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Brain Noradrenergic Responses to Training and to Amnestic Frontal Cortex Stimulation[1]

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GOLD, P. E. AND J. M. MURPHY. *Brain noradrenergic responses to training and to amnestic frontal cortex stimulation.* PHARMAC. BIOCHEM. BEHAV. **13**(2) 257–263, 1980.—Rats were trained in a one-trial inhibitory (passive) avoidance task prior to receiving supraseizure electrical stimulation of frontal cortex, a treatment that results in amnesia. Forebrain and brainstem norepinephrine (NE) concentrations decreased by 23% 10 min after footshock training. Posttraining frontal cortex stimulation resulted in a potentiation of the forebrain NE response (to 31–33% below control values) and in attenuation of the brainstem response (0–5% lower than control values). These results are consistent with previous findings that indicate that good retention performance is predicted by training and treatment conditions that result in approximately a 20% decrease in brain NE content as measured 10 min after training; deviations from this optimal level, presumably reflecting more or less NE release, predict poor retention in comparably trained and treated rats. Thus, memory storage processing appears to be sensitive to many manipulations that alter the endogenous posttraining brain NE response to footshock.

Amnesia Memory storage processes Electroshock Stress Norepinephrine Avoidance training

WHEN administered shortly after training, many acute treatments produce retrograde amnesia. An extensive literature documents this phenomenon in a variety of species and tasks and addresses the theoretical significance of these findings [17, 18, 33, 40, 41, 42]. During the past 30 years, several attempts have been made to determine the neurobiological responses to amnestic treatments that comprise or contribute to the development of amnesia. Some correlates of amnesia include behavioral and electrographic seizures ([12, 14, 16, 43, 51, 52, 55, 56, 57, 58]; cf. [26]), changes in hippocampal theta activity [37], and several measures of neurochemical changes following pharmacological treatments that alter memory (e.g., [2, 8, 10, 28, 29, 32]).

For each of these potential correlates of amnesia, there are indeed some conditions under which the brain response to the treatment is related to amnesia. However, the correlates generally do not extend beyond a particular treatment class. For example, brain seizure activity is, in some cases, correlated with the amnestic effectiveness of electrical stimulation of the cortex (cf. [26]), but seizure activity is not necessary for amnesia produced by electrical stimulation of the amygdala [15], or for amnesia produce by norepinephrine (NE) synthesis inhibitors [28,29]. Protein synthesis inhibition (typically 90–95% inhibition is necessary for amnesia) can be correlated with amnesia produced by antibiotics but does not appear to explain the amnesias produced by electroconvulsive shock (only 10–20% inhibition; [7,8]).

Thus, different amnestic agents may act on memory by initiating different neurobiological responses. Alternatively, however, it is possible that most amnestic agents have some common action that is related to amnesia. For example, most traditional amnestic agents (electroconvulsive shock, analeptic drugs, protein synthesis inhibitors, NE synthesis inhibitors) may be acute general physiological stressors that elicit brain NE, pituitary-adrenal, and sympathetic activity. Therefore, some components of an organism's stress response may be major contributors to the effects of these treatments on memory. This possibility has gained support from several recent findings. First, posttraining subcutaneous injections of ACTH or epinephrine, two hormones often associated with stress [38], can produce retrograde amnesia [20, 21, 22, 25]. Second, brain NE concentrations, which are also sensitive to a variety of stressors [3, 4, 11, 27, 34, 39, 44, 45, 50, 53], decline by approximately 40% within 10 min of training+treatment under those conditions with which subcutaneous epinephrine injections produce amnesia [23,24]. The transient decrease in brain NE can be interpreted as reflecting release of this neurotransmitter (cf. [48]) and is significantly larger than the 20% decrease observed in response to footshock training alone. Therefore, amnesia produced by peripheral epinephrine injections appears to be related to an exaggerated brain NE response. Third, the α-adrenergic antagonist phenoxybenzamine attenuates both the epinephrine-induced amnesia and the brain NE response to epinephrine [24]. Fourth, phenoxybenzamine also attenuates the effects on memory of a wide spectrum of other

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amnestic agents, including subseizure electrical stimulation of the amygdala, pentylenetetrazol, cycloheximide, diethyldithiocarbamate (a NE synthesis inhibitor), as well as supraseizure electrical stimulation of frontal cortex [19], the amnestic agent used in the present experiment.

Although noradrenergic responses appear to be sensitive to avoidance training and to memory-modulating treatments, it should be noted that chronic alterations in brain NE, e.g. with lesions of locus coeruleus, do not generally result in impaired acquisition or retention of learned responses nor do these alterations impair the formation of retrograde amnesia (cf. [1,54]). It appears, then, that animals chronically depleted of NE may be able to compensate for this loss by using other memory-modulating systems. On the other hand, as indicated above, the effects on memory of acute treatments seem to be well-correlated with effects on NE activity.

Collectively, these findings support the hypothesis that catecholamine responses to stress may be involved in retrograde amnesia. In the present study, changes in brain NE content were determined after training and frontal cortex stimulation to assess further the generality of the relationship between the brain NE response and retrograde amnesia. Supraseizure electrical stimulation of frontal cortex was chosen as the amnestic agent because of its similarity to a major amnestic treatment, electroconvulsive shock. Because brain NE has been reported to be involved in convulsions (e.g., [6,49]) and is responsive to electroconvulsive shock [31,47], a secondary purpose was to determine whether a single brain seizure induced by electrical brain stimulation results in a change in brain NE concentrations.

METHOD

Training and Treatment

Male Sprague-Dawley rats (250–300 g, Flow Laboratories) were housed individually with ad lib food and water. All animals initially underwent surgery for electrode implantation. Under sodium pentobarbital (Nembutal, 45 mg/kg) anesthesia, four cortical electrodes (stainless steel screws) were implanted bilaterally over frontal and posterior cortex (either 2 mm anterior or 7 mm posterior to bregma, 2 mm lateral). The electrodes were connected to an Amphenol microminiature connector strip, and the assemblage was cemented in place.

Approximately one week following surgery, the animals were placed on a water deprivation schedule. Each rat received a single daily aliquot of water sufficient to reduce its weight to 80% of its baseline value within 4–6 days. Thereafter, each animal's weight was maintained at that level. After body weights stabilized at the 80% level, each rat received one daily pretraining trial for 4 days. The apparatus was a long alleyway divided into a well-lit start compartment (24×14×12 cm) and a dimly-lit black shock compartment (37×14×12 cm) containing a stainless steel grid floor. A water spout protruded 1 cm from the far end of the black compartment. On each trial, the animal was placed in the white compartment for 10 sec before a sliding white door separating the compartments was opened. The rat was then allowed to approach the water spout and to drink for a 30 sec period following the first lick. By the fourth pretraining trial, all animals traversed the alleyway and began to drink within 15 sec after the door was opened. The water deprivation and pretraining procedures were used both to habituate the animals to the training apparatus and to decrease variability in retention performance above a reliable baseline performance measure. The brain NE content and its responsiveness to footshock in these animals did not differ from similar measures obtained with non-deprived untrained animals (unpublished).

On the fifth day, animals received avoidance training, a single 3 mA, 2 sec scrambled AC footshock administered after the tenth second of drinking. Five seconds after the training footshock, either sham or frontal cortex stimulation (2.5 or 5.0 mA, 60 Hz, 1 sec) was administered. Electrocortical activity was then recorded for 2 min on a Grass Model 7 polygraph to monitor the brain seizure pattern and duration.

Twenty-four hr after training, a set of animals under each footshock and cortical stimulation condition was tested for retention performance (Ns=8/group). Animals were placed in the start compartment and were allowed to turn away from the door. The sliding door was opened and the latency to enter the shock compartment was noted. High latencies were interpreted as good retention performance.

Neurochemistry

Ten minutes after training, a set of animals in each group (Ns=8–15) was decapitated. The brains were rapidly removed and dissected into two portions (forebrain and brainstem) with a midcollicular cut vertical to the ventral brain surface. The cerebellum and olfactory bulbs were discarded.

The brain samples were immediately homogenized (Brinkman Polytron) in 5 ml of 0.1 N cold perchloric acid and centrifuged (Sorvall RC-3) at 12000 rpm for 10 min at 4°C. The supernatants were removed and stored. The pellets were resuspended and rehomogenized in another 5 ml 0.1 N perchloric acid. The samples were centrifuged as before and the supernatants were combined and stored at −20°C until assayed.

A radioenzymatic assay detailed elsewhere [30] was used to determine brain norepinephrine content. The assay utilizes adrenal PNMT and ^{3}H-S-adenosyl methionine to convert NE to labelled epinephrine. Fifty μl aliquots of the brain homogenates were placed in 15 ml conical centrifuge tubes and freshly prepared reaction mix (35 μl of 1 M Tris-HCl, pH=8.6, in 5 g/100 ml EDTA, 0.1 mM dithiothreitol, 5 μl (^{3}H) SAME (2.5 μCi, New England Nuclear) and 10 μl PNMT (Sigma) was added. Internal standard curves were determined in each run by adding known amounts of NE to the samples. The samples were incubated for 30 min at 37°C and the reaction was stopped by the addition of 2.0 ml of 0.5 M sodium phosphate, pH=10.0, containing 5 g/100 ml EDTA and 0.1 mM dithiothreitol. Alumina (180 mg) was added and the samples were vortexed and washed (4 times) with 3–5 ml H_2O. After the last wash, the ^{3}H-epinephrine was extracted by vortexing with 1.0 ml of cold 0.1 N perchloric acid. Fifty μl of freshly mixed 0.2 N acetic acid containing 25 μg epinephrine and 100 μl of a standard phosphotungstic acid solution were added. The samples were placed on ice for 5 min and then centrifuged (2500 rpm for 10 min). A 1 ml aliquot of the supernatant was then added to 15 ml tubes containing 1.0 ml of 1.0 M potassium phosphate (pH=9.15) and 10 ml of 1% (v:v) diethylhexylphosphoric acid—toluene. The tubes were capped, shaken vigorously for 5 min, and centrifuged (2500 rpm, 10 min) to separate phases. Nine ml of the clear organic phase was transferred to a plastic scintillation vial containing 400 μl of Liquifluor (New England

Nuclear). Samples were quantitated in a Beckman Model 3100 P liquid scintillation counter (wide ^3H window) and brain NE concentrations were calculated based on the NE standards.

RESULTS

Behavior and Electrophysiology

Retention latencies of the trained and stimulated groups were significantly lower than those of the trained unstimulated group ($ps<0.02$, Mann-Whitney U-test, two-tailed). All stimulated animals exhibited mild forelimb clonus; no animal had a tonic convulsion. The stimulated animals had brain seizures that fit one of the two general electrographic patterns shown in Fig. 2; 50% of the animals that received 2.5 mA stimulation and 70% of the animals that received 5 mA stimulation had secondary afterdischarges. However, the type of seizure pattern was not related to the degree of retention impairment.

Neurochemistry

Forebrain and brainstem NE concentrations under the six training and treatment conditions are shown in Fig. 3 and 4. The training footshock reliably reduced the forebrain NE concentration to 77% of the nonfootshocked control group ($p<0.02$, t-test, two-tailed). In the absence of footshock, 2.5 and 5.0 mA stimulation decreased brain NE content to 84% and 80% of the comparable non-stimulated group. Under the footshock condition, the stimulated groups had NE concentrations reduced to 82% and 81% of those of the non-stimulated footshock group ($p<0.1$, two-tailed t-tests, $p<0.05$ pooled stimulated vs non-stimulated animals) and to 69 and 67% of those of the nonfootshocked control group ($ps<0.01$). Thus, after either footshock or cortical stimulation, forebrain NE concentrations were reduced, whereas the combined effects of footshock and stimulation resulted in a further reduction in NE concentration.

As observed in the forebrain, brainstem NE concentrations were also reduced after footshock alone to 77% of control values ($p<0.02$). However, the remaining pattern of results obtained in the brainstem samples differed considerably from that of the forebrain. Frontal cortex stimulation in nonfootshocked groups did not significantly alter the brainstem NE concentrations ($ps<0.2$) but, when combined with footshock, frontal cortex stimulation attenuated the 77% NE decrease seen with footshock alone. Thus, footshock-stimulated groups did not evidence a significant change in brainstem NE values compared to untreated animals ($ps>0.2$). Moreover, the footshocked animals that received 2.5 mA cortical stimulation had brainstem NE concentrations that were significantly higher than those of the footshock alone group. The 5.0 mA stimulated animals also had NE concentrations higher than those of the footshock alone group but this increase did not reach statistical significance ($t=1.87$, $p<0.1$, two-tailed). Analysis of the data based on brain seizure pattern (Fig. 2) for individual rats indicated that, within each treatment group, the forebrain and brainstem NE concentrations did not vary with seizure pattern (i.e., primary afterdischarge vs primary+secondary afterdischarge).

DISCUSSION

The present study examined the effect of direct electrical stimulation of frontal cortex on retention of inhibitory (passive) avoidance training and on changes in brain NE concentrations. Consistent with the results of several previous studies [26], the cortical stimulation produced brain seizures and amnesia.

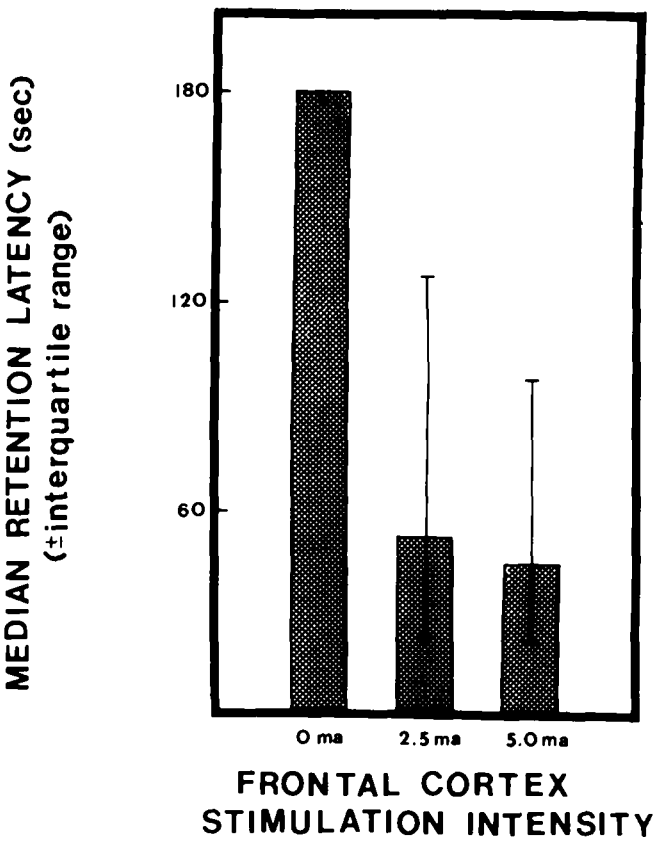

FIG. 1. Retention latencies of animals trained and tested in a one-trial inhibitory (passive) avoidance task. Note that posttrial electrical stimulation of frontal cortex impaired later retention performance.

In further agreement with previous reports the single training footshock produced approximately a 20% decrease in forebrain and brainstem NE concentration, a decrease that is directly related to the intensity of the footshock [23,24]. The findings of the earlier studies indicate that the decrease in NE concentration is transient; the brain NE content returns to control values over a 30–90 min period. Of particular relevance to the present experiment, the previous findings indicated that the extent of the posttraining decrease in NE concentration was correlated with later retention performance. A transient 20% decrease in brain NE content predicted good retention performance observed after a strong training footshock, such as that used in the present experiment, or after a weak footshock followed by an epinephrine injection that enhanced later retention performance. Smaller (0–5%; i.e., after low footshock training) or larger (30–40%; i.e., after high footshock followed by an amnestic epinephrine injection) decreases in NE concentration were seen under conditions that resulted in poor retention performance, i.e., low footshock.

The present study was designed to examine the effects of an amnestic agent, supraseizure frontal cortex stimulation,

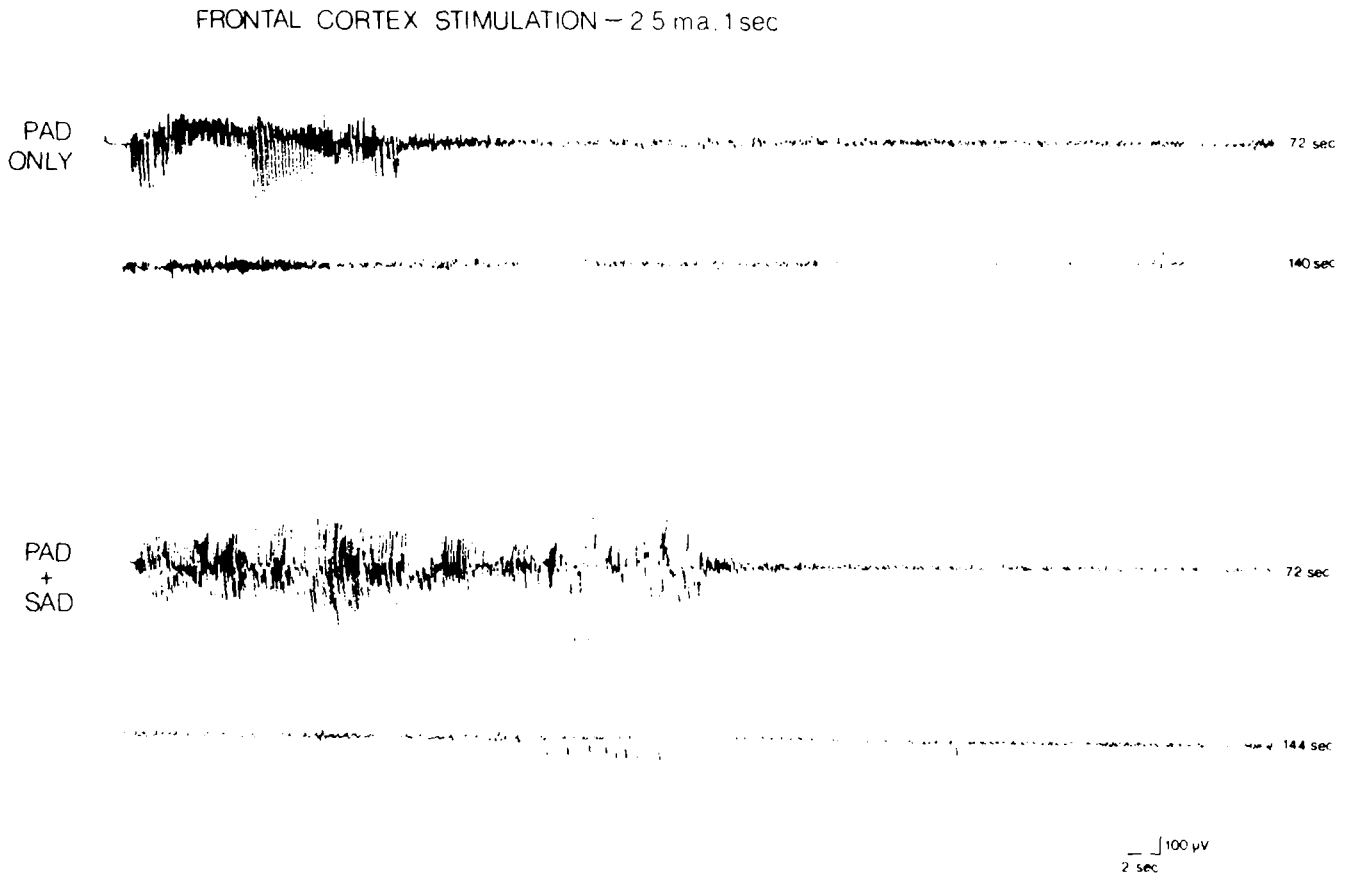

FIG. 2. Afterdischarges recorded between unilateral frontal and posterior cortical electrodes. The two electrographic seizure patterns, primary afterdischarge (PAD) or primary + secondary afterdischarge (PAD+SAD), occurred at each stimulation intensity and were not related to later memory impairment or to the extent of the effects on brain norepinephrine.

on brain NE concentrations in order to determine whether posttraining (+treatment) changes in brain NE content predicted later retention performance under these conditions as well. Our previous findings led us to believe that combined footshock and brain stimulation would have additive effects on NE levels; i.e., amnesic groups would show a decrease in brain NE concentrations that significantly exceeded that of trained but untreated groups. The results obtained with forebrain samples were generally consistent with this view. Frontal cortex stimulation or footshock alone resulted in an approximate 20% decrease in NE values. When footshock and stimulation were combined, forebrain NE concentration was further decreased to 30–40% below that of the untrained, nonstimulated group. In contrast, footshock reduced brainstem NE concentrations by 20% but cortical stimulation resulted in only a minor (nonsignificant) decrease. Moreover, the brainstem and forebrain differed considerably in that the combined effects of footshock and stimulation attenuated the 20% decrease in brainstem NE seen with footshock alone.

This is the first instance, after examination of several training-treatment conditions in which we found a dissociation between the percent change in NE concentrations in different brain regions. The different responses of the forebrain and brainstem may reflect the use of a treatment, frontal cortex stimulation, applied to a particular brain region in contrast to the use of peripherally administered epinephrine in previous reports [23,24]. Because adrenalectomy [5] as well as several peripherally administered adrenergic receptor antagonists may attenuate electroconvulsive shock and frontal cortex stimulation-produced amnesias [19], it seemed possible that the amnestic effects of convulsive agents might be mediated by a peripheral adrenergic response. However, the fact that there are regional differences in the NE response to frontal cortex stimulation, but not to peripheral epinephrine injections, suggests that the effects of frontal cortex stimulation on memory are not mediated by an adrenal epinephrine response. The results of a recently completed experiment add further support to this view: plasma epinephrine concentration is greatly elevated by footshock alone but frontal cortex stimulation does not significantly add to this response [13].

These findings thus indicate that after supraseizure electrical stimulation of some brain regions, changes in NE content are localized to particular brain regions. Such anatomically segregated effects may be important in analyzing amnestic, as well perhaps as antidepressant (cf. [9, 35, 36, 47]), effects of localized electroshock treatments. Although this anatomical differentiation of the NE response seems curious in light of the anatomical evidence for widespread distribution of individual locus coeruleus neurons (cf. [1]), the results are compatible with the possibility that nor-

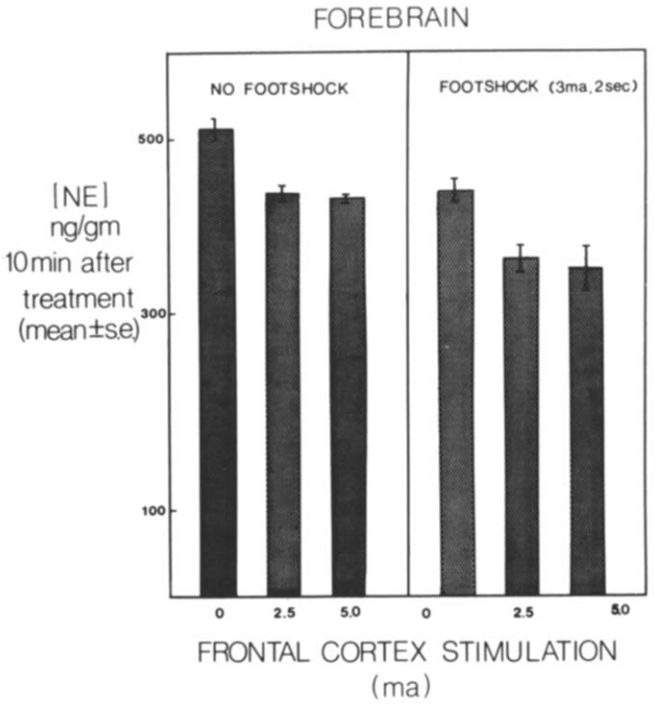

FIG. 3. Forebrain norepinephrine (NE) concentrations measured 10 min after training+treatment. Note that the training footshock or frontal cortex stimulation resulted in an approximately 20% decrease in NE content. The combined treatments resulted in a further reduction (30–35%) as compared to untreated control animals.

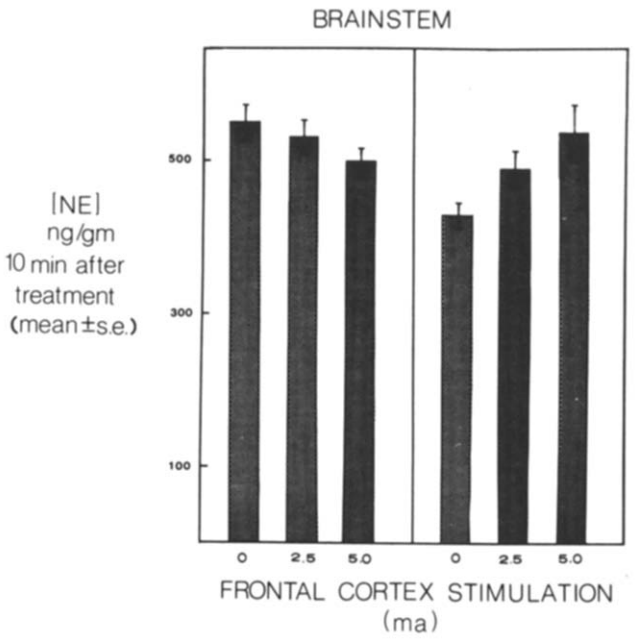

FIG. 4. Brainstem norepinephrine (NE) concentrations measured 10 min after training+treatment. Note that the training footshock resulted in a 23% reduction in NE content. Stimulation alone did not significantly alter brainstem NE concentrations. Furthermore, the combination of footshock+stimulation had no significant effect on braimstem NE content.

epinephrine release may, in some cases, be under local control [46].

In summary, the present results indicate that rats typically exhibit a 20% decrease in forebrain and brainstem NE concentrations after a training footshock. The findings further indicate that supraseizure frontal cortex stimulation, administered shortly after training, alters this brain response—potentiating the footshock-produced change in forebrain NE content and reducing the change in brainstem NE. Therefore, acute manipulations that impair normal memory storage processing may do so by altering the endogenous modulatory activity of certain brain systems, a noradrenergic system in this case. When taken together with previous findings, it appears that activity in the central noradrenergic system predicts later retention performance under a wide variety of training-treatment conditions. The present results add further support to the view that memory processing is sensitive to posttraining noradrenergic activity. In addition, posttraining noradrenergic activity may mediate the enhancing and impairing influences of many amnestic and memory-enhancing treatments.

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