tomy is attributable to the shortage of circulating glucocorticoids rather than mineralocorticoids.

Evidence has accumulated suggesting the importance of PG synthesis in initiation of DCR. Deciduogenic stimulus increases the uterine content of PGs[6,7]. Administration of indomethacin, an inhibitor of PG synthesis[11], interferes with implantation and DCR[4,5]. In the present study, if 2 injections of 1 mg indomethacin were given, one 2 h before and the other 6 h after intraluminal oil instillation, DCR was almost similar in magnitude to that in OX rats with their adrenals intact ($0.2 > p > 0.1$). None of the rats of this group formed deciduomata in the untreated horns. Therefore, it is not inconceivable that the increase in DCR in AX-OX rats as compared to OX rats was due to an increased uterine PG production in the former. Consistent with this view is the finding that glucocorticoids suppress the synthesis and/or release of PGs in a cell culture system, mineralocorticoids being less potent in this respect[8,9]. Anyhow, the present findings suggest the involvement of adrenal secretions in the regulation of DCR. Occasional DCR occurring in the untreated uterine horns contralateral to the treated ones has already been noted[12–14]. In the case of the present experiments, transfer of instilled oil, possibly together with PGs, from the treated horns to the contralateral ones via the uterine cervix or diffusion of secondary effectors, possibly PGs, released from treated horns might be involved in the induction of DCR in the untreated horns. Further studies are needed in order to draw a final conclusion.

Deciduoma formation in rats ovariectomized and ovariectomized-adrenalectomized as adults

Group	Positive response		Mean weight (mg ± SE) of	
	Treated horns	Untreated horns	Treated horns	Untreated horns
OX	9/ 9	0/ 9	305.8 ± 34.6	72.2 ± 1.7
AX-OX	10/10	9/10**	749.7 ± 40.4**	71 (460.9 ± 68.1)[a]
AX-OX + 500 µg CT[b]	10/10	6/10*	436.8 ± 64.4(**)	82.8 ± 8.2 (385.8 ± 110.4)
AX-OX + 50 µg AD[b]	7/ 7	7/ 7**	792.0 ± 36.6**	(626.1 ± 65.3)
AX-OX + 1 mg IN[c]	7/ 7	0/ 7**	229.4 ± 30.4(**)	65.1 ± 5.1

AD, aldosterone; AX, adrenalectomy; CT, corticosterone; IN, indomethacin; OX, ovariectomy. [a] Mean weight of untreated horns bearing deciduomata is given in parenthesis. [b] Given twice daily for 7 days after operation. [c] Given 2 h before and 6 h after deciduogenic stimulus. * $p < 0.01$ and ** $p < 0.001$, significance of difference in DCR incidence (Fisher's exact probability test) and in mean weight of horns (Student's t-test) from OX group, (**) $p < 0.001$, from AX-OX group.

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Facilitation or inhibition of memory by morphine: a question of experimental parameters[1]

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Summary. The effects of morphine on memory are highly controversial. According to some investigators post-trial injections of morphine facilitate memory. Others, however, have reported impairment of memory after morphine injections. To investigate the extent to which this may be due to different experimental parameters, foot-shock intensity and dosage of morphine were systematically varied in a passive-avoidance task. It was found that post-trial administration of medium and relatively high doses of morphine facilitate retention performance following moderate levels of foot-shock. Under other conditions of dose and shock intensity, the drug was not effective or even impaired retention.

The discovery of the endogenous opiates[2,3] has rekindled interest in the effects of morphine on the central nervous system. Many studies have been made of the influence of morphine on learning and memory, but so far the results obtained have been divergent.

Some authors have shown that post-trial treatment with opiate agonists improves retention. Belluzzi and Stein[4], Mondadori and Waser[5], and Stäubli and Huston[6] have all reported that morphine, when given in relatively high doses, improves retention of a one-trial passive-avoidance situation. It also has been demonstrated that an injection of morphine given after a one-trial appetitive task facilitated its memorization.

Other investigators have found that retention is impaired by morphine. Retention of a step-through passive-avoidance task[7,8] or of a shuttle-box avoidance task[9] has been shown to be diminished by low post-trial doses of morphine. Similarly, post-trial administration of Leu-enkephalin or beta-endorphin resulted in poorer retention of a shuttle-avoidance task and inhibited the habituation of rearing in response to an acoustic stimulus[10–12].

Contradictory results are not uncommon in the pharmacology of memory[13]. It has been shown that the effects of drugs on the memory often depend on the nature of the task set[14–16] and the dose used[17,18]. Amongst others, Gold and van Buskirk[19] and

Hall and Mayer[20] have reported that the retest performance of a passive avoidance task can be improved, or impaired by a given dose of a drug, depending on the intensity of the foot-shock.

In the present study, the dose of morphine and the intensity of the foot-shock were systematically varied in order to evaluate the combined effect of these parameters on the acquisition of a one-trial passive-avoidance response.

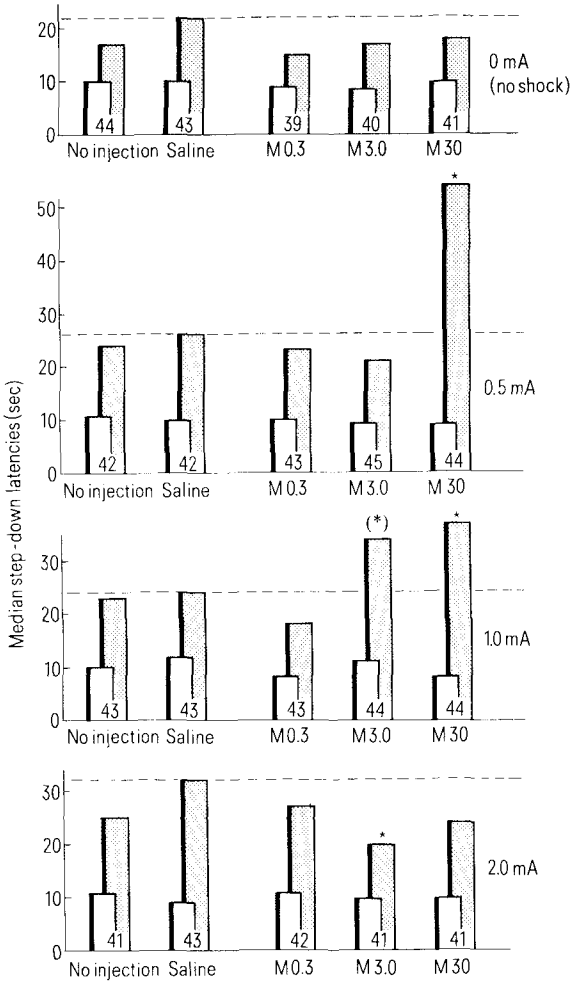
Methods. Animals. About 900 male mice (NMRI, bom-wiga; 20–25 g) were housed in Makrolon cages (42 × 26 × 15 cm) in a room illuminated on a 12/12 h light/darkness cycle. The animals had access to food and water ad libitum throughout the study. They were randomly assigned to different groups (n = 39–45), and all manipulations were performed blind in order to minimize experimental bias.

Apparatus. The step-down apparatus used to test passive avoidance consisted of a box measuring 50 × 50 × 40 cm with an electrifiable grid floor (6-mm stainless-steel rods spaced 13 mm apart). In it was a round, wooden platform 1 cm high and 5.7 cm in diameter, which could be enclosed by a 20-cm-long hollow, plastic cylinder with an inner diameter of 6.8 cm. The foot-shock was a scrambled, 50 Hz, bipolar, square-wave, constant current of 1 sec duration, set at 0, 0.5, 1.0, or 2 mA. Procedure. On day 1, groups of 5 animals were given access to the learning apparatus for 3 min, to familiarize them with the situation. On day 2, the mice were individually placed on the platform inside the cylinder. After 10 sec, the cylinder was removed, and the step-down latency was measured (the mice had to leave a marked safety zone, 2.5 cm wide surrounding the platform, with all 4 legs). Animals that had latencies longer than 30 sec were removed from the study (less than 1%). On day 3, the same procedure was followed as on day 2, except that a 1-sec foot-shock (0, 0.5, 1.0, or 2 mA) was administered as soon as the animal had left the safety zone with all 4 legs. The animal was then promptly removed from the test-box and given an injection of morphine HCl (0.3, 3.0, or 30 mg/kg i.p.), or saline, within 15 sec of the foot-shock. After the injection, the animals were replaced in their home cages. The uninjected controls were replaced in their home cages immediately after the foot-shock. The retention test was performed on day 4 at exactly the same time of day and in exactly the same manner as on day 2. A trial was terminated of the retest latency of an animal exceeded 180 sec.

Statistical procedure. The use of a cut-off design in retest results in non-normally distributed data. This as well as the different sizes of the groups prevented the use of a multifactorial ANOVA for overall statistical analysis. However, by using double admissible baseline latency as criterion for learning, the animals of the various groups can be divided into learners and non-learners. This allows an overall statistical analysis using the likelihood ratio test[21]. In order to evaluate the combined effect of drug dosage and shock intensity on retention performance only saline and morphine injected animals that received a foot-shock were included in the overall statistical analysis. If we assume that the treatment has no influence on the response of an animal (null hypothesis), the probability of a given response is the same for all combinations of drug dosages and shock intensities, provided that the responses of the animals are independent of each other. If the null hypothesis is true, the ratio of the maximum likelihood obtained in the unrestricted model devided by the maximum likelihood under the null hypothesis only rarely attains large values. Twice the natural logarithm of this ratio approximates chi-square distribution. To test a special hypothesis this logarithm can be partitioned into components in a way similar to the sum of squares of deviations in the ANOVA[21]. The most widely used parameter to compare individual groups is retest latency. In order to have results comparable to earlier findings[5] individual comparisons of the retest performance of the various experimental groups with that of their appropriate saline control group were done by using Mann-Whitney U statistics[22].

Results. The table shows the results of the maximum-likelihood quotient test. The most prominent finding emerging from the overall statistical analysis of the data was a highly significant interaction between drug dosage and shock intensity (2 $p < 0.0005$). As expected shock intensity significantly added to the variance (2 $p < 0.001$), whereas drug dosage did not (2 $p > 0.1$) suggesting a non-uniform drug effect.

The figure is a graphical representation of all the data obtained. 0 mA (no shock): In all the groups, the morphine-treated animals tended to leave the platform more quickly than the saline-treated controls (the differences are not significant). 0.5 mA: In the animals treated with 0.3 and 3.0 mg/kg of morphine retention was slightly inhibited, whereas in those given 30 mg/kg, there was a significant facilitation (2 $p < 0.05$, Mann-Whitney). 1.0 mA: Retention was slightly impaired by a dose of 0.3 mg/kg, improved by 3.0 mg/kg (2 $p < 0.07$) and 30 mg/kg (2 $p < 0.05$). 2.0 mA: All doses resulted in impaired retest performance. At 3.0 mg/kg, the effect was significant (2 $p < 0.02$).



Effect of post-trial administration of morphine (0.3, 3.0, and 30 mg/kg) on the retention of a step-down passive-avoidance task performed at different foot-shock intensities (0, 0.5, 1, and 2 mA). Median step-down latencies during baseline (blank columns) and retest (stippled columns) trials for the different experimental and control groups. Numbers in columns represent group size. * $p < 0.05$; (*) $p < 0.1$, two-tailed, Mann-Whitney U test; retest latencies are compared to those of appropriate saline control group).

Overall statistical analysis: Animals are divided into learners and non-learners according to whether their retest latencies are greater or smaller than 60 sec (double maximum admissible baseline latency). Based on these data the importance of the 2 factors (shock intensity and drug dosage) as sources of variation is determined by using the likelihood ratio test

Source of variation	$-2 \ln \lambda^*$	d.f.	$p <$
Treatment effect	24.826	15	0.05
Shock main effect	3.163	6	n.s.
Drug effects	21.663	9	0.0125
Drug main effect	6.740	3	0.05
Interaction (drug dosage × shock intensity)	14.923	6	0.0125

λ, likelihood ratio.
* $-2 \ln \lambda$ approximates chi-square distribution. n.s., not significant.

Discussion. The results show that a single post-trial injection of morphine either facilitates or inhibits the retention performance of a one-trial passive-avoidance situation, depending on the drug dosage and on the intensity of the foot-shock administered. This is, to the best of our knowledge, the first demonstration of facilitating and inhibiting effects of morphine on memory within one and the same experimental setting, and the results, at first glance, seem consistent with those found by other authors: retest performance is improved after high doses, but inhibited after low doses of morphine. However, at some doses we observed inhibition or facilitation depending on the intensity of the foot-shock applied. There are three hypotheses at present which attempt to explain the effects of morphine on memory processing; the opiate-amnesia-receptor hypothesis[9], the morphine-reinforcement hypothesis[5], and the morphine-punishment hypothesis[6]. The interaction of the effects of dose with foot-shock intensity creates some problems in each of them.

Having found that low doses of morphine inhibit the memory, Izquierdo[9] postulated the existence of opiate-amnesia receptors. Conceivably, explanations for the facilitating effects of high doses might be advanced that do not exclude the notion of amnesia receptors. One might argue that morphine, in low doses, interacts specifically with one type of opiate receptor (most probably μ). This effect might be blocked or overrun by one or several other systems coming into action as the dose is increased. However, the fact that in our study either facilitation or inhibition of memory occurred after the same dose of morphine (3 mg/kg), depending on the preceeding shock level, limits the usefulness of this hypothesis.

A hypothesis whereby reinforcers facilitate memory processing has been formulated by Huston and Mondadori[23]. It accounts for the demonstration that post-trial application of various reinforcers, such as food[23,24] or reinforcing hypothalamic stimulation[25,26], facilitates retention performance in passive-avoidance tasks (comparable to that used in this experiment), as well as in a food motivated task[27]. This theory is therefore consistent with the data resulting from the present experiment, since morphine has been shown to act as a reinforcer, inasmuch as animals will learn to administer this drug in certain doses. Further support for the applicability of the reinforcement hypothesis is to be found in the observation that other self-administered drugs, such as apomorphine[28,29], amphetamine[30,31], ACTH[32,33], nicotine[34,35], and alcohol[36,37] have also been shown to facilitate retention in different tasks.

The reinforcement theory can account, in general, for the influence of dosage on the way in which morphine affects the memory, since there would necessarily be a threshold for its reinforcing effect. However, the paradoxical effects of morphine at a given dose are again problematical. One explanation still consistent with the hypothesis could be offered on the assumption that the reinforcing value of any particular dose of morphine is affected by the intensity of the preceding foot-shock, i.e. that the foot-shock influences the state of the animal in such a way as to alter the impact of a consequent stimulus (in this case morphine). This notion, although intuitionally appealing, needs experimental support.

Since morphine injections have also been shown to have punitive effects, especially at higher doses[39], it might be argued that in the present situation 2 consecutive punishments (shock followed immediately by morphine) have been administered. Their additive effects could result in longer step-down latencies. Such an explanation, although favoured by Stäubli and Huston[6], seems rather unlikely, however, as earlier experiments have shown that non-specific punishments, e.g. administration of LiCl[5], or immersion in hot and cold water[39], do not add to the foot-shock to improve learning. Moreover, in the present study, the morphine injected, no-shock groups tended to show shorter retest latencies than the saline-injected controls. This suggests that, if anything, the morphine injections had a positive, reinforcing rather than negative, punishing effect. The reactions of the morphine-injected, no-shock groups also serve as a control for the proactive inhibitory effects of the drug. If post-trial morphine affected retest performance pro-actively (by behavioral inhibition), this should be apparent in the no-shock control groups as well.

More important than how these results fit into the various existing concepts of morphine affecting memory processing is the notion (alluded to above) that the drug is influencing modifiable functional states. The brain and body of an animal shocked with 0.5 mA is presumably different from that of an animal shocked at either 1.0 or 2.0 mA current strength. The difference in the animals' behavioral response to foot-shocks of varying intensity implies that the post-shock brain activity patterns (e.g. arousal, vigilance) are also different. It need hardly be pointed out that all these central processes involve neurotransmitter and hormonal activity. The undrugged brain is able to process the information of the task under every condition of foot-shock intensity, as shown by the non-injected controls. The difference between the non-injected controls and the saline-injected controls demonstrates the influence of the post-shock injection procedure on ongoing memory processes. The fact that even the magnitude of this difference depends on the foot-shock intensity is interesting, but in the light of the above-mentioned hypothesis not surprising. The presence of morphine may modulate some or all of these processes. The functional states resulting from a particular combination of shock intensity and drug dosage may be favorable, indifferent, or unfavorable for the storage (and retrieval) of the kind of information in question (for a more detailed discussion of this view, see Mondadori[13]. Therefore, attempts to generalize results deriving from single sets of experimental parameters can easily be misleading.

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Effects of bombesin, vasoactive intestinal peptide and neurotensin on TRH-induced body shaking in rats[1]

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Summary. Bombesin, vasoactive intestinal peptide (VIP) and neurotensin were found to suppress body shaking behavior caused by intracerebroventricular injection of TRH.

Thyrotropin releasing hormone (TRH) induces a marked body shaking behavior[2-5] which can be suppressed by opioid agonists[6], particularly β-endorphin[4], and neurotensin (NT)[7]. The action mode of body shaking behavior in unknown. The aim of the present report was to study the interactions of TRH with other neuropeptides, bombesin (BBS), vasoactive intestinal peptide (VIP) and NT, using the body shakes as an index of the behavioral effect.

Materials and methods. Male Wistar rats, weighing 250–300 g, were housed at a constant temperature of 25°C under controlled illumination of a 12-h light:dark cycle (lights turned on at 07.00 h), with free access to standard rat biscuits and water. The method of intracerebroventricular (i.c.v.) injection has been described elsewhere[8]. Briefly, with the rat under pentobarbital anesthesia, a stainless steel guide cannula was fixed stereotaxically with dental cement on the skull at an appropriate position for insertion of an injection cannula into the left lateral ventricle. After a 5-day recovery period another 5 days were allowed for the animals to become accustomed to the insertion of the injection cannula in the morning. In the experiment, 5 µl of a peptide solution or physiological saline solution was injected with a microsyringe without anesthesia. After every experiment, the placement of the cannula was determined by injecting 5 µl of 1% Evans blue solution. The frequency of body shakes was counted visually for 30 min after the injection of neuropeptides into the lateral ventricle of the rat. The room temperature was maintained at 25°C.

The compounds used were TRH (Sigma), BBS (Osaka Protein Res. Foundation), VIP (Sigma) and NT (Osaka Protein Res. Foundation). Comparison of the data were performed by the method of Dunnett.

Results. As shown in table 1, 1.6 µg TRH produced vigorous body shake responses during the 30-min period. When 1 or 2 µg BBS, 5 or 10 µg VIP, or 10–40 µg of NT was injected, no body shaking response was observed (table 1).

The body shake scores when BBS, VIP and NT were injected together with 1.6 µg TRH are given in table 2. BBS in doses of more than 0.2 µg, VIP in doses of more than 2 µg and NT in doses of more than 5 µg significantly prevented the body shake responses induced by TRH. The antagonistic effect of BBS was particularly marked, while that of NT was slight.

Discussion. At present the mode and sites of action of neuropeptides on the incidence of body shaking response are obscure. Central actions of TRH have been shown to be related to enhanced turnover of catecholamines[9-12] and TRH-induced body shakes were suggested to be dependent on the brain dopamine[5]. The present results, that TRH-induced body shakes

Table 1. Body-shaking responses to i.c.v. injection of TRH, bombesin (BBS), vasoactive intestinal peptide (VIP) and neurotensin

Peptide	Dose (µg)	No. of rats	No. of shakes during 30 min
Saline		15	2 ± 0.7
TRH	1.6	14	90 ± 5.8**
BBS	1	9	2 ± 0.4
	2	10	2 ± 0.5
VIP	5	8	1 ± 0.9
	10	8	0 ± 0.0
NT	10	8	1 ± 0.3
	20	8	0 ± 0.0
	40	7	9 ± 0.2

** $p < 0.01$ vs saline (Dunnett's test). Means ± SEM.