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Effect of agmatine on long-term potentiation in morphine-treated rats

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ABSTRACT

Agmatine is an endogenous amine derived from L-arginine that potentiates morphine analgesia and inhibits naloxone precipitated abstinent symptoms in morphine dependent rats. In this study, the effects of agmatine on long-term potentiation (LTP) in the lateral perforant path (LPP)-granule cell synapse of the rat dentate gyrus (DG) on saline or morphine-treated rats were investigated. Population spikes (PS), evoked by stimulation of the LPP, was recorded from DG region. Acute agmatine (2.5–10 mg/kg, s.c.) treatment facilitated hippocampal LTP. Acute morphine (30 mg/kg, s.c.) treatment significantly attenuated hippocampal LTP and agmatine (10 mg/kg, s.c.) restored the amplitude of PS that was attenuated by morphine. Chronic morphine treatment resulted in the enhancement of hippocampal LTP, agmatine co-administered with morphine significantly attenuated the enhancement of morphine on hippocampal LTP. Imidazoline receptor antagonist idazoxan (5 mg/kg, i.p.) reversed the effect of agmatine. These results suggest that agmatine attenuated the effect of morphine on hippocampal LTP, possibly through activation of imidazoline receptor.

1. Introduction

Opioids, such as morphine, have been used in the clinical management of pain for about 200 years. Their clinical practice, however, is greatly limited by their powerful potential of tolerance and dependence. Recently, more and more attentions have been paid to the mechanisms of opioid tolerance and dependence. Several lines of evidence suggest that long-term opiate treatment may result in mal-adaptive plasticity in brain structures involved in learning and memory, such as the hippocampus (Robbins and Everitt, 1999; Eisch et al., 2000). Parallels between addiction and learning are reflected in the striking similarities between the signal transduction cascades and molecular adaptations associated with both process (Hyman and Malenka, 2001). In addition, chronic administration of amphetamine or cocaine produces dramatic changes in the morphology of dendritic spines in addiction-related brain regions, which closely resemble those associated with learning (Robinson and Kolb, 1997; Robinson et al., 2001). Learning and memory are thought to be encoded by changes in the usage of interneuronal connections. Moreover, long-term potentiation (LTP) is the most compelling model for studying the synaptic basis of use-dependent changes in the strength of interneuronal connections. Recently, several reports have shown that both acute (Ito et al., 2001) and chronic morphine treatment inhibited LTP (Salmanzadeh et al., 2003; Pu et al., 2002).

Agmatine is an amine synthesized following decarboxylation of L-arginine by the enzyme arginine decarboxylase (ADC). It has modulatory effect on transmitter/hormone release (Li et al., 1994; Kalra et al., 1995), and possibly exerts as a neurotransmitter/modulator in brain (Reis and Regunathan, 2000). Agmatine has weak analgesic effect and enhances morphine-induced antinociception (Kolesnikov et al., 1996; Yesilyurt and Uzbay, 2001). Furthermore, it inhibits tolerance to morphine (Fairbanks and Wilcox, 1997; Li et al., 1999) and attenuates morphine abstinent syndrome in vitro and *in vivo* (Aricioglu-Kartal and Uzbay, 1997; Li et al., 1998; Aricioglu et al., 2003a,b). Agmatine binds to α2-adrenergic and imidazoline receptors with high affinity (Li et al., 1994; Piletz et al., 1995), but neither activates nor inhibits α2-adrenoceptors (Pinthoug et al., 1995); binds to NMDA and inhibits NOS (Yang and Reis, 1999; Galea et al., 1996), which both play important role on LTP. Furthermore, some evidence suggested that agmatine might have an effect on learning and memory. Agmatine facilitates memory consolidation in inhibitory avoidance task (Arteni et al., 2002). However, other research suggested that systemically administered agmatine selectively impairs behavioral inferences in contextual fear learning (Mckay and Persinger, 2003). Such discrepancy could be due to the fact that, given the distinct nature of these tasks, different systems and mechanisms might be involved in the modulation of their memories. In the present study, we hope to determine whether agmatine has any effects on LTP in the lateral perforant path (LPP)-granule cell synapse of the rat dentate gyrus (DG) on saline or morphine-treated rats.

2. Materials and methods

2.1. Animals

Male Wistar (180–220 g) rats were obtained from Beijing Animal Center, China. The rats were housed in groups and maintained on a

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12 h light/dark cycle with food and water available *ad libitum*. All animal treatments were strictly in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

2.2. Drugs

Morphine hydrochloride was purchased from Qinghai Pharmaceutical Factory (Xining, China). Agmatine was obtained from Beijing Institute of Pharmacology and Toxicology (Beijing, China). Idazoxan was purchased from Sigma Chemical Company (Sigma, St. Louis, MO, USA). Morphine and agmatine were injected subcutaneously (s.c.) and idazoxan was administered intraperitoneally (i.p.).

2.3. Electrode implantation

Electrode implantation in rats was undertaken as reference (Fig. 1., Doyle et al., 1996; Xu et al., 1997). Recording was performed under urethane (1.2 g/kg, i.p.) anesthetization. One electrode was served as a ground electrode (7 mm posterior to bregma and 5 mm left of the midline), the second electrode was acted as an anchor (opposite to the ground screw, 7 mm posterior to bregma and 5 mm right of the midline), and the third electrode served as the reference electrode (8 mm anterior to bregma and 1 mm left of the midline). Recording and stimulating electrodes were made by insullac-coated-acupuncture pin. Recording of population spikes (PS) were made from the dentate gyrus in response to stimulation of the LPP. The recording electrode was inserted 4.0 mm posterior to bregma and 2.0 mm right of the midline, and the stimulating electrode was inserted 7.5 mm posterior to bregma and 4.0 mm right of the midline.

2.4. Hippocampal LTP recording protocol

In all experiments, test PS were evoked by a square-wave constant current pulse stimulation of 0.1 ms duration at a frequency of 0.033 Hz. Before each experiment, input–output curves were generated to determine the maximal amplitude of PS, and the intensity of stimulus was set at a level that evoked PS at 55–65% of the maximum amplitude. The amplitude of PS was measured and averaged every 5 min. LTP was induced by high-frequency stimulation using 20 pulses at 200 Hz, repeated three times at a 30 s interval. All recording and stimulation was performed using an on-line computerized oscilloscope-stimulator and data analysis interface system.

2.5. Effect of agmatine on hippocampal LTP

2.5.1. Effect of acute agmatine treatment on hippocampal LTP

To study the effect of acute agmatine treatment on hippocampal LTP, 4 groups of rats were subcutaneously injected with agmatine 0, 2.5, 5, and 10 mg/kg (Arteni, et al., 2002; Aricioglu et al., 2004) at 30 min before LTP induction.

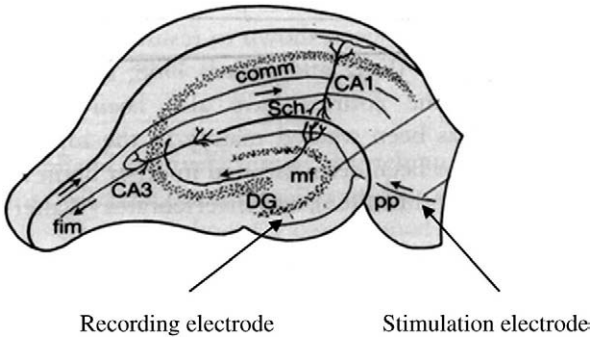

Fig. 1. The locations of stimulation and recording electrodes in the brain.

Idazoxan, an imidazoline receptor antagonist, was used to study the mechanism for the enhancement of agmatine on LTP. Four groups of rats were administrated with saline, idazoxan (5 mg/kg, i.p.) (Wei et al., 2005), agmatine (10 mg/kg, s.c.) or idazoxan + agmatine. In idazoxan + agmatine group, idazoxan was injected 15 min before agmatine injection. LTP was induced 15 min after idazoxan injection or 30 min after agmatine injection.

2.5.2. Effect of chronic agmatine treatment on hippocampal LTP

To study the effect of chronic agmatine treatment on hippocampal LTP, 2 groups of rats were administrated with saline or agmatine 10 mg/kg (three times daily, s.c.) for 5 days. 12 h after the termination of chronic treatment, the rats were stimulated and LTP was recorded.

2.6. Effect of agmatine on hippocampal LTP in morphine-treated rats

2.6.1. Acute effect of agmatine on hippocampal LTP in acute morphine-treated rats

The effect of agmatine on hippocampal LTP in acute morphine-treated rats was studied. Agmatine (10 mg/kg, s.c.) was injected 30 min before morphine injection; morphine (30 mg/kg, s.c.) was injected 30 min before LTP induction.

To clarify the mechanism for the effect of agmatine, idazoxan was also used as a tool. Four groups of rats were administrated with morphine (30 mg/kg), idazoxan (5 mg/kg, i.p.) + morphine, agmatine (10 mg/kg, s.c.) + morphine or idazoxan + agmatine + morphine. In idazoxan + morphine group, idazoxan was injected 15 min before morphine injection. In agmatine + morphine group, agmatine was injected 30 min before morphine injection. In idazoxan + agmatine + morphine group, idazoxan was injected 15 min before agmatine injection; 30 min after agmatine administration, morphine was injected. LTP was induced 30 min after morphine treatment.

2.6.2. Chronic effect of agmatine on hippocampal LTP in chronic morphine-treated rats

The chronic effect of agmatine treatment on hippocampal LTP in chronic morphine-treated rats was investigated. Morphine was administrated at escalating dose (10, 20, 30, 40 and 50 mg/kg, three times daily, s.c.) for 5 days (Hong-jie Xi et al., 2006). Agmatine (10 mg/kg, s.c.) was injected 30 min before morphine injection on each day. The amplitude of LTP was measured 12 h after the termination of chronic treatment.

2.6.3. Acute effect of agmatine on hippocampal LTP in chronic morphine-treated rats

The acute effect of agmatine treatment on hippocampal LTP in chronic morphine-treated rats was investigated. LTP was induced 12 h after the termination of chronic morphine treatment. Saline or agmatine (10 mg/kg, s.c.) was administrated 30 min before LTP induction.

2.7. Data analysis

All data were presented as mean ± S.E.M. The data were subjected to one-way or two-way analysis of variance (ANOVA) followed by Dunnett's *t* test for two groups or multiple comparisons, respectively. Student's *t* test was used when two independent groups were compared. A value of $P<0.05$ was considered to be significant.

3. Results

3.1. Effect of acute agmatine treatment on hippocampal LTP

In saline treated rats, the PS amplitude is 157.5 ± 3.65% of the baseline after high-frequency stimulation using 20 pulses at 200 Hz, which exhibited a significant LTP. In acute agmatine treated rats, the PS amplitude after stimulation was significantly facilitated as compared

to saline control group ($F_{(3,39)}=3.65$; $P<0.05$) at doses of 2.5, 5 and 10 mg/kg, which were 173.7±5.7% to 187.4±10.6% of the baseline. Idazoxan, an imidazoline receptor antagonist, had no effect on hippocampal LTP compared to control, the PS amplitude of which is 162.9±8.3% of the baseline. Pre-treatment with idazoxan (5 mg/kg, i.p.) 15 min before agmatine significantly decreased the PS amplitude to 160.8±8.6% of the baseline ($t=2.22$; $P<0.05$), as compared with agmatine treated rats, which was 192.2±8.6% of the baseline (see Fig. 2). This result implicated that the effect of agmatine is exerted through imidazoline receptor.

3.2. Effect of chronic agmatine treatment on hippocampal LTP

In chronic saline treated rats, the PS amplitude is 156.2±4.9% of the baseline after high-frequency stimulation. After the rats were chronically treated with agmatine for 5 days (10 mg/kg, s.c., three times daily), the PS amplitude is 153.7±5.5% of the baseline, which is not significantly different from that of saline control (see Fig. 3).

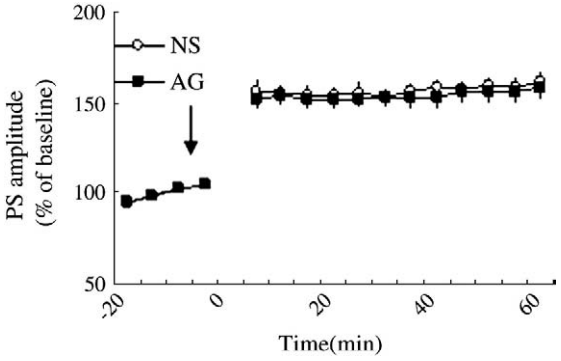

Fig. 3. Effect of chronic agmatine treatment on hippocampal LTP. LTP was induced 12 h after the termination of chronic treatment (s.c., three times daily for 5 d) with NS, or agmatine (10 mg/kg, s.c.) respectively. Tetanic stimulation was added at 0 min. PS amplitude was plotted at intervals of 5 min. *In vivo* recording was performed on anaesthetized rats. Results were summarized from all animals ($n=8$–9). Each value represents the mean±S.E.M. Student's *t* test was used when two independent groups were compared.

3.3. Acute effect of agmatine on hippocampal LTP in acute morphine-treated rats

Acute morphine treatment significantly inhibited the hippocampal LTP. The PS amplitude of the saline treated rats was 164.79±9.76% of the baseline. 30 min after morphine (30 mg/kg, s.c.) injection, the PS amplitude decreased to 130.9±6.5% of the baseline ($t=3.12$, $P<0.05$). Co-administration of agmatine (10 mg/kg, s.c.) and morphine significantly restored the PS amplitude to the level of control, which was 150.8±6.9% of the baseline ($t=2.87$, $P<0.05$) (see Fig. 4A).

After morphine (30 mg/kg, s.c.) injection, the PS amplitude decreased to 130.9±6.5% of the baseline. Agmatine restored the LTP when co-administrated with morphine. Pre-treatment with idazoxan (5 mg/kg, i.p.) 15 min before morphine administration did not influence the inhibition of LTP induced by morphine. However, idazoxan inhibited the effect of agmatine when it was administrated along with agmatine, the PS amplitude decreased from 150.8±2.4% to 122.7±6.6% of the baseline ($t=2.93$; $P<0.05$) (see Fig. 4B). This result inferred the possible role of imidazoline receptor in this procedure.

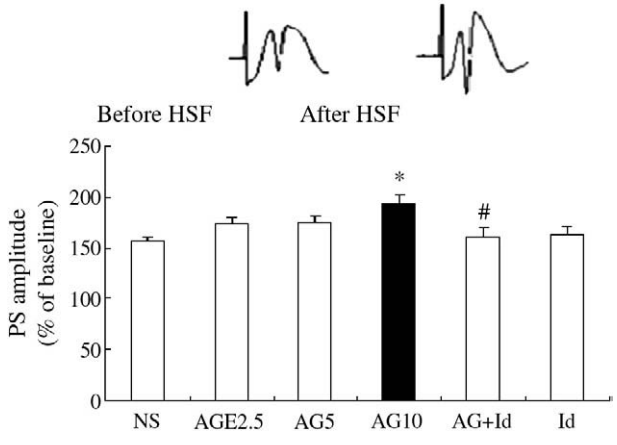

Fig. 2. Effect of acute agmatine treatment on hippocampal LTP (Panel A) and the relationship with imidazoline receptors (Panel B). LTP was induced at 30 min after acute agmatine (0, 2.5, 5, 10 mg/kg, s.c.) treatment (Panel A) or agmatine (10 mg/kg, s.c.), idazoxan (5 mg/kg, s.c.) and idazoxan–agmatine (Panel B) treatment. Response amplitude was expressed as a percentage of change in PS amplitude relative to the baseline. LTP was recorded under anesthetization. Results were summarized from all animals ($n=7$–14). Each value represents mean±S.E.M. The data were subjected to one-way or two-way analysis of variance (ANOVA) followed by Dunnett's *t* test for two groups or multiple comparisons, respectively. $^{*}P<0.05$ as compared to control. $^{\#}P<0.05$ as compared to agmatine group.

3.4. Chronic effect of agmatine on hippocampal LTP in chronic morphine-treated rats

After chronic morphine treatment, PS amplitude is greatly increased under stimulation. The capacity of LTP was measured 12 h after the termination of 5 day's morphine treatment. The PS amplitude in control group is 156.2±4.9% of the baseline, while in chronic morphine-treated group, the PS amplitude reached 180.9±5.8% of the baseline ($t=2.72$, $P<0.05$); which exhibited the

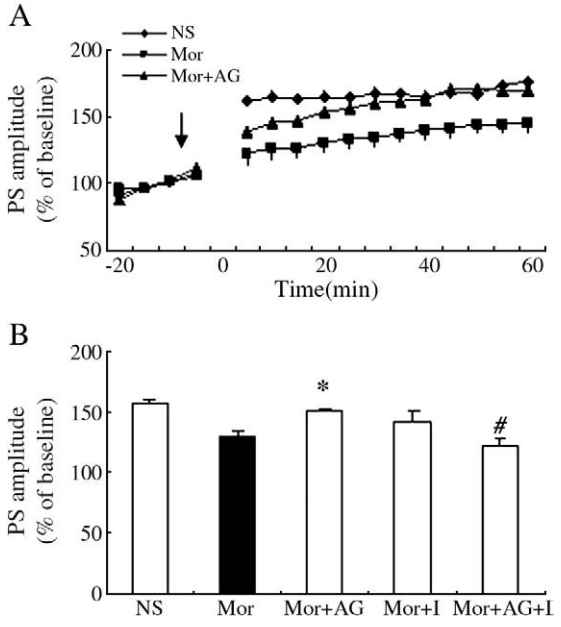

Fig. 4. Acute effect of agmatine on hippocampal LTP in acute morphine-treated rats (Panel A) and the relationship with imidazoline receptors (Panel B). Rats were treated with NS, morphine (30 mg/kg, s.c), agmatine (10 mg/kg, s.c.), and idazoxan (5 mg/kg, i.p.), 30 min before LTP induction. *In vivo* recording was performed on anaesthetized rats. Results were summarized from all animals ($n=7$–14). Each value represents the mean±S.E.M. The data were subjected to two-way analysis of variance (ANOVA) followed by Dunnett's *t* test for two groups or multiple comparisons, respectively. Student's *t* test was used when two independent groups were compared. $^{*}P<0.05$, as compared to NS control. $^{\#}P<0.05$ as compared to Mor + AG.

enhancement of LTP (see Fig. 5). Chronic co-administration of agmatine with morphine restored the PS amplitude to control level at 152.3 ± 8.3% of the baseline ($t = 2.73$, $P < 0.05$).

3.5. Acute effect of agmatine on hippocampal LTP in chronic morphine-treated rats

After chronic morphine treatment, the PS amplitude in hippocampus reached 180.4 ± 18.8%. Acute agmatine (10 mg/kg, s.c.) treatment had no significant effect on the enhancement of LTP by chronic morphine treatment, the PS amplitude was 173.1 ± 13.3% of the baseline, which inferred that acute agmatine treatment had no influence on neuronal plasticity induced by chronic morphine treatment (see Fig. 6).

4. Discussion

Drug addiction has been considered as neuronal adaptation with altered functions of neuronal circuits, including changes in neuronal plasticity. In the present study, we found that acute agmatine treatment facilitated LTP, while chronic treatment had no effect on hippocampal LTP. Acute morphine treatment attenuated LTP, while chronic morphine treatment greatly enhanced the PS amplitude. Chronic co-administration agmatine with morphine inhibited the enhancement of LTP by morphine. The effect of agmatine was exerted through imidazoline receptor.

Agmatine, a new neurotransmitter and/or modulator, plays an important role in CNS. Systemic agmatine administration facilitates memory consolidation in inhibitory avoidance task (Arteni et al., 2002), which might involving the activation of imidazoline receptor in the tractus solitarii (NST)–nucleus paragigantocellularis (PGi)–locus coeruleus (LC) pathway. Local administration of agmatine into LC produces increased neuronal firing, an effect probably not dependent on α2-adrenoceptors activation (Pineda et al., 1996). Local application of clonidine, an α2-adrenoceptor/imidazoline receptor agonist, into PGi causes a rapid and sustained increase in the firing rate of all cells recorded in the LC; this effect was also not dependent on α2-adrenoceptor since they had been previously inactivated (Ruiz-Ortega and Ugedo, 1997). Therefore, the activation of LC could either due to an indirect effect through binding to I1-imidazoline receptors at the PGi, or to a direct effect through activation of I2-imidazoline receptors localized in the LC, once the local application of agmatine increases neuronal activity in this region (Pineda et al., 1996). In coincidence with previous research, our study suggested that acute agmatine treatment facilitated LTP, which evoked a dose-dependent (2.5, 5, and 10 mg/kg) enhancement in the PS amplitude. However, chronic agmatine treatment did not influence the LTP as acute agmatine treatment did. The reasons for the less effect of chronic agmatine treatment on LTP are not clear yet, but adaptation might be one

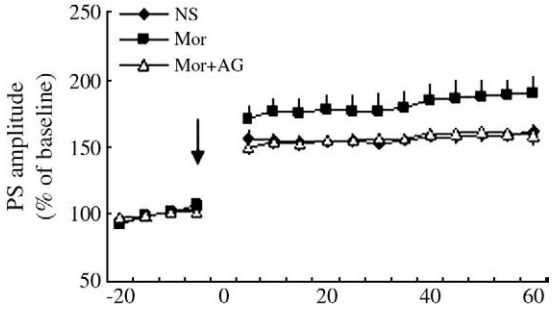

Fig. 5. Chronic effect of agmatine on hippocampal LTP in chronic morphine-treated rats. LTP was induced 12 h after the termination of chronic treatment (s.c., three times daily for 5 d) with NS, morphine or agmatine–morphine, respectively. *In vivo* recording was performed on anaesthetized rats. Results were summarized from all animals ($n = 8$–9). Each value represents the mean ± S.E.M. Student's *t* test was used when two independent groups were compared. $P < 0.05$ as compared to NS control.

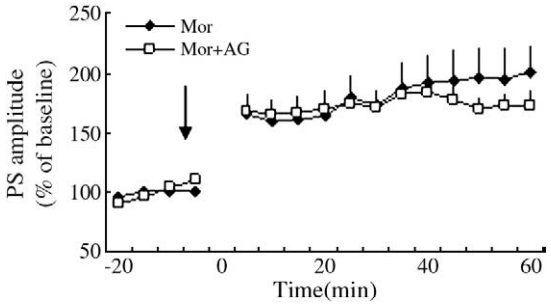

Fig. 6. Acute effect of agmatine on hippocampal LTP in chronic morphine-treated rats. Rats were injected with morphine (s.c., three times daily) for 5 days. 12 h after the termination of chronic morphine treatment, NS or agmatine (10 mg/kg) was injected subcutaneously. 30 min after injection, LTP was induced. *In vivo* recording was performed on anaesthetized rats. Results were summarized from all animals ($n = 5$–6). Each value represents the mean ± S.E.M. Student's *t* test was used when two independent groups were compared.

reason. Idazoxan, an imidazoline receptor antagonist, has no effect on LTP, while it antagonized the acute effect of agmatine on LTP. Different from our result, idazoxan was reported to enhance LTP (Takamatsu et al., 2008), this discrepancy might relate to the different experiment conditions during *in vivo* and *in vitro* studies for lack of neural connection.

In accordance with previous research (Ito et al., 2001), acute morphine treatment attenuated LTP. The effect of morphine might be related to inhibition on cAMP release, which is an important molecule for LTP. The long-term regulation of transmitter release by the cAMP cascade has been observed in many organisms from *Drosophila* to vertebrates (Frank and Greenberg, 1994) and may be one of the most conserved mechanisms that regulate synaptic efficacy.

Chronic morphine treatment enhanced LTP, this phenomenon might relate to a well known biochemical adaptation that the up-regulation of cAMP pathway in the rewarding system correlates with chronic opiate exposure (Bohn et al., 2000). Interactions between chronic morphine treatment and synaptic plasticity at the mossy fiber synapse in the CA3 region of hippocampus are of particular interest since opioid receptors inhibit glutamate release at this synapse (Simmons and Chavkin, 1996; Weisskopf et al., 1993) and the cAMP cascade plays a central role in plasticity at this site (Huang et al., 1994; Weisskopf et al., 1994). Considering the role of adenylyl cyclase in LTP formation at the mossy fiber-CA3 synapse in the hippocampus and the fact that AC1/8 is both up-regulated by chronic morphine, it is possible that this is one site that the long-term effect of opiates will affect plasticity. And some report suggested that in acute withdrawn slices from morphine-treated guinea pigs, LTP at the mossy fiber synapse was enhanced (Harrison et al., 2002). Otherwise, a cAMP-dependent increase in transmitter release during withdrawal has been described in several brain regions, and the interaction between the actions of opioids and activity-dependent plasticity could be critical in many brain regions such as the amygdala and nucleus accumbens. All these brain regions were important in context-dependent learning and had opioid-sensitive synaptic input. The coincidence of an up-regulation of adenylyl cyclase and context-dependent activity at specific synapses in these brain regions may be a potent activator of long-term synaptic plasticity associated with chronic morphine treatment. However, some studies demonstrated that chronic morphine treatment attenuated LTP (Pu et al., 2002; Salmanzadeh et al., 2003), which is different from our results. Such a discrepancy could be due to the fact that, different model and different index at different testing time might be involved in the modulation of neuronal plasticity. For example, Fereshteh uses extra cellular recordings on slices, EPSP as an index, while in this study we have used *in vivo* animal experiment, PS as an index.

Many studies have reported the effects of agmatine in inhibiting morphine withdrawal symptoms (Aricioglu-Kartal and Uzbay, 1997;

Li et al., 1998; Aricioglu et al., 2003a,b), the underlying mechanisms are unclear. Our results provide electrophysiology evidence to support the contribution of agmatine on the synaptic adaptation induced by opioids. As we have known, the most widely studied form of synaptic plasticity is NMDA-dependent LTP. However, more recently, LTP is expressed as an enhancement of postsynaptic AMPA receptor transmission (Wolf, 2002). Fast excitatory glutamate transmission is principally mediated by AMPA subtype receptors that are activated at the resting membrane potential. At most mature excitatory synapses, AMPA receptors coexist with NMDA receptors that are normally blocked by magnesium at the resting membrane potential. To be activated, NMDA receptors require both glutamate binding and membrane depolarization. The repetitive stimulation results in postsynaptic summation of AMPA-EPSCs depolarizing the dendritic spine to relieve the voltage-dependent block of NMDA channels by magnesium. Therefore, AMPA is important for the hippocampal LTP. In addition, both NMDA and AMPA/kainate receptors are involved in the cardiovascular inhibition produced by imidazoline-like drugs, which is probably at least partly dependent on an I1R mechanism in the rostral ventrolateral medulla (Wang et al., 2007). Therefore, it's possible that imidazoline receptor served as a bridge between agmatine and AMPA/NMDA. VTA dopamine neurons recorded from chronic cocaine- or amphetamine-pretreated rats are more responsive to the excitatory of AMPA. But no change in responsiveness to NMDA was observed and the increased responsiveness to AMPA was evident in rats tested three days after discontinuing drug administration (Giorgetti et al., 2001). AMPA may be one site where agmatine mediates opioid dependence though interfering with neuronal circuit. Therefore, the mechanisms for the effect of agmatine on LTP in morphine-treated rats still need further study.

In conclusion, agmatine facilitated LTP itself and restored the PS amplitude that was attenuated by morphine. Chronic morphine treatment resulted in the enhancement of LTP, agmatine co-administered with morphine significantly attenuated the effect of morphine on LTP. Imidazoline receptor antagonist idazoxan reversed the effect of agmatine. These results suggest that agmatine attenuated the effect of morphine on hippocampal LTP possibly through activation of imidazoline receptor.

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