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Adrenocortical suppression blocks the memory-enhancing effects of amphetamine and epinephrine

(catecholamines/glucocorticoids/metyrapone/inhibitory avoidance)

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ABSTRACT **This study examined glucocorticoid–adrenergic interactions in modulating acquisition and memory storage for inhibitory avoidance training. Systemically (s.c.) administered amphetamine (1 mg/kg), but not epinephrine (0.1 mg/kg) or the peripherally acting amphetamine derivative 4-OH amphetamine (2 mg/kg), given to rats shortly before training facilitated acquisition performance in a continuous multiple-trial inhibitory avoidance (CMIA) task. Adrenocortical suppression with the 11β-hydroxylase inhibitor metyrapone (50 mg/kg; s.c.), given to rats 90 min before training, did not block the effect of amphetamine and did not affect acquisition performance of otherwise untreated animals. Retention of CMIA and one-trial inhibitory avoidance was enhanced by either pre- or posttraining injections of amphetamine, as well as 4-OH amphetamine and epinephrine. The finding that injections of amphetamine and epinephrine have comparable effects on memory is consistent with the view that amphetamine may modulate memory storage, at least in part, by inducing the release of epinephrine from the adrenal medulla. Metyrapone pretreatment blocked the memory-enhancing effects of amphetamine, 4-OH amphetamine, and epinephrine but did not affect retention performance of otherwise untreated animals. Posttraining injections of different doses of epinephrine (ranging from 0.0001 to 1.0 mg/kg) produced a dose-dependent memory enhancement for inhibitory avoidance training and metyrapone blocked the memory-enhancing effects of all these doses. These findings provide further evidence that the sympathoadrenal and adrenocortical systems are intimately coupled during processes of memory storage.**

It is well established that adrenal hormones are released during training in emotionally motivated tasks (1–3) and influence neurobiological mechanisms underlying regulation of memory storage (4–6). Systemic injections of the adrenomedullary hormone epinephrine produce dose-dependent enhancement of retention performance when given to rats and mice shortly after training in aversive and appetitive learning tasks (7–10).

Earlier evidence suggesting that peripheral catecholamines modulate memory storage came from experiments examining the effects of systemic injections of amphetamine. In rats and mice, amphetamine produces dose- and time-dependent enhancement of memory storage (11–17). The effects of posttraining injections of amphetamine on memory are attenuated by surgical removal of the adrenal medulla (13), the primary source of circulating epinephrine (18). This finding suggests that the effects of amphetamine on memory storage are due, at least in part, to an influence on the release of catecholamines from peripheral storage sites (19). This view is supported by evidence that 4-OH amphetamine, a derivative of amphetamine with a limited capacity to enter the brain (20), also facilitates retention when given immediately after training (12, 14, 17).

Training in aversively motivated learning tasks is also known to stimulate the adrenocortical system, resulting in increased plasma levels of corticosterone (3, 21). There is extensive evidence that glucocorticoids modulate memory consolidation (22–26). Furthermore, findings of experiments using adrenalectomized (ADX) rats indicate that the level of circulating corticosterone is a major factor in determining the sensitivity of epinephrine in modulating memory storage (27, 28), suggesting an interaction between sympathoadrenal and adrenocortical systems in the modulation of memory storage for emotionally influenced tasks.

The present experiments examined glucocorticoid–adrenergic interactions in the regulation of memory storage in adrenally intact rats. The enhancing effects of systemic injections of amphetamine, 4-OH amphetamine, and epinephrine on memory for inhibitory avoidance training were examined in rats pretreated with a vehicle solution or metyrapone, a drug that inhibits 11β-hydroxylase, a rate-limiting enzyme in corticosterone synthesis (29, 30). Metyrapone treatment does not completely block the release of corticosteroids, but it greatly reduces the elevation of corticosterone during emotionally arousing events such as training in an inhibitory avoidance task. Basal levels of corticosterone are not appreciably affected, even when metyrapone is administered at a very high dose (150 mg/kg) (ref. 31; S. F. de Boer, personal communication).

MATERIALS AND METHODS

Subjects. Male Sprague–Dawley rats (250–275 g on arrival) from Charles River Breeding Laboratories were used. They were individually housed in a temperature-controlled (22°C) colony room and maintained on a standard 12-h light/12-h dark cycle (0700–1900 h lights on) with food and water available ad libitum. The animals were adapted to laboratory conditions for at least 1 week before any treatment. Training and testing were performed between 1000 and 1500 h.

Apparatus and Procedures. Two variants of inhibitory avoidance training were used. For both experiments, the rats were trained in an inhibitory avoidance apparatus (32), consisting of a trough-shaped alley (91 cm long, 15 cm deep, 20 cm wide at the top and 6.4 cm wide at the floor) divided into two compartments separated by a sliding door that opened by retracting into the floor. The starting compartment (31 cm long) was illuminated and the shock compartment (60 cm long) was dark. Training was conducted in a sound-attenuated room.

In a first experiment, metyrapone was administered to rats followed by pretraining injections of amphetamine, 4-OH amphetamine, or epinephrine. Possible interactions of these treatments were studied on acquisition and retention. A

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Abbreviations: ADX, adrenalectomy or adrenolectomized; CMIA, continuous multiple-trial inhibitory avoidance; IA, inhibitory avoidance; GR, glucocorticoid receptor; MR, mineralocorticoid receptor.

second experiment was conducted to exclude the possibility that the effects found on retention performance were due to sensory or motivational influences on acquisition. In this second experiment, rats were pretreated with metyrapone and received injections of the adrenergic agents immediately after training. In a third and last experiment, rats pretreated with metyrapone were injected with different doses of epinephrine immediately after training in the inhibitory avoidance apparatus to investigate whether metyrapone may alter the sensitivity of epinephrine in enhancing memory storage.

A continuous multiple-trial inhibitory avoidance (CMIA) training procedure was used in the first experiment. On the training day, each animal received a s.c. injection of either vehicle or metyrapone (50 mg/kg) 90 min before training. Additional injections of either saline, amphetamine (1.0 mg/kg), or 4-OH amphetamine (2.0 mg/kg) were given 30 min before training, or epinephrine (0.1 mg/kg) was administered 5 min before training. The rat was then placed in the starting compartment of the apparatus facing away from the door. As the rat stepped into the dark compartment, a low-intensity footshock (0.25 mA) was delivered until the rat escaped back into the starting compartment. The door remained open throughout the entire training period, and whenever the rat reentered the dark compartment, shock was again delivered and was terminated when the rat escaped to the starting compartment. The rat was retained in the apparatus until it remained in the starting compartment continuously for 200 s. The animal was then returned to its home cage. The total number of trials (i.e., entries into the shock compartment) required to reach the acquisition criterion of 200 consecutive seconds in the starting compartment was recorded. On the retention test 48 h after training, the rat was placed in the starting compartment, as in the training session, and the latency to step into the dark compartment (maximum, 600 s) was recorded. Shock was not administered on the retention test trial.

In the second experiment conducted in the same inhibitory avoidance (IA) apparatus, the animals received only one training trial. Each animal received a s.c. injection of either vehicle or metyrapone (50 mg/kg) 90 min before training. The rat was placed in the starting compartment of the apparatus facing away from the door, and the rat was allowed to enter the dark. When the rat stepped completely into the dark compartment, the door was closed and a mild inescapable footshock (0.45 mA, 1.0 s) was delivered. The rat was removed from the dark alley 15 s after termination of the footshock and immediately given a s.c. injection of saline, amphetamine (1.0 mg/kg), 4-OH amphetamine (2.0 mg/kg), or epinephrine (0.1 mg/kg). Retention was tested 48 h after training using the same testing procedures as in experiment 1.

The behavioral procedures used for the third experiment were similar to those of the second one, except that different doses of epinephrine were injected immediately after training. Rats received s.c. injections of either vehicle or metyrapone (50 mg/kg) 90 min prior to the start of the one-trial inhibitory avoidance training and immediately after training s.c. injections of saline or either of the five doses of epinephrine (ranging from 0.0001 to 1.0 mg/kg). Retention was tested 48 h after training, with the same testing procedures used in experiments 1 and 2.

Drug Administration. The 11β-hydroxylase inhibitor metyrapone (2-methyl-1,2-di-3-pyridyl-1-propanone; Sigma) was injected s.c. at 50 mg/kg in a vol of 2.0 ml/kg on the dorsal surface of the neck 90 min before training in all tasks. The drug was dissolved in polyethylene glycol and diluted with a 0.9% saline (NaCl) solution to reach the appropriate concentration. The final concentration of polyethylene glycol was 40%. The vehicle control contained the same polyethylene glycol concentration. This dose was selected on the basis of findings of a previous experiment (B.R., B. Bohus, and J.L.M., unpublished observation).

As described above, the memory-enhancing drugs that were used included (+)-amphetamine (1.0 mg/kg; Sigma), (±)-4-hydroxyamphetamine (2.0 mg/kg; 4-OH amphetamine; Smith-Kline Beecham), and epinephrine (0.1 mg/kg; Elkins-Sinn, Cherry Hill, NJ). In the last experiment, five different doses of epinephrine (0.0001, 0.001, 0.01, 0.1, and 1.0 mg/kg) were used. The doses used were selected on the basis of previous experiments in this laboratory (9, 17). All of these agents were dissolved in 0.9% saline and were administered s.c. in a vol of 1.0 ml/kg.

Statistics. Between-group comparisons for all experiments were analyzed with a one-way ANOVA followed by Fisher's post-hoc tests. Values of $P < 0.05$ were considered significant. The number of animals per group is indicated in the figure legends.

RESULTS

CMIA. Fig. 1*A* shows the CMIA acquisition results. A one-way ANOVA of the number of training trials required to reach acquisition criterion revealed a significant group effect ($F_{(7,82)} = 3.19$; $P < 0.005$). Between-group comparisons made with Fisher's post-hoc tests indicated that amphetamine (1.0

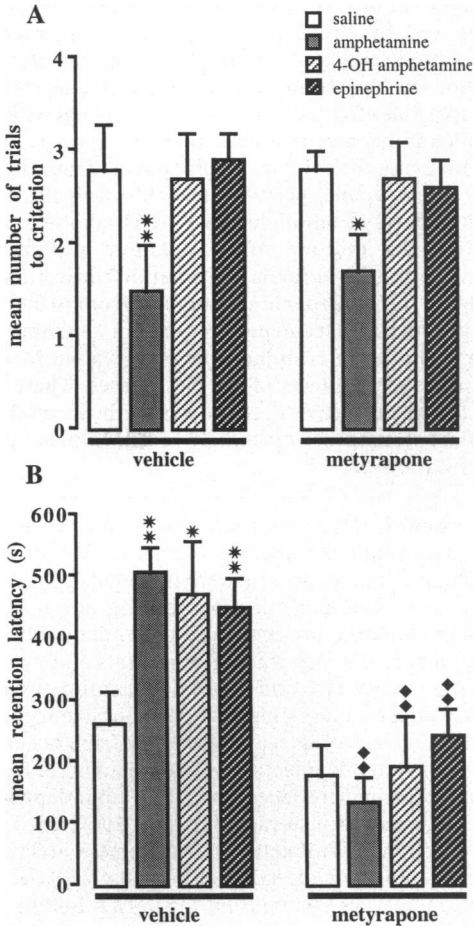

FIG. 1. Effects of corticosteroid synthesis blockade with metyrapone (50 mg/kg) on amphetamine (1.0 mg/kg), 4-OH amphetamine (2.0 mg/kg), or epinephrine (0.1 mg/kg) induced changes in acquisition (*A*) and retention (*B*) in a continuous multiple-trial inhibitory avoidance. Bars represent mean (±SEM) number of trials required to reach acquisition criterion (*A*) or step-through latency (in seconds) on the retention test (*B*). ✱, $P < 0.05$; ✱✱, $P < 0.01$ as compared with the corresponding saline group; ◆◆, $P < 0.01$ as compared with the corresponding vehicle group (n = 7–15 animals per group).

mg/kg) significantly facilitated acquisition ($P < 0.01$ compared with saline-treated controls). In contrast, pretraining injections of either 4-OH amphetamine (2.0 mg/kg) or epinephrine (0.1 mg/kg) did not affect acquisition performance. Metyrapone did not block the amphetamine-induced facilitation of acquisition. Furthermore, the acquisition performance of the metyrapone/saline group did not differ from that of the vehicle/saline controls ($P > 0.95$).

The effects of metyrapone on amphetamine-, 4-OH amphetamine-, and epinephrine-induced enhancement of retention are shown in Fig. 1*B*. A one-way ANOVA revealed a significant overall effect ($F_{(7,82)} = 7.20$; $P < 0.0001$). Between-group comparisons indicated that all three adrenergic treatments produced significant improvements in retention performance relative to saline-treated controls [amphetamine and epinephrine (both $P < 0.01$), and 4-OH amphetamine ($P < 0.05$)].

Metyrapone significantly attenuated the retention enhancement produced by pretraining administration of amphetamine, 4-OH amphetamine, and epinephrine. The retention latencies of all these groups were significantly shorter after metyrapone treatment than after vehicle injections (all $P < 0.01$). The retention latencies of the animals in the three metyrapone adrenergic groups did not differ from those of the metyrapone/saline control group. Furthermore, the retention performance of the metyrapone/saline group did not differ from that of the vehicle/saline group ($P > 0.20$).

IA. The IA retention test latencies are shown in Fig. 2. A one-way ANOVA of data revealed a significant treatment effect ($F_{(7,102)} = 7.18$; $P < 0.0001$). Between-group comparisons with the Fisher tests indicate that retention latencies were significantly enhanced by posttraining injections of amphetamine, 4-OH amphetamine, and epinephrine (all $P < 0.01$) in comparison with saline-treated rats. Metyrapone blocked the memory-enhancing effects of amphetamine, 4-OH amphetamine, and epinephrine (all $P < 0.01$). Furthermore, retention latencies in the metyrapone/saline group did not differ from those in the vehicle/saline control group ($P > 0.75$).

The retention test latencies of rats injected with different doses of epinephrine immediately after training on a one-trial inhibitory avoidance task are shown in Fig. 3. A one-way ANOVA of data revealed a significant treatment effect ($F_{(11,136)} = 3.76$; $P < 0.0001$). Post-hoc analysis revealed that epinephrine showed a dose-dependent effect on memory: The

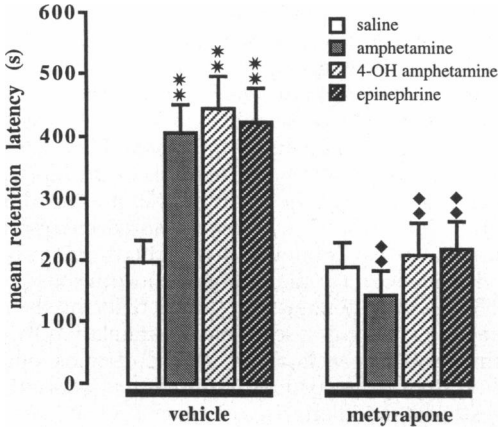

FIG. 2. Effects of corticosteroid synthesis blockade with metyrapone (50 mg/kg) on amphetamine (1.0 mg/kg), 4-OH amphetamine (2.0 mg/kg), or epinephrine (0.1 mg/kg) induced memory enhancement in an inhibitory avoidance task. Bars represent mean (±SEM) step-through latency (in seconds) on the retention test. ✱✱, $P < 0.01$ as compared with the corresponding saline group; ◆◆, $P < 0.01$ as compared with the corresponding vehicle pretreatment group (n = 9–20 animals per group).

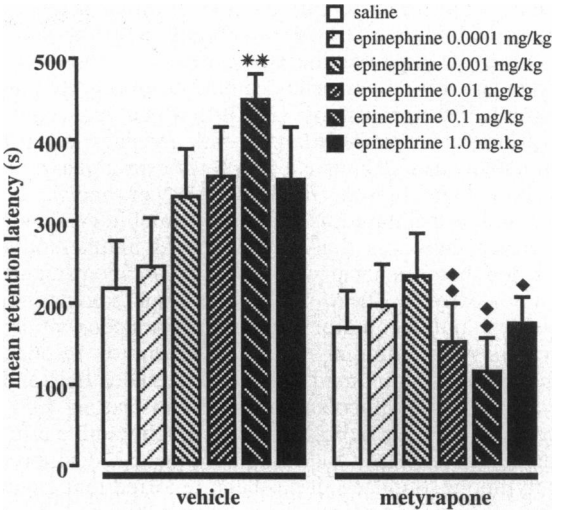

FIG. 3. Effects of corticosteroid synthesis blockade with metyrapone (50 mg/kg) on epinephrine-induced memory enhancement in an inhibitory avoidance task. Bars represent mean (±SEM) step-through latency (in seconds) on the retention test. ✱✱, $P < 0.01$ as compared with the corresponding saline group; ◆, $P < 0.05$; ◆◆, $P < 0.01$ as compared with the corresponding vehicle pretreatment group (n = 11–14 animals per group).

0.1 mg/kg dose of epinephrine significantly enhanced retention compared to saline-injected rats ($P < 0.01$). Other doses were not statistically significant (the P values of the 0.01 and 1.0 mg/kg doses of epinephrine were both 0.06). Metyrapone blocked the memory-enhancing effect of epinephrine. The retention latencies of metyrapone-treated animals with different doses of epinephrine did not differ from those of the metyrapone/saline group or from each other. Furthermore, the retention latencies of metyrapone-treated rats injected with the three higher doses of epinephrine were significantly shorter than those of the corresponding vehicle/epinephrine groups (0.01 and 0.1 mg/kg; $P < 0.01$; 1.0 mg/kg; $P < 0.05$). Retention latencies of the metyrapone/saline group did not differ from those of the vehicle/saline control group ($P > 0.50$).

DISCUSSION

These experiments examined whether metyrapone influenced the enhancing effects of systemic injections of epinephrine, amphetamine, and its peripherally acting derivative 4-OH amphetamine on acquisition and retention in inhibitory avoidance tasks. Amphetamine, but not 4-OH amphetamine and epinephrine, given to rats before training facilitated acquisition performance in a CMIA task. Metyrapone did not block the effect of amphetamine on acquisition. On the other hand, injections of amphetamine, as well as 4-OH amphetamine and epinephrine, enhanced retention in the CMIA and IA tasks. Metyrapone pretreatment blocked the memory-enhancing effects of all these treatments. Acquisition and retention performance of rats were not affected by metyrapone administration alone.

The findings that only rats that received injections of amphetamine, but not 4-OH amphetamine and epinephrine, required fewer trials in a CMIA task to reach acquisition criterion suggest that the enhancing effect of amphetamine on acquisition is independent of its function in stimulating the release of epinephrine from the adrenal medulla. These results are consistent with the finding that a depletion of peripheral epinephrine by adrenomedullectomy also fails to affect acquisition performance in an IA task (13, 33). Systemically administered amphetamine readily enters the brain and may

modulate acquisition performance by a direct activation of central dopaminergic (12, 34) or noradrenergic systems (12, 35). Doses of amphetamine comparable to those found to facilitate acquisition performance have been reported also to increase locomotor activity (36–39), which may confound acquisition performance in an IA task. An increase in locomotor activity can, of course, easily be interpreted as a poorer acquisition. The present findings, however, indicated that amphetamine facilitated acquisition of inhibitory avoidance. This clearly indicates that the effects of amphetamine on acquisition performance were not due to an influence on locomotor activity. The view that the amphetamine-induced acquisition and locomotor effects are independent is also supported by the finding that the locomotor response to amphetamine is attenuated following adrenalectomy and can be restored with glucocorticoid administration (36, 37), whereas our findings indicate that the amphetamine effect on acquisition is unaltered following adrenocortical suppression by metyrapone. Similarly, it has been reported that enhanced arousal states and attention to amphetamine, which may directly influence acquisition performance, were not related to amphetamine-induced changes in locomotor activity (40). These findings suggest that the amphetamine-induced facilitation of acquisition performance found may be due to enhanced arousal states or attention, possibly enhancing short-term memory processing.

Retention was enhanced by amphetamine, 4-OH amphetamine, and epinephrine administered to rats either shortly before or immediately after training. The finding that these retention effects were obtained with both pretraining and posttraining injections indicates that the enhanced retention is due to modulation of memory storage and not to influences on sensory or motivational processes during the training experience (41). This view is further supported by the absence of any consistent effects of the adrenergic drug injections on acquisition performance in the CMIA task. Our findings are also consistent with previous evidence that amphetamine- and 4-OH amphetamine-induced enhancement of memory storage depends on the integrity of the adrenal medulla (13, 14). The memory-enhancing effect of epinephrine is mediated via an activation of central noradrenergic mechanisms (9, 17). This view is supported by the finding that peripheral injections of amphetamine, 4-OH amphetamine, and epinephrine reduce levels of norepinephrine in the hippocampus and amygdala (14). However, since epinephrine is a rather polar substance, it seems unlikely that peripherally released or injected epinephrine reaches the central nervous system in an amount sufficient to exert a direct influence on brain systems involved in memory (42). The 4-OH amphetamine effects on memory are initiated by the release of peripheral epinephrine. Epinephrine may activate adrenergic receptors in the periphery that, in turn, stimulate noradrenergic systems in the brain via visceral, probably vagal, afferents (43, 44). This hypothesis is supported by the findings that sotalol, a peripherally acting β-noradrenergic antagonist, blocks the memory-enhancing effects of peripheral injections of epinephrine (17, 45).

Pretreatment with metyrapone, a corticosterone-synthesis inhibitor, blocked the memory enhancement induced by epinephrine, amphetamine, and 4-OH amphetamine. Moreover, metyrapone treatment blocked the enhancing effects of epinephrine in a wide range of doses. These findings suggest that a stress-induced increase in corticosterone is essential for producing memory-enhancing effects and the effect is not due to corticosterone-induced changes in the sensitivity of epinephrine. Corticosterone readily crosses the blood–brain barrier and binds directly to mineralocorticoid (MRs or type I) and glucocorticoid (GRs or type II) receptors in the brain (46–48). GR's affinity for corticosterone is lower than that of MR. Basal levels of corticosterone activate MRs, whereas stress-induced increases in circulating corticosterone levels also activate GRs. Metyrapone is known to block the increases in corticosterone levels during stress, but basal levels are not appreciably affected (ref. 31; S. F. de Boer, personal communication). Such evidence suggests that metyrapone treatment results primarily in reductions of corticosterone binding to GRs, whereas the binding to MRs remains at least partially spared (B.R., B. Bohus, and J.L.M., unpublished observation).

Our findings conflict to some degree with those of previous studies. Borrell *et al.* (27, 28) reported that although epinephrine interacts with glucocorticoids in modulation of memory storage, the epinephrine effect on memory could be seen in the absence of circulating corticosterone. They reported that epinephrine administered to ADX rats attenuated the ADX-induced impairment of retention of IA training. They also reported that adrenomedullectomy or concurrent administration of corticosterone to ADX rats decreased the effectiveness of epinephrine in modulating memory storage. Because dexamethasone, a potent GR agonist, did not change the sensitivity of epinephrine in attenuating the ADX-induced memory deficit, these findings suggest that corticosterone suppresses the effectiveness of epinephrine in the modulation of memory storage in ADX rats, and the interaction is mediated primarily via MRs, and not GRs.

The differences between the latter and present studies may be attributed to the ADX treatment used in the Borrell studies, a treatment depleting both MRs and GRs, while metyrapone probably affected only binding to GRs. Accordingly, there are obvious differences in these experiments in the occupancy or balance of MRs and GRs. Another difference, but related to the first one, is that in the present study the effects of epinephrine were examined in the enhancement of memory, whereas in the studies by Borrell and colleagues the effects of epinephrine were investigated in the attenuation of an ADX-induced memory deficit. An alternative explanation for the differences observed is that metyrapone may induce the release of deoxycorticosterone (30), which, in turn, can be converted in tetrahydroxydeoxycorticosterone or other neurosteroids. These neurosteroids may block the memory-enhancing effects of epinephrine and amphetamine.

The mechanisms modulating the glucocorticoid–adrenergic interaction on memory in our study and the other studies described above need further inquiry. One interpretation of the present results is that corticosterone may exert a tonic inhibitory influence on the synthesis and release of epinephrine from the adrenal medulla (49). However, this possibility is very unlikely because pretreatment with the dosage of metyrapone used in the present study does not increase plasma levels of epinephrine (S. F. de Boer, personal communication), and metyrapone does not facilitate memory when administered alone. Another, more likely mechanism is a direct interaction of the glucocorticoid and adrenergic systems in limbic areas involved in memory processes. High densities of MRs and GRs are present in the neurons of the hippocampus and amygdala (50–52). In light of the presumed role of epinephrine in activation of central noradrenergic mechanisms, it is of particular interest that corticosterone also has a profound influence on noradrenergic neurotransmission in the brain (53–55). The finding that the activity of the central noradrenergic system is susceptible to stimulation by peripheral epinephrine as well as by glucocorticoids opens the possibility that glucocorticoid–adrenergic interactions on memory storage modulation may be localized, at least in part, at the locus of the central noradrenergic system. Corticosterone might also influence the activity of other neurotransmitter systems in the hippocampus and amygdala, such as the GABAergic, serotonergic, and peptidergic systems (54), which, in turn, interact with the noradrenergic system in regulating memory storage (56).

In conclusion, the findings of this study indicate that suppression of the release of corticosterone blocks the effects of

amphetamine and epinephrine in the modulation of memory formation. These findings provided further evidence that the sympathoadrenal and adrenocortical systems are intimately coupled during processes of memory storage.

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1. de Boer, S. F., Koopmans, S. L., Slangen, J. L. & van der Gugten, J. (1990) *Physiol. Behav.* **47,** 1117–1124.
2. McCarty, R. & Gold, P. E. (1981) *Horm. Behav.* **15,** 168–182.
3. Roozendaal, B., Koolhaas, J. M. & Bohus, B. (1991) *Physiol. Behav.* **50,** 771–775.
4. Bohus, B. (1994) in *The Memory System of the Brain*, ed. Delacour, J. (World Scientific, New Jersey), Vol. 4, pp. 337–364.
5. Gold, P. E. & McGaugh, J. L. (1975) in *Short-Term Memory*, eds. Deutsch, D. & Deutsch, J. A. (Academic, New York), pp. 355–378.
6. McGaugh, J. L. (1983) *Annu. Rev. Psychol.* **34,** 229–241.
7. Gold, P. E. & van Buskirk, R. (1975) *Behav. Biol.* **13,** 145–153.
8. Izquierdo, I. (1984) in *Neurobiology of Learning and Memory*, eds. Lynch, G., McGaugh, J. L. & Weinberger, N. M. (Guilford, New York), pp. 333–350.
9. Liang, K. C., Juler, R. G. & McGaugh, J. L. (1986) *Brain Res.* **368,** 125–133.
10. Sternberg, D. B., Isaacs, K. R., Gold, P. E. & McGaugh, J. L. (1985) *Behav. Neural Biol.* **44,** 447–453.
11. Krivanek, J. & McGaugh, J. L. (1969) *Agents Actions* **1,** 36–42.
12. Martinez, J. L., Jr., Jensen, R. A., Messing, R. B., Vasquez, B. J., Soumireu-Mourat, B., Geddes, D., Liang, K. C. & McGaugh, J. L. (1980) *Brain Res.* **182,** 157–166.
13. Martinez, J. L., Jr., Vasquez, B. J., Rigter, H., Messing, R. B., Jensen, R. A., Liang, K. C. & McGaugh, J. L. (1980) *Brain Res.* **195,** 433–443.
14. Martinez, J. L., Jr., Ishikawa, K., Liang, K. C., Jensen, R. A., Bennett, C., Sternberg, D. B. & McGaugh, J. L. (1983) *Behav. Neurosci.* **97,** 962–969.
15. Packard, M. G., Williams, C. L. & McGaugh, J. L. (1992) *Psychobiology* **20,** 280–285.
16. Strupp, B. J., Bunsey, M., Levitsky, D. & Kesler, M. (1991) *Behav. Neural Biol.* **56,** 62–76.
17. Williams, C. L., Packard, M. G. & McGaugh, J. L. (1994) *Psychobiology* **22,** 141–148.
18. Viveros, O. H., Diliberto, J. R., Hazum, E. & Chang, K. J. (1980) in *Neural Peptides and Neuronal Communication: Advances in Biochemical Psychopharmacology*, eds. Costa, E. & Trabucchi, M. (Raven, New York), pp. 191–204.
19. Weiner, N. (1985) in *The Pharmacological Basis of Therapeutics*, eds. Goodman, A. G., Goodman, L. S., Rall, T. W. & Murad, F. (MacMillan, New York), pp. 120–144.
20. Day, M. D. (1979) *Autonomic Pharmacology: Experimental and Clinical Aspects* (Churchill Livingstone, New York).
21. Harvey, S., Philips, J. G., Rees, A. & Hall, T. R. (1984) *J. Exp. Zool.* **232,** 633–645.
22. Bohus, B. & de Kloet, E. R. (1981) *Life Sci.* **28,** 433–440.
23. Gold, P. E., Rose, R. P., Spanis, C. W. & Hankins, L. L. (1977) *Horm. Behav.* **8,** 363–371.
24. Oitzl, M. S. & de Kloet, E. R. (1992) *Behav. Neurosci.* **106,** 62–71.
25. Roozendaal, B. & McGaugh, J. L. (1996) *Neurobiol. Learning Memory*, in press.
26. Sandi, C. & Rose, S. P. R. (1994) *Brain Res.* **647,** 106–112.
27. Borrell, J., de Kloet, E. R., Versteeg, D. H. G. & Bohus, B. (1983) *Behav. Neural Biol.* **39,** 241–258.
28. Borrell, J., de Kloet, E. R. & Bohus, B. (1984) *Life Sci.* **34,** 99–107.
29. De Nicola, A. F. & Dahl, W. (1971) *Endocrinology* **89,** 1236–1241.
30. Strashimirov, D. & Bohus, B. (1966) *Steroids* **7,** 171–180.
31. Freo, U., Holloway, H. W., Kalogeras, K., Rapoport, S. I. & Soncrant, T. T. (1992) *Brain Res.* **586,** 256–264.
32. McGaugh, J. L., Introini-Collison, I. B. & Nagahara, A. (1988) *Brain Res.* **446,** 37–49.
33. Silva, M. T. A. (1973) *Behav. Biol.* **9,** 553–562.
34. Ivens, J. A., Janak, P. H. & Martinez, J. L., Jr. (1992) *Proc. West. Pharmacol. Soc.* **35,** 165–169.
35. Kuczenski, R. & Segal, D. S. (1992) *Synapse* **11,** 164–169.
36. Cador, M., Dulluc, J. & Mormède, P. (1993) *Neuroscience* **56,** 981–988.
37. Cole, B., Cador, M., Stinus, L., Rivier, C., Rivier, J., Vale, W., Le Moal, M. & Koob, G. F. (1990) *Life Sci.* **47,** 1715–1720.
38. Gelowitz, D. L. & Kokkinidis, L. (1993) *Brain Res. Bull.* **32,** 561–565.
39. Pauly, J. R., Robinson, S. F. & Collins, A. C. (1993) *Brain Res.* **620,** 195–202.
40. Jones, G. H., Mittleman, G. & Robbins, T. W. (1989) *Behav. Neural Biol.* **51,** 80–91.
41. McGaugh, J. L. & Herz, M. J. (1972) *Memory Consolidation* (Albion, San Francisco).
42. Weil-Marherbe, H., Axelrod, J. & Tomchick, R. (1959) *Science* **129,** 1226–1228.
43. Williams, C. L. & Jensen, R. A. (1991) in *Peripheral Signaling of the Brain: Role in Neural-Immune Interactions, Learning and Memory*, eds. Frederickson, R. C. A., McGaugh, J. L. & Felten, D. L. (Hogrefe & Huber, New York), pp. 467–472.
44. Williams, C. L. & McGaugh, J. L. (1993) *Behav. Neurosci.* **107,** 1–8.
45. Introini-Collison, I. B. & McGaugh, J. L. (1991) in *Peripheral Signaling of the Brain: Role in Neural-Immune Interactions, Learning and Memory*, eds. Frederickson, R. C. A., McGaugh, J. L. & Felten, D. L. (Hogrefe & Huber, New York), pp. 275–302.
46. Chao, H. M., Choo, P. H. & McEwen, B. S. (1989) *Neuroendocrinology* **50,** 365–372.
47. Herman, J. P., Patel, P. D., Akil, H. & Watson, S. J. (1989) *Mol. Endocrinol.* **3,** 886–894.
48. Reul, J. M. H. M. & de Kloet, E. R. (1985) *Endocrinology* **117,** 2505–2512.
49. Kvetnansky, R., Fukuhara, K., Pacak, K., Cizza, G., Goldstein, D. S. & Kopin, I. J. (1993) *Endocrinology* **133,** 1411–1419.
50. Fuxe, K., Cintra, A., Härfstrand, A., Agnati, L. F., Kilia, M., Zoli, M., Wikström, A. C., Okret, S., Aronsson, M. & Gustafsson, J. Å. (1987) *Ann. N.Y. Acad. Sci.* **512,** 362–393.
51. Honkaniemi, J., Pelto-Huikko, M., Rechardt, L., Isola, J., Lammi, A., Fuxe, K., Gustafsson, J. Å., Wikström, A. C. & Hökfelt, T. (1992) *Neuroendocrinology* **55,** 451–459.
52. van Eekelen, J. A. M., Jiang, W., de Kloet, E. R. & Bohn, M. C. (1988) *J. Neurosci. Res.* **21,** 88–94.
53. Nicoll, R. A. (1988) *Science* **241,** 545–551.
54. de Kloet, E. R. (1991) *Front. Neuroendocrinol.* **12,** 95–164.
55. McEwen, B. S. (1987) *Biochem. Pharmacol.* **36,** 1755–1763.
56. McGaugh, J. L., Introini-Collison, I. B., Cahill, L., Kim, M. & Liang, K. C. (1992) in *The Amygdala: Neurobiological Aspects of Emotion, Memory, and Mental Dysfunction*, ed. Aggleton, J. P. (Wiley–Liss, New York), pp. 431–451.