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Role of the basolateral amygdala in memory consolidation

Denis Paré*

Center for Molecular & Behavioral Neuroscience, Rutgers State University, 197 University Avenue, Newark, NJ 07102, USA

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Abstract

Typically, emotionally charged events are better remembered than neutral ones. This paper reviews data indicating that the amygdala is responsible for this facilitation of memory by emotional arousal. Pharmacological and behavioral studies have shown that the release of adrenal stress hormones facilitates memory consolidation. The available evidence suggests that this effect depends on a central action of stress hormones involving the release of the neuromodulators noradrenaline (NA) and acetylcholine in the basolateral complex of the amygdala (BLA). Indeed, BLA lesions block the memory modulating effects of stress hormones. Moreover, microdialysis studies have revealed that BLA concentrations of NA and acetylcholine are transiently (2 h) elevated following emotionally arousing learning episodes. Last, post-learning intra-BLA injections of β-adrenergic or muscarinic receptor antagonists reduce retention. These results have led to the hypothesis that NA and acetylcholine increase the activity of BLA neurons in the hours *after* the learning episode. In turn, the BLA would facilitate synaptic plasticity in other brain structures, believed to constitute the storage sites for different types of memory. Consistent with this, post-learning treatments that reduce or enhance the excitability of BLA neurons respectively decrease or improve long-term retention on various emotionally charged learning tasks. However, a number of issues remain unresolved. Chief among them is how the BLA facilitates synaptic plasticity elsewhere in the brain. The present review concludes with a consideration of this issue based on recent advances in our understanding of the BLA. Among other possibilities, it is suggested that rhythmic BLA activity at the theta frequency during arousal as well as the uniform conduction times of BLA axons to distributed rhinal sites may promote plasticity in co-active structures of the temporal lobe.

Contents

Abbreviations: ACh, acetylcholine; BLA, basolateral complex of the amygdala; CEA, central nucleus of the amygdala; CNQX, 6-cyano-7-nitroquinoxaline-2,3-dione; CREB, cAMP response element-binding; LTP, long-term potentiation; NA, noradrenaline; NTS, nucleus tractus solitarius; PKA, protein kinase A

* Tel.: +1-973-353-1080x3251; fax: +1-973-353-1272.
E-mail address: pare@axon.rutgers.edu (D. Paré).

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1. Introduction

Probably everyone has realized that emotions affect memory. This commonplace experience was confirmed in controlled laboratory studies: emotional arousal generally improves memory (Heuer and Reisberg, 1990; Burke et al., 1992; reviewed in Christianson, 1992). The present review examines data suggesting that the amygdala is responsible for the modulation of memory by emotions. It also considers the cellular mechanisms that might underlie this phenomenon. However, it will not address whether the amygdala is a critical site of plasticity for some forms of learning such as in Pavlovian fear conditioning. For reviews on this issue, see Blair et al. (2001) and Walker and Davis (2002).

2. Memory consolidation and emotions

2.1. Memories form slowly over time

From invertebrates (Krasne, 1978) to humans (Cahill, 2000), long-term memory for an event can be enhanced or reduced by manipulations performed in the minutes to hours after learning. This has led to the suggestion that memories form slowly over time, a process termed memory consolidation. The first evidence of this came when Mueller and Pilzecker (1900) reported that memory of recently learned information is disrupted by learning of other material shortly after the first learning. Later on, susceptibility of recently formed memories to post-learning manipulations was also seen with electroconvulsive shocks (Duncan, 1949; Gerard, 1949), protein synthesis inhibitors (Agranoff et al., 1966), drug injections (McGaugh, 1966) and electrical stimulation of discrete brain regions (reviewed in McGaugh and Gold, 1976).

Moreover, it was found that depending on the type of post-learning manipulations, memory consolidation could not only be reduced but also enhanced (McGaugh and Gold, 1976). A key feature of these studies was that the effect of the post-learning treatments decreased as the interval between the learning and the treatment increased (McGaugh, 1973; McGaugh and Gold, 1976). Also, the fact that these treatments were applied after training (but days before testing) excluded the possibility that they affected performance during acquisition or retention tests.

2.2. Emotional arousal facilitates memory consolidation

Various interpretations were proposed for these results. However, the observation that emotionally arousing events are often remembered vividly whereas others are forgotten (reviewed in Christianson, 1992) led Gold and McGaugh (1975) to suggest that post-learning treatments might be interfering with or potentiating a mechanism regulating memory. They reasoned that there would be a biological advantage to delay memory consolidation until the significance of an experience could be evaluated. Thus, they hypothesized that the brain is endowed with systems that affect the development and maintenance of memories even though they are not their storage sites. By facilitating or dampening memory consolidation, these modulatory systems would serve a highly adaptive process allowing "... organisms [to] select from recent experiences those that should be permanently stored" (Gold and McGaugh, 1975, p. 375).

This proposal was supported by studies showing that administration of adrenal stress hormones after learning could facilitate retention (Gold et al., 1975a) in appetitively or aversively motivated tasks (reviewed in McGaugh, 2002a). However, there was an inverted-U relationship between hormonal levels and retention performance (Gold and van Buskirk, 1978a,b). As predicted by the consolidation hypothesis, the effects of stress hormones and their pharmacological analogs were time-dependent, their impact on retention decreasing as the interval between training and hormone treatment increased. Moreover, systemic administration of β-adrenergic receptor antagonists blocked the effects of emotional arousal on long-term declarative memory (Cahill et al., 1994; Nielson and Jensen, 1994). These results raised the possibility that, when released during a stressful episode, these hormones could act retrogradely to affect memory of that event. In other words, the extent of consolidation would depend on the motivational or arousing consequences of an experience, as expressed by the release of stress hormones (Gold and McGaugh, 1975).

3. The amygdala mediates the effect of arousal on memory consolidation

3.1. The facilitating effects of stress hormones on memory depend on the amygdala

Early studies relying on electrical stimulation of discrete brain structures first hinted that the amygdala can modulate memory consolidation (Goddard, 1964; McDonough and Kesner, 1971; Gold et al., 1975b; reviewed in Gold and McGaugh, 1975). However, lesion studies provided definite

evidence that the amygdala mediates the facilitating effects of stress hormones on memory. Indeed, it was found that lesion or inactivation of the basolateral complex of the amygdala (BLA) but not of the central nucleus of the amygdala (CEA) block the memory modulating effects produced by adrenalectomy (Roozendaal et al., 1998) as well as peripheral glucocorticoid (Roozendaal and McGaugh, 1996a; Roozendaal et al., 1996) or diazepam (Tomaz et al., 1992) administration. Moreover, similar results were observed with stria terminalis lesions (Liang and McGaugh, 1983; Liang et al., 1990; Roozendaal and McGaugh, 1996b), a major output pathway of the amygdala.

In addition, it was observed that post-learning treatments that presumably reduced or enhanced excitability of the BLA but not the CEA respectively decreased or improved retention. For instance, reduced retention was seen with local intra-amygdala injections of lidocaine (Salinas et al., 1993; Parent and McGaugh, 1994), GABAa and GABAb agonists (Castellano et al., 1989; Coleman and McGaugh, 1995; Salinas and McGaugh, 1995, 1996), 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX); Mesches et al., 1996), and β-adrenergic receptor antagonists (Roozendaal et al., 1999). Enhanced retention was seen with intra-amygdaloid injections of bicuculline (Dickinson et al., 1993), agonists of β-adrenergic (Ferry et al., 1999; Ferry and McGaugh, 1999; Hatfield and McGaugh, 1999) and muscarinic (Salinas et al., 1997) receptors.

3.2. The amygdala is not the storage site of emotionally-facilitated memories

Although altering amygdala activity immediately after learning affects long-term retention, BLA lesions performed later have no effects (Liang et al., 1982; Parent et al., 1995). This implies that the amygdala is not the storage site of these memories. Otherwise stated, this observation suggests that the memory modulating effects of the amygdala manipulations listed in Section 3.1 do not result from alterations of memory storage in the amygdala but in other structures that presumably constitute the storage site of particular forms of memories (reviewed in Cahill and McGaugh, 1998). In this context, it should be pointed out that the BLA has an astonishingly promiscuous connectivity, especially in primates (Young et al., 1994).

Another factor supporting the view that the amygdala is not the storage site of many of the emotionally-modulated memories is the sheer variety of learning tasks in which this phenomenon was observed. The list includes aversively and positively motivated tasks, hippocampal-dependent and independent tasks, as well as inhibitory avoidance (reviewed in McGaugh, 2002b).

The study of Packard et al. (1994) nicely illustrates this point. They showed that immediate post-learning injection of amphetamines in the BLA increases hippocampal storage of spatial information (hidden platform water maze task) and caudate storage of response information (visible platform water maze task). Yet, intra-amygdala injections of lidocaine just before testing retention had no effect on either task (Packard et al., 1994). Moreover, pre-retention lidocaine injection in the hippocampus or caudate only blocked the memory potentiating effects of intra-amygdala amphetamine injection in the hidden or visible platform water maze task, respectively (Packard and Teather, 1998).

Collectively, these results suggest that, in emotionally arousing conditions, the amygdala, under the direct or indirect influence of peripheral stress hormones, facilitates long-term memory consolidation in other brain structures where memories are actually stored.

3.3. The BLA-mediated modulation of memory consolidation occurs in humans

It appears that the modulation of memory by the BLA is also present in humans. For instance, emotionally arousing stories are better recalled than neutral ones, and this effect is absent in subjects with amygdala lesions (Cahill et al., 1995; Adolphs et al., 1997). In further agreement with animal work, the beneficial effect of emotional arousal on long-term memory is abolished by systemic post-training administration of β-adrenergic receptor antagonists in humans (Cahill et al., 1994) while epinephrine facilitates memory (Cahill and Alkire, 2003). Moreover, imaging studies have found a high correlation between long-term recall of emotionally arousing or neutral material and the amount of amygdala activation observed when these stimuli were first presented (Cahill et al., 1996; Canli et al., 2000; Hamann et al., 1999). These and other findings suggest that, in emotionally arousing conditions, the amygdala promotes memory storage processes in brain areas that are involved in declarative memory (Cahill, 2000; Cahill and McGaugh, 1998).

Although ethical considerations limit the scope of investigations in human subjects, access to introspective reports offers insights into the mechanisms underlying the facilitation of memory by emotions. Much anecdotal evidence indicates that emotional stress is followed by intrusive re-experiencing of the arousing event. Following a car accident for instance, subjects report repetitive and involuntary mental re-enactment of the events leading to the crash. Cahill (2000) has proposed that this “ruminative” process may be critical to understand the effect of emotional arousal on memory. He pointed out that this delayed and protracted reaction to emotional stress is reminiscent of the time course of emotional responses evoked by repetitive amygdala stimulation: they develop gradually during the stimulus and outlast the period of stimulation (Zbrozyna, 1972), for hours according to some reports in humans (Mark et al., 1972).

While the origin of these ruminative thoughts remains unknown, their importance for memory consolidation is obvious. Such rehearsal can only facilitate memory. Whether a

similar phenomenon occurs in animals also remains to be determined.

4. What is the link between the release of adrenal stress hormones and the basolateral amygdala?

4.1. Anatomical data

Glucocorticoids freely pass the blood brain barrier and there is a moderate density of glucocorticoid receptors in the BLA (Sarrieau et al., 1986; Honkaniemi et al., 1992). Thus, direct glucocorticoid actions in the BLA are possible. Unfortunately, to the best of my knowledge, the electrophysiological effects of glucocorticoids have not been investigated in the amygdala so far. In the hippocampus, glucocorticoids were reported to reduce inhibitory chloride currents by enhancing desensitization of GABAa receptors (Shen et al., 2000) and presynaptically reducing GABA release probability (Teschemacher et al., 1997). In addition, glucocorticoids were reported to increase NMDA currents (Wong and Moss, 1994). Both effects are consistent with the possibility that glucocorticoids enhance BLA excitability during stress.

While glucocorticoids cross the blood brain barrier, adrenaline does not. Then, how does peripheral adrenaline alter memory consolidation? Based on evidence that there are β-adrenergic receptors on the ascending vagus (Schreurs et al., 1986), it was proposed that peripheral adrenaline might cause noradrenaline (NA) release in the amygdala via projections of the vagus to noradrenergic neurons of nucleus tractus solitarius (NTS; McGaugh, 2002a). Consistent with this idea, it was found that reversible NTS lesions attenuate the memory modulating effects of post-training adrenaline (Williams and McGaugh, 1993). Moreover, adrenergic activation of the NTS potentiates amygdala NA release and enhances retention performance in emotionally arousing and spatial memory tasks (Clayton and Williams, 2000). However, tract-tracing studies have revealed that NTS projects to the CEA but not the BLA (Ricardo and Koh, 1978), suggesting that another target of NTS must be involved. One likely possibility is the direct projection of NTS to the locus coeruelus (Van Bockstaele et al., 1999), the main source of NA inputs to the amygdala (Fallon and Ciofi, 1992). This is consistent with the fact that intra-amygdaloid injections of β-adrenergic antagonists interfere with the memory modulating effects of peripheral adrenaline (see above).

However, the response to stress presumably has a central origin. Thus, when attempting to explain the facilitating effects of emotional arousal on memory, we should not only look for the indirect effects of stress hormones, but also for direct modulatory effects in the BLA that might be generated centrally as part of the stress response. To gain insight into this possibility, we will consider the results of microdialysis studies.

4.2. Microdialysis and pharmacological studies implicate noradrenaline and acetylcholine

A variety of neuromodulators are released in larger quantities during emotional arousal than in control conditions. These include serotonin (Kawahara et al., 1993; Amat et al., 1998), dopamine (Hori et al., 1993; Young and Rees, 1998; Inglis and Moghaddam, 1999), NA (Tanaka et al., 1991; Quirarte et al., 1998; Williams et al., 2000), and acetylcholine (ACh; McIntyre et al., 2003). Of these various modulators, only antagonists of β-adrenergic (reviewed in Ferry and McGaugh, 2000) and muscarinic receptors (Power et al., 2000; Salinas et al., 1997) were reported to block the potentiating effects of arousal on memory. Consequently, I now consider the origin and actions of NA and ACh in the BLA.

4.2.1. Noradrenaline effects in the basolateral amygdala

Most NA inputs to the BLA originate in the locus coeruleus (Pickel et al., 1974; Fallon et al., 1978). Abundant evidence indicates that the discharge rate of locus coeruleus neurons increases during stress (Abercrombie and Jacobs, 1987a,b). Moreover, there is high correlation between the firing rate of locus coeruleus neurons and NA concentration in their projection sites (Berridge and Abercrombie, 1999). Thus, the increased NA concentration observed in the amygdala following stress (see references above) constitutes a likely candidate for BLA mobilization during emotional arousal.

Yet, NA was reported to have overall inhibitory effects on BLA neurons. Indeed, NA inhibits epileptiform discharges in the amygdala of kindled rats (McIntyre and Wong, 1986; Stoop et al., 2000). This effect of NA results from a predominant α_2-mediated presynaptic inhibition of glutamate release in the BLA. According to Ferry et al. (1997), the effects of β-adrenoreceptor activation are comparatively less important: they include (1) a reduction in spike frequency accommodation via the inhibition of some subtypes of Ca^{2+}-dependent K^+ currents and (2) a presynaptic facilitation of excitatory synaptic transmission (Huang et al., 1996; Ferry et al., 1997) resulting from a potentiation of some voltage-gated Ca^{2+} channels subtypes (P and/or Q; Huang et al., 1996). These studies suggest that cAMP-dependent protein kinase A (PKA) mediates both effects, but in different cellular compartments.

4.2.2. Effects of acetylcholine in the basolateral amygdala

Since muscarinic receptor activation in the amygdala has been implicated in memory consolidation (see above), we now consider the effects of ACh on plasticity. Cholinergic projections from the basal forebrain to the cerebral cortex have been implicated repeatedly in cortical plasticity (Bakin and Weinberger, 1996; Bjordahl et al., 1998; Kilgard and Merzenich, 1998). For instance, paired presentation of noxious and auditory stimuli produce a long-lasting shift in the best frequency of auditory cortical neurons toward the frequency of the conditioned stimulus (Weinberger, 1998).

Moreover, this effect is blocked by cortical applications of muscarinic antagonists (Gao and Suga, 2000; Ji et al., 2001).

Because the BLA is reciprocally connected to the substantia innominata (Krettek and Price, 1978; Jolkkonen et al., 2002; reviewed in Amaral et al., 1992), it is not only in a position to facilitate ACh release in the cerebral cortex (Dringenberg and Vanderwolf, 1996) but also to be influenced by basal forebrain cholinergic inputs. Data consistent with both possibilities were obtained (Power and McGaugh, 2002; Power et al., 2002). Also, single unit studies of immunohistochemically identified basal forebrain neurons have revealed that cholinergic cells increase their firing rate during EEG activation (Duque et al., 2000; Manns et al., 2000). Presumably, the same occurs during stress (McIntyre et al., 2003).

Like NA, ACh has complex pre- and postsynaptic actions on BLA neurons. Muscarinic receptor activation produces a profound presynaptic inhibition of excitatory synaptic transmission (Yajeya et al., 2000), the reduction of various K^+ conductances (K^+ leak, M-current, $gK_{Ca^{2+}}$; Washburn and Moises, 1992), the potentiation of a hyperpolarization-activated inward rectifier K^+ current and the activation of a Ca^{2+}-independent mixed cationic conductance (Yajeya et al., 1999). In addition, activation of nicotinic receptors produces a rapid depolarization of GABAergic BLA interneurons (Washburn and Moises, 1992) and presynaptically enhances glutamate and GABA release (Girod et al., 2000; Barazangi and Role, 2001). On the basis of these results, it is unclear whether the net effect of ACh is a facilitation or a depression in the BLA.

4.3. Long-term effects of neuromodulators

The studies reviewed above focused on the immediate effects of NA and ACh. Yet, several lines of evidence suggest that the memory enhancing effects of NA and ACh depend on increases in excitability that outlast the period of behavioral arousal and persist after the concentration of these modulators has returned to control levels. Indeed, the time-window when intra-amygdala injections of β-adrenergic and muscarinic antagonists can reduce retention is shorter than that observed with lidocaine injection (at least 6 h; Parent and McGaugh, 1994) or tetrodotoxin (2 days; Sacchetti et al., 1999). This is consistent with the fact that NA levels return to baseline values within 2 h of an emotionally arousing event (Quirarte et al., 1998). These considerations raise the possibility that NA and/or ACh, in addition to the effects described above, have delayed and long-lasting excitatory actions that persist long after emotionally arousing events. Consistent with this, there is evidence implicating the activation of β-adrenoreceptors and the classical cAMP pathway in long-term regulation of neuronal excitability and synaptic transmission.

Indeed, a number of neuromodulators that are positively coupled to adenylyl cyclase and cAMP formation can affect the behavior of neurons by activating cAMP-dependent PKA (Levitan, 1994). The particular response produced by PKA activation depends on substrate proteins that are specific to each cell type, but include proteins taking part in neurotransmitter release and synthesis, ionotropic receptors and ionic channels (Gray et al., 1998; Soderling and Derkach, 2000). Although previous studies have generally focused on the immediate actions of these neuromodulators, much data suggest that their effect can outlast the period of agonist application. For instance, PKA activation by serotonin in aplysia neurons produces long-term inhibition of two types of K^+ channels (Klein et al., 1982; Siegelbaum et al., 1982), partly accounting for the sensitization of the gill withdrawal reflex (Kandel and Schwartz, 1982). Similarly, in colliculi neurons, transient application (<5 min) of β-adrenergic receptor agonists produces a long-lasting (>2 h) inhibition of a non-inactivating K^+ current, leading to a prolonged enhancement of excitability (Fagni et al., 1992; Ansanay et al., 1995; Milhaud et al., 1998). Analysis of the biochemical steps involved revealed that the K^+ channel inhibition resulted from a transient increase in cAMP formation and PKA activation (<10 min) associated with a prolonged inhibition of phosphatase activity. However, protein synthesis could not be ruled out (Ansanay et al., 1995).

Evidence for such long-term modulation of neuronal excitability by the β-adrenoreceptor–cAMP–PKA pathway was also obtained in the BLA. In these studies, β-adrenergic receptor antagonists and inhibitors of cAMP-dependent PKA prevented the late phase of long-term potentiation (L-LTP) whereas isoproterenol, a β-adrenergic receptor agonist, as well as forskolin, an adenylyl cyclase activator, induced L-LTP and stimulated the phosphorylation of cAMP response element-binding (CREB) proteins (Huang and Kandel, 1998; Huang et al., 2000). The involvement of this transcription factor (reviewed in Mayr and Montminy, 2001) is consistent with the fact that protein synthesis inhibition prevented L-LTP in the same experiments (Huang et al., 2000).

In summary, there is abundant evidence supporting the notion that activation of β-adrenergic receptors can have long-term effects in the BLA, at first through protein phosphorylation and, in the long-term, through protein synthesis. However, it remains unclear whether NA, as opposed to pure β-adrenergic receptor agonists, would have the same effect.

5. How does increased basolateral activity facilitate memory consolidation?

In addition to the problem of identifying the neuromodulators that mobilize the BLA during and after emotional arousal, another unresolved issue is how does the BLA facilitate memory consolidation in target structures? This enigma can be broken down in a number of related questions.

5.1. Relation between task requirements and the particular population of basolateral amygdala neurons involved in memory modulation

First, are distinct populations of BLA cells recruited in different types of tasks or do all BLA cells, irrespective of their projection site(s), behave similarly during emotional arousal? The finding that not only BLA but also stria terminalis lesions block the memory modulating effects of adrenal stress hormones (Roozendaal and McGaugh, 1996a,b) implies that BLA actions in target structures are involved. Because different nuclei of the BLA (lateral, basolateral and basomedial nuclei) have distinct extrinsic projections (reviewed in Pitkänen, 2000), one would anticipate that different subsets of BLA cells are involved depending on the storage site of the particular memory that is probed by the task. For instance, in the visible platform water maze task believed to depend on a striatal storage site (Packard and Teather, 1998), one would predict that the lateral amygdala is not involved since it has little if any striatal projections (Royce, 1978; Russchen et al., 1985). However, little work has been done to test this idea.

Another possibility is that the memory modulating effects of the BLA depend on projections to one or more structures with promiscuous projections. In support of this scenario, recent work suggests that interfering with prefrontal activity with local injections of the glutamate receptor antagonist CNQX blocks the memory enhancing effects of post-training NA injections in the BLA and reciprocally (Liang, 2001). Similarly, immunotoxic lesions of basal forebrain cholinergic neurons block the BLA-mediated enhancement of memory consolidation in the inhibitory avoidance task (Power et al., 2002).

Yet, other data suggests that, in some circumstances at least, specific groups of BLA neurons might be involved in the modulation. In several studies, BLA lesions were reported to abolish the memory facilitation produced by drug injections in particular projection sites of the BLA. To cite a few examples, this is the case of the facilitated inhibitory avoidance retention produced by 8-Br-cAMP injections in the entorhinal cortex (Roesler et al., 2002) or by glucocorticoid infusions in the hippocampus (Roozendaal and McGaugh, 1997). Although these experiments lend themselves to other interpretations, they are compatible with the idea that these entorhinal or hippocampal manipulations recruited a subset, by opposition to the entire pool, of BLA neurons.

Finally, even though different pools of BLA neurons might be critical for the memory modulating effect depending on the task, it is possible that emotional arousal recruits BLA cells indiscriminately. According to this scenario, the BLA would send the same signal in all emotionally arousing tasks; the particular environmental contingencies and neuronal networks involved in coding them would determine which type of memories is (are) facilitated.

5.2. Changes in basolateral activity produced by emotional arousal

Irrespective of where the BLA acts to facilitate memory consolidation, it appears unlikely that emotional stress involves a dramatic and general increase in the firing rate of BLA neurons. Indeed, electrophysiological studies have revealed that BLA neurons are subjected to powerful inhibitory pressures: (1) interneurons that generate large-amplitude inhibitory synaptic potentials (Lang and Paré, 1997a; Samson et al., 2003) and (2) projection cells endowed with a Ca^{2+}-dependent K^{+} current that can be activated by sub-threshold synaptic inputs (Lang and Paré, 1997b; Danober and Pape, 1998; Chen and Lang, 2000). Moreover, the reversal potential of GABAa responses is much closer to spike threshold in BLA interneurons than in projection cells (Lang and Paré, 1998; Martina et al., 2001). This difference arises from cell type specific chloride homeostatic mechanisms whereby the prevalent regulators of the intracellular chloride concentration are cation-chloride cotransporters that accumulate chloride in interneurons and extrude chloride in projection cells (Martina et al., 2001).

As a result, the spontaneous firing rate of BLA projection cells is unusually low (Paré and Gaudreau, 1996). In fact, emotional arousal produced by the anticipation of a noxious stimulus is only accompanied by a modest increase in firing rate (Paré and Collins, 2000). However, the discharges of simultaneously recorded BLA neurons were reported to become more synchronized through a modulation at the theta frequency (Paré and Collins, 2000).

Two non-exclusive factors probably contribute to the appearance of theta oscillations in the BLA during the anticipation of noxious stimuli. First, BLA neurons are endowed with intrinsic membrane properties that predispose them to oscillate or reverberate in this range of frequencies (Paré et al., 1995b; Pape and Driesang, 1998). Second, the BLA receives synaptic inputs from the rhinal cortices and hippocampal formation (reviewed in McDonald, 1998) where rhythmic neuronal activity in the theta range has been observed (Mitchell and Ranck, 1980; Buzsáki et al., 1983; Alonso and Garcia-Austt, 1987; Collins et al., 1999). Finally, it should be noted that the propensity of rhinal and hippocampal areas to generate theta activity increases during EEG-activated states and arousal (Green and Arduini, 1954; Collins et al., 1999).

Therefore, it is possible that the theta activity of amygdala neurons during emotional arousal promotes memory by facilitating interactions between neocortical storage sites and the declarative memory system of the temporal lobe.

How would periodic amygdala activity at the theta frequency play this role? First, as mentioned above, glutamatergic projection neurons of the BLA have extremely low firing rates (Paré and Gaudreau, 1996), even during emotional arousal (Paré and Collins, 2000). Thus, the temporal clustering of neuronal discharges at the theta frequency greatly enhances the depolarization produced by BL activity on

target structures. Second, it is important to realize that much of the temporal lobe is oscillating at the theta frequency during emotional arousal (Paré and Gaudreau, 1996; Alonso and Garcia-Austt, 1987) and that amygdala and hippocampal theta are highly correlated (Paré and Gaudreau, 1996; Pape and Stork, 2003). Third, coherent oscillations cause short recurring time-windows that facilitate synaptic interactions between phase-locked oscillators. Fourth, coincident presynaptic versus postsynaptic activity is critical to synaptic plasticity (Malenka, 1994).

It is thus possible that by telescoping the periods of effective synaptic interactions in short time-windows, amygdala oscillations at the theta frequency exert a depolarizing action that promotes synaptic plasticity in co-active structures of the temporal lobe and neocortex. Consistent with this idea, the conduction times of BLA axons to the rhinal cortices are adjusted to compensate for variations in distance between the BL complex and distinct rostrocaudal rhinal sites (Pelletier and Paré, 2002). As a result, BL neurons can generate simultaneous rhythmic depolarizations at spatially distributed rhinal sites and facilitate hebbian associations between coincident activity patterns.

In rats, intra-amygdala lidocaine injections up to 6 h post-learning interfere with the facilitating effects of emotion on recall assessed days later (Parent and McGaugh, 1994). Since rats normally spend significant amounts of time sleeping in 6 h, this finding raises the possibility that the activity of amygdala neurons during sleep also contributes to the consolidation of emotional memories.

Indeed, much work indicates that the BLA and perirhinal cortex generate highly synchronized slow oscillatory activity associated with prominent fluctuations in firing probability during EEG-synchronized states (Paré and Gaudreau, 1996; Collins et al., 2001). In addition, the BLA generates synchronized population bursts during slow-wave sleep and under barbiturate anesthesia (Paré et al., 1995a). These synchronized population discharges give rise to brief, large-amplitude potentials, termed sharp potentials, in the rhinal cortices (Paré et al., 1995a; Collins et al., 1999) and, after a brief delay, in the dentate gyrus (Paré et al., 1995a).

It is possible that the synchronized activity of BLA neurons during sleep also contributes to the consolidation of emotional memories. According to this view, despite storage facilitation by amygdala theta during wakefulness, representations would remain labile. Subsequent sleep activity would, through a still undefined mechanism, consolidate these representations.

In support of this idea, much evidence suggests that sleep plays a pivotal role in synaptic plasticity and memory (reviewed in Benington and Frank, 2003). For instance, slow-wave sleep enhances cortical reorganization of ocular dominance columns following monocular deprivation (Frank et al., 2001). Moreover, it was shown that sleep after training is essential for the consolidation of some forms of procedural memory such as visual discrimination skills (Gais et al., 2000; Stickgold et al., 2000). However, the facilitating effect of sleep is not limited to procedural memory as sleep deprivation produces marked impairments of episodic memory (Plihal and Born, 1999).

It was proposed that the facilitating effect of sleep on memory consolidation depends on the synchronized neuronal events taking place during this state of vigilance. For instance, one model of episodic memory (Buzsáki, 1989) postulates that during waking, information is initially stored in the CA3 region of the hippocampus via changes in the strength of connections between pyramidal neurons. Later on during SWS, synchronized population discharges of CA3 neurons in relation to events known as sharp waves would "replay" the representations stored in the CA3 network and via the rhinal cortices, reactivate associative cortical neurons representing features of the event of interest. Ultimately, this replay of stored representations would lead to long-term synaptic changes in associative cortical networks.

Such models are consistent with the fact that the medial temporal lobe plays a time-limited role in memory (Squire and Cohen, 1979). Moreover, they are supported by electrophysiological studies where evidence of sleep replay of waking activity patterns was obtained (Wilson and McNaughton, 1989).

In the case of the amygdala however, there is no need to invoke actual storage of waking activity in the intra-amygdaloid network. Sleep events would not "replay" waking activities, but would recruit cortical neurons randomly. Specificity of the consolidation process might be ensured by activity-dependent "tagging" of particular groups of synapses in wakefulness (Frey and Morris, 1998).

5.3. Effect of increased basolateral activity on target neurons

The above section emphasized the poor spontaneous activity of BLA neurons. Although arousal produces some increase in BLA activity and a modification of firing pattern, the change remains modest. How could such subtle alterations have a significant impact on synaptic plasticity? A possible solution to this enigma might reside in the particular cell type contacted by amygdalofugal axons.

Electron microscopic observations have revealed that the axon terminals of BLA projection cells are enriched in glutamate (Smith and Paré, 1994) and that they only form asymmetric synapses, typically (and in some cases exclusively), with dendritic spines (perirhinal cortex, Smith and Paré, 1994; insula, Paré et al., 1995c; striatum, Kita and Kitai, 1990). For electron microscopists, these are code words for excitatory inputs to projection neurons as inhibitory local-circuit cells are generally spineless (Ribak, 1978; Freund et al., 1983). These ultrastructural findings suggest that what might distinguish BLA axons from other glutamatergic inputs is the paucity of inhibitory interneurons they contact. Unfortunately, too few ultrastructural studies have been completed to determine whether this applies to all BLA projections.

There are other possibilities, all of which remain to be investigated. They are mentioned here in the hope that this might stimulate experimentation. First, the dynamic release properties of BLA axon terminals might favor high fidelity transfer. In the cerebral cortex for instance, pyramidal to pyramidal synapses show a rapid depression when repetitively activated (Thomson and Deuchars, 1997). Perhaps BLA axons are more resistant to activity dependent depression due to a different release machinery and/or distinct presynaptic inhibitory influences.

Another possibility is that the density and/or particular complement of glutamate receptors found postsynaptic to BLA axon terminals differs from other inputs to target neurons. For instance, a higher NMDA to non-NMDA receptor ratio would favor NMDA-dependent plasticity. It has been proposed that a higher NMDA/AMPA ratio contributes to the ability of prefrontal cortical neurons to generate persistent delay activity, a property often equated to short-term memory (Fuster and Alexander, 1971; Chafee and Goldman-Rakic, 1998). Although this hypothesis was not supported in the prefrontal cortex (Myme et al., 2003), it remains to be tested for BLA synapses.

Finally, as will become clear in the next section, it is possible that the BLA does not facilitate memory consolidation via direct interactions with storage sites, but indirectly, via the recruitment of modulatory cell groups. This scenario is supported by the fact that immunotoxic lesions of cholinergic basal forebrain neurons block the memory enhancement produced by BLA injections of NA (Power et al., 2002).

In thinking about this issue, it should be kept in mind that, depending on the task, the BLA might modulate memory via different mechanisms.

5.4. Facilitation of hippocampal long-term potentiation by the basolateral complex

Although the particular properties that allow BLA synapses to facilitate memory remain unidentified, a wealth of data indicate that the BLA does facilitate synaptic plasticity. A rapidly growing literature indicates that the BLA facilitates LTP of perforant path inputs to the dentate gyrus, a cellular model of memory. Indeed, it was reported that BLA but not CEA stimulation facilitates (Ikegaya et al., 1995, 1996; Akirav and Richter-Levin, 1999; Frey et al., 2001) whereas BLA lesions reduce LTP of perforant path inputs to the dentate gyrus (Ikegaya et al., 1994). Moreover, intra-amygdaloid injections of β-adrenergic and muscarinic receptor antagonists have the same effects (Ikegaya et al., 1997; Frey et al., 2001).

In a detailed analysis of this phenomenon, Frey et al. (2001) reported that BLA stimulation only affects weak and transient forms of LTP. LTP produced by a strong tetanus does not require the BLA for its induction nor its maintenance. Since the BLA does not project to the dentate gyrus (Pikkarainen et al., 1999), the BLA influence on LTP of perforant path inputs to the dentate gyrus must be indirect. Presumably, it involves activation of noradrenergic and cholinergic cell groups projecting to the hippocampus. However, the BLA does not project directly to the medial septum and locus coeruleus, the main source of cholinergic and NA inputs to the hippocampus. Thus, even the recruitment of these modulatory cell groups by the BLA must be indirect.

6. Conclusions

To sum up, the available evidence indicates that the BLA facilitates memory consolidation in a wide variety of emotionally arousing tasks, whether their affective valence is positive or negative. It is also clear that the BLA is not the storage site for most of these facilitated memories. Rather the BLA seems to affect synaptic plasticity elsewhere in the brain. While the link between emotional arousal and BLA activation remains uncertain, it seems to involve ACh and NA release in the BLA.

Challenges for future studies include identifying how the BLA affects memory consolidation and synaptic plasticity. Different avenues of investigation are worth considering. First, it is possible that BLA synapses have particular properties such as preferential contacts with projection cells, high reliability release probability, or different complements of postsynaptic glutamatergic receptors. However, as suggested by LTP studies and the effects immunotoxic lesions of basal forebrain cholinergic neurons, it is possible that the memory modulation produced by BLA stimulation depends on the indirect recruitment of modulatory ACh and NA systems.

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