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Involvement of α_1-adrenoceptors in the basolateral amygdala in modulation of memory storage

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Abstract

These experiments examined the involvement of α_1-adrenoceptors in the basolateral amygdala and their interaction with β-adrenoceptors in modulating memory storage. In Experiment 1, male Sprague–Dawley rats, implanted with bilateral cannulae in the basolateral amygdala, were trained in a one-trial inhibitory avoidance task and immediately after training, were given microinfusions (0.2 μl/side) of the selective α_1-adrenoceptor antagonist, prazosin (0.1–1.0 μg). Retention was tested 48 h later. Prazosin induced a dose-dependent impairment in retention performance. In Experiment 2, animals received post-training intra-basolateral amygdala infusions of phenylephrine (a non-selective α-adrenoceptor agonist; 1.0–10.0 μg) alone or in combination with yohimbine (a selective α_2-adrenoceptor antagonist; 0.2 μg) to examine the effects, on memory storage, of selective α_1-adrenoceptor activation. Low doses of phenylephrine alone tended to impair retention performance, whereas the highest dose was non-effective. In contrast, phenylephrine infused together with yohimbine induced a dose-dependent enhancement of retention performance, suggesting that a selective activation of α_1-adrenoceptors enhances memory formation. In Experiment 3, animals received intra-basolateral amygdala infusions of phenylephrine (1.0–10.0 μg) and yohimbine (0.2 μg) in combination with atenolol (a β_1-adrenoceptor antagonist; 1.0 μg). Atenolol blocked the memory-enhancing effects induced by infusions of phenylephrine together with yohimbine. Considered together, these findings suggest that α_1-adrenoceptors in the basolateral amygdala are implicated in mediating the effects of norepinephrine on memory storage and that their action depends on concurrent β-adrenoceptor activation.

Keywords: Noradrenergic system; Basolateral amygdala; Memory storage; α-Adrenoceptor; β-Adrenoceptor

1. Introduction

Extensive evidence indicates that stress hormones and neuromodulatory systems affect memory storage via an interaction with noradrenergic mechanisms in the amygdala (see McGaugh et al., 1996 for review). The memory-modulating effects of stress hormones or drugs affecting adrenergic, gamma-aminobutyric acid, opioid peptidergic and glucocorticoid systems are blocked by intra-amygdala infusions of β-adrenoceptor antagonists (Liang et al., 1986; McGaugh et al., 1988; Introini-Collison et al., 1989, 1995; Quirarte et al., 1997). Post-training intra-amygdala administration of norepinephrine or β-adrenoceptor agonists enhances inhibitory avoidance retention (Liang et al., 1986, 1995; Introini-Collison et al., 1989). Furthermore, post-training infusions of the β-adrenoceptor antagonist, propranolol, into the amygdala produce retention deficits that are attenuated by concurrent infusions of norepinephrine (Gallagher et al., 1977). Considered together, these findings suggest that noradrenergic effects on memory storage are mediated, at least in part, by an activation of β-adrenoceptor mechanisms in the amygdala.

Recent findings from our laboratory indicate that the memory-modulating effects of norepinephrine as well as other drugs are selectively mediated by the basolateral amygdala and not other amygdala nuclei (Parent and McGaugh, 1994; Roozendaal and McGaugh, 1996; Quirarte et al., 1997; Ferry and McGaugh, in press; Hatfield and McGaugh, in press). These behavioral findings are generally consistent with evidence indicating a high density of

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β-adrenoceptor subtypes within the amygdala (Alexander et al., 1975; Bylund and Snyder, 1976). However, the amygdala also contains α-adrenoceptors (U'Prichard et al., 1980; Unnerstal et al., 1984; Zilles et al., 1993). Like the β-adrenoceptor, the α_1-adrenoceptor subtype is located post-synaptically and activated by norepinephrine (see Hardman et al., 1996 for review). In contrast, α_2-adrenoceptors are predominantly located pre-synaptically and activation of these receptors inhibits the release of norepinephrine (Langer, 1974; Starke, 1979).

Studies examining the role of amygdaloid α-adrenoceptors in memory storage have not, as yet, yielded a consistent pattern of results. Post-training infusions of the non-selective α-adrenoceptor antagonist, phentolamine, into the amygdala were reported to induce dose-dependent enhancement of inhibitory avoidance retention (Gallagher and Kapp, 1981), whereas administration of the selective α_1-adrenoceptor antagonist, prazosin, did not induce significant effects (McGaugh et al., 1988), although the findings of Liang et al. (1995) showed a tendency towards impairment. The present study examined further the role of α_1-adrenoceptors in consolidation of memory for inhibitory avoidance training. A second objective of these experiments was to determine whether the basolateral amygdala is involved in mediating the effects induced by α-adrenergic manipulations. A first experiment examined the effects of immediate post-training intra-basolateral amygdala infusions of several doses of the selective α_1-adrenoceptor antagonist, prazosin, on memory for inhibitory avoidance training. A second experiment examined the effects on memory storage of selective activation of α_1-adrenoceptors in the basolateral amygdala. To our knowledge, no selective agonist for α_1-adrenoceptors is available. Thus, phenylephrine (a non-selective α-adrenoceptor agonist; Wikberg, 1973; Flavahan and McGrath, 1981; van Meel et al., 1981) was infused alone or together with the selective α_2-adrenoceptor antagonist, yohimbine.

Previous behavioral findings have suggested that the memory-modulating effects of norepinephrine may be mediated by an interaction between α- and β-adrenoceptors (Sternberg et al., 1986). This view is consistent with pharmacological evidence indicating that norepinephrine stimulates the formation of the second messenger cyclic adenosine 3′,5′-monophosphate (cAMP) via an interaction between both receptor types. Whereas β-adrenoceptors are coupled to the adenylate cyclase system and directly stimulate the formation of cAMP in the brain, α_1-adrenoceptors are not coupled directly to cAMP, but their activation potentiates the generation of cAMP by influencing β-adrenoceptor efficacy (Perkins and Moore, 1973; Schultz and Daly, 1973; Leblanc and Ciaranello, 1984; Johnston and Minneman, 1986; Pilc and Enna, 1986). Therefore, we examined in Experiment 3 whether the effects of α_1-adrenoceptor activation in the basolateral amygdala on memory storage depend on β-adrenoceptor activity. Rats received immediate post-training infusions of phenylephrine and yohimbine (resulting in a selective activation of α_1-adrenoceptors) together with the β-adrenoceptor antagonist, atenolol, into the basolateral amygdala.

2. Materials and methods

2.1. Animals

Male Sprague–Dawley rats ($n = 174$; 270–300 g at the time of surgery) from Charles River Laboratories were used. After arrival, they were housed individually in a temperature-controlled (22°C) colony room and maintained on a 12-h light period (light on at 0700 h) with free access to food and water. All experiments were carried out during the light phase of the cycle between 1000 and 1400 h. The numbers of animals in each group are shown in the figure legends.

2.2. Surgery

One week after arrival, the animals were anesthetized with sodium pentobarbital (50 mg/kg body weight, i.p.) and given atropine sulfate (0.4 mg/kg, i.p.) to suppress salivation. The skull was fixed in a flat position to a stereotaxic frame (Kopf Instruments, Tujunga, CA) and stainless steel guide cannulae (23 gauge, 15 mm long) were implanted bilaterally 2 mm dorsal to the basolateral amygdala (coordinates: anteroposterior, -2.8 mm from bregma; mediolateral, ± 5.0 mm from midline; dorsoventral, -6.7 mm from the skull surface) according to the atlas of Paxinos and Watson (1986). The cannulae and two anchoring screws were affixed to the skull with dental cement. Stylets (15-mm long 00 insect dissection pins) were inserted into each cannula to maintain patency and were removed only for the infusion of drugs. The rats were allowed to recover from surgery a minimum of 7 days before training was initiated.

2.3. Inhibitory avoidance apparatus and procedures

The inhibitory avoidance apparatus consisted of a trough-shaped alley (91 cm long, 15 cm deep, 20 cm wide at the top, 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 (McGaugh et al., 1988). The apparatus was located in a light- and sound-attenuated room.

The rat was placed in the starting compartment, with the door opened, and was allowed to enter the dark compartment. After the rat stepped completely into the dark compartment, the door was closed and a mild inescapable footshock with a duration of 1.0 s was administered. Animals showing entrance latencies longer than 30 s

were eliminated from the study. The footshock intensity was adjusted for each experiment (0.5 mA for Experiment 1; 0.4 mA for Experiments 2 and 3). The rat was removed from the dark alley 15 s after termination of the footshock, and immediately given bilateral microinfusions of adrenergic drugs into the basolateral amygdala. On the 48-h retention test trial, the rat was placed in the starting compartment, as in the training session, and the latency to reenter the dark compartment (maximum latency of 600 s) was recorded and used as the measure of retention. Shock was not administered on the retention test trial.

2.4. Drugs

For Experiment 1, prazosin (0.1, 0.3 or 1.0 μg; Sigma, St. Louis, MO), a selective α_1-adrenoceptor antagonist, was dissolved in 0.9% saline solution. Control animals received saline only. The doses of prazosin were selected on the basis of previous behavioral experiments (Liang et al., 1995).

For Experiment 2, L-phenylephrine, a non-selective α-adrenoceptor agonist and yohimbine, a selective α_2-adrenoceptor antagonist, were used. Both drugs were purchased from Sigma. Some animals received saline or increasing doses of phenylephrine (0.1, 1.0 or 10.0 μg), whereas other animals received increasing doses of phenylephrine (0.1, 1.0 or 10.0 μg) together with yohimbine (0.2 μg). The doses of the drugs were selected on the basis of previous behavioral experiments (McGaugh et al., 1988; Liang et al., 1995).

For Experiment 3, L-phenylephrine, yohimbine and atenolol (Sigma), a selective β_1-adrenoceptor antagonist, were dissolved in 0.9% saline. Animals received infusions of yohimbine (0.2 μg) and one of several doses of phenylephrine (0.1, 1.0 or 10.0 μg) in combination with atenolol (1.0 μg). The dose of atenolol was selected on the basis of previous behavioral experiments (Quirarte et al., 1997). Solutions of all drugs were prepared freshly before each experiment.

2.5. Infusion procedures

Bilateral immediate post-training infusions of adrenergic agonists and antagonists into the basolateral amygdala were administered through 30-gauge injection needles connected to a 10-μl Hamilton microsyringe by polyethylene tubing. The needles protruded 2 mm beyond the cannula tips to reach the basolateral amygdala. A 0.2-μl injection volume per side was infused for 23 s by an automated syringe pump (Sage Instruments, Boston, MA). To allow diffusion of the drug, the injection needles were retained within the cannulae for an additional 50 s after drug infusion. The infusion volume was based on our findings that selective neurotoxically induced lesions of the basolateral amygdala are produced with an infusion volume of 0.2 μl (Roozendaal and McGaugh, 1996). Furthermore, drug infusions of this volume into either the basolateral amygdala or the adjacent central amygdala induce differential effects on memory storage (Parent and McGaugh, 1994; Roozendaal and McGaugh, 1997a).

2.6. Histology

After completion of behavioral testing, the rats were anesthetized with an overdose of sodium pentobarbital (100 mg/kg, i.p.) and perfused intracardially with 0.9% saline (w/v) solution followed by 10% formaldehyde (v/v). At least 24 h before sectioning, the brains were placed in a 15% sucrose (w/v) solution for cryoprotection. Sections of 40 μm were made (using a freezing microtome) and stained with Cresyl violet. The sections were examined under a light microscope and determination of the location of injection needle tips in the basolateral amygdala was made according to the standardized atlas plates of Paxinos and Watson (1986).

2.7. Statistics

The retention test latencies of Experiment 1 were analyzed with a one-way analysis of variance (ANOVA) with dose of prazosin (four levels) as between-subject variable. Mean retention latencies of Experiment 2 were analyzed with a two-way ANOVA with dose of phenylephrine (four levels) and yohimbine (two levels) both as between-subject variables. For statistical analysis of Experiment 3, mean retention latencies were compared with the retention latencies obtained in the phenylephrine and yohimbine group of Experiment 2 using a two-way ANOVA with dose of phenylephrine (four levels) and atenolol (two levels) both as between-subject variables. Post-hoc comparisons for all experiments were performed with Fisher's tests. A probability level of < 0.05 was accepted as statistically significant.

3. Results

3.1. Experiment 1: effects of basolateral amygdala α_1-adrenoceptor blockade

Histological examination revealed that 34 rats had correct cannulae placements in the basolateral amygdala (the data of four animals with placements outside the basolateral amygdala were excluded from the analyses). A representative cannula placement in the basolateral amygdala is shown in Fig. 1.

The retention test latencies are shown in Fig. 2. A one-way ANOVA revealed a significant effect of prazosin [$F(3,30) = 21.99$; $P < 0.001$]. The mean ($\pm$S.E.M.) retention latency of the saline control group was 484.8 ± 36.5 s, indicating that the footshock induced strong retention of the inhibitory avoidance training. Between-group compar-

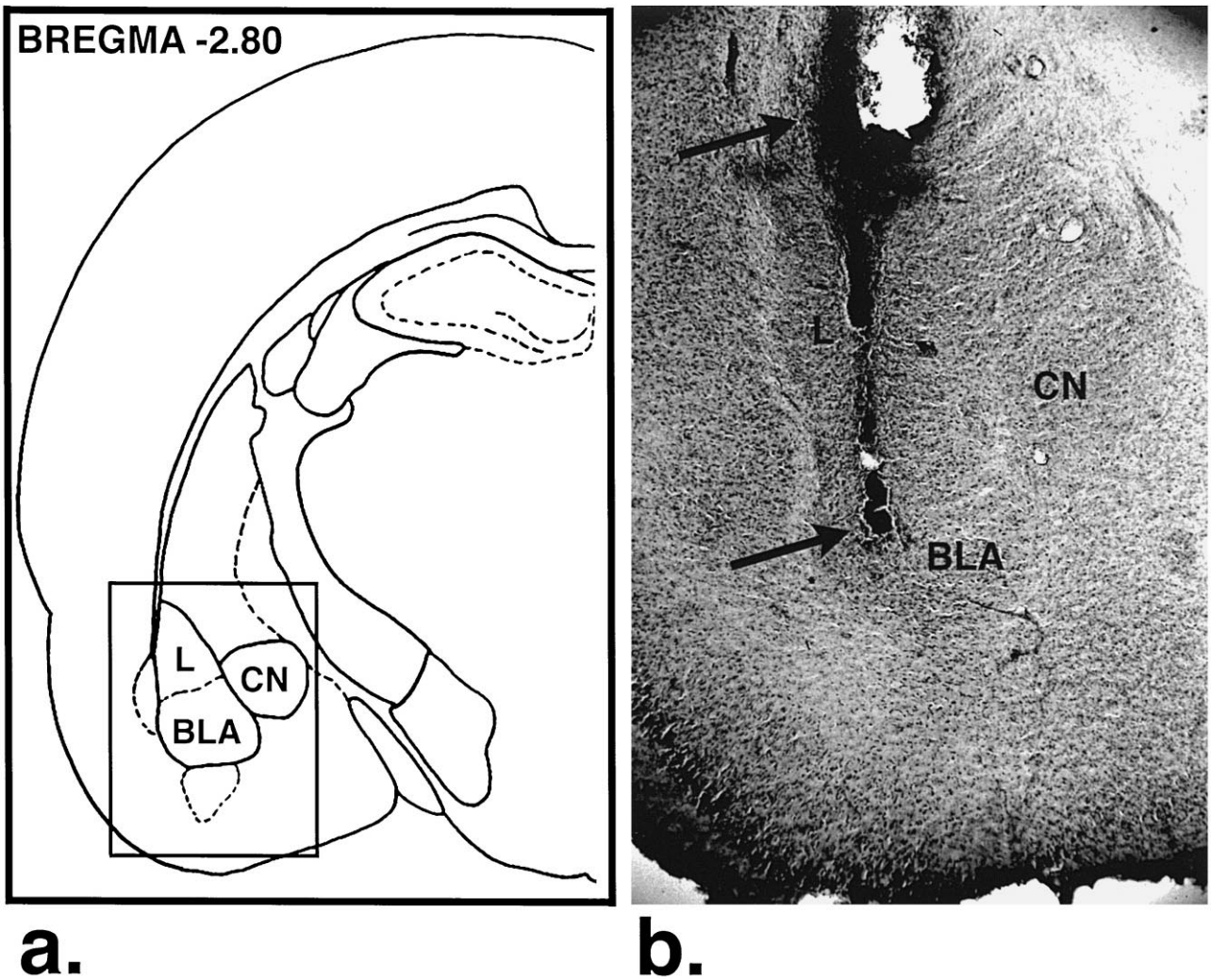

Fig. 1. (a) Schematic representation of the amygdaloid complex. The solid lines indicate the position of the photomicrograph (b) representing the cannula (upper arrow) and the injection tip (lower arrow) placement. BLA: basolateral nucleus of the amygdala; CN: central nucleus of the amygdala; L: lateral nucleus of the amygdala.

isons indicated that all three prazosin groups had significantly shorter latencies than those of the controls (all, $P < 0.001$). Moreover, the animals infused with the highest dose of prazosin (1.0 μg) showed significantly shorter retention latencies than those infused with either the 0.1 or 0.3 μg doses of prazosin (both, $P < 0.05$).

3.2. Experiment 2: effects of basolateral amygdala α_1-adrenoceptor activation

Histological examination revealed that 79 rats had correct cannulae placements in the basolateral amygdala. Fifteen animals that had placements outside the basolateral amygdala were not included in the analyses.

The retention test latencies are shown in Fig. 3. Two-way ANOVA revealed significant phenylephrine [$F(3,71) = 5.93$; $P < 0.01$] and yohimbine effects [$F(1,71) = 27.65$; $P < 0.001$] as well as a significant interaction between these two factors [$F(3,71) = 4.74$; $P < 0.01$]. The mean (±S.E.M.) retention latencies of the control groups infused with either saline (113.6 ± 19.9 s) or yohimbine (146.8 ± 12.7 s) did not differ significantly ($P = 0.16$). Phenylephrine alone did not significantly affect retention performance. However, infusion of the two lower doses of phenylephrine (0.1 and 1.0 μg) tended to impair retention ($P = 0.07$; $P = 0.08$, respectively). Phenylephrine infused together with the α_2-adrenoceptor antagonist, yohimbine (thus resulting in a selective activation of α_1-adrenoceptors), induced a dose-dependent enhancement of retention latencies. Post-hoc comparisons revealed a significant enhancement of the two higher doses of phenylephrine (1.0 and 10.0 μg) as compared to their corresponding controls ($P < 0.01$; $P < 0.001$, respectively). Moreover, yohimbine significantly reversed the tendency of the two lower doses of phenylephrine to impair retention ($P < 0.01$; $P < 0.001$, respectively).

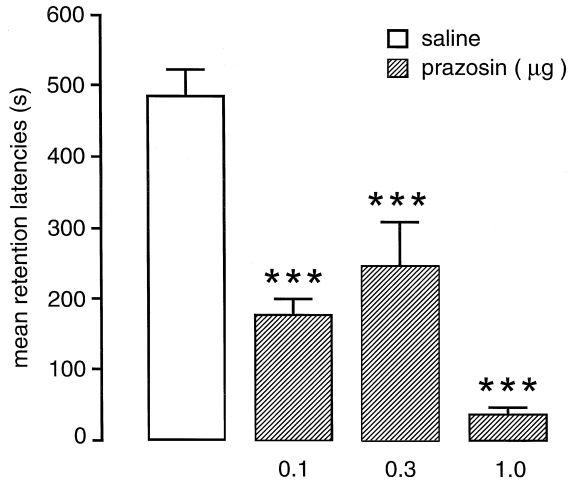

Fig. 2. The effects of immediate post-training infusions of various doses of prazosin (a selective α_1-adrenoceptor antagonist) into the basolateral amygdala on the mean latency (±S.E.M.) to enter the dark compartment on the retention test (***$P < 0.001$ as compared with vehicle-injected group) ($n = 7–9$/group).

3.3. Experiment 3: effects of concurrent activation of α_1-adrenoceptors and blockade of β-adrenoceptors in the basolateral amygdala

Histological examination revealed that 36 rats had correct cannulae placement in the basolateral amygdala. Four animals that had placements outside the basolateral amygdala were discarded from the analysis. The retention test latencies are shown in Fig. 4. In order to depict the effects of β-adrenoceptor blockade on the memory enhancement induced by α_1-adrenoceptor activation, the results obtained

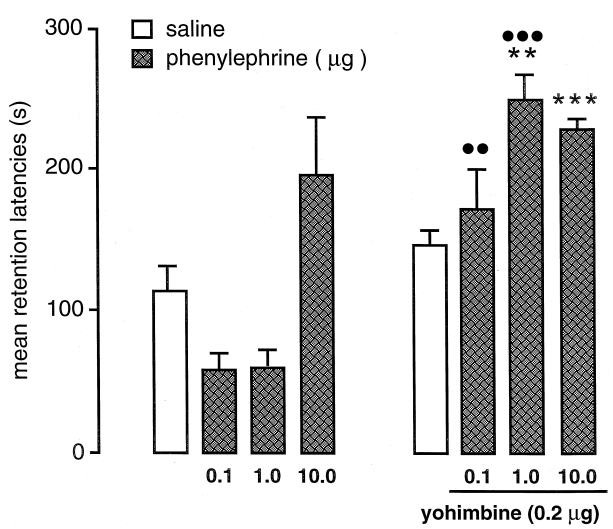

Fig. 3. The effects of immediate post-training infusions of various adrenergic agents into the basolateral amygdala on the mean latency (±S.E.M.) to enter the dark compartment on the retention test. Phenylephrine (an α-adrenoceptor agonist) was injected alone, or in combination with 0.2 μg of yohimbine (a selective α_2-adrenoceptor antagonist) (**$P < 0.01$, ***$P < 0.001$ as compared with each corresponding control group; •• $P < 0.01$, ••• $P < 0.001$ as compared with the corresponding groups injected with phenylephrine alone) ($n = 8–12$/group).

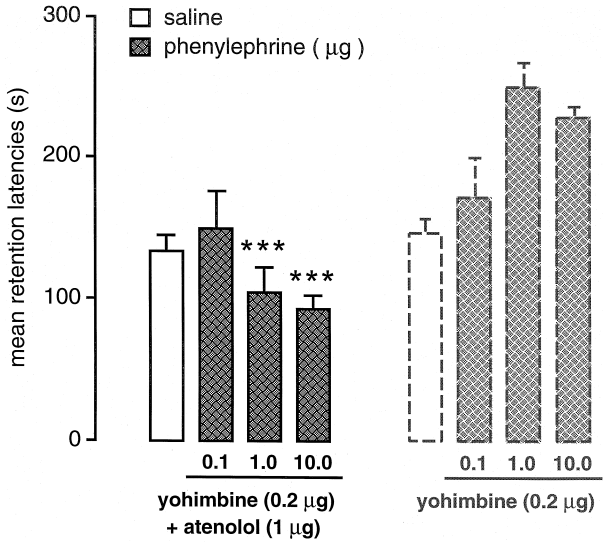

Fig. 4. The effects of immediate post-training infusions of various doses of phenylephrine together with 0.2 μg of yohimbine and 1.0 μg of atenolol (a β-adrenoceptor antagonist) into the basolateral amygdala on the mean latency (±S.E.M.) to enter the dark compartment on the retention test. The dotted graph represents the results obtained in Experiment 2 (***$P < 0.001$ as compared with the corresponding groups injected with phenylephrine and yohimbine in Experiment 2) ($n = 8–10$/group).

in the group infused with phenylephrine and yohimbine (Experiment 2) are shown on the right of this figure (in dashed lines for the bars). A two-way ANOVA revealed no phenylephrine effect [$F(3,66) = 1.218$; n.s.], but a significant atenolol effect [$F(1,66) = 29.13$; $P < 0.001$] and a significant interaction between these two factors [$F(3,66) = 6.72$; $P < 0.01$]. Atenolol blocked the enhancing effects induced by a selective activation of α_1-adrenoceptors (i.e., induced by infusion of phenylephrine and yohimbine) on retention performance observed in Experiment 2 (both, $P < 0.01$). Post-hoc comparisons showed that in animals given atenolol, phenylephrine and yohimbine did not increase retention latencies.

4. Discussion

The findings of these experiments support the hypothesis that post-synaptic α_1-adrenoceptors in the basolateral amygdala are involved in modulating memory for inhibitory avoidance training. Immediate post-training inactivation of α_1-adrenoceptors with prazosin impaired later retention performance (Experiment 1), whereas an activation of these receptors enhanced retention (Experiment 2). These findings are consistent with those implicating the α-component of the amygdala adrenoceptor system in regulating memory storage. Liang et al. (1995) reported that a selective blockade of α_1-adrenoceptors in the amygdala tended to impair inhibitory avoidance retention. The failure to reach significance in that study may have been due to the small number of animals used and, perhaps,

because the manipulations were directed to the whole amygdala rather than selectively to the basolateral amygdala. Other studies reported that α-adrenoceptor manipulation in the amygdala influenced the memory-modulating effects induced by norepinephrine (Gallagher and Kapp, 1981). Norepinephrine is released in the amygdala by stressful or arousing stimulation of the kind used in inhibitory avoidance training (Galvez et al., 1996; Quirarte et al., 1998) and is hypothesized to be a critical component of the endogenous mechanism mediating the enhancing influences of emotional arousal on memory consolidation (McGaugh et al., 1996). Our findings are consistent with the view that amygdaloid α-adrenoceptors are involved in modulating retention of the inhibitory avoidance task, and also suggest that these receptors participate in mediating the effects of training-induced or experimentally administered norepinephrine on memory storage. Moreover, although the present findings do not exclude the possibility that amygdaloid nuclei other than the basolateral amygdala may be involved in mediating α-adrenergic effects on memory storage, they are consistent with previous findings indicating a selective involvement of the basolateral amygdala in adrenergic influences on memory storage (Roozendaal and McGaugh, 1996, 1997a; Quirarte et al., 1997).

Activation of α-adrenoceptors with the non-selective agonist, phenylephrine, induced a complex pattern of effects. Although none of the doses induced significant effects, low doses of phenylephrine tended to impair whereas the highest dose did not show this tendency. These results are in accordance to the lack of significant effect induced by post-training infusion of phenylephrine into the amygdala (Liang et al., 1995). Despite the fact that phenylephrine has been described as a selective α_1-adrenoceptor agonist (Hardman et al., 1996), there is evidence that phenylephrine also stimulates pre-junctional α_2-adrenoceptors (Wikberg, 1973; Flavahan and McGrath, 1981; van Meel et al., 1981). Therefore, the complex dose–response effects of phenylephrine are likely due to a combined activation of α_1- and α_2-adrenoceptors, which may have opposite effects on memory storage. Anatomical findings have reported a higher density of α_2-adrenoceptors as compared to α_1-adrenoceptors in the amygdala (Unnerstal et al., 1984; Zilles et al., 1993). Additionally, activation of pre-synaptic α_2-adrenoceptors blocks norepinephrine release (Langer, 1974; Starke, 1979). Such findings suggest that lower doses of phenylephrine predominantly activate α_2-adrenoceptors, resulting in retention impairment, whereas at higher doses, phenylephrine also activates α_1-adrenoceptors, counterbalancing the α_2-adrenergic inhibitory effect on retention. Coactivation of α_2-adrenoceptors by phenylephrine is supported by our finding that a blockade of these receptors with yohimbine significantly enhanced retention performance. Such impairing effects of α_2-adrenoceptor activation on memory storage are also consistent with previous findings indicating that intra-amygdala infusions of the non-selective α-adrenoceptor antagonist, phentolamine, enhance memory when administered in low doses (probably by acting on α_2-adrenoceptors), whereas this enhancing effect was not seen at higher doses (probably by acting on both α_2- and α_1-adrenoceptors) (Gallagher and Kapp, 1981).

The second major finding of this study is that post-synaptic α_1-adrenoceptors interact with β-adrenoceptors in regulating memory storage. The results of Experiment 3 show that inactivating β-adrenoceptors in the basolateral amygdala with atenolol blocked the memory-enhancing effects of α_1-adrenoceptor activation. Such a functional interaction between both receptor types has been suggested only indirectly in previous behavioral studies. For example, Sternberg et al. (1986) reported that pre-training systemic injections of phentolamine (a non-selective α-adrenoceptor antagonist) blocked the memory-enhancing effect of systemically administered epinephrine. More interestingly, the dose of phentolamine that blocked the adrenoceptors did not affect retention performance by itself, suggesting that the effects of norepinephrine on memory storage are mediated by an interaction between α- and β-adrenoceptors. Our findings are consistent with extensive evidence from pharmacological studies indicating that α_1- and β-adrenoceptors interact in regulating noradrenergic signal transduction. As noted above, norepinephrine stimulates the formation of the second messenger cAMP in the rat brain via an activation of both β- and α_1-adrenoceptors. Whereas β-adrenoceptors are known to be coupled directly to adenylate cyclase to stimulate cAMP production, α_1-adrenoceptors are not coupled to this enzyme but act indirectly by potentiating the response of β-adrenergic activation (Perkins and Moore, 1973; Daly et al., 1981; Leblanc and Ciaranello, 1984; Johnston and Minneman, 1986; Pilc and Enna, 1986). Interestingly, the memory-enhancing effects of the opioid peptidergic antagonist, naloxone (among other drugs), are blocked by administration of β-adrenoceptor, but not α-adrenoceptor, antagonists in the amygdala (McGaugh et al., 1988). Such findings are consistent with the view that β-adrenoceptor is the primary noradrenergic receptor involved in modulating memory storage and that α-adrenoceptor manipulation merely acts by modulating β-adrenergic activity.

The basolateral amygdala is not likely to be the locus of neural changes underlying long-term memory, but may regulate memory consolidation processes occurring in other brain regions through the activation of its noradrenergic system. Lesions of the stria terminalis, a major afferent/efferent amygdala pathway, block the memory enhancement of post-training systemic injections of the adrenergic agonist, clenbuterol, as well as post-training intra-amygdala infusions of norepinephrine (Liang et al., 1990; Introini-Collison et al., 1991). Recent findings indicate that the noradrenergic system of the basolateral amygdala plays a role in enabling the processing of hippocampal-dependent memory consolidation (Roozendaal and McGaugh, 1997b;

Roozendaal et al., 1998) as well as hippocampal synaptic plasticity (Ikegaya et al., 1997). Although the pathway(s) through which the basolateral amygdala affects hippocampal memory and neuroplasticity are not known, some anatomical and behavioral evidence support the view that the basolateral amygdala–nucleus accumbens pathway may mediate basolateral amygdala influences on memory involving the hippocampus (O'Donnell and Grace, 1995; Setlow et al., 1998).

In summary, these findings have provided some new insights into the involvement of adrenergic mechanisms in the basolateral amygdala in mediating norepinephrine effects on memory storage. The present findings suggest that adrenergic influences on memory consolidation are mediated by an interaction between β- and α_1-adrenoceptor activation.

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