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# Acute and chronic intracerebroventricular morphine infusions affect long-term potentiation differently in the lateral perforant path

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**Abstract**

Experiments were performed to investigate the effects of acute and chronic intracerebroventricular (icv) morphine infusions via osmotic minipumps on long-term potentiation (LTP) in the lateral perforant path (LPP)-granule cell synapse of the rat dentate gyrus. Although significant antinociceptive activity was observed when morphine was infused (25 nmol/μl/h) for 30 min or 1 h, the activity was not observed in rats receiving morphine chronically for 72 h, and the tail-flick latency of this group was comparable to that of rats receiving saline. LTP induction was significantly attenuated after acute morphine infusion (1 h) in LPP-granule cell synapses of the dentate gyrus. In contrast, LTP induction was augmented after chronic morphine infusion for 72 h. Bath-perfused morphine augmented the baseline population spike (PS) amplitude in rats treated with saline, whereas it attenuated the LTP induced by chronic morphine infusion. Returning the LTP to the level of saline infusion after in vitro morphine perfusion suggests that enhancement of the LTP is a withdrawal-like phenomenon. These results suggest a difference between the effects of acute and chronic intracerebroventricular morphine infusions on synaptic plasticity in the LPP-granule cell synapses of the dentate gyrus. 

*Keywords:* Long-term potentiation; Morphine; Intracerebroventricular infusion; Lateral perforant path

## 1. Introduction

Long-term potentiation (LTP), a sustained increase in synaptic efficacy, was originally discovered in the dentate gyrus of the hippocapus after short-term and high-frequency stimulation of the perforant path (Bliss and Lomo, 1973). Since then, studies on LTP have been extended to the other areas of the hippocampus and other regions of the brain. LTP in the hippocampus is considered the primary experimental model for investigating the synaptic basis of learning and memory in vertebrates (Bliss and Collingridge, 1993).

A growing body of evidence has shown that acute and chronic administration of morphine affects learning in rodents (Aguilar et al., 1998; Smith, 1985; Westbrook et al., 1997). A single administration of morphine has been shown to decrease the avoidance response (Smith, 1985). When it was given chronically, tolerance developed for a decreased avoidance response (Aguilar et al., 1998).

It has been shown that endogenous opioids and GABA play a role in several hippocampal functions including the induction of LTP (Lupica, 1995; Piguet and North, 1993; Xie and Lews, 1990). Opioid peptides that coexist with glutamate have emerged as one factor in LTP induction in several hippocampal pathways. In the lateral perforant path (LPP), low-frequency stimulation evokes an excitatory postsynaptic potential (e.p.s.p.) on granule cells by released glutamate. This stimulation also activates nearby GABAergic interneurons. This leads to the inhibitory postsynaptic potential (i.p.s.p.), which curtails the e.p.s.p., and, thus, LTP is not established. The release of opioid peptides by these fibers may be considered as a frequency-dependent factor. During high-frequency stimulation, enkephalins and glutamate are coreleased from the terminal of the LPP. The released enkephalins activate μ-and δ-opioid receptors on GABAergic interneurons, resulting in a transient suppression of GABA release (Bramham and Servay, 1996; Derrick et al., 1992). The loss of GABAergic inhibition leads to a shift in the balance of excitation and inhibition, and, thus, boosting postsynaptic depolarization on granule cells and facilitating LTP induction.

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The mossy fibers, which originate from granule cells in the dentate gyrus and terminate in the CA3 area of the hippocampus, also display LTP (Yamamoto and Chujo, 1978), and opioid receptor activation is one factor underlying the frequency-dependent mossy fiber LTP (Derrick et al., 1992). Although opioid receptor activation contributes to mossy fiber LTP induction, this effect is not dependent on the suppression of GABAergic interneurons, but on increasing presynaptic $Ca^{2+}$ levels at mossy fiber terminals (Derrick and Martinez, 1985).

The above observations also suggest that synaptic plasticity could be affected not only by endogenous but also exogenously applied opioids. Chronic in vivo morphine administration has been shown to augment the LTP in the Schaffer collateral-CA1 synapses of the hippocampus, without changing the baseline population spike (PS) (Mansouri et al., 1997, 1999). These reports suggest that synaptic plasticity could be influenced by chronic administration of opioids in the CA1 area. However, the effect of chronic morphine treatment on LTP induction in other areas of the hippocampus has not been examined. Therefore, we hypothesized that chronic morphine administration could affect LTP induction in LPP-granule cell synapses of the dentate gyrus, where opioid peptides and their receptors have been shown to be abundant (McLean et al., 1987).

## 2. Methods

### 2.1. Materials

Morphine hydrochloride was purchased from Sankyo (Tokyo, Japan). Other chemicals were purchased from the following companies: picrotoxin and naloxone hydrochloride, Sigma; sodium pentobarbital (Nembutal), Dynabot; and dental acrylic cement, GC.

### 2.2. Animals

Male Wistar rats weighing 150–280 g were used. They were kept in a room maintained at a temperature of 24 °C and relative humidity 55%, illuminated for 12 h from 8:00 a.m. to 8:00 p.m., and were allowed food and water ad libitum.

### 2.3. Administration of morphine

Rats were anesthetized by sodium pentobarbital and stereotaxically implanted with an indwelling stainless-steel guide cannula (26 gauge, 10 mm long) into the lateral cerebral ventricle (AP: −0.5 mm from the bregma; L: +1.3 mm from the midline; and DV: +4.5 mm below the skull surface) according to a brain map (Paxinos and Watson, 1986) for the infusion of morphine via an osmotic pump. After surgery, the rats were allowed at least 4 days to recover before infusion. Each animal was administered saline or 25 nmol/μl morphine into the cerebroventricle at a rate of 1 μl/h for the indicated time periods via an osmotic minipump (Alzet 2001, Alza, Palo Alto, USA), which had been implanted subcutaneously between the scapulae, under ether anesthesia, as described previously (Makimura et al., 1996, 1997). Saline and morphine solutions were passed through a 0.25-mm filter before being introduced into the pump, and the delivery apparatus was assembled under sterile conditions.

### 2.4. Preparation of hippocampal slices

The brains of the rats were removed quickly and cooled in ACSF (124 mM NaCl, 2.5 mM KCl, 26 mM $NaHCO_3$, 2 mM $CaCl_2$, 1.25 mM $NaH_2PO_4$, 1 mM $MgCl_2$, 10 mM glucose). Hippocampi were dissected out, blocked and cut using a rotor slicer (Dosaka EM, Japan) into 400-μm sections. The slices were maintained in the chamber at 32 °C in ACSF, which was aerated with a gas mixture of 95% $O_2$/5% $CO_2$. After recovery in the chamber for 1 h, these slices were transferred to a submersion chamber and perfused at a rate of 2 ml/min at 32 °C.

### 2.5. Stimulation and recording

A bipolar enamel-coated stimulating electrode was placed on the surface of the slice in the outer third of the suprapyramidal blade of the dentate gyrus for selective stimulation of the LPP. PSs were recorded with glass micropipettes (2–6 Ω) filled with NaCl. ACSF and drugs were perfused into the chamber through an in-line heater (Warner Instrument, USA) by a peristaltic pump.

### 2.6. Experimental protocol

Background stimuli (single pulses, 0.1–0.3 mA) were delivered at intervals of 30 s until stabilized responses were observed (for at least 20 min). Then, a baseline input–output (I/O) curve was constructed by derivation of the graded stimuli (25–300 μA) to the LPP. The stimulus intensity, which evoked a PS of 50% of the baseline maximum, was chosen for subsequent stimuli (test stimulation). PS amplitude was measured as the difference between the peak negativity and midway of the first and second peak positivities.

### 2.7. Morphine perfusion in vitro

Hippocampal slices prepared from rats subjected to saline and morphine infusions were perfused with morphine 10 μM for 10 min. Tetanic stimulation was applied in the presence of morphine, and then morphine was washed out immediately.

### 2.8. Induction of LTP

Tetanic stimulation for production of LTP consisting of 100 pulses at 100 Hz was applied at the same stimulus intensity as used for test stimulation. Each slice received a

single stimulus of train at 0 min through the same electrode as used for test stimulation. Response amplitude was expressed as a percentage of change in PS amplitude relative to the baseline response. Signals were digitized, displayed on an LTP system (Furusawa Lab. Appliance, Japan), and stored on computer disk for data processing.

### 2.9. Statistics

One-way ANOVA with the Bonferroni test for post hoc comparison was used when more than three groups were compared. Student's *t* test was used when two groups were compared.

## 3. Results

### 3.1. Antinociceptive effect of intracerebroventricular (icv) morphine infusion by the tail-flick test

When morphine was infused (25 nmol/μl/h) for 30 min or 1 h, the tail-flick latency was dramatically prolonged, and significant antinociceptive activity was observed (Fig. 1). At 24 and 48 h after infusion, the antinociceptive effect could still be seen, but activity gradually decreased. At 72 h after infusion, tolerance occurred, and antinociceptive activity of morphine was no longer observed.

### 3.2. Effect of in vitro morphine perfusion on baseline PS amplitude and LTP induction in rats continuously infused with saline

In rats continuously infused with saline, LTP was evident as a stable potentiation of PS amplitude, and the response amplitude after LTP induction (for the average of 30–40 min) was 179.3 ± 8.3% of the baseline (Fig. 2; Table 1). When morphine (10 μM) was applied to the slices for 10 min, baseline PS amplitude was significantly increased in 10 min (Fig. 2; Table 1). The PS amplitude for the average for 10 min of morphine perfusion period was 136.5 ± 5.0% as compared to that for before morphine perfusion. When tetanic stimulation was applied to induce LTP in the presence of morphine and morphine was washed out immediately, LTP was apparently enlarged by morphine (Fig. 2; Table 1).

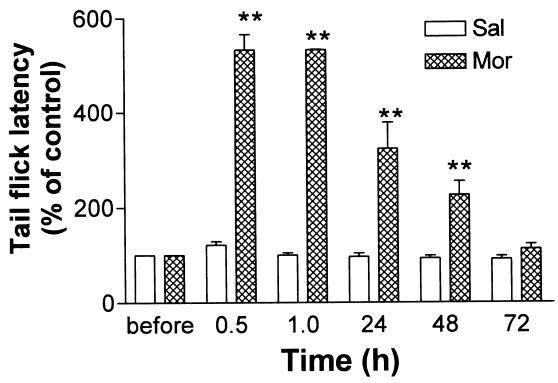


Fig. 1. Time course of antinociceptive effect of morphine intracerebroventricular infusion. Each animal was infused with saline or 25 nmol/μl morphine at a rate of 1 μl/h for the indicated time periods via an osmotic minipump implanted subcutaneously between the scapulae, under ether anesthesia. Antinociceptive effect was measured at the indicated time after the start of administration, and was expressed as tail-flick latency (%). Each value represents the mean ± S.E.M. for 10 rats. ** $P < .01$ as compared with respective saline value.

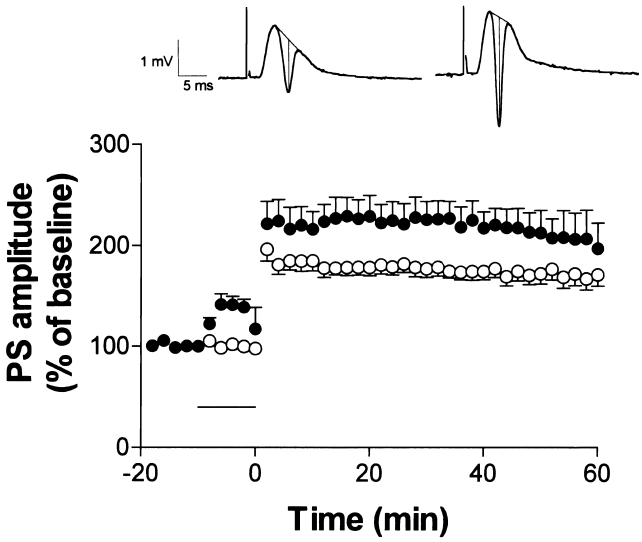


Fig. 2. LTP in control rats (infused with saline) and effects of morphine on basal PS and LTP induction. Saline was infused into the cerebral ventricle for 72 h as described in the Methods. Normal ACSF (○, $n = 11$) or ACSF containing 10 μM morphine (●, $n = 6$) was perfused for 10 min. Tetanic stimulation (100 pulses at 100 Hz) was added at 0 min before the end of the 10 min (horizontal bar) of perfusion. PS amplitude was plotted at intervals of 2 min. Response amplitude in morphine perfused group was expressed as a percentage of change in PS amplitude relative to the baseline response before morphine perfusion. Each value represents the mean ± S.E.M. The traces represent typical evoked potentials of control rat before (left) and after (right) addition of tetanic stimulation.

### 3.3. Effects of acute and chronic morphine infusions on baseline PS amplitude and LTP induction

#### 3.3.1. Induction of LTP

Intracerebroventricular infusions of morphine for 1 and 72 h affected neither the stimulus intensity, which evoked a PS of 50% of the baseline maximum (data not shown) nor baseline PS amplitude (Fig. 3A). After acute infusion of morphine, the LTP was significantly suppressed (Fig. 3A) and the response amplitude for the average of 30–40 min was 116.8 ± 11.8% of the baseline (Table 1). In contrast, chronic infusion of morphine significantly facilitated LTP induction (Fig. 3A), and the response amplitude for the average of 30–40 min was 220.5 ± 23.0% of the baseline (Table 1).

Table 1
Effects of in vitro morphine perfusion on basal PS amplitude and LTP in rats sunjected amd morohine infusions

| Intracerebroventricular infusion | Perfusion in vitro | Baseline | LTP |
|---|---|---|---|
| Saline (control) | saline (11) | – | 179.3 ± 8.3 |
| Saline | morphine (6) | 136.5 ± 9.1* | 224.5 ± 18.7** |
| Morphine (1 h) | saline (7) | – | 116.8 ± 11.8** |
| Morphine (72 h) | saline (10) | – | 220.5 ± 23.0** |
| Morphine (72 h) | morphine (6) | 115.3 ± 5.0 | 165.2 ± 6.7*** |

Intracerebroventricular infusions were performed as described in the Methods. Hippocampal slices prepared from rats subjected to saline and morphine infusions were perfused with morphine 10 μM for 10 min. The PS amplitude for the average for 10 min of morphine perfusion period (baseline) was expressed as a percentage relative to the baseline response before morphine application. Tetanic stimulation was applied before the end of the 10 min perfusion, and then morphine was washed out immediately. In the case of LTP, average values of 30–40 min after tetanic stimulation were presented. LTP was expressed as a percentage of change in PS amplitude relative to the baseline response. In morphine-perfused groups, the baseline response before morphine perfusion was used for the calculation of LTP. Each value represents the mean ± S.E.M. Numbers in parentheses indicate the number of rats.

* $P < .05$ as compared with before morphine.

** $P < .05$ as compared with control (saline–saline).

*** $P < .05$ as compared with morphine 72 h–saline.

### 3.3.2. Effect of morphine perfusion in vitro

Slices prepared from the group infused chronically with morphine were perfused with ACSF containing 10 μM morphine for 10 min, and tetanic stimulation was added before the end of the 10 min perfusion (Fig. 3B). Morphine-induced increase in baseline PS amplitude was dramatically attenuated in the group infused chronically with morphine (115.3 ± 5.0%; Fig. 3B; Table 1.) as compared to that (136.5 ± 5.0%, Table 1). Furthermore, morphine (10 μM) suppressed the potentiated LTP in slices from the group infused chronically with morphine, and the LTP was comparable to that of saline-infused control rats (Fig. 3B; Table 1), thus, suggesting that enhancement of LTP is a withdrawal-like phenomenon due to storing of the slices in morphine-free ACSF (spontaneous withdrawal).

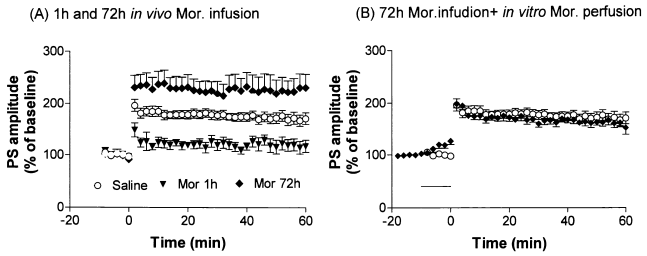


Fig. 3. LTP in rats subjected to acute and chronic morphine infusion (icv) and the effects of in vitro morphine perfusion on baseline PS amplitude and LTP induction after long-term morphine infusion. (A) Morphine was infused into the cerebral ventricle for 1 h (acute, ▼, $n = 7$) or 72 h (chronic, ✦, $n = 10$). After infusion, hippocampi were dissected out, blocked and cut using a rotor slicer (Dosaka EM) into 400-μm sections. The slices were maintained in the chamber at 32 °C in ACSF, which was aerated with a gas mixture of 95% $O_2$/5% $CO_2$. After recovery in the chamber for 1 h, these slices were transferred to a submersion chamber and perfused at a rate of 2 ml/min at 32 °C. Tetanic stimulation (100 pulses at 100 Hz) was added at 0 min. Response amplitude was expressed as a percentage of change in PS amplitude relative to the baseline response. (B) Hippocampal slices prepared from rats subjected to chronic morphine infusion were perfused with morphine 10 μM for 10 min (✦, $n = 6$). After recovery in the chamber for 1 h, these slices were transferred to a submersion chamber and perfused at a rate of 2 ml/min at 32 °C. ACSF containing 10 μM morphine was perfused for 10 min (horizontal bar in this figure). Tetanic stimulation (100 pulses at 100 Hz) was added before the end of morphine perfusion (at 0 min). Response amplitude was expressed as a percentage of change in amplitude relative to the baseline response before morphine perfusion. The time course of LTP in saline-infused rats (○) is derived from Fig. 2 (normal ACSF) for comparison.

### 3.4. Effects of bath-applied naloxone and picrotoxin on LTP in continuous saline- or morphine-infused (icv) rats

The LTP in saline-infused control rats was attenuated by the perfusion of a μ-opioid antagonist, naloxone. Although picrotoxin (1 μM) did not affect the baseline PS amplitude or LTP in the saline-treated groups, it reversed the inhibitory effect of naloxone (10 μM, Fig. 4A). In the group infused chronically with morphine, naloxone also suppressed LTP dramatically, and the LTP was comparable to that in the presence of naloxone in saline-treated groups. Unlike saline-infused groups, this inhibition was not completely reversed by the same concentration of picrotoxin (Fig. 4B).

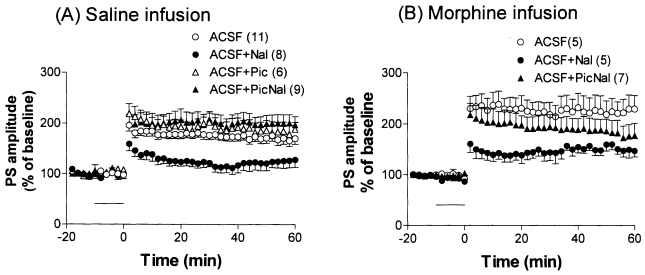


Fig. 4. Effects of naloxone and picrotoxin perfusion in vitro on LTP in saline- (A) and morphine-infused (B) rats. Saline (A) or morphine (B) was continuously infused (icv) for 72 h as described in Fig. 1. Hippocampal slices were prepared as described in the Methods. Tetanic stimulation was added at 0 min before the end of a 10-min (horizontal bar in this figure) application of 10 μM naloxone (Nal, ●, $n = 8$ for salime and $n = 5$ for morphine), 1 μM picrotoxin (Pic, △, $n = 6$) or a picrotoxin/naloxone mixture (PicNal, ▲, $n = 9$ for salime and $n = 7$ for morphine). Response amplitude was expressed as a percentage of change in PS amplitude relative to the baseline response before perfusion. Each value represents the mean ± S.E.M. The time courses of LTP in rats subjected to continuous saline (○ in A) and morphine infusions (○ in B) are derived from Figs. 2 (normal ACSF) and 3 (normal ACSF), respectively, for comparison.

## 4. Discussion

In the LPP-granule cell synapses of the rat hippocampal slices, LTP induction seems to be controlled by μ and δ opioid receptors (Bramham and Servay, 1996; Xie and Lews, 1990). Fig. 2 shows that in vitro morphine perfusion enhances the baseline PS amplitude in the LPP-granule cell synapses. Although LTP was apparently enlarged by the treatment, it was possible that this effect was due to a morphine-induced increase in basal neuronal activity. Our previous data showed that this enhancement of LTP was not observed after PS amplitude was adjusted in the presence of morphine to the basal level by reducing the stimulus intensity (Akaishi et al., 2000). Taken together, our findings demonstrate that in vitro morphine perfusion did enhance basal neurotransmission but not LTP in the LPP-granule cell synapses.

As reported previously (Makimura et al., 1996, 1997), continuous intracerebroventricular infusion of morphine via osmotic minipumps for 72 h developed tolerance to the drug. This was demonstrated by the tail-flick latency in 72-h morphine-infused rats being comparable to that in saline-infused rats. Although in vitro morphine perfusion significantly increased basal neurotransmission in saline-infused control rats, this effect was dramatically attenuated in rats chronically treated with morphine, suggesting the development of tolerance in basal neuronal activity in the LPP-granule cell synapses after continuous morphine infusions. The present study also demonstrates that chronic infusions of morphine significantly augment LTP in the LPP-granule cell synapses. In addition, bath-perfused morphine attenuates the LTP in the group infused chronically with morphine, and the LTP is comparable to that in saline-infused control groups. These results suggest that enhancement of the LTP in the chronically morphine-infused group is a withdrawal-like phenomenon due to storing of the slices in morphine-free ACSF. Brain slices from opioid-dependent animals undergo withdrawal-like changes when incubated in the absence of morphine for 1–6 h (Ingram et al., 1998).

It has been shown that the LTP induced by the primed-bursts tetanic stimulation is augmented in the Schaffer collateral-CA1 pyramidal cell synapses in morphine dependent rats (Mansouri et al., 1997, 1999). In contrast, acute morphine treatment does not affect LTP (Mansouri et al., 1997, 1999). Present data demonstrate the enhancement of the LTP in the LPP-granule cell synapses in the group infused chronically with morphine followed by spontaneous withdrawal. These results suggest that morphine dependence and withdrawal cause changes in hippocampal neuronal circuitry that induces synaptic plasticity, which are manifested during tetanic stimulation as augmented LTP.

Present results also demonstrate that acute intracerebroventricular infusions of morphine dramatically attenuated LTP in the LPP-granule cell synapses. Endogenous opioids released during high-frequency stimulation play an important role in the induction of LTP at the LPP-granule cell synapses (Xie and Lews, 1990). Recent evidence suggests that the LTP-controlling effects of μ- and δ-opioid receptors are attributable to suppression of GABAergic inhibition, resulting in facilitation of NMDA receptor activation (Bramham and Servay, 1996; Hanse and Gustafsson, 1992). One possible mechanism for the attenuated LTP response is the desensitization of the opioid receptors on GABAergic interneurons after acute infusions of morphine. The enkephalins released during tetanic stimulation would not activate the desensitized opioid receptors on the GABAergic interneurons, resulting in an increase in GABA release. This would lead to the increased i.p.s.p. and failure to establish LTP. Further work is needed to substantiate this hypothesis.

The role of GABAergic inhibition was examined by comparing the effects of naloxone on LTP induction in control slices with those on LTP induction in the spontaneously withdrawing slices. Naloxone attenuated LTP in both the control and spontaneously withdrawing slices. These findings suggest that opioid peptides released during tetanic stimulation serves as endogenous disinhibitory substances in spontaneously withdrawing slices, as well as in control slices. Although the inhibitory effect of naloxone in control slices was completely blocked by picrotoxin at the concentration that had no effect on basal PS amplitude and LTP, naloxone-induced inhibition in the spontaneously withdrawing slices was not completely reversed. These results suggest that the disinhibitory effect of picrotoxin is attenuated by long-term morphine infusion followed by spontaneous morphine withdrawal. It seems likely that a change in the balance of excitation and inhibition plays a role in increased plastic changes in LPP-granule cell synapses during morphine withdrawal. This leads to the enhancement of glutamatergic neurotransmission in the LPP-granule cells synapse of the dentate gyrus. Alternatively, the signal transduction mechanisms of GABAergic interneurons could be altered by morphine dependence and withdrawal. In the periaqueductal gray, chronic morphine treatment has shown to induce coupling of μ-opioid receptors to adenylyl cyclase- and protein kinase A-dependent processes that is not prominent in GABAergic nerve terminals in control animals (Ingram et al., 1998). Increased opioid inhibition of GABA release by the activation of adenylyl cyclase during morphine withdrawal was also reported in the nucleus accumbens (Chieng and Williams, 1998). Such a switch of signal transduction mechanisms by morphine dependence and withdrawal may be involved in the LTP enhancing effect and altered picrotoxin sensitivity in the LPP-granule cell synapses of the dentate gyrus.

LTP induction in the perforant path-dentate granule cell synapse is known to be NMDA receptor dependent. Recent studies have investigated the role of NMDA-dependent LTP hypothesis of spatial leaning and failed to obtain consistent support for the hypothesis (Cain et al., 1997; Saucier and Cain, 1995; Sutherland et al., 1993). It has recently been reported that voluntary running selectively enhances LTP in medial perforant path-dentate gyrus synapses, and improved

water maze performance (van Praag et al., 1999). The significance of LTP induction in the LPP-granule cells on memory and other functions in relation to opioid dependence/withdrawal needs to be determined.

In summary, we have demonstrated the following: (1) although acute intracerebroventricular morphine infusion for 1 h attenuated LTP induction, chronic morphine infusion followed by spontaneous morphine withdrawal facilitated LTP induction in LPP-granule cell synapses of the dentate gyrus; (2) bath-perfused morphine attenuated the enhanced LTP in rats continuously infused with morphine, whereas it augmented baseline PS amplitude without obvious effects on LTP in control groups.

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