which has been described [16], were produced from breeding stocks obtained from the Jackson Laboratory, Bar Harbor, ME.

All animals were 56+3 days of age at the time these experiments began. Approximately equal numbers of males and females were used. All the mice were maintained under standard conditions of temperature (23–24°C) and controlled lighting (12 hr light cycle, 7 a.m.–7 p.m.) with ad lib access to Purina Mouse Breeder Chow and tap water. The experiments were performed between 11 a.m. and 4 p.m. to avoid possible circadian effects.

Behavioral Assays

Passive avoidance conditioning. Animals were tested for passive avoidance conditioning in an apparatus essentially identical to one described by Jarvik and Kopp [15] consisting of a two-chamber box, one chamber being well lighted and the other remaining dark. The walls and floor of the dark "shock" chamber were made of black opaque Plexiglas, and were covered by two metal plates. The metal plates were connected to an alternating current generator. The illuminated chamber was constructed of transparent plastic and was brightly lighted. The bright "start" chamber was connected to the shock chamber by a round hole 3 cm in diameter, located flush with the floor. The two compartments were separated by a guillotine door.

Training was begun by placing the mouse in the start chamber, the animal facing away from the guillotine door. The mouse was allowed to enter the dark compartment spontaneously. The guillotine door was then lowered and the mouse received a footshock of 0.4 mA for 5 sec. Exactly 24 hours later the procedure was repeated, except that the animals were not given a second footshock.

Step-through latencies were recorded both at the time of training and retesting. Each animals was assigned a "retention" score, defined as the trial 2 minus trial 1 latency. A constant was added to each score to make them all positive numbers.

Active avoidance conditioning. Animals were trained for active avoidance conditioning in an apparatus identical to one described by Schlesinger and Wimer [27]. The training apparatus was constructed of plastic and consisted of a chamber 19 cm high, 25 cm wide, and 24.5 cm long. The floor of the compartment consisted of 2.4 mm brass rods, the centers of which were separated by 8.5 mm. An escape shelf, 2.5 cm wide, was mounted 7.3 cm above the grid floor and ran completely around the inside walls of the apparatus. The compartment was covered with a removable plastic lid.

Pressing a microswitch activated a buzzer and a 100-W light bulb for 3 sec. If the mouse did not jump to the escape shelf, a response timer and a shock generator were activated for the duration of the trial. The buzzer, attached to the outside of the box, made a sound and vibrated the box slightly. The light was mounted over the compartment and illuminated the box.

All animals were trained individually. Each mouse was given 30 sec to explore the grid floor. The light and buzzer conditioned stimuli (CS) were then presented for 3 sec, beginning the first trial. Termination of the CS was followed by the onset of the 0.2 mA electric shock unconditioned stimulus (US), delivered through the grid floor. The US was never delivered for more than 15 sec/trial. The animals were left on the escape shelf during the 15 second intertrial interval. Training was continued until the animals reached some predetermined acquisition criterion. Two such criteria were used in these experiments. One was a "weak criterion," defined as training the animals to make 3 out of 5 consecutive avoidance responses. The second, or "strong criterion" was defined as training animals to make 8 out of 10 consecutive avoidance responses. The animals were randomly assigned to these two conditions of testing. An avoidance response was defined as jumping to the escape shelf during the CS interval.

The animals were given extinction training exactly 24 hours later. This training was identical to acquisition training, except that the US was not turned on. Extinction training was continued until the animals reached some predetermined extinction criterion, either 3 out of 5, or 8 out of 10, consecutive failures to jump to the escape shelf.

Each mouse was assigned an acquisition and an extinction score, defined as the number of trials necessary to reach the learning and extinction criteria, respectively.

Drug Regimens

SP was dissolved in 0.01 N acetic acid in 0.9% saline; this vehicle was used for all control injections. SP was injected subcutaneously at doses ranging from 0.46 to 4.64 ng/g body weight. Naltrexone HCl was dissolved in phosphate buffered saline (pH 7.4), and this vehicle was used in all control injections. Naltrexone was injected subcutaneously at a dose of 5 mg/kg. Volumes of all injections were 0.01 ml/g body weight.

In all of the passive avoidance experiments SP or the vehicle were injected immediately after the training trial. In the active avoidance experiments SP or the vehicle were injected either 10 minutes prior to the beginning of training or immediately after training. Naltrexone or the vehicle was injected 1 hour before the training trial.

It is important to point out that all drug administration was blind, the person performing the experiment not knowing whether the drug or the vehicle had been injected. The

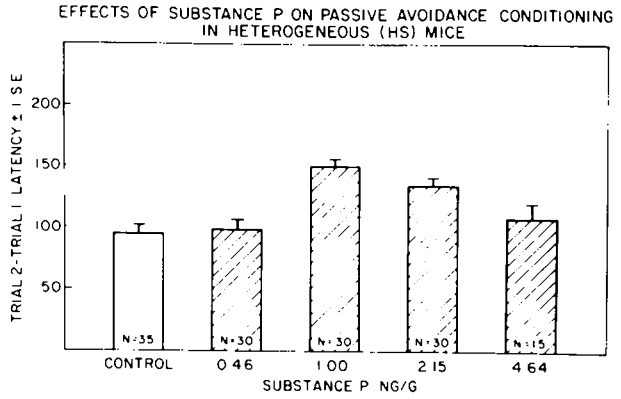

FIG. 1. Effects of SP on the retention of a single-trial passive avoidance response in HS mice. SP was injected immediately after the training trial.

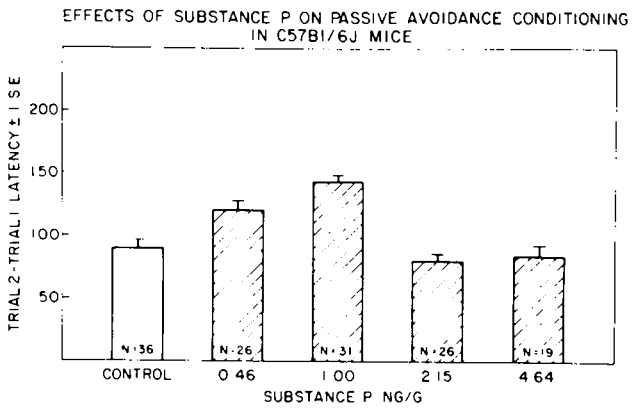

FIG. 2. Effects of SP on the retention of a single-trial passive avoidance response in C57Bl/6J mice. SP was injected immediately after the training trial.

drug code was not broken until all the experiments reported here had been completed.

Surgical Procedure

Surgery was performed under Nembutal anesthesia (85 mg/kg). All the animals were 42 days of age at the time of surgery. They were given two weeks to recover before being used in the learning experiments. Bilateral adrenalectomies were performed in a one stage operation. Sham operations were identical, except that no adrenal tissue was removed. Following surgery, all the adrenalectomized animals and the sham-operated controls were maintained on a 0.9% saline in 0.5% sucrose solution.

When behavioral testing had been completed, all of the adrenalectomized mice were sacrificed and autopsies were performed to determine whether any adrenal tissue had been spared. Only 1 out of 40 operated mice had to be discarded because some adrenal tissue had been spared.

Statistical Analyses

The data obtained in each of the 7 experiments reported below were analyzed by means of completely randomized 1- or 2-way analyses of variance. Where appropriate, subsequent protected Student's t-tests were performed to compare the average scores of individual groups of subjects.

RESULTS

Experiment 1

In the first experiment we studied the effects of post-trial administration of SP on the retention of a single-trial passive avoidance habit in HS mice. SP was injected in doses ranging from 0.46 to 4.64 ng/g; control animals were injected with diluent vehicle. The number of animals used in this study ranged from 15 to 35 mice per treatment group. The data obtained in this study are summarized in Fig. 1.

Analysis of variance of these data yielded a significant SP effect; $F(4,135)=4.92$, $p<0.01$. Individual t-tests comparing the average performance of animals given the various concentrations of SP with the vehicle injected control group indicated that the groups receiving 1.0 and 2.15 ng/g of SP retained the passive avoidance habit significantly better than did the mice injected with the vehicle ($p<0.001$ and <0.01, respectively). Furthermore, the animals receiving 1 ng/g of SP retained the passive avoidance habit significantly better than did mice injected with either 0.46 or 4.64 ng/g ($p<0.01$ and 0.05, respectively).

Experiment 2

Our second experiment was essentially a replication of the first study, except that the effects of SP on the retention of a single trial passive avoidance habit was studied in C57Bl/6J mice. Animals of this genotype were given injections of SP in doses ranging from 0.46 to 4.64 ng/g; control animals were injected with diluent vehicle. The number of mice used in this experiment ranged between 19 to 36 animals per treatment group. The results of this second experiment are summarized in Fig. 2.

Analysis of variance of these data indicated that SP significantly enhanced the retention of this habit in animals of this genotype; $F(4,133)=4.92$, $p<0.01$. Individual t-tests showed that only animals injected with 1 ng/g of SP retained this habit significantly better than did the mice in the vehicle injected control group ($p<0.01$). In addition, mice receiving 1 ng/g retained the passive avoidance habit significantly better than did animals receiving either 2.15 or 4.64 ng/g ($p<0.001$ and <0.01, respectively).

Experiment 3

The effects of SP on the acquisition and extinction of an active avoidance habit were studied in our third experiment, the results of which are summarized in Fig. 3. The animals were trained to two criteria of acquisition, a weak and a strong criterion. Exactly 10 minutes prior to training the animals were injected with 1 ng/g of SP or with vehicle. This dose was chosen because in our previous studies this amount of SP maximally enhanced the retention of a passive avoidance habit. Twenty-four hours after acquisition training, the animals were extinguished as follows: The animals that had been trained to the weak acquisition criterion were extinguished to a weak extinction criterion, and the animals that had been trained to the strong acquisition criterion were

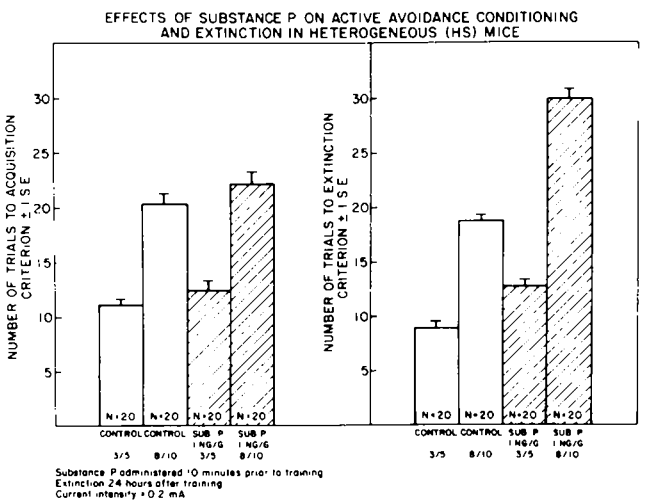

FIG. 3. Effects of SP on the acquisition and extinction of an active avoidance task. SP was injected 10 minutes before training. Animals were trained and extinguished to two criteria: 3 out of 5 consecutive or 8 out of 10 conseuctive avoidance response. HS animals were used.

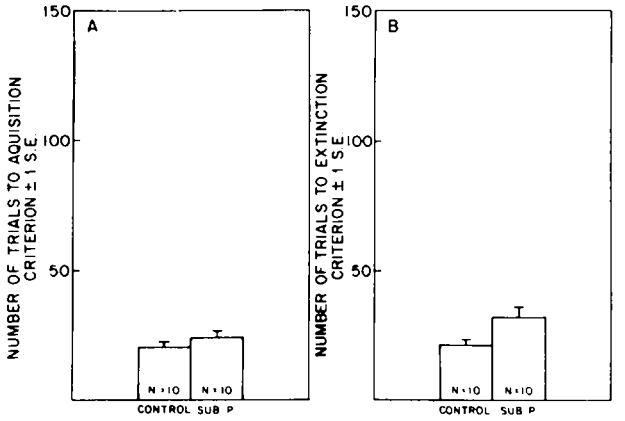

FIG. 4. Effects of SP on the extinction of an active avoidance task in C57Bl/6J mice. SP was injected immediately after the animals had been trained to make 8 out of 10 consecutive avoidance responses.

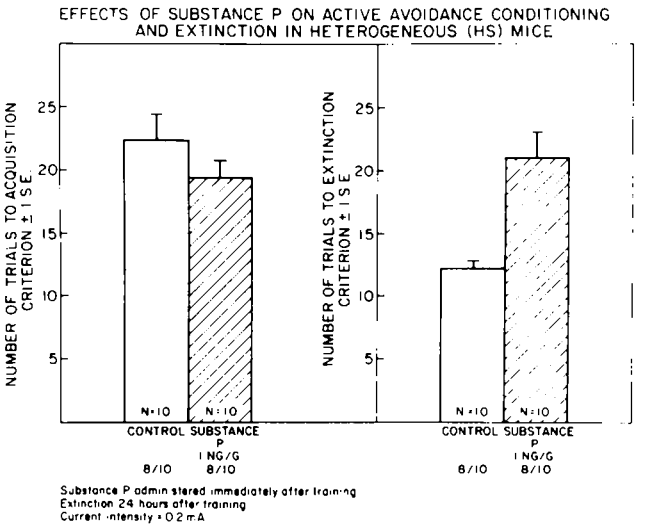

FIG. 5. Effects of SP on the extinction of an active avoidance task in HS mice. SP was injected immediately after the animals had been trained to make 8 out of 10 consecutive avoidance responses.

extinguished to a strong extinction criterion. Twenty HS mice were tested per treatment condition.

Two separate 2×2 factorial analyses of variance were performed on these data, one for the results obtained during the acquisition phase of this experiment and a second analysis for the results obtained during the extinction phase of the study. Analysis of variance on the acquisition data yielded an expected and significant criterion effect, $F(1,76)=36.50$, $p<0.001$. However, SP did not significantly facilitate the acquisition of this habit, notwithstanding the fact that the peptide was injected 10 minutes prior to training. Analysis of variance of the extinction data again yielded an expected and significant criterion effect, $F(1,76)=44.21$, $p<0.001$. With respect to extinction, however, SP was found to delay significantly the rates of extinction of this habit, $F(1,76)=12.08$, $p<0.001$. Subsequent t-tests indicated that this extinction effect was largely due to the effects of the peptide on the extinction of the strongly entrained habit ($p<0.001$); the effect of SP on the extinction of the weakly entrained habit did not reach statistical significance.

Experiment 4

The fourth experiment was a replication of our third study. We again studied the effects of SP on the acquisition and extinction of an active avoidance habit, but C57Bl/6J, instead of HS mice, were used as subjects. SP, 1 ng/g, or diluent vehicle was injected 10 minutes prior to training, and 10 C57Bl/6J mice were used per treatment condition. The results of this study are shown in Fig. 4.

Two separate analyses of variance were performed on these data, one for the acquisition and the other for the extinction phase of the study. These analyses revealed that SP did not significantly affect the acquisition of this habit in animals of this genotype. However, the peptide did significantly retard the extinction of this habit, $F(1,18)=23.60$, $p<0.001$.

Experiment 5

In our fifth experiment we again examined the effects of SP on the acquisition and extinction of an active avoidance habit in HS mice. The only difference between this and the previous experiment was that the animals were injected with SP or with vehicle immediately after training. The animals were all trained and extinguished to the strong criterion. Ten HS mice were tested per treatment condition, and the results obtained in this study are summarized in Fig. 5.

Analysis of variance of the extinction data indicated that SP significantly delayed the extinction of this habit, $F(1,18)=4.44$, $p<0.05$.

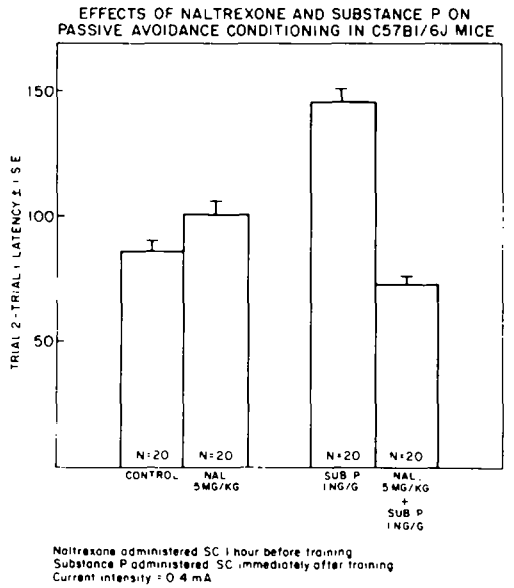

FIG. 6. Effects of SP and naltrexone on the retention of a single-trial passive avoidance habit. Naltrexone was injected 1 hour before training. SP was injected immediately after training. C57Bl/6J mice were used.

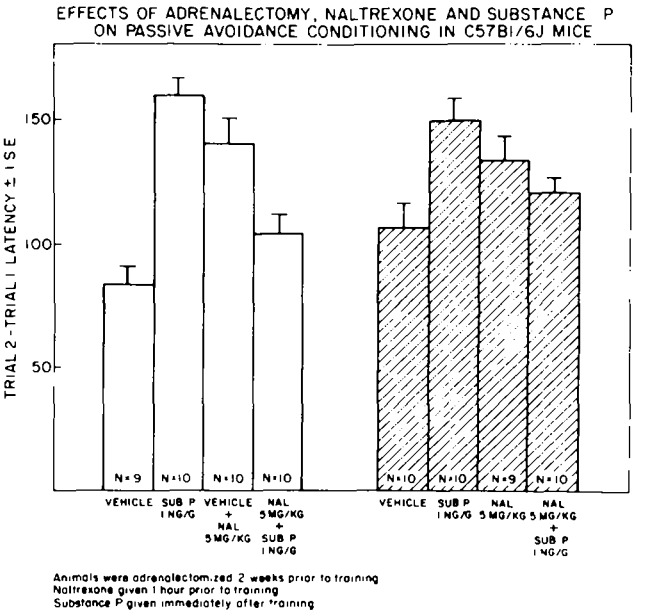

FIG. 7. Effects of SP and naltrexone on the retention of a single-trial passive avoidance habit in sham-operated (open bars) and adrenalectomized (hatched bars) C57Bl/6J mice. Naltrexone was injected 1 hour before training; SP was injected immediately after training.

Experiment 6

In the sixth experiment we again used the passive avoidance paradigm, and the effects of SP on the retention of this habit were studied in C57Bl/6J animals. Two additional groups of mice were tested in this study in an attempt to determine whether or not the effects of SP on retention could be mediated via interactions between SP and opioid systems in the brain. Thus, one group of subjects received naltrexone and then the diluent vehicle, while the other group received naltrexone and then SP. Naltrexone was injected 1 hour before training, whereas SP or vehicle was injected immediately after the training trial. Twenty C57Bl/6J mice were used in each treatment condition. The data obtained in this study are summarized in Fig. 6.

An overall analysis of variance of these data revealed a significant drug effect, $F(3,76)=9.12$, $p<0.001$. Subsequent protected t-tests showed that SP significantly enhanced the retention of this habit ($p<0.001$). In addition, this analysis showed that naltrexone when given in combination with SP completely reversed the memory enhancing effect of SP ($p<0.001$).

Experiment 7

The seventh experiment in the series was essentially a replication of Experiment 6, except that the effects of SP and naltrexone on the retention of a passive avoidance habit were studied in sham-operated and adrenalectomized C57Bl/6J mice. Between 9 and 10 animals of this genotype were used in each treatment group, and the results of this study are summarized in Fig. 7.

An overall 2×4 analysis of variance of these data yielded the following results: The sham-operated animals did not differ from the adrenalectomized mice. However, a significant drug effect was obtained, $F(3,70)=4.68$, $p<0.01$. For the sham-operated animals, subsequent protected t-tests indicated that both SP and naltrexone significantly enhanced the retention of this passive avoidance habit, $p<0.01$ and 0.05, respectively. In addition, naltrexone, when given in combination with SP, decreased the memory enhancing effects observed when either compound was given singly ($p<0.05$). Subsequent protected t-tests on the data obtained in the adrenalectomized mice yielded no statistically significant results. However, visual inspection of the data shown in Fig. 7 suggests that the trends obtained in this study are similar to those observed in our other experiments.

DISCUSSION

This series of experiments have yielded data consistent with the hypothesis that the peripheral administration of SP alters memory functions in experimental animals. The results obtained in these studies can be summarized as follows:

(1) The peripheral post-trial administration of SP can enhance the retention of a single-trial passive avoidance habit in both HS and C57Bl/6J mice. Since SP was administered after training, this increased retention cannot easily be explained in terms of any effect that SP might have on either responsiveness or sensitivity of the animals to the aversive stimuli used during training.

(2) The memory enhancing effects of SP are dose dependent; 1 ng/g of SP increased the retention for this passive avoidance habit, whereas lower and higher doses are either less effective or ineffective. In this respect, the effects of SP on memory are similar to results obtained with other peptides. A similar peak in the dose-response curve has also

been seen for the effects of SP [5] and SP (1–7) on antinociception [33, 34, 35] in mice and on motor activity in rats [2].

(3) The administration of SP before animals are trained on an active avoidance task did not significantly alter the rates at which mice acquired this habit, at least not at the doses and time parameters used in these studies.

(4) The administration of SP before training on an active avoidance task significantly delayed the rates at which this habit could be experimentally extinguished. Further, the administration of SP after training also delayed extinction of this habit. These findings could indicate that SP somehow facilitates the consolidation of memory, an interpretation consistent with our findings that the peripheral administration of SP reverses the amnestic effects of cycloheximide and electroconvulsive shock-induced amnesia [26].

(5) In two of the experiments reported above, we tested for the effects of naltrexone on the retention of a passive avoidance habit. Three comparisons were made; in only one of these, namely in Experiment 7, and only in the sham-operated animals, did naltrexone significantly enhance memory. This may be due to the fact that we used only one dose of naltrexone (5 mg/kg), which may be in excess of the optimal dose necessary to facilitate the retention of passive and active avoidance habits [7,22]. It may be for this reason that our data differ from those reported in other studies which show that naloxone, another opiate antagonist, facilitated the retention of active and passive avoidance habits [20]. Another reason that our data are not in good agreement with other results may be due to procedural differences in our studies and those cited above.

(6) Naltrexone, when used in combination with SP, significantly reduced the memory enhancing effects of SP, at least insofar as the retention of a passive avoidance habit is concerned. These data are somewhat perplexing as they may indicate either that the memory enhancing effects of SP are mediated via an opioid system in the brain, or that the memory enhancing effects of naltrexone are mediated via a SP system in the brain, or both.

Our data may also be explained in terms of the heterogeneous effects observed after the peripheral administration of SP. Gallagher and Kapp [8] have shown that the retention of a passive avoidance habit is enhanced by naloxone and impaired by levorphanol when these compounds are injected into the amygdala. Injection of SP into this structure has been shown to cause amnesia, a result opposite to that observed with opiate antagonists [13]. If the diverse effects of peripheral administration of these substances are due to a summation of their various effects in different anatomical regions, the net result on memory may be unclear, despite the fact that each compound, when administered singly, may enhance memory.

(7) Finally, SP and naltrexone did not produce significantly different effects from acidified saline in adrenalectomized mice. These two compounds did, however, produce the same effects in sham-operated and intact animals. The results obtained in adrenalectomized animals are somewhat unclear because we tested only a single dose of naltrexone and SP. Since the dose-response curves for both compounds are U-shaped, removal of the adrenal glands may have attenuated or sensitized the animals to the effects of these drugs. Until a dose-response curve is completed on adrenalectomized animals, it is not possible to make a statement about the interaction between arousal effects or ACTH secretion and the memory enhancing effects of SP. Such experiments are in progress. Many different interpretations of these data are possible. With respect to SP's ability to facilitate the retention of passive and active avoidance habits it is possible, for example, that this peptide directly affects memory processing in the central nervous system. Alternatively, it seems possible that the memory enhancing effects of SP might be mediated via interactions between this peptide and endogenous opioid systems in the brain. Our data showing that naltrexone inhibits the actions of SP on memory processes suggest such a possibility. Stewart and Hall [35] have shown that several effects of SP on behavior are apparently mediated via some components of the endogenous opioid systems. Another interpretation might be that SP produces its memory enhancing effects via interactions with catecholaminergic transmitter systems in the brain. Such interactions are known to occur after SP is injected systemically [30]. SP is also known to alter neural activity in pathways connecting the hypothalamus and the pituitary that have been interpreted as an increase in afferent impulse traffic between these areas [1]. Thus, SP might increase the release of neurohypophyseal hormones, some of which have already been shown to enhance memory. At present we know of no data that would allow us to distinguish critically between these, or other, alternatives.

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