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Cholinergic modulation of memory in the basolateral amygdala involves activation of both m1 and m2 receptors

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Muscarinic cholinergic activation is a critical component of basolateral amygdala (BLA)-mediated modulation of memory consolidation. The receptor(s) mediating this activation during consolidation have not been elucidated. This study investigated the roles of muscarinic subtype 1 (m1) and subtype 2 (m2) receptors in memory enhancement, by post-training intra-BLA infusions of the non-selective muscarinic agonist oxotremorine. Rats received intra-BLA infusions of either oxotremorine alone (10 μg in 0.2 μl per side), oxotremorine together with the selective m1 antagonist telenzipine (1.7, 5.0, 17 or 50 nmol/side), oxotremorine with the selective m2 antagonist methoctramine (1.7, 5.0, 17 or 50 nmol/side), oxotremorine with a combination of the above doses of telenzipine and methoctramine, or only vehicle, immediately after inhibitory avoidance training. Performance on a 48-hour retention test was significantly enhanced in oxotremorine-treated rats relative to vehicle-infused controls. Intra-BLA co-infusion of oxotremorine with either telenzipine (5, 17 or 50 nmol/side) or methoctramine (17 or 50 nmol/side) blocked the oxotremorine-induced enhancement. Combinations of these antagonists did not act additively to block memory enhancement by oxotremorine. These findings indicate that modulation of memory consolidation induced by cholinergic influences within the BLA requires activation of both m1 and m2 receptor synapses. Plausible mechanisms for m1- and m2-mediated influences on BLA circuitry are discussed. *Behavioural Pharmacology* **14:207–213**

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Introduction

Extensive evidence indicates that post-training drug and hormone treatments modulate memory consolidation (McGaugh, 1966, 1989; Gold and van Buskirk, 1978; Sternberg *et al.*, 1985) and that such memory modulatory effects are mediated by the basolateral group of nuclei in the amygdala (BLA) (Gallagher and Kapp, 1978; Gallagher *et al.*, 1981; Liang *et al.*, 1986a, b; Cahill and McGaugh, 1991; Parent and McGaugh, 1994; McGaugh *et al.*, 1993; Roozendaal *et al.*, 1996, 1997; Roozendaal and McGaugh, 1997; Power *et al.*, 2002). Post-training memory modulatory treatments have been shown to involve activation of muscarinic cholinergic receptors in the BLA (Baratti *et al.*, 1984 Dalmaz *et al.*, 1993, Introini-Collison *et al.*, 1996; Vazdarjanova and McGaugh, 1999; Power *et al.*, 2000; Passani *et al.*, 2001; Cangioli *et al.*, 2002), by afferent cholinergic projections from the nucleus basalis magnocellularis (Power and McGaugh, 2002).

Subtype 1 muscarinic (m1) and subtype 2 muscarinic (m2) receptors are generally considered to induce excitatory and inhibitory responses, respectively (Brann *et al.*, 1987; Peralta *et al.*, 1988;). There are high densities of both the m1 and m2 receptor types in the BLA (Spencer *et al.*, 1986). Transmission electron microscope imaging has demonstrated both asymmetric (presumed excitatory) and symmetric (presumed inhibitory) cholinergic synapses in the BLA (Wainer *et al.*, 1984; Li *et al.*, 2001). Although m2 receptors may function as presynaptic autoreceptors (Starke, 1981; Briggs and Cooper, 1982; Galarraga *et al.*, 1999), the prevalence of symmetric cholinergic synapses in the BLA (Wainer *et al.*, 1984; Li *et al.*, 2001) suggests that m2 receptors in the BLA may directly mediate a sizable portion of cholinergic signals to postsynaptic neurons in the BLA. The specific contributions of m1 and m2 receptor signaling pathways in the BLA, in mediating the critical role of muscarinic cholinergic signaling in the BLA during memory modulatory processes (Dalmaz *et al.*, 1993, Introini-Collison *et al.*, 1996; Power *et al.*, 2000; Power and McGaugh, 2002; McIntyre *et al.*, 2003), has not as yet been investigated.

The current experiment investigated whether enhancement of memory with increased intra-BLA muscarinic cholinergic activation, immediately after training, re-

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quires activation of m1, m2 or both m1 and m2 receptors in the BLA. Rats with bilateral guide cannulae aimed at the BLA were trained in a one-trial learning inhibitory avoidance (IA) task. Immediately after the training, rats received selective pharmacological stimulation of m1, m2 or both m1 and m2 receptors in the BLA. Receptor types were selectively activated by administering a general muscarinic agonist together with selective muscarinic receptor antagonists. This procedure permits greater selectivity in the activation of receptor subtypes than does administration of selective muscarinic agonists. Antagonists were used because with administration of selective agonists, the non-targeted receptor type would still be activated at normal levels by endogenous acetylcholine. If cholinergic-mediated memory modulatory processes in the BLA involves only, or primarily, either the m1 or m2 receptors, then selective activation of that receptor type (m1 or m2), but not the other, should enhance memory, as assessed by performance on a 48-hour retention test. However, if both are directly involved and necessary, then animals that received selective activation of either type alone should not show enhanced memory on the retention test. If m2 receptors mediate primarily an autoreceptor, negative feedback function in BLA memory modulatory processes, then selective activation of m1 receptors may have a stronger memory-enhancing effect than co-activation of both receptor types.

Methods

Subjects

One hundred and sixty-nine male Sprague–Dawley rats from Charles River Laboratories (Wilmington, Massachusetts, USA) were used in this study. The rats weighed approximately 300 g at the time of surgery and were housed individually in a temperature-controlled (22°C) vivarium. Food and water were freely available and the lights were on from 07.00 h to 19.00 h. Rats were given 1 week to be acclimatized to the vivarium before surgery. All behavioral procedures were conducted between 09.00 h and 15.00 h. All procedures were in accordance with the NIH guidelines and were approved by the IACUC.

Surgery

Rats were prepared for surgery with administration of sodium pentobarbital anesthetic (50 mg/kg, i.p.), atropine sulfate to maintain respiration (0.1 mg/ 2 ml, i.p.), and 0.9% sterile saline to prevent dehydration (2.5 ml, s.c.). Each rat was placed in a small animal stereotaxic frame (Kopf Instruments, Tujunga, California, USA) and implanted with bilateral 15 mm guide cannulae (23 gauge) aimed at the BLA. The following stereotaxic coordinates were used, according to the atlas of Paxinos and Watson (1997): 2.8 mm posterior and 5.0 mm lateral to bregma, and 6.5 mm ventral to the skull surface. The cannulae were fixed in place with dental cement and two anchoring surgical screws (Small Parts Inc., Miami Lakes, Florida, USA). After the surgery, 15 mm-long stylets (00 insect dissection pins) were inserted into the cannulae to maintain patency. Rats were kept in an incubator until they awoke from the anesthesia.

Inhibitory avoidance

The IA apparatus was a trough-shaped alley (91 cm long and 20 cm deep), divided by a sliding door into a lit safe compartment (31 cm long) and a dark shock compartment (60 cm long). Behavioral training and testing were conducted in a light- and sound-attenuated room. Rats were allowed 1 week to recover from the surgery before IA training, and were handled on the 3 days prior to training for 60 s each day, to allow habituation to the post-training drug administration procedure.

Rats were removed from their home cages, placed directly into the lit safe compartment, facing away from the dark compartment, and allowed to enter the dark shock compartment. After each rat stepped into the dark compartment with all four paws, the sliding door was closed behind it and it received a single inescapable mild footshock (0.5 mA, 1.0 s). Fifteen seconds after the shock, rats were removed from the dark shock compartment and given intra-BLA infusions. Rats were replaced into their homecages immediately after drug administration. Retention for IA training was tested 48 h later. During retention testing, rats were placed into the lit safe compartment and allowed to enter the dark compartment just as during training. The latency (s) for each rat to step completely into the dark compartment with all four paws was recorded. Enhanced memory was inferred from longer retention latencies relative to vehicle-infused controls. The experimenter was blind to the group designations of the rats during behavioral training and testing procedures.

Drug administration

Drug solutions were administered directly into the BLA immediately after training, to selectively affect the consolidation phase of memory. Control animals received infusions of only the vehicle solution (0.9% sterile saline). All other animals received either the non-selective muscarinic agonist oxotremorine alone (OXO; sesquifumarate salt, 10 μg/side), OXO (10 μg/side) together with the selective m1 receptor antagonist telenzipine 2HCl (TEL, 1.7, 5.0, 17 or 50 nmol) in a cocktail, OXO (10 μg/side) together with the selective m2 receptor antagonist methoctramine tetrahydrochloride (MET, 1.7, 5.0, 17 or 50 nmol) in a cocktail, or OXO (10 μg/side) together with both a subeffective dose of TEL and a subeffective dose of MET in a cocktail. The dose of OXO used in this study has been shown previously to enhance memory for shock avoidance training when administered into the BLA post-training (Vazdarjanova and McGaugh, 1999). The highest

present doses (50 nmol) of TEL and MET were shown previously to selectively affect amygdalar muscarinic receptor subtypes in a study that demonstrated selective m1 but not m2 mediation of intraventricular carbachol-induced pressor responses (Aslan *et al.*, 1997). All drugs were purchased from RBI (Natick, Massachusetts, USA).

The drug solutions (0.2 µl/side) were infused into the BLA at a constant rate over 25 s by automated syringe pumps (Sage Instruments, Boston, Massachusetts, USA), via 30-gauge injection needles connected to 10 µl Hamilton microsyringes by PE-20 polyethylene tubing. The needles were left in place for an additional 30 s after infusion to allow diffusion of the solutions into the BLA. This drug infusion volume is small enough to selectively affect the BLA region of the amygdala (Roozendaal and McGaugh, 1997; Da Cunha *et al.*, 1999).

The present study used a pharmacological strategy to isolate the roles of m1 or m2 receptor subtypes. An m1 or an m2 receptor antagonist, respectively, was combined with a nonselective muscarinic agonist shown previously to enhance memory storage (Baratti *et al.*, 1984; Dalmaz *et al.*, 1993; Introini-Collison *et al.*, 1996; Salinas *et al.*, 1997; Vazdarjanova and McGaugh, 1999; Cangioli *et al.*, 2002). The rationale for this approach, rather than the use of selective m1 or m2 agonists, was twofold. First, whereas direct stimulation of one receptor type with a putative selective agonist would presumably produce disproportionately greater activation of that receptor type, the other receptor type might still be activated by endogenous acetylcholine. Therefore, such an approach would not rule out a contribution by a receptor type not targeted by an agonist. Second, the selectivity and affinity of TEL and MET as muscarinic subtype-specific antagonists are particularly well documented. TEL has a tenfold greater affinity than, and a selectivity equal to, that of the widely used m1 receptor antagonist pirenzipine (Schudt *et al.*, 1988), coupled with an unusually slow dissociation rate (at 37°C, $t_{1/2} = 35$–46 min), (Schudt *et al.*, 1988; Galvan *et al.*, 1989). MET has been described as the most selective m2 antagonist currently available (Melchiorre *et al.*, 1987; Giraldo *et al.*, 1988; Michel and Whiting, 1988) and has been used extensively *in vitro* (Sugita *et al.*, 1991) and *in vivo* (Massi *et al.*, 1989; Smolders *et al.*, 1997).

Histology

The rats were anesthetized with an overdose of sodium pentobarbital (100 mg/kg) and perfused intracardially with 0.9%. saline solution followed by 4% weight/volume formaldehyde solution. The fixed brains were removed and placed into formaldehyde solution. Two days later, the brains were transferred to 30% sucrose solution, where they were stored for at least 2 days before slicing. Forty-micron thick coronal sections were collected with a freezing microtome. Sections were mounted onto gelatin-coated glass slides and stained with thionin to visualize the infusion needle tracks. Behavioral data from animals that did not have both infusion needle tracks terminating within the BLA were excluded from statistical analysis.

Statistics

The behavioral data were analyzed with a two-way analysis of variance (ANOVA), with intra-BLA drug treatment as the between-subjects variable. Specifically, the mean retention latencies, for the range of doses of each antagonist or combination of antagonists, were compared to vehicle controls and rats that received only OXO. Fisher's *post-hoc* tests were performed to determine the sources of detected significance. Probability levels of less than 5% were considered significant. Retention latencies are reported with standard errors of the means.

Results

Histology

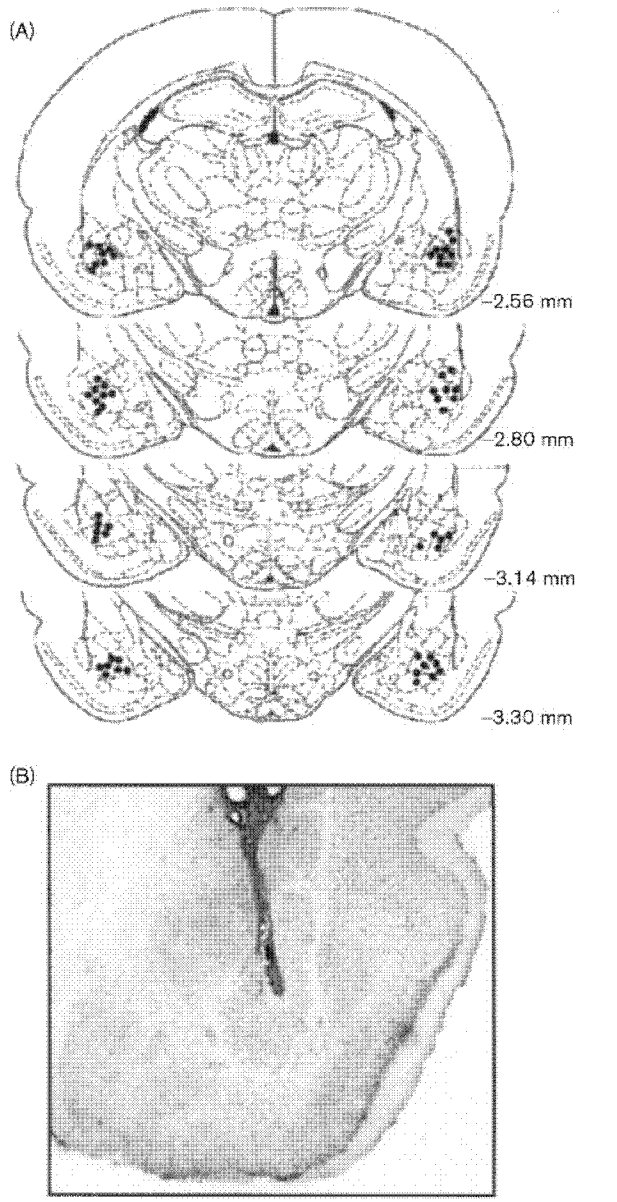
One hundred and twenty-seven rats were confirmed to have both infusion needle tracks terminating within the BLA and were included in the behavioral data analysis. A representative example of infusion needle termination sites of 30 randomly selected rats included animals (A) and a photomicrograph of a representative example of an intra-BLA infusion needle track (B) are shown in Fig. 1.

Inhibitory avoidance

The behavioral data are summarized in Fig. 2. Two-way ANOVAs revealed a significant effect of the intra-BLA TEL treatment [$F(5,70) = 10.27$; $P < 0.001$], and a significant effect of the intra-BLA MET treatment [$F(5,70) = 7.68$; $P < 0.001$]. The OXO treatment significantly increased the mean retention latency (164.82 ± 25.81 s, $n = 22$) relative to vehicle-infused controls (49.28 ± 7.30 s, $n = 21$; $P < 0.001$). The 5 nmol (99.86 ± 29.33 s, $n = 7$), 17 nmol (37.50 ± 9.07 s, $n = 6$) or 50 nmol (31.19 ± 4.60 s, $n = 16$) doses of TEL blocked OXO-induced memory enhancement ($P < 0.05$, $P < 0.001$ and $P < 0.001$, versus OXO alone, respectively). The mean retention latency of the 1.7 nmol dose of TEL together with OXO group (201.25 ± 25.44 s) did not differ from that of rats that received OXO alone (NS). The 17 nmol (83.00 ± 17.94 s) or 50 nmol (50.80 ± 11.39 s) doses of MET blocked OXO-induced memory enhancement ($P < 0.05$ and $P < 0.001$, versus OXO alone, respectively). The mean retention latencies of the 1.7 nmol (151.40 ± 24.06 s) and 5 nmol (218 ± 65.05 s) doses of MET together with OXO groups did not differ from those of rats that received OXO alone (NS). Thus the memory-enhancing effect of OXO could be blocked by the sufficient presence of either an m1 receptor antagonist or an m2 receptor antagonist.

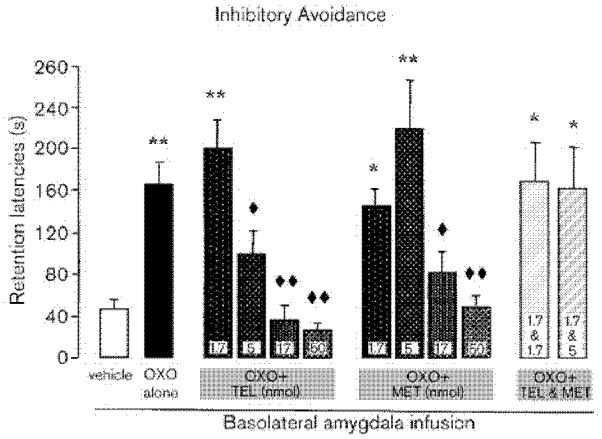
Administration of the 1.7 nmol dose of TEL together with the 1.7 or 5.0 nmol doses of MET did not combine

Fig. 1



Data from 127 rats with both infusion needles that terminated within the basolateral amygdala (BLA) were included. Coordinates are posterior to bregma. (A) The locations of acceptable needle tips from a random sample of 30 rats whose retention latencies were included in the statistical analysis of the behavioral data are indicated by the solid circles. (B) Photomicrograph of a representative example of an infusion needle track terminating in the BLA.

Fig. 2



Oxotremorine (OXO; 10 μg in 0.2 μl/side) infused into the basolateral amygdala (BLA) immediately after inhibitory avoidance (IA) training enhances memory on a 48-hour retention test. Co-infusion of the selective m1 receptor antagonist telenzipine (TEL) at 5.0, 17 or 50 nmol doses, or the selective m2 receptor antagonist methoctramine (MET) at 17 or 50 nmol doses, blocked the OXO-induced memory enhancement. The retention performance of the OXO + 1.7 nmol TEL and OXO + 1.7 or 5.0 MET groups did not differ from that of the vehicle-infused control group. $*P<0.05$ and $**P<0.001$ versus vehicle-infused controls; ◆$P<0.05$ and ◆◆$P<0.001$ versus OXO alone.

additively to block OXO-induced memory enhancement [$F(3,57) = 5.519$, $P < 0.01$]. The mean retention latencies of OXO + 1.7 nmol TEL + 1.7 nmol MET (152.33 ± 40.18 s) and of OXO + 1.7 nmol TEL + 5.0 nmol MET (160.40 ± 45.68 s) were greater than those of vehicle-infused controls ($Ps < 0.01$), but did not differ from that of rats that received OXO alone (NS).

The drug infusions produced no observable nonspecific behavioral effects, such as ataxia or seizures. Furthermore, our findings that intra-BLA memory modulatory drug treatments, such as those included in this study, modulate memory for appetitive (Sternberg *et al.*, 1985; Oscos *et al.*, 1988; Salinas and McGaugh, 1996) as well as aversive tasks indicate that the infusions themselves do not act as negative reinforcers. And because all drugs were given immediately after training they could not have directly affected behavior or performance during acquisition (training) or retrieval (testing). Rats that received OXO infusions outside the BLA due to misplaced cannulae ($n = 4$) did not show enhanced IA retention (41 ± 13.08 s).

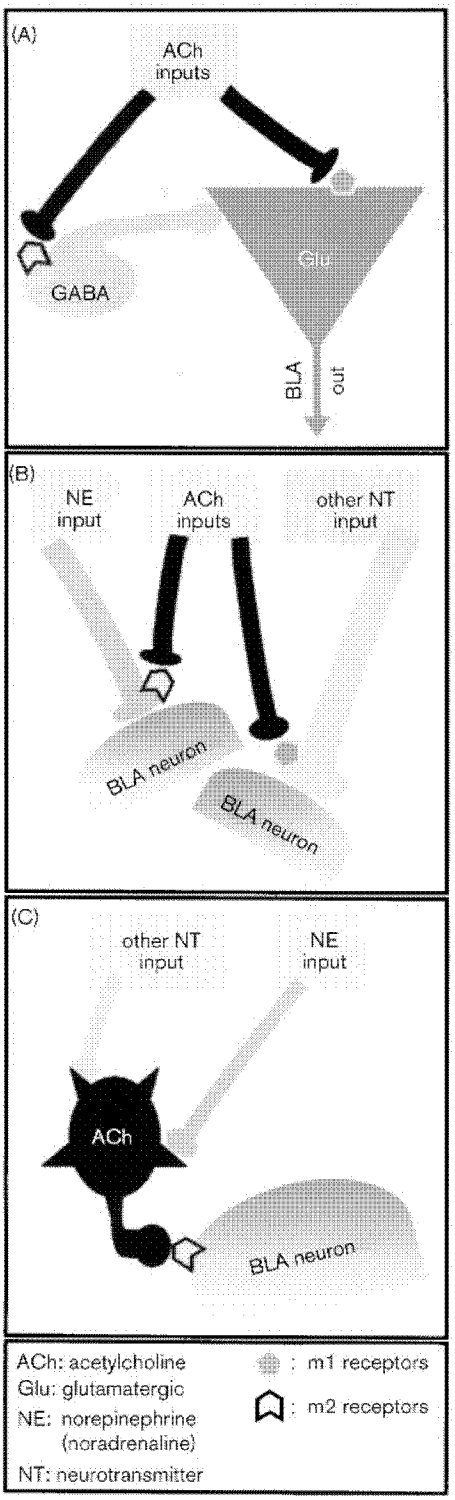
Discussion

This study investigated the involvement of two major muscarinic receptor subtypes in BLA-mediated memory modulatory processes. Post-training intra-BLA infusions of OXO enhanced retention for IA. This finding is consistent with previous reports that muscarinic cholinergic drugs enhance memory when administered into the amygdala (Dalmaz *et al.*, 1993; Riekkinen *et al.*, 1993; Introini-Collison *et al.*, 1996; Salinas *et al.*, 1997) or administered selectively into the BLA (Vazdarjanova and McGaugh, 1999; Cangioli *et al.*, 2002; Power and McGaugh, 2002). This finding is also consistent with numerous reports that cholinergic activation in the amygdala is important for retention of IA training

(Duméry and Blozovski, 1987; Decker *et al.*, 1990; Riekkinen *et al.*, 1993; Passani *et al.*, 2001; Power and McGaugh, 2002).

Memory enhancement with post-training intra-BLA OXO treatment was blocked by concurrent blockade in the BLA of either m1 receptors with TEL or m2 receptors with MET. Co-administration of the subeffective doses of each selective antagonist together with OXO into the BLA did not combine to attenuate the memory-enhancing effect of intra-BLA OXO. Therefore it is unlikely that the effects of m1 and m2 receptor activation may simply summate to produce effects on memory consolidation. Rather, these findings suggest that activation of each receptor subtype may provide a dissociable contribution to BLA processing during consolidation. If both receptor types are critically involved in BLA-mediated muscarinic cholinergic modulation of memory, as the present findings suggest, then post-training administration of a selective m1 or m2 agonist also should not enhance memory with the opposite antagonist co-administered into the BLA.

Fig. 3



It is worth noting that none of the TEL- or MET-treated groups had mean retention latencies significantly lower than that of vehicle-infused controls. Thus, none of these selective antagonist doses prevented consolidation of the fundamental context-shock association learned during IA training. Such pharmacological blockade of enhancement, without completely inhibiting consolidation of the context–shock association, has been shown previously with intra-BLA infusions of the general muscarinic antagonist atropine, at doses that did not impair IA retention alone (Dalmaz *et al.*, 1993; Introini-Collison *et al.*, 1996; Power *et al.*, 2000). However, the possibility that the present effective doses of TEL and/or MET may further impair IA memory in the absence of pharmacologically augmented muscarinic receptor agonism was not tested in the present study. Similarly, it may be that higher, as yet untested doses of TEL and MET may result in IA memory worse than that of controls.

It is possible that memory modulation requires either a threshold level of activation of each receptor subtype or a proper balance of m1- and m2-receptor-mediated influences in the BLA during consolidation. In the latter case, disruption of this balance by either antagonist alone may prevent memory enhancement. In either case, the

Both m1 and m2 receptors are involved in basolateral amygdala (BLA)-mediated memory modulation, a variety of cholinergic elements have been described in the BLA, and cholinergic stimulation of the BLA has robust eects on electrical activity in the BLA and behavior. Several possible mechanisms of muscarinic cholinergic influences in the BLA that may combine to mediate these eects are represented here. (A) Direct excitation of postsynaptic cells in the BLA: cholinergic inputs [i.e. from the nucleus basalis magnocellularis] may synergistically inhibit γ-aminobutyric acid (GABA) interneurons and glutamatergic projection neurons, or vice versa. (B) Influencing neurotransmitter release: axo-axonic cholinergic synapses may regulate the release of neurotransmitters in the BLA from other neuromodulatory systems, such as norepinephrine, and perhaps glutamate from cortical inputs. (C) Local signaling: cholinergic local circuit neurons, postsynaptic to BLA input neurons and presynaptic to other BLA neurons, may participate in information processing.

present findings further suggest that the m2 receptors in the BLA are involved in critical cell–cell signaling, rather than or in addition to simple autoreceptor-regulation of acetylcholine release from cholinergic terminals.

There are many possible mechanisms by which cholinergic signaling via m1- and m2-mediated synapses may function in memory modulatory processes in the BLA. There are both asymmetric and symmetric axo-somatic cholinergic synapses within the BLA (Wainer *et al.*, 1984; Li *et al.*, 2001). Considered together with the present findings, and as illustrated in Fig. 3A, those observations suggest that both m1 and m2 receptor synapses directly influence the activity of postsynaptic neurons in the BLA. Inhibitory cholinergic 'serial synapses' have also been identified in the BLA (Li *et al.*, 2001), in which cholinergic inputs to the BLA formed symmetric axo-axonic synapses on noncholinergic presynaptic terminals. Therefore muscarinic receptors in the BLA could also mediate cholinergic regulation of the release of other neurotransmitters in the BLA, as illustrated in Fig. 3B. Consistent with this hypothesis is the finding that, in the lateral nucleus of the BLA, administration of cholinergic agonists has been reported to reduce glutamatergic and GABAergic synaptic transmission *in vitro* (Sugita *et al.*, 1991). Additionally, small local-circuit cholinergic neurons have been observed within the BLA (Carlsen and Heimer, 1986), which are postsynaptic to noradrenergic and other noncholinergic terminals (Li *et al.*, 2001). These observations suggest that cholinergic synapses originating from such cholinergic interneurons, as illustrated in Fig. 3C, are also involved in neuronal processing downstream of noradrenergic and other neurotransmitter type inputs to the BLA. Previous findings from this laboratory, indicating that muscarinic cholinergic antagonism in the BLA blocks memory modulation induced by post-training noradrenergic (Dalmaz *et al.*, 1993; Introini-Collison *et al.*, 1996) and noradrenergic-dependent (Roozendaal, 2000) glucocorticoid (Power *et al.*, 2000) treatments, are consistent with this view.

In summary, the current findings suggest that both m1 and m2 receptors are important mediators of memory modulatory processes in the BLA. The necessity for both presumptive excitatory and inhibitory cholinergic synapses in OXO-induced enhancement of memory consolidation, together with the variety of cholinergic elements described in the BLA (Wainer *et al.*, 1984; Li *et al.*, 2001), indicate that the cholinergic system has multiple roles in BLA-influenced information processing. The evidence summarized above suggests that these roles may include a combination of: (1) directly influencing postsynaptic cells in the BLA (such as glutamatergic projection neurons and GABAergic interneurons); (2) influencing the release of other neurotransmitters in the BLA; and (3) participating in processing signals from noradrenergic and other inputs to the BLA (summarized in Fig. 3).

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