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Retrieval Effects of Both Post- and Presession β-Endorphin Administration in a Three-Session Paradigm

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NETTO, C. A., M. MALTCHIK AND M. NUNES. *Retrieval effects of both post- and presession β-endorphin administration in a three-session paradigm.* PHARMACOL BIOCHEM BEHAV **37**(1) 47–51, 1990.—Rats were submitted to three sessions, with a 24-hr interval between, of step-down inhibitory avoidance task using a 60-Hz, 0.3-mA footshock, or of two-way active avoidance task using 25 presentations of a 5-sec, 1-kHz tone and a 0.4-mA footshock. Animals received intraperitoneal injections of either saline or β-endorphin (2.0 μg/kg) after the first session, and before the second or the third sessions, in a 2×2×2 design. β-Endorphin given before the second or the third sessions improved retention for both tasks, but when administered after the first session, it impaired retention for the second session. The administration of β-endorphin after the first session prevented the retrieval enhancement by the opioid given before the third session. Rats receiving β-endorphin both after the first and before the second sessions, whilst showing no retrieval impairment on the second session, also did not show the pre-third session β-endorphin retrieval enhancing effect. These data suggest that the post-first session exaggeration of the endogenous opioid state by β-endorphin administered after the first session causes a long-lasting change in retrievability for the active and inhibitory avoidance tasks, as shown by the lack of the retrieval enhancing effect of β-endorphin given before the third session.

Endogenous state dependency β-Endorphin Enhancement of retrieval Three-session paradigm Amnesia Memory files Asymmetric dissociation

β-ENDORPHIN is an endogenous opioid peptide with powerful behavioral modulatory effects (7, 17–20, 22, 29). Several physiological and pharmacological findings suggest that β-endorphin may induce a peculiar form of endogenous state dependency with asymmetric dissociation (7, 9, 12, 30), i.e., that an endogenous neurohumoral opioid state is present after the training of newly acquired tasks, but is not physiologically present at the time of testing/retrieval. Firstly, novel tasks are followed by a decrease of hypothalamic β-endorphin-like immunoreactivity in rats, which is currently interpreted as an activation of the hypothalamic β-endorphin system (12,19). Secondly, posttraining β-endorphin administration causes retroactive amnesia for a variety of tasks, and this effect is independent for the presence of pain during training (17), and of the response requirements of tasks (17,22). Thirdly, naloxone, the competitive opiate receptor antagonist, counteracts β-endorphin effect and produces retrograde memory facilitation (3–5, 12, 14). Fourthly, the administration of ECS (27), a treatment which causes a massive decrease of hypothalamic β-endorphin (1,18), or of β-endorphin (8,9) before the test session reverses the retrieval deficit caused by posttraining administration of either β-endorphin or of ECS. Finally, the pretest administration of β-endorphin (10,11) improves retention performance for avoidance tasks, an effect that is not seen if the tasks have been acquired with previous depletion of β-endorphin (11).

However, all these studies employ only two sessions of a task, which casts doubt on their interpretation in terms of state dependency. Actually, Overton (30) has already suggested that some data provided by 2×2 experiments may be misinterpreted as asymmetrical dissociation. To overcome this limitation, we are currently employing a design using three sessions of a task, where the third session is actually a second test session. Using this paradigm, it has been shown that ECS and β-endorphin cause amnesia when administered after the first, but not the second, session of active and inhibitory avoidance tasks (28). As it has also been demonstrated that naloxone fails to cause retrieval enhancement when injected after the second session (25), it is tempting to propose that either facilitatory or inhibitory retrieval effects dependent on the brain β-endorphin system cannot be elicited by treatments administered after the second session of a task (25, 26, 28). These findings can be regarded as more clear-cut evidence for an asymmetrical state dependency than that obtained using two-session paradigms (7, 9, 12, 30).

We have recently shown that the endogenous opioid β-endorphin, given either before the second or the third session,

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improves retention for both inhibitory and active avoidance tasks (26), suggesting that retrieval enhancement involves opioid state dependency induced by the activation of brain β-endorphin in the first session (12, 13, 15, 16, 26). However, another recent study demonstrated that the endogenous opioid leucine-enkephalin administered after the training session produced a long-lasting amnesia for an avoidance task (2), suggesting that opioids can also have long-term detrimental effects on memory. Thus, a pharmacologically induced change in the posttraining opioid state may produce a long-lasting disruption of retrieval of newly acquired memories. This may, in turn, influence the ability of β-endorphin, given before the third session, to enhance retrieval. Therefore, we decided to investigate the effect of β-endorphin, administered after the first session, on the retrieval enhancement elicited by β-endorphin given before the third session on two avoidance tasks.

METHOD

One hundred and ninety-two Wistar-derived male and female rats from our breeding stock were used (age, 80 to 90 days; weight, 140 to 220 g). No sex differences in behavioral performances of the tasks under study have been detected. Eighty rats were used in the two-way active avoidance task, and the remainder in the step-down inhibitory avoidance task.

Behavioral

The two-way active avoidance task was carried out in a 50 × 25 × 25-cm automated acrylic box (Albarsch) whose floor was a series of 0.1 cm caliber parallel bronze bars divided at the midline by a 1 cm high acrylic hurdle. The conditioned stimulus was a 5-sec, 70-dB, 1-kHz tone, delivered through a loudspeaker attached to the rear wall of the box. Each tone was immediately followed by a scrambled 0.4-mA footshock (unconditioned stimulus, maximum duration of 5 sec) applied until animals crossed the midline (escape response). Animals avoided the shock by crossing the hurdle during the tone (conditioned/avoidance response) (7, 27, 28). Three consecutive sessions were given, one session per day, using an identical procedure. Animals were left to explore the box for 3 minutes and then received 25 tone-footshock trials with a random intertrial interval varying from 10 to 50 seconds. The recording of the number of avoidance responses and of intertrial crossings was automatic. Retention was measured as the difference in the number of avoidance responses between the second and the first sessions, and between the third and the second sessions (27,28). There were no differences in the number of intertrial crossing between any of the sessions (F values<0.93, $p>0.1$; mean of crossings: 8.13 ± 1.49; 8.09 ± 1.69; 7.69 ± 1.75, for the first, the second and the third sessions, respectively).

The inhibitory avoidance procedure was carried out in an automatically operated, brightly illuminated, 30 cm high, 25 cm deep, 50 cm wide wood box with a glass wall in front. The floor was a series of parallel 0.1 cm caliber stainless steel bars spaced 0.8 cm apart, and the left edge of the grid was covered by a 7 cm wide, 5 cm high formica platform. Animals were gently placed on the left rear corner of the platform and their latencies to step down onto the grid were measured with an automatic digital timer. Immediately upon placing their four paws on the grid, a 0.3-mA, 60-Hz, 6-sec scrambled footshock was delivered. Three consecutive sessions were carried out, one session per day, using an identical procedure, except that the footshock was omitted in the third session. Animals avoided the shock by staying on the platform (9,24). The second and the third sessions were terminated after 300 sec plus the latency of the previous session. Animals which did not step down on the second session within this period received no footshock. The difference in latencies between second and first session, and between third and second session, was used as a measure of retention (27,28).

TABLE 1

SCHEDULE OF TREATMENTS, SALINE (1 ml/kg) OR β-ENDORPHIN (2 μg/kg), EMPLOYED IN THREE SESSIONS OF BOTH TWO-WAY ACTIVE AND STEP-DOWN INHIBITORY AVOIDANCE TASKS

	Treatments		
Group Number	After-1st Session	Before-2nd Session	Before-3rd Session
1	Saline	Saline	Saline
2	Saline	β-endorphin	Saline
3	Saline	Saline	β-endorphin
4	Saline	β-endorphin	β-endorphin
5	β-endorphin	Saline	Saline
6	β-endorphin	Saline	β-endorphin
7	β-endorphin	β-endorphin	Saline
8	β-endorphin	β-endorphin	β-endorphin

Pharmacological Treatment

β-Endorphin (Sigma), 2.0 μg/kg and saline were administered intraperitoneally, IP, in a volume of 1 ml/kg. This dose of β-endorphin is twice the ED_{50} (18) and has consistent memory modulation effects for both active and inhibitory avoidance tasks (9–12, 17–19, 26–28). Animals were randomly assigned to 8 groups ($N = 10$ per group for active avoidance; $N = 14$ per group for inhibitory avoidance). Each group received different treatment schedules after the first, before the second, and before the third sessions, in a $2 \times 2 \times 2$ design as shown in Table 1. All treatments were given 1 min or less after the first session, and 6 min before both second and third sessions. These intervals for pre- and postsession injections has been demonstrated to be adequate and effective ones (4, 5, 9–12, 17–19, 25–28).

Statistics

Data of the two-way active avoidance task were analyzed by individual one-way ANOVAs for each session followed by Duncan multiple range tests when indicated. Data of the inhibitory avoidance task were analyzed by a Kruskal-Wallis analysis of variance for each session followed by Dunn multiple comparison tests when indicated (6). Comparisons between performances across consecutive sessions used a Friedman two-way analysis of variance followed by a multiple comparison test based on Friedman rank sums (6, 25–28).

RESULTS

Two-Way Active Avoidance

Table 2 shows the mean number of avoidance responses made by the eight groups in the experiment. There were no differences between groups in performance on the first session [$F(7,72) = 0.49$, $p>0.1$; mean $= 8.01 \pm 1.09$ of conditioned responses for all groups]. However, there were significant differences between

TABLE 2

EFFECTS OF POST- AND PRESESSION β-ENDORPHIN ADMINISTRATION UPON PERFORMANCE ON TWO-WAY ACTIVE AVOIDANCE TASK

Group Number	Performance (Mean ± SEM of the Number of Avoidance Responses) 1st Session	2nd Session	3rd Session
1*	8.14 ± 0.87	11.54 ± 1.25	15.74 ± 1.14
2*	8.21 ± 0.91	14.10 ± 1.21†	18.40 ± 1.16†
3*	8.86 ± 1.45	12.26 ± 1.35	19.06 ± 1.02†
4*	8.57 ± 1.45	14.91 ± 0.95†	19.37 ± 1.35†
5	6.93 ± 1.33	7.33 ± 1.38‡	13.83 ± 1.39
6	9.07 ± 1.02	9.17 ± 1.21‡	15.17 ± 1.18
7*	7.60 ± 0.88	11.10 ± 1.26	16.50 ± 0.96
8*	8.08 ± 1.51	12.53 ± 1.88	15.63 ± 1.49

N = 10 rats per group. Groups numbered according to the schedule shown in Table 1.

*Significant differences in performance across consecutive sessions Duncan multiple range tests ($p<0.05$).

†Different from non-noted groups in the same session by Duncan multiple range test ($p<0.05$).

‡Same as †, and not significantly different from the group first session performance by Duncan multiple range test ($p<0.05$).

TABLE 3

EFFECTS OF POST- AND PRESESSION β-ENDORPHIN ADMINISTRATION UPON RETENTION OF STEP-DOWN INHIBITORY AVOIDANCE TASK

Group Number	Performance [Median (Interquartile Range) of Step-Down Latencies] 1st Session	2nd Session	3rd Session
1*	2.9 (2.2/5.4)	81.3 (25.5/100.4)	235.1 (114.2/276.1)
2*	2.8 (1.8/4.2)	136.5 (120.1/170.5)†	436.5 (304.3/470.5)†
3*	3.5 (1.7/3.8)	74.3 (37.6/125.3)	374.3 (258.2/425.3)†
4*	4.0 (2.3/5.1)	163.2 (73.7/209.7)†	463.2 (326.4/500)†
5	2.6 (2.0/4.4)	12.3 (1.3/26.3)‡	159.1 (109.2/217.2)
6	3.6 (2.5/5.1)	5.5 (3.1/14.0)‡	145.1 (117.6/243.9)
7*	3.9 (2.2/5.6)	73.5 (36.3/121.0)	256.2 (161.0/421.1)
8*	3.8 (2.5/6.9)	61.2 (33.1/111.2)	203.1 (157.2/303.2)

N = 14 rats per group. Groups numbered according to the schedule shown in Table 1.

*Significant differences in performance across consecutive sessions by multiple comparison tests based on Friedman rank sums ($p<0.05$).

†Different from nonnoted groups in the same session by a Kruskal-Wallis Analysis of Variance ($p<0.05$) followed by a Dunn multiple comparison test ($p<0.05$).

‡Same as †, and not significantly different from the group first session performance by multiple comparison tests based on Friedman rank sums ($p<0.05$).

groups in the second ($F=4.36$, $p<0.05$) and the third sessions ($F=4.95$, $p<0.05$). Duncan multiple range tests indicated that Groups 5 and 6, which had received β-endorphin after the first session and saline before the second, had impaired avoidance performances on the second session, while Groups 2 and 4, which had saline after the first session and β-endorphin before the second, showed improved avoidance on session 2. Groups 2, 3 and 4, which had received β-endorphin before the second and/or the third session, all showed increased number of avoidance responses in the third session. All rats showed improved avoidance across consecutive sessions, except those for Groups 5 and 6 ($p<0.05$, Duncan test).

Inhibitory Avoidance

Table 3 shows the median step-down latencies in the eight experimental groups. There were no differences between groups in the first session, $H(7)=1.02$, $p>0.1$, Kruskal-Wallis test. However, there were significant differences in scores between groups in the second, $H(7)=12.45$, $p<0.05$, and in the third sessions, $H(7)=14.91$, $p<0.05$. A Dunn multiple comparison test indicated that Groups 5 and 6, which had received β-endorphin after the first session and saline before the second, had impaired step-down latencies for the second session, whilst Groups 2 and 4, which had received saline after the first session and β-endorphin before the second, showed increased latencies ($p<0.01$). Groups 2, 3, and 4, receiving β-endorphin before the second and/or the third session, had increased step-down latencies for the third session. The Friedman two-way analysis of variance indicated differences within groups (all $\chi^2_r>14.81$, $p<0.01$), and free multiple comparison tests based on Friedman rank sums indicated an increase in performance across consecutive sessions ($p<0.01$) for all but Group 5, which had been given β-endorphin after the first session and saline thereafter, and Group 6, which had additionally received β-endorphin before session 3.

DISCUSSION

Since results for both active and inhibitory avoidance tasks were similar they will be discussed together. β-Endorphin given either before the second (Group 2) or the third session (Group 3) caused an improvement of retention scores, confirming previous evidence that presession β-endorphin enhances retrieval, probably through a state dependency mechanism (25). This interpretation is supported by findings that pretest exposure to novel stimuli enhances retrieval in mice (10,11) and rats (15), probably through activation of the hypothalamic β-endorphin system, since the effect is blocked by the concomitant administration of naloxone. Furthermore, the presession β-endorphin retrieval enhancing effect is not seen in animals receiving naloxone after the first session (14,26). The pre-second session β-endorphin retrieval enhancing effect carried over to the performance of the third session. This carryover effect has been previously shown for facilitatory treatments administered after the first session (25), and the current interpretation is that of an irreversible strengthening of memory trace (8,21).

The finding that animals receiving β-endorphin both before the second and the third sessions (Group 4) showed no additional enhancement of performance on the third session when compared to Group 3, which received β-endorphin only before the third session, argue against an endogenous state-dependent interpretation. However, this result may be attributable to a ceiling effect. Indeed, pilot studies conducted with four, rather than three, sessions showed that fourth session performances of active and inhibitory avoidance tasks were not significantly different from those of the third session in groups which received β-endorphin before the second and/or the third sessions. This implies that there is a limit to the extent of improvement over trials under our present experimental parameters, so that further enhancement of retrieval would not be detected.

Animals receiving β-endorphin after the first session and saline before the second one (Groups 5 and 6) showed the usual opioid-induced retrieval impairment/amnestic effect expressed in the performance of the second session. It is worth noting that rats in Group 5 reached control performance levels in the third session. This implies that although they showed a retrieval deficit, some rehearsal or latent access to information occurred in the second session (28). An interpretation in terms of disruption of consolidation by β-endorphin administered after the first session can be dismissed because animals would be likely to be naive in the second session, so that their performances on the third session would be inferior to that of the control group. Results from Group 6 clearly show that β-endorphin administered after the first session prevented the pre-third session β-endorphin retrieval enhancing effect. This can be explained in two distinct ways: Firstly, the exaggeration of the posttraining opioid state may cause a long-lasting change in retrievability of these tasks. Alternatively, the impairment of second session performance may be responsible for the failure of β-endorphin given before the third session to enhance retrieval. However, the latter explanation is quite improbable because animals receiving the opioid after the first and before the second sessions showed normal performance in the second session (Groups 7 and 8), corroborating previous studies (7, 9, 12, 13, 27), and did not exhibit the retrieval enhancing effect for the opioid given before the third session (Group 8).

Another possible explanation for the lack of effect of β-endorphin given before the third session in groups 6 and 8 is that the three-sessions paradigm works as overtraining: It has been shown that morphine is less effective in abolishing a classically conditioned nictitating membrane response in overtrained animals (23). However, if animals were overtrained it would not have been possible for Groups 2, 3, and 4 to show enhancement of retrieval in the third session.

The main finding of the present study is that the administration of a single dose of β-endorphin after the first session proactively counteracts the pre-third session β-endorphin retrieval enhancing effect. This long-lasting change in retrievability of these tasks is not due to a low performance on the second session, but it is likely to be due to a pharmacologically induced alteration on the endogenous opioid state dependency associated to these tasks. Dana and Martinez (2) previously reported a long-term memory effect for another endogenous opioid, leucine-enkephalin: Mice injected after the first session of an avoidance task showed retrieval impairment when tested both 2 and 5 days later. However, a high dose of leucine-enkephalin was employed, and its amnestic effect was not blocked by naloxone (2), which makes its effects distinct from those reported for β-endorphin (3, 4, 7–13, 15–18, 26). Moreover, in the present study, animals receiving β-endorphin after the first session (Group 5) showed spontaneous recovery of performance to control levels in the third session. Despite these discrepancies, both our experiments and the findings of Dana and Martinez (2) point to a long-lasting memory effect of a single dose of endogenous opioids.

According to the endogenous state dependency hypothesis (7, 9, 12, 30), the administration of β-endorphin after the first session of both tasks increases the asymmetry between training and testing opioid states (8, 12, 15). This exaggerated neurohumoral asymmetry affects availability for retrieval in two distinct ways: 1) it causes amnesia for the second session, and 2) it prevents the retrieval enhancing effect of β-endorphin administered before the third session. The former effect is reversed by β-endorphin administered before the second session, while the latter is not. This indicates that an alteration in the opioid state after the training can cause a long-lasting change in retrievability for avoidance tasks in a three-session paradigm.

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