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Roles of $GABA_A$, NMDA and muscarinic receptors in induction of long-term potentiation in the medial and lateral amygdala in vitro

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Abstract

We have studied mechanisms underlying long-term potentiation (LTP) in the medial and lateral amygdala using in vitro slice preparations. In normal bathing medium, LTP was not induced by tetanic stimulation (100 pulses at 100 Hz). However, in the presence of a $GABA_A$ blocker, picrotoxin or bicuculline, LTP was reproducibly induced in both medial and lateral amygdala. In the medial amygdala, the LTP induced in the presence of picrotoxin was blocked by 2-amino-5-phosphonovalerate (APV), an NMDA receptor antagonist, and was significantly reduced by scopolamine, a muscarinic receptor antagonist. On the other hand, the LTP in the lateral amygdala was not affected by APV, but was significantly reduced by scopolamine. These results suggest that both NMDA receptors and muscarinic receptors are involved in the induction of medial amygdala LTP, while muscarinic receptors, but not NMDA receptors, are involved in the induction of lateral amygdala LTP.

Keywords: Long-term potentiation; Medial amygdala; Lateral amygdala; $GABA_A$ receptor; NMDA receptor; Muscarinic receptor; Brain slice; Rat

1. Introduction

The amygdala is thought to be involved in certain types of learning and memory besides emotional and motivational aspects of behavior (Sarter et al., 1985; McGaugh et al., 1990). It has been reported that the synapses of the amygdala display long-term potentiation (LTP) (Chapman et al., 1990; Chapman and Bellavance, 1992; Gean et al., 1993; Shindou et al., 1993), a long-lasting increase of synaptic strength that is widely believed to be a cellular basis of learning and memory (Bliss and Collingridge, 1993). The LTP in the amygdala may thus contribute to learning processes mediated by these brain structures. However, the mechanisms of the amygdala LTP have not yet been well understood. In the hippocampus, where LTP has been best characterized to date, the induction of LTP requires the activation of *N*-methyl-D-aspartate (NMDA) receptors in the CA1 region and in the dentate gyrus (Collingridge et al., 1983; Harris et al., 1984; Errington et al., 1987; Mizutani et al., 1991), and is influenced by γ-aminobutyric acid A ($GABA_A$) receptor-mediated inhibition (Wigstrom and Gustaffson, 1983). Moreover, the induction of hippocampal LTP is regulated by cholinergic inputs through muscarinic receptors (Tanaka et al., 1989; Burgard and Sarvey, 1990; Abe et al., 1994). Similarly, several lines of evidence suggest that NMDA receptors (Miserendino et al., 1990; Falls et al., 1992; Kim and McGaugh, 1992) and muscarinic receptors (Quillfeldt et al., 1990; Ohno et al., 1992) are involved in amygdala-related learning in living animals. Therefore, in the present study, we investigated the roles of $GABA_A$, NMDA and muscarinic receptors in the induction of LTP in the medial and lateral amygdala by using brain slice preparations in vitro.

2. Materials and methods

Whole brain isolated from male Wistar rats, 7–9 weeks old, was placed in ice-cold artificial cerebrospinal fluid (ACSF), and trimmed to a block containing the

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amygdala. The composition of ACSF was as follows: 124.0 mM NaCl, 5.0 mM KCl, 2.4 mM $CaCl_2$, 1.3 mM $MgSO_4$, 1.24 mM KH_2PO_4, 26.0 mM $NaHCO_3$ and 10.0 mM glucose. The brain block was cut into coronal slices of 400–500 μm thickness with a Vibratome. The slices were allowed to recover for more than 1 h in an incubation chamber containing ACSF which was maintained at 34°C, and continuously bubbled with 95% O_2/5% CO_2. One slice containing the desired subnuclei of the amygdala was transferred into a submersion chamber (3 ml) where warmed (34°C) and oxygenated (95% O_2/5% CO_2) ACSF was continuously perfused at a rate of 1 ml/min. A bipolar tungsten electrode was placed on the stria terminalis or the external capsule to stimulate the afferent fibers, and the evoked potential was extracellularly recorded from the medial amygdaloid nucleus or the lateral amygdaloid nucleus, respectively (Figs. 1A and C). A glass capillary microelectrode filled with 0.9% NaCl (tip resistance 2–3 Mohms) was used for the recording. A single test stimulation (0.05 ms duration) was applied at intervals of 20 s, and the evoked potential was sequentially monitored on a digital oscilloscope. For off-line analysis, the wave form of the evoked potential was recorded on an ink-writing oscillograph only when necessary (usually every 5 min). The stimulus intensity was adjusted to produce a population spike of about 50% of the maximum amplitude. The responses were allowed to equilibrate until stable baseline values were obtained for at least 10 min before application of drugs or tetanic stimulation. All drugs were delivered by perfusion. Tetanic stimulation to induce LTP was applied at the same stimulus intensity through the same electrode as used for test stimulation.

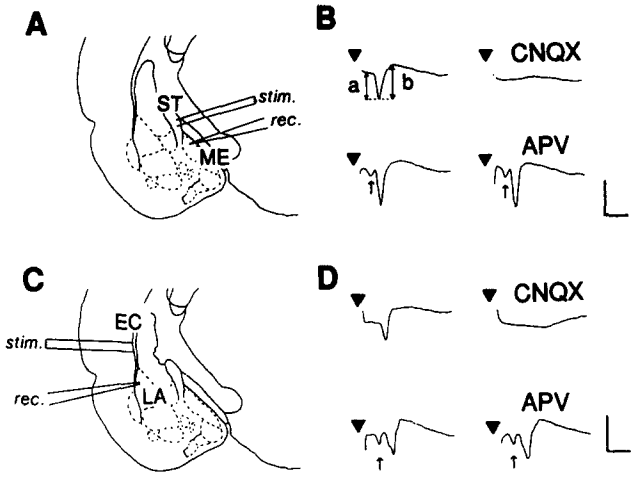

Fig. 1. Evoked potentials in the medial and lateral amygdaloid nuclei of rat brain slices. A and C: schematic illustrations of coronal amygdala slices showing locations of stimulating and recording electrodes. The stimulating electrode was placed on the stria terminalis (A, ST) or the external capsule (C, EC) and the field potential was recorded from the medial amygdaloid nucleus (A, ME) or the lateral amygdaloid nucleus (C, LA), respectively. B and D: effects of CNQX and APV on the evoked potentials in the ST-ME synapses (B) and in the EC-LA synapses (D). CNQX (30 μM) and APV (30 μM) were applied by adding to the perfusing ACSF. The left and right records in each panel are the evoked potentials 5 min before and 20 min (CNQX) or 60 min (APV) after perfusion of drugs. Test stimulation was delivered at the time indicated by arrowheads. Calibration bars: vertical 1 mV, horizontal 5 ms. The voltage difference between the sharp negative onset and the negative peak (a) and that between the negative peak and succeeding positive peak (b) were measured, and the amplitude of the population spike was calculated as (a+b)/2. The signal designated by an arrow is a non-synaptic response, since this component remained unchanged in Ca^{2+}-free ACSF.

As shown in Figs. 1B and D, stimulation of afferent fibers evoked the sharp negative-going field potential in the amygdaloid nuclei. In control experiments, we carried out intracellular recordings of evoked potentials and confirmed that the latency of peak negative field potentials (5–6 ms) corresponded well with that of intracellularly-recorded action potentials, indicating that the extracellularly-recorded sharp negativity is a population spike. A very small non-synaptic response (as indicated by arrows in Figs. 1B and D) was sometimes recorded, but this signal did not affect the induction of LTP and the effects of drugs. To quantitate changes of synaptic responses, the amplitude of population spike was measured from the data recorded on an ink-writing oscillograph. The population spike amplitude was measured as shown in Fig. 1B. In control experiments, we monitored baseline-evoked potentials for 30 min in the absence of tetanus and confirmed that the variability of baseline population spike amplitude was at most ±10%. Therefore, LTP was considered to have occurred if the potentiated spike amplitude remained at least 20% higher than the baseline value 30 min after tetanus. All data are represented as the mean ± S.E.M. of the values obtained from different slices. In the text, '*n*' indicates the number of slices tested.

3. Results

The medial amygdala field potential evoked by stimulation of the stria terminalis was completely blocked by 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX), a non-NMDA receptor antagonist, but not affected by 2-amino-5-phosphonovalerate (APV), an NMDA receptor antagonist (Fig. 1B). Similarly, the lateral amygdala field potential evoked by stimulation of the external capsule was blocked by CNQX but not by APV (Fig. 1D). These results suggest that, in both the medial and lateral amygdala, the excitatory synaptic transmission is mediated by non-NMDA receptors in our recording condition.

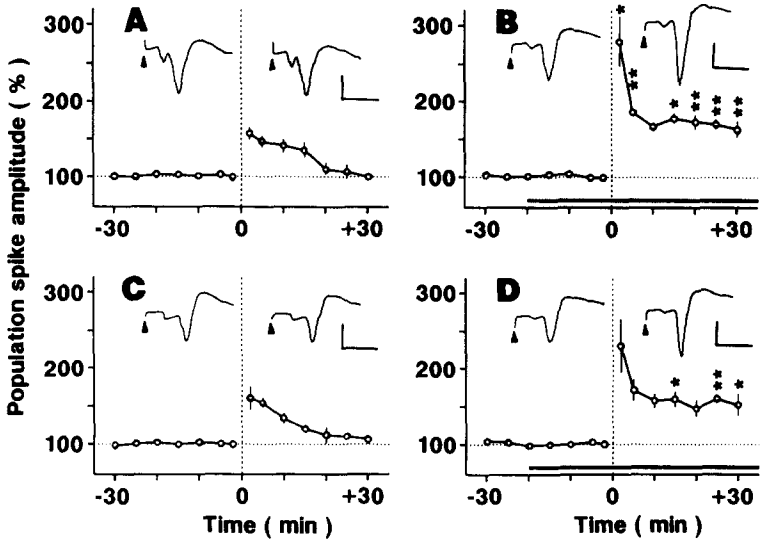

Fig. 2. Tetanus-induced potentiation of evoked potentials in the medial (A, B) and lateral amygdala (C, D) in normal ACSF (A, C) and in the presence of 10 μM picrotoxin (B, D). Abscissae indicate time (min) after application of tetanic stimulation (100 pulses at 100 Hz). Ordinates indicate population spike amplitude expressed as a percentage of baseline values immediately before tetanic stimulation. In B and D, picrotoxin (10 μM) was perfused during the time indicated by bold, horizontal bars. Typical evoked potentials recorded from one slice are shown as inset of each graph (left, immediately before tetanus; right, 30 min after tetanus). Calibration bars: vertical 0.5 mV, horizontal 5 ms. Open circles and vertical bars indicate the means and S.E.M. of the data obtained from five slices. Asterisks indicate significant differences from the data in normal ACSF (A or C): $*P < 0.05$, $**P < 0.01$; Mann-Whitney's U-test.

Next we tried to induce LTP in the medial and lateral amygdala. As shown in Fig. 2A, in normal ACSF, application of a tetanic stimulation (100 pulses at 100 Hz) to the stria terminalis increased the subsequent synaptic responses in the medial amygdala, but the potentiation declined to the baseline level within 20 min, which was regarded as short-term potentiation (STP). LTP was not induced by a 100-pulse, 100 Hz tetanus in any of five slices tested. Similarly, application of a 100-pulse, 100 Hz tetanus produced only STP in the lateral amygdala synapses (Fig. 2C). We applied various patterns of tetanic stimulations (30–1000 pulses at 50–200 Hz), but LTP was not induced by any conditions tested. Perfusion of 10 μM picrotoxin, a $GABA_A$ chloride channel blocker, did not affect the medial amygdala synaptic potentials evoked by test stimulation. However, the magnitude of potentiation induced by a 100-pulse, 100 Hz tetanus in the presence of picrotoxin was significantly larger than that under normal conditions (Fig. 2B). Moreover, the potentiation lasted longer than 30 min in all slices tested, indicating that LTP was induced in the presence of picrotoxin. Similarly, in the lateral amygdala, picrotoxin (10 μM) significantly enhanced the amplitude of tetanus-induced potentiation and facilitated the generation of LTP in all slices tested (Fig. 2D). The application of picrotoxin (10 μM) had no effects on the baseline synaptic potentials in the medial and lateral amygdala for over 50 min ($n = 3$, data not shown), ruling out the possibility that the LTP is due to the gradual increase of baseline synaptic responses caused by picrotoxin. Bicuculline (0.1 μM), a $GABA_A$ receptor antagonist, also facilitated the induction of LTP in the medial and lateral amygdala. In bicuculline-treated slices, the population spike amplitudes 30 min after a 100-pulse, 100 Hz tetanus were 167.1% ± 12.2% (% of baseline, mean ± S.E.M., $n = 5$) and 158.5% ± 10.3% ($n = 5$), in the medial and lateral amygdala, respectively.

We examined the effect of picrotoxin on the synaptic responses during high-frequency stimulation (Fig. 3). In both the medial and lateral amygdala, when repetitive stimulus pulses were applied at 10 ms intervals (100 Hz in frequency), the synaptic potentials evoked by secondary stimulations were greatly depressed. Picrotoxin (10 μM) did not affect the responses evoked by the primary stimulation, but significantly reduced the depression of population spikes to secondary stimulations. The disinhibitory effect of picrotoxin was similar between the medial and lateral amygdala synapses (Fig. 3).

In the following experiments, we investigated the roles of NMDA receptors and muscarinic receptors in LTP induction in the presence of picrotoxin. In the medial amygdala, perfusion of 30 μM APV did not affect the baseline synaptic potentials, but significantly blocked the induction of LTP (Fig. 4A). On the other hand, the induction of LTP in the lateral amygdala was not blocked by 30 μM APV (Fig. 4B). Scopolamine (3 μM), a muscarinic receptor antagonist, did not affect the baseline synaptic responses recorded before the tetanus, but

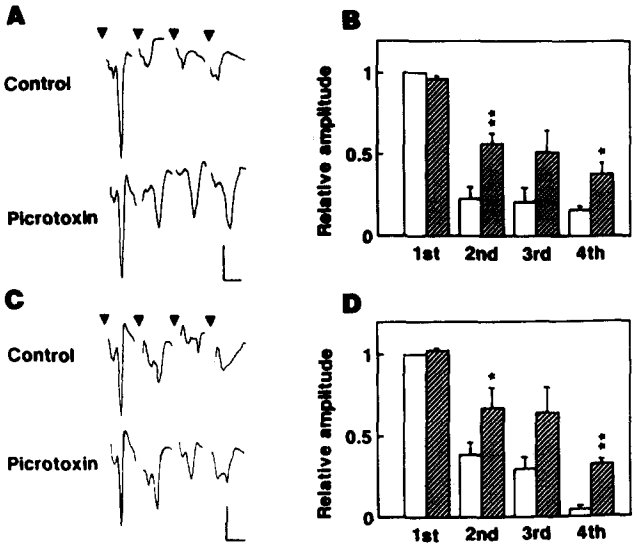

Fig. 3. Effects of picrotoxin (10 μM) on depression of evoked potentials by high-frequency repetitive stimulation (4 pulses at 100 Hz) in the medial (A, B) and lateral amygdala (C, D). A and C: sample records. The upper and lower in each panel are the records 5 min before and 20 min after perfusion of 10 M picrotoxin. Arrowheads indicate the time of stimulation. Calibration bars: vertical 0.5 mV, horizontal 5 ms. B and D: collected data from four different slices. The amplitude of population spikes evoked by primary (1st) and following stimuli (2nd, 3rd and 4th) in normal ACSF (white columns) and in the presence of picrotoxin (hatched columns) were expressed as relative values, taking the population spike amplitude evoked by primary stimulation in normal ACSF as 1, and collected as the means ± S.E.M. Asterisks indicate a significant difference from the control (white columns): $*P < 0.05$, $**P < 0.01$; Paired t-test.

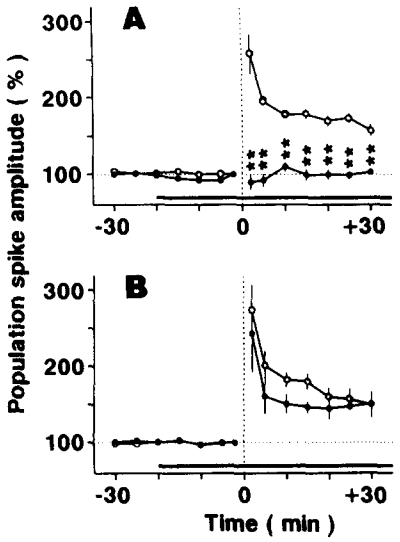

Fig. 4. Effects of APV on LTP in the medial (A) and lateral amygdala (B). During the time indicated by bold bars, 10 μM picrotoxin alone (O) or picrotoxin plus 30 μM APV (●) was perfused and tetanic stimulation (100 pulses at 100 Hz) was applied at time 0. Abscissae and ordinates are as in Fig. 2. The data are represented as the mean ± S.E.M. of the values from five different slices. Asterisks indicate a significant difference from the control data (O): $**P < 0.01$; Mann-Whitney's U-test.

significantly blocked the induction of LTP in both the medial amygdala (Fig. 5A) and the lateral amygdala (Fig. 5B). Similarly, pirenzepine (3 μM), a muscarinic M_1 receptor antagonist, significantly blocked the induction of LTP in both the medial and lateral amygdala. In picrotoxin- and pirenzepine-treated slices, the population spike amplitudes 30 min after tetanus were 114.8% ± 14.7% (n = 5) and 112.9% ± 13.5% (n = 5) in the medial and lateral amygdala, respectively.

4. Discussion

In this study, we found that the amygdala LTP is reliably induced in the presence of $GABA_A$ blockers. This observation should facilitate future studies of the amygdala LTP using in vitro slice preparations. In addition, this result suggests that the amygdala LTP is strongly influenced by inhibitory processes. $GABA_A$ receptor-mediated inhibition appears not to be involved in synaptic responses evoked by low frequency stimulation, as picrotoxin did not affect the baseline synaptic potentials. It is likely that the GABAergic mechanism specifically affects events during or immediately following high-frequency stimulation. In fact, we observed that depression of synaptic potentials during a 100 Hz

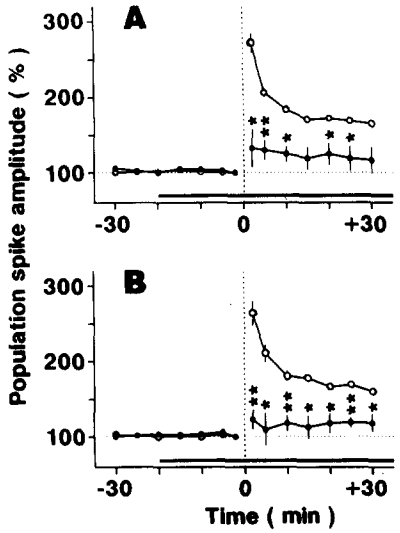

Fig. 5. Effects of scopolamine on LTP in the medial (A) and lateral amygdala (B). During the time indicated by bold bars, 10 μM picrotoxin alone (O) or picrotoxin plus 3 μM scopolamine (●) was perfused and tetanic stimulation (100 pulses at 100 Hz) was applied at 0 min. The data are represented as the mean ± S.E.M. of the values from five different slices. Asterisks indicate significant differences from the control data (O): $*P < 0.05$, $**P < 0.01$; Mann-Whitney's U-test.

stimulus train was reduced by picrotoxin. Postsynaptic inhibition probably works as a feedback mechanism during a repetitive stimulus train to limit depolarization of neurons. When the inhibitory mechanism is blocked by $GABA_A$ blockers, depolarization during a train would be enhanced and consequently facilitate LTP induction.

The nature of amygdala LTP in vivo is unknown. We found that disinhibition facilitated LTP induction in the amygdala. If the amygdala LTP occurs in vivo, there must be a mechanism whereby the amygdala synapses are released from the GABAergic inhibition. The disinhibition may be mediated by extrinsic inputs from the brain region other than the amygdala. In the hippocampus, the disinhibitory function of extrinsic inputs has been well demonstrated. For example, septal projections to the hippocampus increase excitability of hippocampal neurons by inhibiting the GABAergic interneurons (Bikley and Goddard, 1985; Krnjevic et al., 1988) and seem to contribute to the generation of the characteristic hippocampal theta rhythm (Buzsaki et al., 1983). Plasticity of hippocampal synapses are heightened during the theta rhythmic state (Heurta and Lisman, 1993). It remains to be investigated whether such a disinhibitory mechanism is involved in the amygdala LTP in vivo, and, if so, which extrinsic neural input controls the plasticity of amygdala synapses.

In contrast to our present results, three other laboratories (Chapman et al., 1990; Gean et al., 1993; Shindou et al., 1993) reported that the amygdala LTP could be elicited in vitro without GABA blockers. The discrepancy may be due to differences in experimental conditions such as the positioning of a stimulating electrode, the intensity of stimulus current, etc. Alternatively, procedures for the slice preparation or the size of slices with respect to inclusion of brain regions other than the amygdala should influence neural network preservation in the slices. Since we could reproducibly observe LTP in the presence of GABA blockers, GABAergic neurons might have been highly active in our experimental conditions or the slices prepared by our procedures might have lacked the disinhibitory neural inputs.

The evoked potentials in the medial and lateral amygdala were completely blocked by CNQX, indicating that synaptic transmission in both synapses are mediated by non-NMDA receptors under normal recording conditions. APV did not affect the baseline synaptic responses, but blocked the induction of LTP in the medial amygdala, suggesting that the medial amygdala LTP requires the activation of NMDA receptors. The mechanism of LTP in the medial amygdala may be, at least in part, similar to that in the hippocampal CA1 region or the dentate gyrus. In contrast, the LTP in the lateral amygdala was not affected by APV; thus NMDA receptors are not required for the lateral amygdala LTP. These differential effects of APV on the medial (Shindou et al., 1993) and lateral amygdala LTP (Chapman and Bellavance, 1992) have been previously reported, but it remained possible that the differences were caused by the variability of experimental conditions; Shindou et al. (1993) observed LTP in the absence of GABA blockers, whereas Chapman and Bellavance (1992) conducted all LTP experiments in the presence of picrotoxin. Since we compared the medial and lateral amygdala LTPs under the identical experimental conditions, the present data undoubtedly demonstrate that the mechanisms of LTP are different in the medial and lateral amygdala.

The cholinergic system in the amygdala plays an important role in certain types of learning and memory (Quillfeldt et al., 1990; Ohno et al., 1992). In the present study, we have shown for the first time that scopolamine and pirenzepine block the amygdala LTP, suggesting that acetylcholine regulates amygdala synaptic plasticity through muscarinic receptors. Considering that muscarinic receptors are involved in both NMDA receptor-dependent LTP in the medial amygdala and NMDA receptor-independent LTP in the lateral amygdala, the cholinergic system may widely control synaptic functions in the amygdala.

The mechanism by which the cholinergic system regulates the induction of amygdala LTP is unknown. Since scopolamine and pirenzepine do not affect normal synaptic transmission, it is unlikely that low frequency test stimulations activate cholinergic inputs. It is possible that spontaneously released acetylcholine regulates synaptic transmission only during or following the application of tetanic stimulation or that cholinergic fibers are activated by the tetanic stimulation. Heurta and Lisman (1993) have reported that hippocampal CA1 synapses are in a state of heightened plasticity during theta-frequency oscillation induced by a cholinergic agonist. It has also been reported that acetylcholine has a depolarizing action associated with blockade of K^+ currents (Dutar and Nicoll, 1988), and potentiates NMDA receptor-mediated responses (Markrain and Segal, 1992). At least, in the lateral amygdala, it is unlikely that the cholinergic system regulates the induction of LTP by modulating NMDA receptor-mediated responses, since activation of NMDA receptors is not required for the lateral amygdala LTP.

Initial potentiation produced by the tetanus consists mainly of the component generally termed post-tetanic potentiation (PTP), which usually lasts for a few minutes. We have previously observed that PTP in the hippocampal synapses is not blocked by APV (Abe et al., 1990) or protein kinase inhibitors (Abe and Saito, 1993). However, in the present study, both APV and muscarinic antagonists blocked not only LTP but also PTP. Gean et al. (1993) have also shown that 50 μM APV blocked both PTP and LTP in the basolateral amygdaloid nucleus. In addition, Chapman and

Bellavance (1992) have reported that APV at 50 μM did not block LTP in the lateral amygdala but at 100 μM, APV blocked both PTP and LTP. Taken together, these results suggest that, unlike in the hippocampal synapses, the PTP and LTP in the amygdala synapses may share, at least in part, the same underlying mechanisms.

In conclusion, in the present study, we have shown the following: (1) the amygdala LTP in vitro can be more reliably induced in the presence of $GABA_A$ blockers; (2) the induction of LTP requires the activation of NMDA receptors in the medial amygdala but not in the lateral amygdala; and (3) muscarinic receptors are involved in both the medial and lateral amygdala LTP. Further investigations of the regional differences in the mechanism of synaptic plasticity will provide a new understanding of different roles played by the subnuclei of the amygdaloid complex in learning and memory.

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