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Chapter 8

Role of Norepinephrine in Modulating Inhibitory Avoidance Memory Storage: Critical Involvement of the Basolateral Amygdala

Barbara Ferry and Gina L. Quirarte

Additional information is available at the end of the chapter

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1. Introduction

The relationship between noradrenergic function, stress, and memory has long been a subject of interest. What is normally adaptive during situations of extreme physical threat, including increases in heart rate and blood pressure, increased vigilance, hyperarousal, exaggerated startle, and enhancement of memory storage are considered to be part of a response elicited in a stressful situation [1]. Indeed, emotionally arousing experiences tend to be well remembered, and studies over the past five decades have provided considerable evidence suggesting that hormones released by stressful emotional experiences play an important role in mediating the effects of emotional arousal on lasting memory. One of the brain regions involved in the stress response is the amygdala, and neuromodulatory influences occurring selectively within this structure have been widely shown to regulate memory consolidation of newly acquired information through its projections to other brain structures. This review will focus on evidence from research findings investigating the relationship between stress-elicited noradrenergic brain activation and the role of the amygdala in mediating the effects of norepinephrine (NE) on memory consolidation. Furthermore, our findings suggest that this noradrenergic activation of the amygdala or, more precisely, of the basolateral nucleus of the amygdala, serves to modulate memory storage in other brain regions.

2. Adrenergic catecholamines and stress

The locus coeruleus (LC) noradrenergic system plays an important role in the fear response and anxiety. Other brain systems are also involved in the fear response and anxiety; these

include the corticotrophin-releasing factor hypothalamic-pituitary-adrenal axis system and the benzodiazepine, dopamine, opiate, and serotonergic systems. These neuropeptide and neurotransmitter systems function in a coordinated manner with NE, as reviewed elsewhere [2-4].

Diverse adaptive behavioral responses are evoked by acute exposure to a variety of stressful events. In coordination with neuroendocrine and autonomic responses induced by such events, behavioral adaptations serve to maintain homeostasis and, by enabling optimal functioning, ensure survival in the face of threat. In addition to the primary neural circuits mediating contextually specific responses, acute stress also activates other brain systems that play a modulatory role, serving to bring together the complex response of the organism to any stress. Of the systems modulated by stress, the brain noradrenergic system has been shown to be one of the most important.

The noradrenergic system originates in a relatively small number of cells located in the LC and in other cell groups in the medulla and pons that utilize NE as a neurotransmitter. Nonetheless, the extensive network of noradrenergic terminals projecting from these few cells innervates essentially the entire neural axis. This widespread and divergent anatomical organization allows this system to influence the activity of the entire nervous system under conditions of elevated noradrenergic release during stress.

Activation of the noradrenergic system alters the ''signal to noise ratio'' of responses evoked by other afferents (both excitatory and inhibitory), rather than inducing simple inhibition or excitation, thus enhancing synaptic transmission in target circuits [5]. Such modulatory effects of NE have been described in many brain circuits and have been shown to be mediated, via different transduction mechanisms, by both β and α-adrenergic receptors [6-9]. Given the anatomical organization of the central noradrenergic system, it is suggested that stimuli that activate the small population of hindbrain noradrenergic neurons result in the release of NE in many widespread target regions throughout the brain, altering the reactivity of many neural circuits mediating a variety of behavioral and physiological responses. Furthermore, the anatomical organization and potential modulatory effects of the NE system suggest that it may facilitate a number of responses evoked by other afferents. As a consequence, the observed effects of increased noradrenergic release in a particular structure will depend on the set of specific neural circuits recruited and the set of specific behavioral responses elicited by the stressful stimulus which provoked the increase in NE release.

Noradrenergic neurons are activated by specific sensory stimuli of several modalities [10, 11], suggesting that information from the external, as well as the internal, environment is transduced by a variety of sensory systems before gaining access to the noradrenergic system. Moreover, some data suggest that the strength of a stimulus in a particular context is an important factor in determining the noradrenergic response [11-13]. Both electrophysiological and neurochemical studies (i.e., in vivo microdialysis) have shown that the brain noradrenergic system is phasically and robustly activated by a diverse array of acutely stressful stimuli [14-21].

3. Adrenergic catecholamines and memory storage

Strong memories are often based on experiences that were emotionally arousing [22]. There is a large body of evidence suggesting that stress hormones released by emotional experiences play an important role in mediating the effects of emotional arousal on lasting memory. There is now extensive evidence supporting the hypothesis that the strength of long-term memories is influenced by hormonal systems activated by experience [23, 24], i.e., memory formation may involve stress-released hormones as endogenous modulators of the neurobiological processes underlying memory consolidation.

Gold and van Buskirk [25] were the first to suggest the involvement of central NE in memory. Their study showed that inhibitory avoidance (IA) training increases brain NE levels under conditions that result in good retention, suggesting an enhanced release of this neuromodulator during training. In support of this view, Haycock et al. [26] showed that intraventricular infusion of NE facilitates retention, providing further evidence for the view that central NE function modulates memory. Other studies, e.g., those of Jensen et al. [27], reported that intracerebroventricular administration of diethyldithiocarbamate (DDC), a drug that decreases central catecholamine levels, impairs IA retention when administered post-training. Furthermore, concurrent infusion of NE into the ventricles or systemic injection of NE or epinephrine blocks the retention impairment produced by peripheral administration of DDC [28-30].

Further evidence suggesting that peripherally released catecholamines may influence memory consolidation came from experiments using amphetamines. Amphetamine is known to influence the release of catecholamines from peripheral storage sites [31]. Numerous studies [e.g. 32-34] have shown that amphetamine enhances memory when administered systemically either shortly before, or shortly after training. Enhancing effects of amphetamine have been observed in a variety of tasks, such as IA, active avoidance, discriminated avoidance, and appetitive discrimination [34-36]. Moreover, the fact that amphetamine enhances memory when administered post-training supports the view that it enhances retention by influencing memory storage processes. Since amphetamine crosses the blood-brain barrier, other studies have examined whether its memory-modulating effects involve influences on peripheral or central catecholamines. Post-training systemic injection of 4-OH amphetamine (an amphetamine derivative that does not cross the blood-brain barrier) was also found to enhance IA retention, whereas central injection of amphetamine was ineffective. The effects of systemic injection of amphetamine and 4-OH amphetamine do not seem to involve peripheral sympathetic neurons, the primary source of peripheral NE, as sympathetic denervation induced by 6-hydroxydopamine hydrobromide induced 24 hours before training does not attenuate the memory-enhancing effects of either drug. In contrast, adrenal demedullation, i.e., elimination of peripheral epinephrine, blocks the effects of both amphetamine and 4-OH amphetamine on memory for active avoidance and IA training [37].

More recently, Williams et al. [38] showed that the memory-enhancing effects of systemic injection of 4-OH amphetamine are blocked by the peripherally acting β-adrenoceptor

antagonist sotalol. These findings provide strong support for the view that amphetamine influences memory storage, at least in part, through effects involving the release of peripheral epinephrine from the adrenal medulla.

Systemic administration of epinephrine also enhances retention in different tasks, including IA [39], multitrial avoidance [40], a one-trial appetitive task [41], and an aversively motivated discrimination task [42]. Epinephrine is effective when given immediately after training; moderate doses produce the greatest enhancement, larger doses being less effective or even impairing retention, and the doses of epinephrine found to enhance retention produce plasma epinephrine levels comparable to those found after IA training [43].

Retention enhancement induced by epinephrine is blocked by injection of the β-adrenoceptor antagonist propranolol, a drug that readily enters the brain [41] as well as by sotalol, a β-adrenoceptor antagonist that does not enter the brain [44]. Post-training administration of β-adrenoceptor agonists that enter the brain, including dipivefrin and clenbuterol, also enhances memory consolidation, and the memory enhancement induced by dipivefrin and clenbuterol is blocked by propranolol, but not by sotalol [44]. Moreover, the memory-enhancing effect of clenbuterol is selectively blocked by centrally, but not peripherally, acting β-adrenoceptor antagonists [45]. Although the use of systemic nonspecific antiadrenergic agents has clearly implicated NE in learning and memory, the results obtained by Introini-Collison and Baratti [45] indicate that the effects of epinephrine on memory storage are initiated by activation of peripheral β-adrenoceptors, but also involve activation of β-adrenoceptors in the brain.

4. Route of stress-induced brain activation: from the LC to higher brain structures

As epinephrine does not readily cross the blood–brain barrier [46], its effects on memory consolidation appear to be initiated, at least in part, by activation of β-adrenoceptors in the periphery. This conclusion is supported by the finding that sotalol, a β-adrenoceptor antagonist that does not readily enter the brain, blocks the enhancing effects of peripherally administered epinephrine on memory [44].

A large number of studies have suggested that the effects of epinephrine on memory are most likely mediated by activation of β-adrenoceptors located on vagal afferents. For example, anatomical data have provided evidence that the dorsal and ventral branches of the vagus nerve innervate the adrenal gland [47]. In another study, Niijima [48] showed that electrical stimulation of the adrenal nerve evokes action potentials in the vagus nerve. More recently, Miyashita and Williams [49], using electrophysiological recordings of vagus nerve activity, showed that systemically administered epinephrine produces a significant increase in vagal nerve firing that is blocked by concurrent administration of the β-adrenoceptor antagonist sotalol. These data clearly show that the effects of epinephrine on the brain are mediated, at least in part, by the activation of ascending fibers of the vagus nerve and that these effects of epinephrine on vagal neural discharge are mediated through influences on peripheral β-adrenergic receptors.

Information regarding somatosensory activity, including that induced by footshock, is transmitted by ascending vagal fibers to the nucleus of the solitary tract (NTS), a brainstem structure with a high population of noradrenergic neurons [50-52]. In response to vagal nerve activation, NTS neurons influence central noradrenergic activity through direct synapses on neurons in the LC. Vagal afferents send noradrenergic projections directly and indirectly via the LC to forebrain regions [53-55], including the amygdala [56, 57]. Moreover, the finding that intra-NTS infusion of the β-adrenoceptor antagonist propranolol [58] or inactivation of the NTS with lidocaine [59] prevents epinephrine enhancement of memory provides evidence that the NTS is part of a brain stem system that, together with the LC, enables epinephrine-induced memory enhancement. Taken together, these data suggest that central noradrenergic neurons arising in the NTS mediate the effects of peripheral physiological influences on memory consolidation. This implication is supported by evidence that post-training infusion of the local anesthetic lidocaine into the NTS impairs IA retention [59]. Moreover, injection of lidocaine into the NTS blocks the memory-enhancing effects of systemic post-training injection of epinephrine [55]. Thus, the NTS appears to be an interface between peripheral adrenergic activation and brain processes regulating memory consolidation.

5. The noradrenergic system of the amygdala is involved in modulating memory storage

The amygdala is principally responsible for fear and anxiety responses to threatening environmental stimuli, including the increase in activity of the sympathetic nervous system in response to threat [60-62]. The LC densely innervates the amygdala [63, 64] and, in particular, projects to the central and basal nuclei [65-68].

Activation of the LC by electrical stimulation or administration of drugs (e.g. yohimbine) results in increased anxiety [69-72], probably as a result of the potentiation of this excitatory pathway from the LC to the amygdala. In addition to a role in anxiety, the LC projection to the amygdala may also play a role in forming and retrieving emotional memories [73, 74]. Interestingly, level of arousal, which is highly correlated with LC activity, determines the likelihood of a memory being encoded and subsequently retrieved.

Moreover, microdialysis data have shown that acute stressful immobilization induces increased NE release in the stria terminalis [15, 78], an important amygdala NE afferent, and in the medial and central nuclei of the amygdala [75-77].

Although the first evidence suggesting the involvement of the amygdala in learning and memory was published over 65 years ago [79], it is only in recent years that the amygdala has become a central focus of inquiry in studies of learning and memory. There is now extensive evidence suggesting that it is involved in the effects of attentional and reward processes [80-82] and that it may be a locus of the neural changes underlying the acquired association of cues with emotional responses, especially the somatosensitive responses elicited by fearful stimuli [83-85]. In addition, there is a strong consensus that it is involved in mediating the effects of emotional arousal on memory.

Extensive evidence indicates that the effects of peripheral epinephrine on memory are mediated by influences involving noradrenergic activation of the amygdala. For example, post-training intra-amygdala infusion of the β-adrenoceptor antagonist propranolol blocks the memory-enhancing effects of systemically administered epinephrine [86, 87] and the retention deficits induced by post-training infusion of propranolol into the amygdala are attenuated by concurrent infusion of NE [88]. Additionally, post-training infusion of NE or the β-adrenoceptor agonist clenbuterol into the amygdala induces a dose-dependent enhancement of retention [89-91] and attenuates retention deficits induced by adrenal demedullation [87]. Together, these findings strongly suggest that the amygdala mediates the effects of epinephrine on memory storage and that the effects involve activation of β-adrenergic mechanisms.

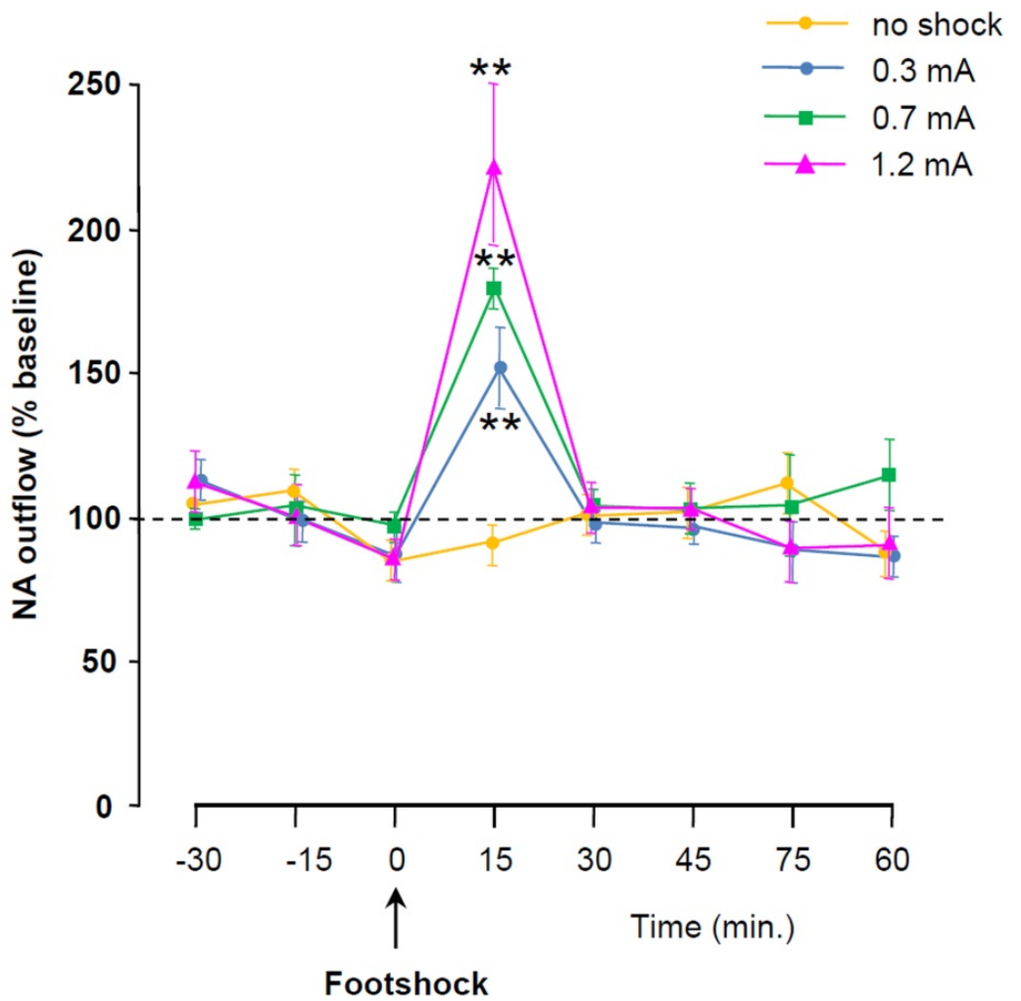

Figure 1. Effect of low- and high-intensity footshock on NE release in the amygdala assessed by in vivo microdialysis and HPLC. The data are shown as the mean (±SEM) NE levels expressed as a percentage of basal levels before footshock. **, $p < 0.01$ as compared to the no footshock group [94].

Studies using *in vivo* microdialysis and high performance liquid chromatography support these findings. The figure 1 illustrates one of the results we obtained in an experiment where a significant increase in NE levels was measured in the dialysis sample collected after

exposure to footshocks of variable intensities. Other findings in our laboratory have shown that training conditions that evoke emotional arousal (e.g. footshock stimulation) or direct injection of epinephrine or corticosterone in doses that facilitate memory significantly increases NE release in the amygdala and this effect is directly related to the stimulus intensity [92-96].

Interestingly, it has been shown that the relative severity of the stressor and its physiologic impact can vary between individuals [93]. Thus, the severity of stress produced by a stimulus, whether physiologic or psychogenic, has typically been defined in terms of the magnitude of the physiological response it elicits, e.g., by measuring activation of the hormonal hypothalamic–pituitary–adrenal (HPA) stress axis or of the peripheral sympathoadrenal autonomic response system. Whereas the brief bursts of electrical activity elicited by distinct, innocuous stimuli occur over a period of 100's of milliseconds, phasic activation of noradrenergic neurotransmission by acutely stressful stimuli is much longer lasting, of the order of seconds to minutes or hours, depending on the stimulus, often outlasting the duration of the stimulus itself, and correlates temporally with peripheral physiological indicators of the stress response [77, 97].

For example, McIntyre et al. [98] examined NE release induced by IA training and, as expected on the basis of our previous studies of the effects of footshock stimulation [92, 94], found that NE levels were increased following training. However, in their study, perhaps somewhat surprisingly, the duration of the increased NE levels was greater than that previously found with footshock stimulation given without IA training [92, 94, 99]. Their findings suggest that the combination of footshock and the novel contextual information provided by training may have increased amygdala noradrenergic activation. Additionally, they showed that the extent of the increase in amygdala NE levels after training predicted the 24-h retention performance, as animals with a larger increase in NE release after training had longer retention latencies than those with smaller increases. These findings, taken together with those of studies of drug effects on NE levels, provide strong support for the hypothesis that NE release in the amygdala may play a critical role in modulating memory consolidation [100].

Studies using *in vivo* electrophysiological recordings in the cat also demonstrated that delivery of a footshock during IA training significantly increases the firing rate of lateral/basolateral amygdala neurons for 2 h following training [101]. These findings fit well with evidence that memory-modulating drugs can be effective when infused into the amygdala within hours after training [102]. Furthermore, NE release in the amygdala is potentiated by peripheral injection of epinehrine, the opiate antagonist naloxone, or amphetamine [94, 96, 103], findings consistent with evidence that intra-amygdala infusion of β-adrenoceptor antagonists blocks the effect of naloxone on memory storage [104, 105] and that opiate agonists inhibit the release of NE in other brain regions [106]. Moreover, the finding that inactivation of the NTS blocks the effects of systemic epinephrine injection on NE release in the amygdala supports the view that the noradrenergic fibers terminating in the amygdala may originate from soma in the NTS [95].

6. Different adrenoceptors in the basolateral amygdala are involved in memory storage modulation

Noradrenergic receptors on cells receiving an afferent input from the LC can be classified as α_1-, α_2-, or β-adrenoceptors. Activation of α_1-adrenoceptors by NE generally leads to excitation of the follower cells [107] and there is some evidence that β-adrenoceptors are also excitatory [108]. In contrast, activation of α_2-adrenoceptors leads to inhibition of the follower cells [107], and also of the noradrenergic neurones themselves ("autoreceptors"). The consequences of autoreceptor activation can be detected as changes in the firing rate of amygdala neurons and in the release of NE. Alpha$_2$-adrenoceptors are widely distributed in the brain [109, 110] and there are regional differences in their role in modulating NE release [111].

Several findings indicate that the memory-modulating effects of NE and other neuromodulatory and neurotransmitter systems are selectively mediated by the basolateral nucleus of the amygdala (BLA). The first series of experiments demonstrating a selective involvement of the BLA in memory storage showed that lesions of the BLA, but not of the central nucleus of the amygdala, block the memory impairment induced by systemic injection of benzodiazepines [112]. Furthermore, benzodiazepines infused into the BLA impair retention [113], whereas infusion of a benzodiazepine antagonist into the BLA enhances memory [114]. The findings of subsequent experiments suggested a selective involvement of the BLA in mediating noradrenergic influences on memory for many kinds of tasks [115, 116]. For example, Hatfield and McGaugh [117] showed that post-training infusion of NE into the BLA enhances memory for spatial learning in a water maze. In other studies, we found that infusion of the β-adrenoceptor agonist clenbuterol into the BLA enhances IA retention [119], whereas intra-BLA infusion of propranolol impairs memory of the same task [117].

Further studies demonstrated that NE in the BLA also interacts with glucocorticoids. Quirarte et al. (1997) showed that systemic injection of dexamethasone enhances IA retention when administered after training with a relative low footshock intensity and that infusion of a β1 or β2-adrenergic antagonist into the BLA, but not into the central nucleus of the amygdala, blocks the memory-enhancing effects of systemically administration of glucocorticoids (Fig. 2a). They also showed that the glucocorticoid receptor agonist RU 28362 dose-dependently increases IA retention performance when infused into the BLA and that this effect is blocked by post-training co-infusion of the β1-adrenoceptor antagonist atenolol into the BLA (Fig. 2b). These findings strongly suggest that β-adrenergic mechanisms in the BLA mediate the effects of epinephrine on memory storage and that β-adrenergic receptor activation in the BLA is required in order for glucocorticoids to modulate memory storage processes [118] (Fig. 2a and b).

Other findings indicate that α-adrenoceptors within the BLA are involved in the regulation of memory processes via an interaction with β-adrenergic mechanisms. Both α_1- and α_2-adrenoceptor subtypes are expressed at high levels in the amygdala [120, 121], though α_1-adrenoceptors predominate [122-127]. Thus, the tendency to impair IA retention that we

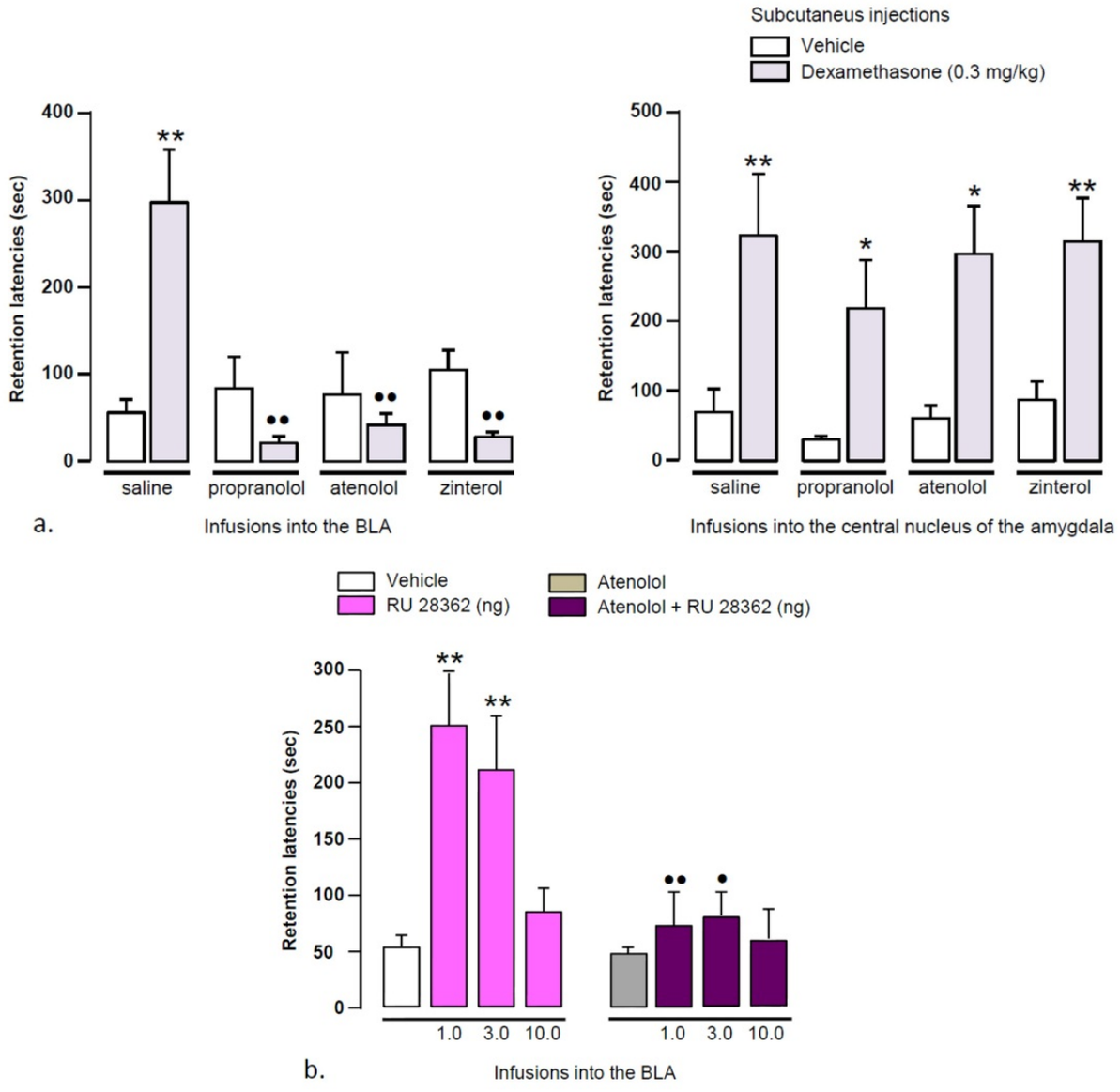

Figure 2. a. Inhibitory avoidance retention latencies of animals that received pretraining infusion of the nonspecific β-adrenergic antagonist propranolol (0.5 μg), the β_1-adrenergic antagonist atenolol (0.5 μg), or the β_2-adrenergic antagonist zinterol (0.5 μg) into the BLA or the central nucleus of the amygdala, followed by immediate post-training subcutaneous injection of dexamethasone (0.3 mg/Kg). The columns and bars show the mean (± SEM) latency in seconds. *, $p < 0.05$, **, $p < 0.01$ compared to the corresponding vehicle group; ●●, $p < 0.01$ compared to the vehicle-dexamethasone group (n=8-14/group) [118].

b. Inhibitory avoidance retention latencies of animals that received concurrent administration of the glucocorticoid receptor agonist RU 28362 (1.0, 3.0, or 10 ng) and the β_1-adrenergic antagonist atenolol (0.5 μg) into the BLA. The columns and bars represent the mean (± SEM) latency in seconds. **, $p < 0.01$ compared to the vehicle group; ●, $p < 0.05$; ●●, $p < 0.01$ compared to the corresponding RU 28362 group (n = 9-13 per group) [118].

obtained in our series of experiments with post-training intra-BLA infusion of low doses of the nonselective α-adrenoceptor agonist phenylephrine [128] very likely resulted from a combined activation of α_1- and α_2-adrenoceptors. In order to clarify the role of each

component of the α-adrenergic system in the BLA, we tested the effect of selective activation and/or blockade of these receptors in the BLA during IA training. Our results showed that post-training α_1-adrenoceptor inactivation using the selective antagonist prazosin impaired IA retention and that selective activation of α_1-adrenoceptors by infusion of a fixed concentration of the α_2-adrenoceptor antagonist yohimbine together with increasing concentrations of phenylephrine dose-dependently enhanced IA retention i.e., yohimbine reversed the tendency of phenylephrine to impair retention. Given the higher affinity of NE for α_2-adrenoceptors [151] and the fact that α_2-adrenoceptors are mostly located presynaptically [142], our results suggest that the IA memory impairing effects produced by phenylephrine alone are mainly due to presynaptic α_2-adrenoceptor activation [152]. This hypothesis is consistent with evidence that activation of presynaptic α_2-adrenoceptors blocks NE release [129 130].

The α_1-adrenergic influence on memory seems to be mediated by an interaction with β-adrenoceptors within the BLA. Indeed, intra-BLA post-training infusion of atenolol blocks the memory enhancement induced by selective activation of α_1-adrenoreceptors [128]. Moreover, we showed that intra-BLA infusion of the α_1-adrenoceptor antagonist prazosin right-shifts the dose-response effects of the β-adrenoceptor agonist clenbuterol when the two drugs are infused together into the BLA post-training [131]. These results suggest that α_1-adrenergic activity in the BLA facilitates the effects of β-adrenergic activation on memory formation. In a subsequent experiment, intra-BLA infusion of the synthetic cyclic adenosine monophosphate (cAMP) analog 8-bromo-cAMP was found to enhance retention in a manner similar to clenbuterol, but the effect induced by 8-bromo-cAMP was not affected by prazosin [131]. These findings are consistent with pharmacological evidence suggesting that β-adrenoceptors modulate memory storage by a direct coupling between Gs protein and adenylate cyclase and that α_1-adrenoceptors may act indirectly on this process by influencing the β-adrenergic-induced synthesis of cAMP [132-134].

As mentioned above, the amygdala contains α_2-adrenoceptors [125-127], which might be located on particular subsets of neurones involved in the autonomic response to stressful stimuli. In order to investigate the role of these receptors in memory for IA, we performed a series of experiments aimed at evaluating the effect of activation or blockade of these receptors in the BLA on IA retention processes. The behavioral data obtained in these experiments showed that bilateral microinfusion of the selective α_2-adrenoceptor antagonist idazoxan into the BLA immediately after training induces dose-dependent enhancement of retention performance of IA when tested 24 h later (Figure 3), whereas post-training intra-BLA infusion of the selective α_2-adrenoceptor agonist UK 14,304 induces dose-dependent impairment of retention performance (Figure 4).

These results are consistent with those of studies in which systemic injection of selective α_2-adrenergic drugs was found to disrupt and enhance consolidation of IA learning in the rat [136]. In addition, they fit with previous reports suggesting that the effects of peripheral administration of α_2-adrenergic compounds on learning and memory performance are mediated through a direct action on central NE release [136-139] and with previous results implicating amygdala α_2-adrenoceptors in footshock-based learning [140, 141]. Moreover,

they clearly indicate that, in addition to involvement of α_1- and β-adrenoceptors, α_2-adrenoceptors in the BLA are involved in mediating the effects of training-induced or experimentally administered NE on memory storage [128, 131]. As pre-synaptic α_2-negative feedback is known to regulate NE release [142], including NE release in the amygdala [127, 129, 130, 140], the present findings provide additional evidence that memory consolidation is regulated by noradrenergic activation within the BLA.

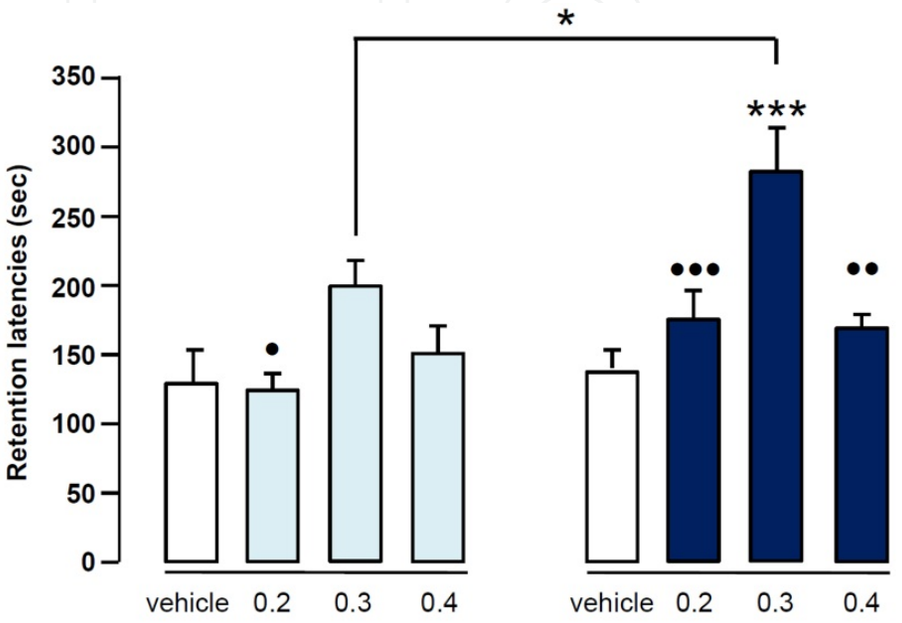

Figure 3. Effect of pre- or post-training infusion of various doses of idazoxan (a selective α_2-adrenoceptor antagonist) into the basolateral amygdala on inhibitory avoidance retention latencies. The columns and bars represent the mean ± SEM latency (in seconds) in entering the dark compartment during the retention test. The pre-training groups were infused 20 min before training, whereas the post-training groups were infused immediately after footshock administration. *, $p < 0.05$ compared to the corresponding value in the other group; ***, $P < 0.001$ compared to the vehicle-injected group; ●, $p < 0.05$; ●●, $p < 0.01$; ●●●, $p < 0.001$ compared to the value using 0.3 μg of idazoxan in the same group. n = 9–13 per group [135].

It is difficult to speculate when, and for how long, a single infusion of an adrenergic drug induces its effect on NE release, since the minimal time interval between sample collection using the microdialysis technique is about 15 min. However, the maximal effect of α_2-adrenergic drugs on NE release has been observed 30 min after infusion [143, 144]. Since the effect of α_2-adrenergic drugs on NE release in the brain and the effect of a footshock on NE release are both maximal after 30 min [98], it is likely that the effects of pre-training local injection of UK 14,304 or idazoxan into the BLA mainly results from binding to α_2-adrenergic autoreceptors, which regulate the stress-induced release of NE. The fact that retention latencies were only influenced by the highest dose of UK 14,304 [135 and Fig. 4] suggests that the pool of NE release induced by footshock within seconds or minutes after shock administration is sufficient to enable the conditioned stimulus (CS)-unconditioned stimulus (US) association. Our finding, shown in Fig. 4, that pre-training intra-BLA infusion of UK 14,304 or idazoxan induces effects on memory that are similar, but of a smaller

amplitude, to those obtained in post-training groups suggests that, during IA, the α_2-adrenoceptor system in the BLA is more probably involved in very fine memory-modulated tuning control of IA consolidation, rather than in the encoding of CS-US association, as suggested previously [141]. The post-training effects are clearly consistent with the hypothesis that IA consolidation depends critically on the training-induced prolonged release of amygdala NE.

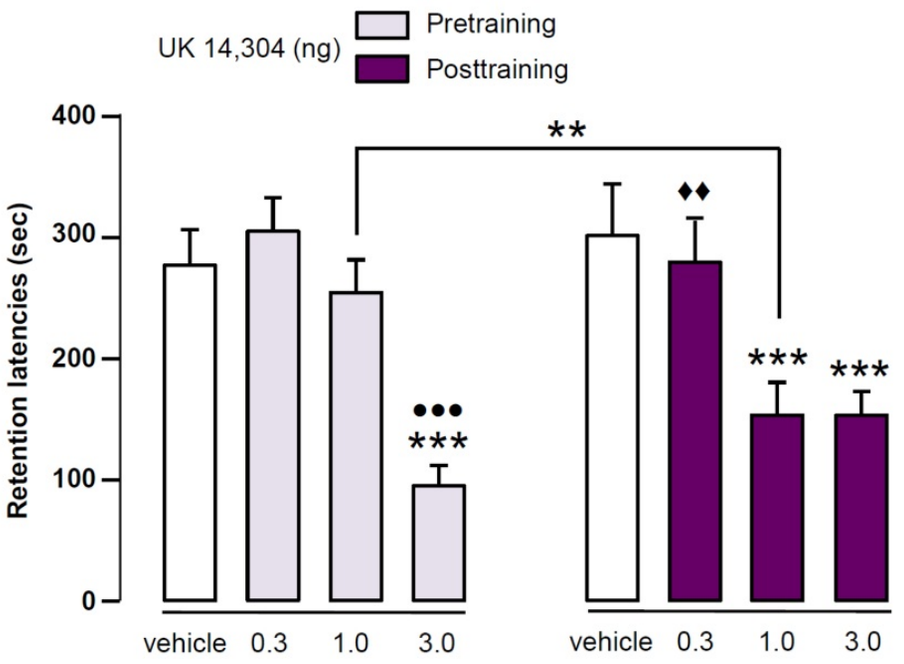

Figure 4. Effect of immediate post-training infusion of various doses of UK 14,304 (a selective α_2-adrenoceptor agonist) into the basolateral amygdala on inhibitory avoidance retention latencies. The columns and bars bars represent the mean ± SEM latency (in seconds) in entering the dark compartment during the retention test. The pre-training groups were infused 20 min before training, whereas the post-training groups were infused immediately after footshock administration. **, $p < 0.01$ compared to the corresponding value in the other group; ***, $p < 0.001$ compared to the vehicle-injected group; ●●●, $p < 0.001$ compared to the groups injected with 0.1 or 1.0 ng of UK 14,304; ♦♦, $p < 0.01$ compared to the groups injected with 1.0 or 3.0 ng of UK 14,304; $n = 9–12$ per group. [135]

In order to test this hypothesis, we investigated the effects of systemic and intra-BLA blockade or activation of α_2-adrenoceptors on the dynamics of NE in the BLA.

In the first study, anesthetized animals were microdialysed in the BLA while receiving systemic infusions of the α_2-adrenoceptor antagonist dexefaroxan or the α_2-adrenoceptor agonist UK 14,304. Results obtained in this study showed that dexefaroxan and UK 14,304 induced respectively a rapid and reversible significant increase and decrease, in NE levels in the BLA (Figure 5).

In a second study using retrodialysis, anesthetized animals received local infusion of dexefaroxan or UK 14,304 and the results showed that dexefaroxan induced a significant and reversible increase in NE levels in the BLA, whereas UK 14,304 caused a significant reduction (Figure 6).

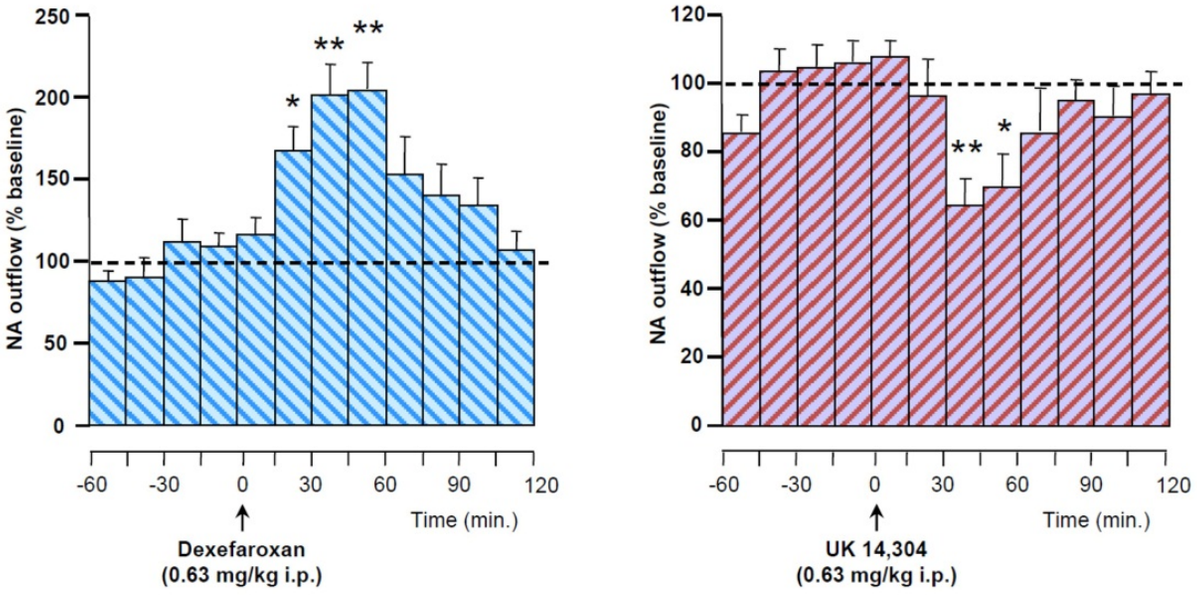

Figure 5. Effect of systemic α_2-adrenoreceptor blockade with the antagonist dexefaroxan (0.63 mg/kg) or activation with the agonist UK 14,304 (0.63 mg/kg) on NE levels in the basolateral amygdala in anesthetized animals assessed by in vivo microdialysis and HPLC. Norepinephrine levels are expressed as a mean (±SEM) value expressed as a percentage of basal levels; $n = 7–9$ per group. $*$, $p < 0.05$; $**$, $p < 0.01$ compared to baseline levels [145].

Our retrodialysis data indicate that drugs infused into the BLA post-training cause maximal NE release about 15 min after infusion. Moreover, this time interval has been described to be critical for the involvement of the amygdala during consolidation of IA [146, 147]. It is therefore likely that the enhancing and inhibitory effects caused, respectively, by post-training injection of idazoxan or UK 14,304 on IA retention were due to modulation of the prolonged training-induced increase in NE levels [98]. Additionally, and importantly, our findings are consistent with those of Pelletier et al. [101] showing that a single footshock increases the firing of neurons in the basolateral amygdala and that the increase peaks after 30 min, but remains high for 2 h.

In summary, our findings show that α_2-adenoreceptor-induced modulation of NE release during post-trial consolidation significantly influences IA retention performance. Providing additional evidence of the memory-modulating role of NE release in the BLA, they also suggest that α_2-adrenoceptors in the BLA are a critical component in the modulating influence of NE on IA memory consolidation and that the effect is probably due to a prolongation of the increase in training-induced levels of NE within the BLA. However, and in reference to previous results showing that NE activates three types of adrenoceptors, each involved in a different signaling pathway, a better understanding of the mechanisms by which NE in the BLA modulates the process of IA retention memory requires a detailed characterization of the signaling pathways downstream of NE binding. Indeed, NE activates β-, α_1-, and α_2-adrenoceptors, all of which are known to be metabotropic receptors. Beta-adrenoreceptors are associated with activation of the protein Gs, which activates adenylate cyclase, leading to production of cAMP, which then activates cAMP response

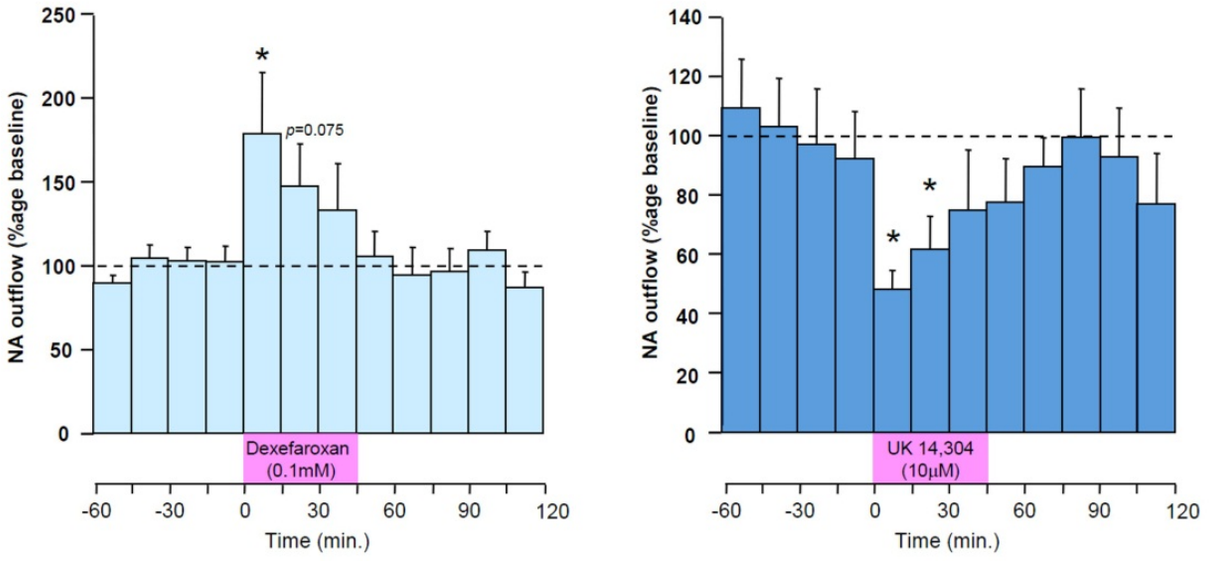

Figure 6. Effect of local α_2-adrenoreceptor blockade with the antagonist dexefaroxan or activation with the agonist UK 14,304 on norepinephrine levels in the basolateral amygdala in anesthetized animals assessed by in vivo retrodialysis and HPLC. Norepinephrine levels are expressed as the mean (±SEM) value expressed as a percentage of basal levels. n = 7-8 per group; ∗, $p < 0.05$ compared to baseline levels [145].

element-binding (CREB) protein. Alpha$_1$-adrenoceptors can mobilize calcium ions from intracellular stores, as well as increase calcium entry *via* voltage-gated calcium channels. Their stimulation leads to hydrolysis of membrane phospholipids *via the* G protein-mediated activation (Gq protein) of phospholipase Cβ and the resultant production of inositol triphosphate (IP3) induces α_1-adrenoceptor-elicited calcium release from intracellular stores, thereby increasing the cytosolic calcium concentration. The simultaneously produced diacylglycerol (DAG) activates protein kinase C (PKC) [148], which phosphorylates many cellular substrates, including membrane channels, pumps, and ion-exchange proteins. Alpha$_1$-adrenoceptors have also been reported to modulate other signaling pathways, resulting in increased accumulation of cAMP and cGMP, potentiation of cAMP responses elicited by the Gs-linked receptors, activation of phospholipase A2 and phospholipase D, activation of cAMP phosphodiesterase, adenosine release, and stimulation of arachidonic acid release [149]. Alpha$_2$-adrenoceptors are classically linked to Gi/o protein, with an action opposite to that of Gs, and act by inhibiting adenylate cyclase *via* a Gi protein and thereby inhibit cAMP production, while the βγ subunits of Gi protein increase potassium ion conductance. Alpha$_2$-adrenoceptors also suppress voltage-activated calcium channels *via* Go protein, thus reducing the flow of extracellular calcium ions into target cells. Moreover, there is increasing evidence suggesting that α_2-adrenoceptors are linked not only to the activation of the Gi/o cascade, but also, for example, to the activation of phospholipase C (PLC) and PKC, at least in some cell types [150].

Although pharmacological data show that α_2-receptors have a higher affinity than α_1-receptors for NE and that both α_2- and α_1-receptors have a higher affinity for NE than β-receptors [151], little is known about the distribution of the three receptors subtypes within

the BLA and further research is clearly needed to determine the signaling cascades initiated by the binding of NE to each of these subtypes linked to the various G proteins, which mediate the activation of specific signal transduction pathways.

A comparison of the differences and similarities between the three adrenoceptors in terms of specificity, signaling, and trafficking [152] would result in a better understanding of the dynamics of NE action on the intracellular cascade of event in the BLA leading to plastic changes underlying memory modulation of IA.

7. Conclusions

These studies indicate that adrenal stress hormones and the amygdala, especially the BLA, are involved in regulating memory consolidation. Because of its anatomical position, the amygdala is able to translate sympathetic arousal into synaptic plasticity that is distributed throughout the brain. Thus, the amygdala appears to be the core of the system involved in the physiological mechanisms promoting brain plasticity and rapid consolidation of memory for major events that drive and condition the survival of the animal. In our review, we suggest that the sympathetic response to a particular emotional or stressful event is driven along the peripheral nervous system by activating the β-adrenoceptor system on vagal afferents, which bridge the peripheral and central nervous systems by stimulating the NTS in the brainstem. As a result, adrenergic stimulation of vagal afferents that project to the NTS, induces activation of the NE system in forebrain structures either directly or indirectly via the LC onto which the NTS projects. It is therefore likely that activation of the vagal nerve will induce NE release in the amygdala through these two pathways.

The evidence that memory for various kinds of tasks is not lost when the amygdala is inactivated or lesioned [146,147,153,154] indicates that it is not the final storage site for emotionally arousing memories, but modulates memory storage in efferent brain regions [155, 156]. Indeed, several subsequent findings suggested that amygdala stimulation modulates memory consolidation and does so through influences mediated by amygdala efferents, and it has been shown that lesion of the stria terminalis, which carries both afferent and efferent projections of the amygdala, blocks the impairing effects of post-training electrical stimulation of the amygdala on memory [157]. In addition, stria terminalis lesions block the memory enhancement induced by post-training systemic injection of clenbuterol or intra-amygdala infusion of NE [89, 91]. These results strongly suggest that modulatory influences on memory involve projections from the amygdala to other brain regions. Consistent with this view, the amygdala shares extensive connections with cortical and subcortical regions implicated in memory storage processes [158-160]. Concerning this point, a large body of data shows that memory consolidation results from the direct interaction of the amygdala with many brain regions, including the nucleus accumbens [161, 162], insular cortex [163], entorhinal cortex [164, 165], rostral anterior cingulate cortex [166], and medial prefrontal cortex [167], and most extensively the hippocampus [168]. With regard to the dynamic interactions between the amygdala and limbic and temporal lobe structures in human and non-human animals, it has been suggested that emotional arousal-

induced NE release in the amygdala will induce modulation of synapses in the target areas that are engaged in memory processing. Despite the growing literature on the memory-modulating role of the interaction between the amygdala and other brain regions, one must bear in mind that the present theoretical operating system is very simplistic, since memory is also modulated by the interaction between many neuromodulatory systems in the BLA. The roles of these latter interactions in memory modulation have been extensively documented and considered in recent reviews [155, 168, 169]. Very briefly, findings have shown that opioid peptides and gamma amino butyric acid both regulate NE release in the amygdala. Moreover, the acetylcholine and glutamate systems play a role in memory modulation at steps beyond the activation of β-adrenoceptors. The effects of glucocorticoids on memory consolidation are indirectly mediated by activation of the NTS and LC, both representing afferent NE projections to the amygdala, and directly by potentiating the noradrenergic signal cascade within the amygdala.

In summary, the epinephrine and NE systems, which rise, respectively from the vagus nerve and the NTS, to the amygdala, form a complicated network of critical mechanisms leading to the emergence of a memory-modulation process. Although this cannot be a complete representation, our data show that the memory-modulated role of NE is mediated differently by the various adrenergic receptors in the BLA, each of which is involved in a specific process. Eventually, through the activation of all of these systems, interacting inside and outside the amygdala, the strength of our emotional memories is determined by the weight of their emotional significance.

Author details

Barbara Ferry
Center for Research in Neuroscience of Lyon, UMR 5292 CNRS – INSERM U 1028 – Université Claude Bernard Lyon 1, Lyon, France

Gina L. Quirarte
Behavioral and Cognitive Neurobiology Department, Institute of Neurobiology, National Autonomous University of México, Campus Querétaro, Qro, México

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