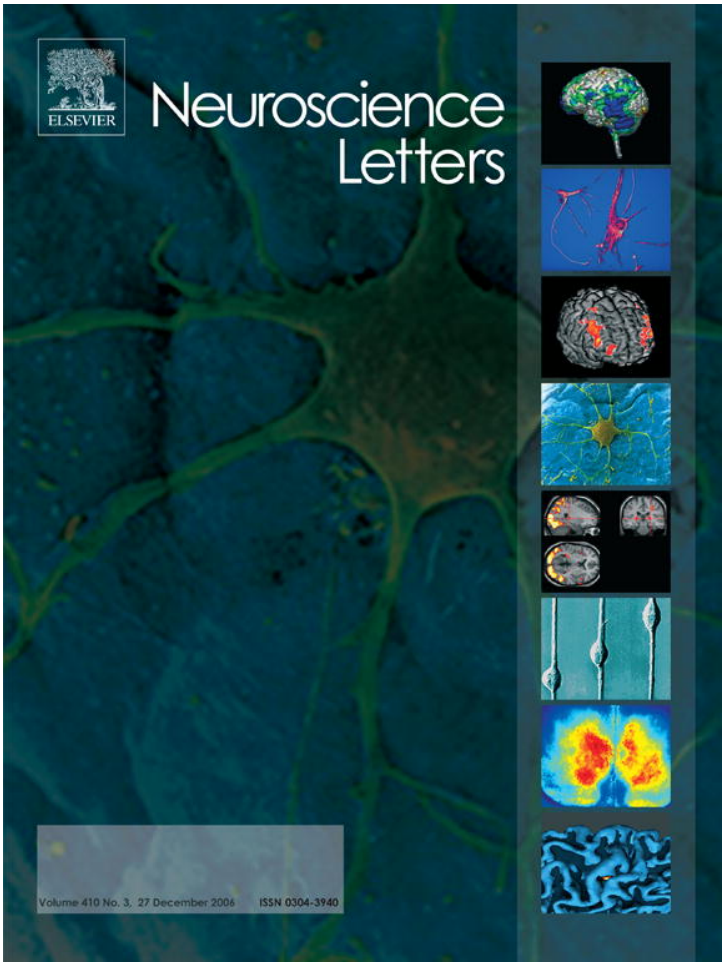

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# Chronic morphine exposure impairs short-term synaptic depression of geniculo-cortical visual pathway *in vivo*

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**Abstract**

Chronic morphine exposure can induce addiction and affect synaptic plasticity, but the underlying neuronal mechanisms remain unknown. Two forms of short-term synaptic depression (paired-pulse depression (PPD) and frequency depression) were investigated *in vivo* in the geniculo-cortical visual pathway of morphine-treated and saline-treated (as control) adult rats. Acute exposure to morphine had no effect on paired-pulse synaptic depression and 10–40 Hz induced frequency synaptic depression. However, chronic morphine exposure reduced markedly the paired-pulse depression and frequency depression at 40 Hz. The effect of chronic morphine exposure on short-term synaptic plasticity in the geniculo-cortical visual pathway was sensitization given that morphine re-exposure further significantly reduced the short-term synaptic depression. Interestingly, the further reduction in short-term synaptic depression due to re-exposure of morphine was recovered to normal (control) levels at 3 to 6 h after morphine re-exposure. These findings suggest that chronic morphine treatment could significantly degrade the short-term synaptic plasticity of geniculo-cortical visual pathway.


*Keywords:* Morphine; Addiction; Short-term synaptic plasticity; Rat; Geniculo-cortical

Drug addiction is a disease of the brain [12], and can be defined as tolerance to and dependence on the drugs of abuse [18]. It is also believed that neural systems become sensitized after chronic exposure to drugs. Once formed, an addiction can be a life-long condition in which individuals show intense drug craving and increased risk for relapse after years and even decades of abstinence. This suggests that addiction involves extremely stable changes in the brain that are responsible for these long-lived behavioral abnormalities [17].

Synaptic plasticity plays a critical role in normal brain function. The thalamocortical pathway of the rodent somatosensory system is a model system for the study of synaptic plasticity. However, recent studies suggest that the geniculo-cortical pathway of the rodent visual system is ideally suited for studying the effects of synaptic plasticity. For example, frequency-dependent depression of the rat visual cortex provides an automatic, dynamic gain-control mechanism and affects some of the specific temporal-filtering properties of the visual cortex [1]. Moreover, short-term synaptic plasticity can increase the reliability of neural information transmission, adjust the balance between cortical excitation and inhibition, modulate the spatio–temporal properties of neuronal activity, and influence coherent oscillations observed in cortico–thalamic networks [4,27,30]. There is increased evidences that chronic exposure to morphine can significantly alter synaptic plasticity and normal brain function *in vivo* and *in vitro* [19,25,31], resulting in the development of dependence on and tolerance to opiates. However, despite considerable advancement in our understanding of the effects of chronic morphine exposure on long-term synaptic plasticity, the effect of this exposure on short-term synaptic plasticity is still unknown.

Previous studies have shown that GABAergic synaptic transmission is influenced by opiates [3,5,7,10], and that the GABAergic system may be crucial to the short-term synaptic plasticity observed in the geniculo-cortical visual pathway [8]. The projections from the dorsal lateral geniculate nucleus

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(dLGN) to the primary visual cortex have been intensively studied and play an important role not only in the relay of visual information from retina to visual cortex, but also in visual information processing and neuronal plasticity [24]. Therefore, understanding the effects of chronic morphine exposure on this projection's neuronal plasticity and information processing is critical.

In the present study, we test the hypothesis that chronic morphine exposure modulates short-term synaptic plasticity in the geniculo-cortical visual pathway. Furthermore, we discuss potential mechanisms for this process.

Adult male Sprague–Dawley (200–300 g) rats were housed in groups and maintained on a 12 h light/dark cycle (7:00–19:00 h) with food and water available. All animal treatments were strictly in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals. Rats were treated by subcutaneous injection of morphine (10 mg/kg) twice per day at 12 h intervals for 10 days as described previously [29]. Control rats were treated similarly with saline instead of morphine.

Before experiments, rats were anaesthetized with urethane (20%, 1.2 g/kg, i.p.) and were then mounted in a stereotaxic apparatus. Body temperature was kept at $37 \pm 0.5$ °C. The eyes were covered throughout the experiment, except during positioning of a stimulating electrode into dLGN [23].

A concentric bipolar electrode (FHC, USA) was positioned 3.8 mm posterior and 3.5 mm lateral to bregma for stimulating the dLGN ipsilateral to the visual cortex recorded. To aid in the positioning of the stimulating electrode in the dLGN, visually driven multiunit activity was monitored as it was being advanced down through the neocortex and overlying hippocampus. The final depth of the stimulating electrode tip was within 100–200 μm of first encountering visually responsive neurons. Glass recording electrodes (tip size 3 μm, with an impedance of 2–3 MΩ while filled with saline) were introduced into the primary visual cortex (7.0 mm posterior to bregma; 3.0–4.0 mm lateral to the midline; 800–1000 μm ventral to dura). Paired-pulse depression (PPD) was investigated by stimulating the LGN using two electrical pulses separated by interstimulus intervals ranging from 25 to 1000 ms (25, 50, 100, 200, 500, 700 and 1000 ms). Intervals between pairs of stimulus were at least 30 s. It is generally impossible to predict steady-state behavior from paired-pulse behavior. Therefore, a 15-pulse train stimulation delivered at three different frequencies (10, 20, 40 Hz) was used to investigate the dynamic trend and steady-state behavior of synaptic transmission. Intervals between trains of stimulus were at least 60 s [8]. Histological analysis confirmed that the stimulating electrode tip was positioned within the first 200 μm of the dorsal surface of the dLGN. Evoked responses with the largest amplitude and shortest latency were recorded in layer IV of the visual cortex after electrical stimulation in the dLGN. Before the beginning of each experiment, a full input–output series was performed, and a stimulation intensity yielding 50–60% of maximum was used for the remainder of the experiment.

The paired-pulse depression ratio was expressed as the size of the second postsynaptic potential (PSP) amplitude relative to the first PSP amplitude. The frequency depression ratio was expressed as the averaged size of the last three PSPs' amplitude relative to the first PSP amplitude.

Data are presented as means ± standard error of means (S.E.M.). Statistical significance was assessed ($P < 0.05$) using a *t*-test analysis.

In the present study, we first investigated, *in vivo*, the effect of chronic morphine exposure on the short-term synaptic plasticity of the projections from the dorsal lateral geniculate nucleus to the primary visual cortex in rats. At 12 h after the termination of injections, the short-term synaptic plasticity of geniculo-cortical projections exhibited depression in NS-treated and morphine-treated rats. We analyzed the paired-pulse depression ratio and the frequency depression ratio following chronic morphine exposure. The PPD ratio was generally higher in morphine-treated rats than in NS-treated rats. Morphine-treated rats showed a significant increase of the PPD ratio at stimulation intervals of 25 ms (NS: $0.47 \pm 0.02$; Mor: $0.61 \pm 0.04$, $P < 0.01$), 200 ms (NS: $0.76 \pm 0.02$; Mor: $0.86 \pm 0.03$, $P < 0.01$), 500 ms (NS: $0.67 \pm 0.02$; Mor: $0.74 \pm 0.02$, $P < 0.05$), 700 ms (NS: $0.74 \pm 0.02$; Mor: $0.83 \pm 0.02$, $P < 0.05$) and 1000 ms (NS: $0.82 \pm 0.01$; Mor: $0.86 \pm 0.01$, $P < 0.05$) when compared with NS-treated rats ($n = 16$, Fig. 1A). Similarly, morphine-treated rats had a higher frequency depression ratio compared with

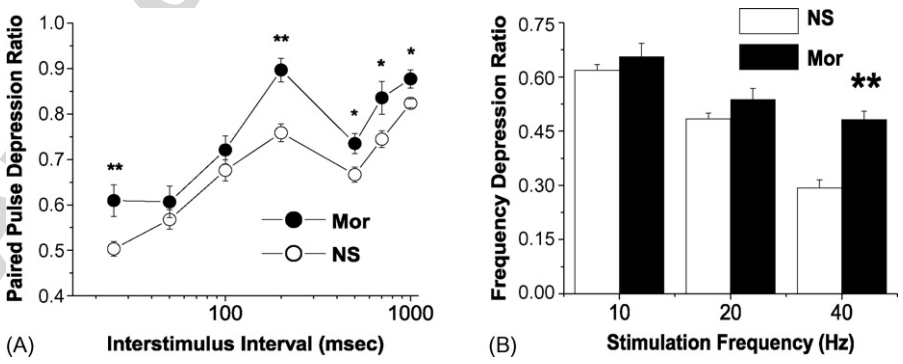


Fig. 1. Chronic morphine exposure reduced the short-term synaptic plasticity of the geniculo-cortical visual pathway. Field potentials were recorded 12 h after termination of chronic treatment with either morphine (subcutaneously, twice per day for 10 days) or NS (treated similarly with saline instead of morphine). Results were summarized from all animals. (A) The paired-pulse depression ratio of the geniculo-cortical visual pathway was increased in morphine-treated rats ($n = 16$). (B) The frequency depression ratio of the geniculo-cortical visual pathway was also increased in morphine-treated rats ($n = 16$). Compared with NS control, $^{*}P < 0.05$; $^{**}P < 0.01$ *t*-test.

NS-treated rats particularly at higher stimulation frequencies of 40 Hz (NS: 0.29 ± 0.02; Mor: 0.48 ± 0.02, $P < 0.01$) ($n = 16$, Fig. 1B). The increased PPD ratio and frequency depression ratio indicate the decline of depression capability in morphine-treated rats, suggesting that chronic exposure to morphine leads to the degradation of short-term depression in the geniculo-cortical pathway of rats.

Neural systems can function normally in the presence of morphine after repeated morphine exposure [9]. In order to determine if the impairment of the geniculo-cortical synaptic depression can be restored by re-exposure to morphine, we gave a single injection of morphine (10 mg/kg) 12 h after the termination of chronic morphine treatment. Prior to testing for depression, we used a single pulse to test baseline field potential activity thirty minutes after morphine re-exposure. We found no change in baseline activity prior to or following morphine re-exposure. Fig. 2 illustrates the effects of morphine exposure and re-exposure recorded in visual cortex. Surprisingly, the PPD ratio and frequency depression ratio were further increased following re-exposure ($n = 16$, Fig. 3A, C and E). Compared with morphine-treated rats, there was a significant increase in the paired-pulse depression ratio at stimulus intervals of 25 ms (Mor: 0.61 ± 0.04; Mor/Mor: 0.71 ± 0.02, $P < 0.05$) and 50 ms (Mor: 0.61 ± 0.03; Mor/Mor: 0.70 ± 0.01, $P < 0.01$). Additionally, the frequency depression ratio at stimulation frequencies of 10 Hz (Mor: 0.66 ± 0.03; Mor/Mor: 0.74 ± 0.03, $P < 0.05$) and 40 Hz (Mor: 0.48 ± 0.02; Mor/Mor: 0.55 ± 0.02, $P < 0.05$) was also increased. The depression ratio of all stimulus intervals and frequencies were significantly higher in morphine re-exposure rats compared with NS-treated rats. Acute saline injection did not influence the PPD ratio or the frequency depression ratio of morphine-treated rats. Moreover, acute morphine injection did not influence the PPD ratio or the frequency depression ratio of NS-treated rats ($n = 12$–14, Fig. 3B, D and E). These results indicate that the short-term synaptic plasticity is sensitive to morphine after chronic morphine exposure.

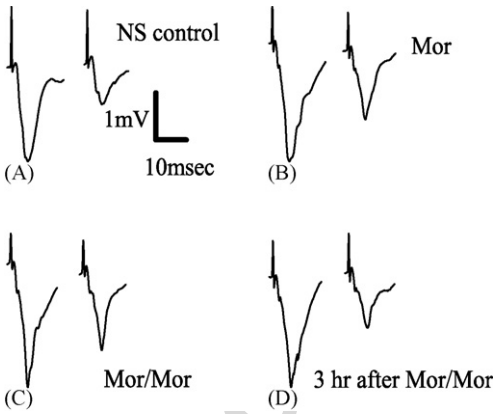


Fig. 2. Sample traces recorded in layer IV of primary visual cortex. The stimulus interval between paired pulses is 25 ms. (A) A sample trace of paired-pulse depression recorded in NS control rats. (B) Compared with NS rats, chronic morphine exposure reduced the paired-pulse depression ratio. (C) After morphine re-exposure there was no change in the first field potential amplitude, but the second field potential amplitude was increased than that of before morphine re-exposure. (D) Interestingly, the morphine's effects on the second field potential recover to NS levels 3 h after morphine re-exposure ((B), (C), (D) come from the same experiment).

It is well established that drug-induced changes in brain function vary with time [16]. In light of the surprising results presented above, we further explored the manifestation of short-

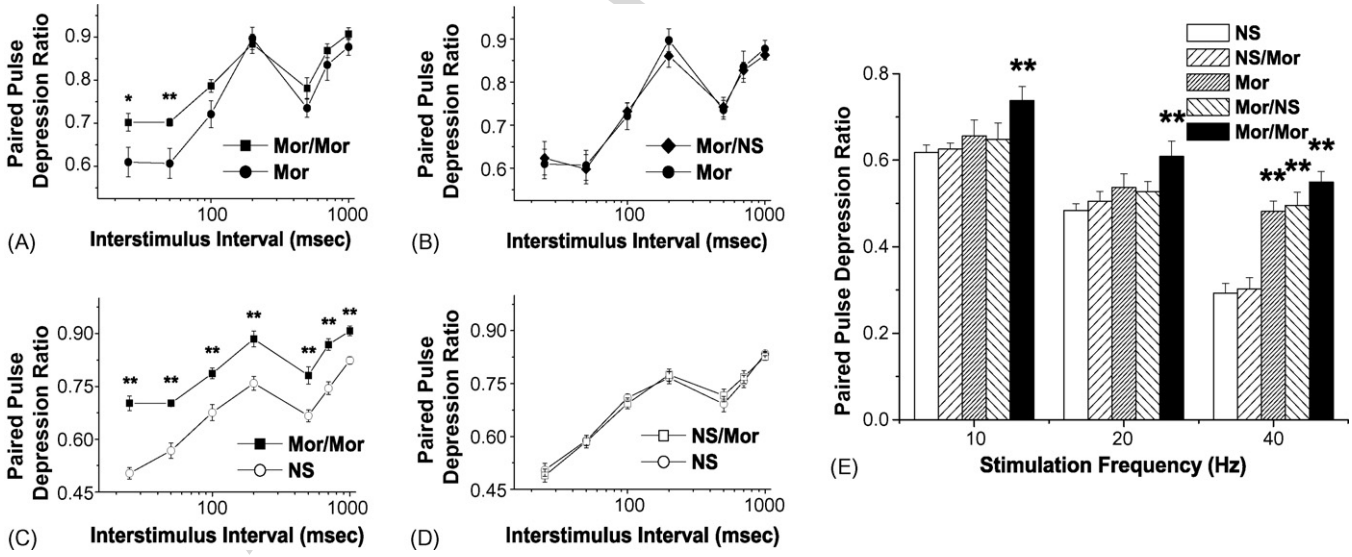


Fig. 3. Re-exposure to morphine further reduced short-term synaptic plasticity (data was collected at half an hour after morphine exposed). (A) Re-exposure to morphine further increased the PPD ratio at stimulus interval of 25 and 50 ms compared with that before morphine re-exposure ($n = 16$). (B) A single exposure to saline of morphine-treated rats had no influence on PPD ratio ($n = 13$). (C) Compared with NS-treated rats, re-exposure to morphine increased PPD ratio of all stimulus intervals significantly ($n = 16$). (D) There was no effect on PPD ratio when the NS control group was acutely exposed to morphine ($n = 12$). (E) There was no effect on frequency depression ratio when NS-treated rats were acutely exposed to morphine. At the stimulus frequency of 40 Hz, the frequency depression ratio was markedly increased in morphine-treated rats compared with NS control and a single injection of saline did not influence the increased frequency depression ratio. Re-exposure to morphine had a significant effect on frequency depression ratio for all frequencies of stimulation compared with NS control ($n = 12$–16 in each group), $^{*}P < 0.05$; $^{**}P < 0.01$, $t$-test.

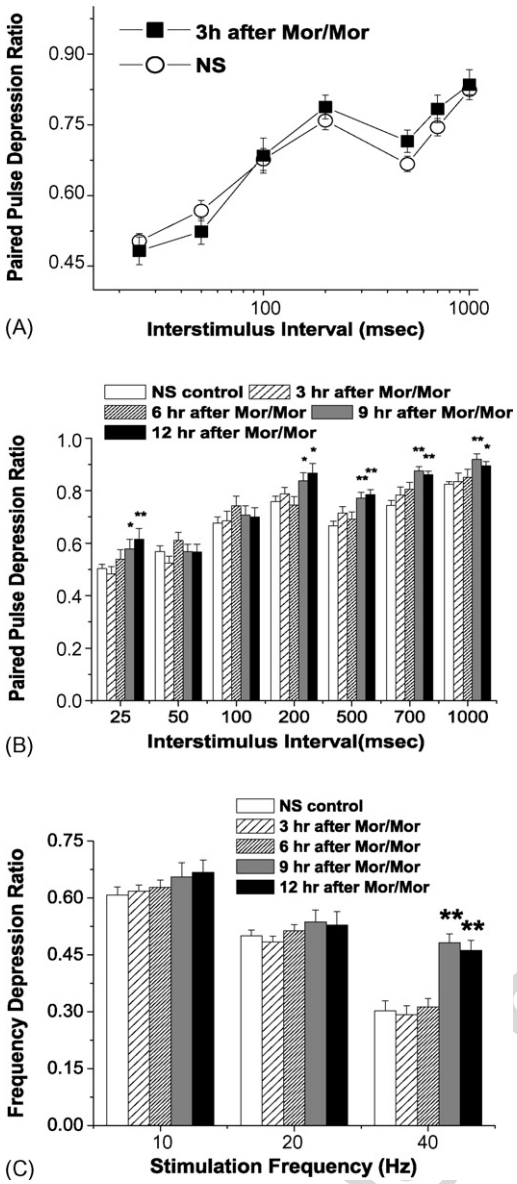


Fig. 4. After morphine re-exposure, the short-term depression recovered to the NS control levels at 3 to 6 h but after 9 to 12 h returned to pre-morphine re-exposure levels. (A) At 3 h after morphine re-exposure, the PPD ratio returned to NS control levels ($n = 10$) (B) PPD ratio at 3 to 6 h after morphine re-exposure recovered to the normal (NS control) levels. At 9 and 12 h after morphine re-exposure, the PPD ratio at stimulus intervals of 25, 200, 500, 700 and 1000 ms was significantly increased compared to that of the NS control group ($n = 8$–10 in each group). (C) Frequency depression ratio was recovered to the normal (NS control) levels 3 to 6 h after morphine re-exposure. Frequency depression ratio at the stimulus frequency of 40 Hz was significantly increased compared with that of the NS control group 9 and 12 h after morphine re-exposure ($n = 8$–10 in each group). $^{*}P < 0.05$; $^{**}P < 0.01$, $t$-test.

term depression at different time intervals following morphine re-exposure. Interestingly, the impaired PPD and frequency depression in morphine-treated rats recovered to NS control levels at 3 to 6 h after morphine re-exposure (Fig. 2D and Fig. 4A). However, at 9 and 12 h after morphine re-exposure, the PPD ratio was significantly increased compared with that of the NS control group at the stimulus intervals of 25 ms (NS: $0.47 \pm 0.02$; 9 h: $0.58 \pm 0.04$, $P < 0.05$; 12 h: $0.61 \pm 0.04$, $P < 0.01$), 200 ms (NS: $0.76 \pm 0.02$; 9 h: $0.84 \pm 0.03$, $P < 0.05$; 12 h: $0.83 \pm 0.04$, $P < 0.01$), 500 ms (NS: $0.67 \pm 0.02$; 9 h: $0.75 \pm 0.02$, $P < 0.01$; 12 h: $0.77 \pm 0.02$, $P < 0.01$), 700 ms (NS: $0.74 \pm 0.02$; 9 h: $0.87 \pm 0.02$, $P < 0.01$; 12 h: $0.83 \pm 0.01$, $P < 0.01$), and 1000 ms (NS: $0.82 \pm 0.01$; 9 h: $0.89 \pm 0.02$, $P < 0.01$; 12 h: $0.86 \pm 0.01$, $P < 0.05$) ($n = 8$–10, Fig. 4). The frequency depression ratio measured at 40 Hz (NS: $0.29 \pm 0.02$; 9 h: $0.48 \pm 0.02$, $P < 0.01$; 12 h $0.46 \pm 0.02$, $P < 0.01$) was also significantly increased. In contrast, the short-term depression ratio of the NS group did not change when tested 12 h after re-exposure to saline. These data indicate that the short-term synaptic plasticity of morphine-treated rats becomes morphine dependent.

As a kind of brain disorder, drug addiction has been considered to be a neuronal adaptation that alters the function of the neuronal circuit, including changes in neuronal plasticity and synaptic transmitter release [16,21]. Recent research suggests that addiction is an aberrant form of memory associated with alterations of synaptic plasticity [14]. Additionally, morphine addiction affects the pattern of synaptic connectivity [2,22]. For instance, acute exposure to morphine could change the strength or "weight" of existing connections that might lead to changes in short-term plasticity. Furthermore, if chronic exposure to morphine induces synapse formation or elimination along with the remodeling of the structure of dendrites or axons, then long term plasticity may also altered. These morphine induced changes in neuronal plasticity could be long-lasting affecting an individual's behavioral adaptation after addiction. In this paper, we provide direct experimental evidence that chronic morphine exposure significantly influences the short-term synaptic plasticity of the visual cortex. These results indicate that chronic morphine exposure induces changes not only in long-term synaptic plasticity [19], but also in short-term synaptic plasticity.

In the present work, we found significantly decreased PPD and frequency depression in primary visual cortex following chronic morphine treatment in rats. Previously we found that postsynaptic GABAergic inhibition may be crucial for short-term depression in the geniculo-cortical pathway. Iontophoresis of the $GABA_B$ receptor antagonist (2-hydroxy-saclofen) in the primary visual cortex had no obvious effect on the amplitude of field potentials but significantly reduced the PPD at stimulus intervals of 200, 500, and 700 ms [8]. This reduced depression resembles the alteration of short-term depression after chronic morphine exposure. Previous research has also revealed that intermittent morphine treatment results in the downregulation of the $GABA_B$ receptor in the mouse [13]. Furthermore, the $GABA_B$ receptor agonist baclofen has been found to be an effective treatment for morphine addiction [6,11,13]. Thus, the downregulation of $GABA_B$ receptors may account for the short-term depression observed at relatively long stimulus intervals (200–1000 ms) in the geniculo-cortical pathway of rats following chronic morphine exposure.

On the other hand, there are both physiological and anatomical evidence suggesting that thalamocortical afferent synapses strongly and monosynaptically excite GABAergic inhibitory interneurons in the cortex [26,28]. Therefore, it is possible that weakened GABAergic inhibition in the chronic morphine-treated rats, leads to weakening of the strong disynaptic

inhibitory inputs that shunt excitatory postsynaptic potentials. It is also possible that IPSPs reduce field potentials by simple summation with EPSPs. Thus, chronic morphine treated rats could exhibit reduced short-term depression under these conditions.

During the development of drug addiction, environmental cues are able to trigger drug seeking behavior leading to relapses in abstinence. Sensitization, which is the opposite of tolerance, describes the situation where a response to a drug escalates during repeated drug exposure [15]. Sensitization may play a key role in triggering compulsive opiate seeking behavior leading to relapse. Previous studies of morphine addiction focused on brain regions such as the prefrontal cortex, nucleus accumbens, ventral tegmental area, and the striatum, which are generally thought to be major components of the reward system which may play key roles in sensitization [20,21]. In the present study, we found that short-term synaptic depression of the geniculo-cortical visual pathway was sensitized to morphine following chronic morphine exposure. This pathway has been shown to play an important role not only in the relay of visual information from retina to visual cortex, but also in visual information processing and neuronal plasticity [24]. The influence of morphine on this projection may contribute to the mediation of sensitized responses to drugs of abuse or environmental cues that trigger compulsive opiate seeking behavior leading to relapse. The underlying mechanism may involve the upregulation of the cAMP pathway. It is well know that acute morphine exposure downregulates the cAMP pathway to decrease the probability of GABA release while chronic morphine exposure compensates by upregulating the cAMP pathway to induce an increased probability of GABA release [3,7]. The summation effect caused by the general influence of chronic morphine exposure on presynaptic GABA release and postsynaptic GABA receptors, likely decreases short-term depression in the geniculo-cortical visual pathway in our study. Accordingly, we propose that morphine re-exposure further reduces the short-term depression observed in the geniculo-cortical visual pathway by further inhibiting the activity of adenylyl cyclase, leading to a decreased probability of GABA release. The recovery of the short-term depression 3 to 6 h after morphine reapplication implies that morphine re-exposure may trigger an unknown mechanism that eventually leads to the restoration of normal short-term depression.

In summary, our results, together with that of others suggest that a change in inhibitory neurotransmission contributes to the degradation of short-term synaptic plasticity in morphine-treated rats. The effect of chronic morphine exposure is complex affecting not only the GABAergic system, but the entire CNS and the peripheral nervous system as well. Further studies will be required to elucidate the underlying mechanisms responsible for this complex process.

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