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Morphine augments excitatory synaptic transmission in the dentate gyrus through GABAergic disinhibition

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Abstract

The present study investigated the effect of morphine on synaptic transmission and long-term potentiation (LTP) in the dentate gyrus using rat hippocampal slice preparations. Field excitatory postsynaptic potential (fEPSP) and population spike (PS), evoked by stimulation of the perforant path, were recorded from the dentate molecular layer and the stratum granulosum, respectively. Following application of 10 μM morphine, PS amplitude increased gradually in 10 min and was eventually potentiated by ≈50%. The phenomenon showed a concentration-dependent manner and was completely canceled by naloxone, a μ opioid receptor antagonist. Furthermore, morphine-induced PS augmentation was not detected in disinhibited hippocampal slices, which suggests that the inhibitory input to the dentate granule cells was required for the facilitatory effect of morphine. Neither fEPSP nor tetanus-induced LTP of PS was altered by morphine application. The data support the hypothesis that μ opioid receptor activity modulates inhibitory recurrent circuits in the dentate gyrus and thereby, indirectly plays a regulatory role for hippocampal excitatory neurotransmission.

Keywords: Long-term potentiation; Hippocampus; Dentate gyrus; Morphine; μ Opioid receptor; $GABA_A$ receptor

1. Introduction

Entorhinal cortical cells excite granule cells in the dentate gyrus via the perforant path, which subsequently activate CA3 pyramidal cells via the mossy fibers. This circuit is constructed by excitatory or inhibitory amino acids and also by other modulatory neurotransmitters. Opioid peptides and their receptors are abundant in the hippocampus, particularly in the lateral perforant path (LPP), the dentate gyrus and the mossy fibers (McLean et al., 1987) and are therefore thought to exert diverse physiological functions of the hippocampal neurotransmission (Simmons and Chavkin, 1996). Indeed, μ opioid receptor activation excites the LPP-granule cell synapses (Neumaier et al., 1988), while κ opioid receptor activation suppresses them (Wagner et al., 1993). The μ opioid-mediated excitation may be attributable to indirect actions through the interneuronal disinhibition (Neumaier et al., 1988) because μ opioid agonists have been reported to elicit hyperpolarization of the hippocampal interneurons and inhibit release of γ-aminobutyric acid (GABA) from inhibitory presynaptic terminals (Madison and Nicoll, 1988; Cohen et al., 1992).

Long-term potentiation (LTP) is a long lasting increase in synaptic strength that results from high frequency stimulation of afferent fibers (Bliss and Collingridge, 1993). Therefore, LTP in the hippocampus in vitro is widely used as a model of synaptic plasticity and considered to be the primary experimental model for investigating the cellular basis of learning and memory in the vertebrates. The involvement of opioids in LTP of the LPP-dentate granule cell synapses has also been suggested, i.e. the facilitatory effects of μ and δ_1 opioids (Xie and Lewis, 1991; Bramham and Sarvey, 1996) and the inhibitory effects of κ opioids (Wagner et al., 1993; Terman et al., 1994). Particularly, Xie and Lewis (1995) indicated that the

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depression of LTP by the μ opioid antagonist naloxone is reverted by pharmacological blockade of $GABA_A$ receptors, suggesting again that μ opioids modulate synaptic plasticity in the dentate gyrus through GABAergic innervations.

Taken together, opioids might modulate neurotransmission and synaptic plasticity of the dentate gyrus. Nonetheless, very little was known about the effect of morphine on synaptic transmission and synaptic plasticity in the LPP-granule cell synapses. On the other hand, there are numerous indications that acute administration and chronic abuse of morphine alter the cognitive abilities of primates (Holtzman, 1976) or rodents (Davis and Smith, 1975; Ageel et al., 1976; Babbini et al., 1980; Smith, 1985; Westbrook et al., 1997; Aguilar et al., 1998). Therefore, to evaluate the influence of this exogenous opioid on the hippocampal physiology would be important in order to clarify the mechanism underlying the cognitive modification. In the present study, hence, we addressed the possibility that exogenous morphine modulates excitatory synaptic transmission in the dentate gyrus in vitro and found that acute application of morphine enhanced the neurotransmission without affecting LTP induction.

2. Materials and methods

2.1. Preparation of hippocampal slices

Male Wistar rats (120–250 g) were deeply anesthetized with ether and the brains were quickly removed and immersed in ice-cold artificial cerebrospinal fluid (ACSF) of the following composition (in mM): NaCl 124.0, NaH_2PO_4 1.25, KCl 2.5, $CaCl_2$ 2.0, $MgCl_2$ 1.0, $NaHCO_3$ 26.0 and glucose 10.0, which was aerated continuously with a gas mixture of 95% O_2/5% CO_2. The hippocampi were dissected out and cut into 400-μm-thickness sections using a rotor slicer (Dosaka EM Co. Ltd., Osaka, Japan). After recovery in the chamber filled with ACSF at 30°C for >1 h, the slices were transferred into a submersion chamber and perfused with ACSF at a rate of 2 ml/min at 32°C.

2.2. Electrophysiology

A bipolar enamel-coated stainless steel electrode was placed on the surface of the slice in the outer one-third of the molecular layer of the dentate gyrus for stimulation of the LPP. Extracellular potentials were recorded with glass micropipettes filled with 2 M NaCl (2–8 MΩ). Field excitatory postsynaptic potential (fEPSP) and population spike (PS) were recorded from different slices. A glass electrode was placed in the molecular layer or the stratum granulosum of the dentate gyrus for recording fEPSP and PS, respectively. Signals were digitized and stored on a computer disk for data processing. PS amplitude was defined as the average of the amplitude from the first positive peak to the succeeding negative peak and the amplitude from the negative peak to the second positive peak. All drugs were dissolved with ACSF and were applied into the chamber through a line heater.

Single test stimulation (100-μs duration) was applied at intervals of 30 s. After the responses were stabilized, the stimulus intensity was adjusted in each experiment (also in a disinhibited slice) to produce fEPSP slope or PS amplitude of $\approx 50\%$ of the maximum responses. To induce LTP, tetanic stimulation (100 pulses at 100 Hz) was applied at the same stimulus intensity through the same electrode as used for test stimulation. To construct an input–output (I/O) curve (a stimulation–response correlation), stimulus intensities were changed in a range from 25 to 300 μA. All data are indicated as the means $\pm$ S.E.M. of the values obtained from different slices. In the text, N indicates the number of slices tested.

3. Results

3.1. Effect of morphine on basal synaptic transmission

When 10 μM morphine was applied to slices, PS amplitude was enhanced, but fEPSP slope was not changed (Fig. 1). PS amplitude gradually increased in 10 min and was eventually potentiated by $\approx 50\%$. The potentiation was maintained for >90 min in the continuous presence of morphine. As we compared PS amplitude immediately before and 10 min after morphine application, the facilitatory effect on PS was statistically significant (paired t-test: $t(10) = 3.38$, $P = 0.007$) (Fig. 2A) and it showed a concentration dependency in a range from 0.1 to 10 μM (Fig. 2B). Because the solubility of morphine for ACSF did not allow us to examine the effect at higher concentrations, it remained to be determined whether 10 μM morphine rendered the maximal effect. However, the concentration of 10 μM was used in the following experiment because 10 μM morphine showed a robust and significant effect so that the phenomenon could be analyzed. We next investigated the I/O profile for the effect of morphine. The amplitude of PS evoked at increasing stimulus intensity was measured immediately before and 10 min after the perfusion with 10 μM morphine and I/O curve was constructed (Fig. 3A). Although morphine enhanced PS amplitudes at stimulus intensities of 50–100 μA, the responses evoked at intensities of >100 μA were not significantly changed (Fig. 3A). Thus, each plot was normalized as a percentage to the maximal response and, as a consequence, we noticed that I/O curve was shifted to a lower current (Fig. 3B);

Stimulus intensity to produce the half maximum of PS amplitude was 69.3 ± 2.0 μA in normal ACSF and 51.3 ± 1.8 μA in morphine (t-test: $t(10) = 6.77$, $P < 0.001$). Next, morphine was washed out after perfusion with 10 μM morphine for 10 min (Fig. 4). After the withdrawal, the potentiated PS amplitude gradually declined and reverted to the baseline level ≈60 min after the washout. This indicates the reversibility of the effect of morphine. Next, to examine the involvement of μ opioid receptor, slices were pre-treated with 10 μM naloxone. Naloxone alone did not affect the baseline responses. Then 10 μM morphine was applied, but no significant change was observed (Fig. 5A). Therefore, the morphine-induced PS potentiation was possibly mediated by μ opioid receptor activation.

In the present study, fEPSP was recorded from the dendrites of the dentate granule cells on which the LPP directly makes its excitatory synapses, whereas PS was recorded from the cell body, where the membrane potential is more strongly controlled by inhibitory interneurons. Thus, the result that morphine enhanced PS amplitude without affecting fEPSP slope suggests that morphine facilitates the excitability of the dentate granule cells via interneuronal modulation. Indeed, μ opioid agonists are known to hyperpolarize GABAergic interneurons (Madison and Nicoll, 1988) and to decrease GABA release from presynaptic terminals in the hippocampus (Cohen et al., 1992). Therefore, we next investigated the effect of morphine using disinhibited hippocampal slices, which were prepared with >1 h incubation in ACSF containing the $GABA_A$ receptor antagonist picrotoxin 50 μM and then transferred into a recording chamber perfused with the same ACSF. The baseline PS amplitude in these slices was significantly larger than that in intact slices; half maximal PS amplitude was 2.89 ± 0.31 mV in the disinhibited slices ($N = 7$) and 2.04 ± 0.23 mV in control slices ($N = 7$) (t-test: $t(12) = 2.20$, $P = 0.049$). Under these conditions, morphine failed to increase PS amplitude (Fig. 5B). The result suggests that morphine did not have the effect in the absence of GABAergic activities. Therefore, morphine possibly modulated the GABAergic innervations and thereby facilitated excitatory synaptic transmission in the dentate gyrus.

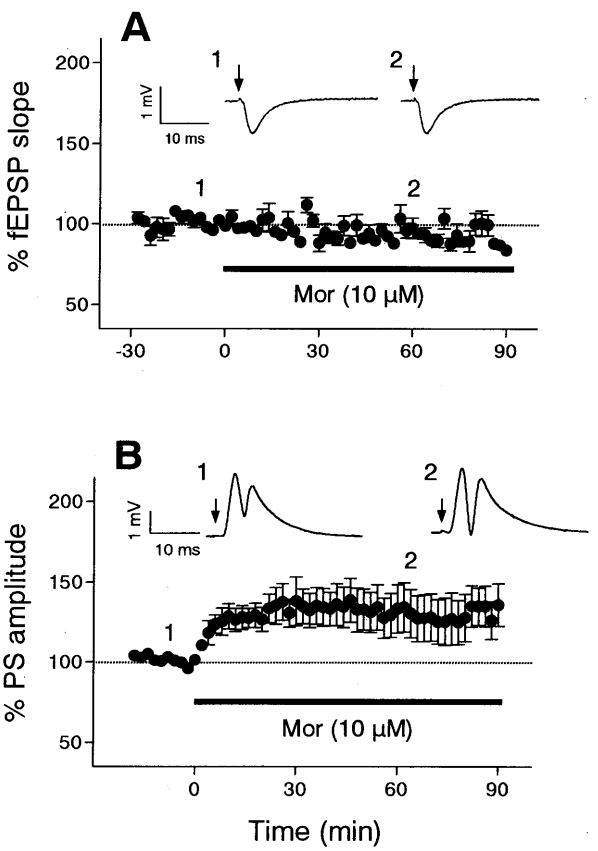

Fig. 1. Time course of changes in field potentials recorded from the dentate molecular layer (A) or the stratum granulosum (B) following application of 10 μM morphine (Mor). (A) Effect of morphine on fEPSP slope ($N = 5$). (B) Effect of morphine on PS amplitude ($N = 8$). The ordinates are expressed as a percentage of field potentials to the average of the baseline responses before morphine application. The traces 1 and 2 in each panel represent typical evoked potentials immediately before and 60 min after morphine perfusion. Test stimulation was delivered at the time indicated by arrows. Each value represents the mean ± S.E.M. of N cases.

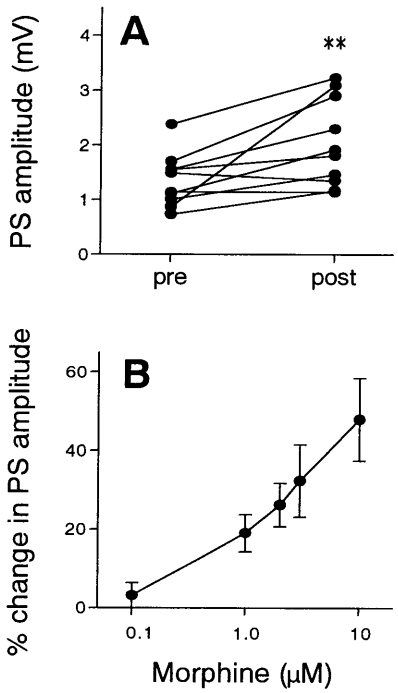

Fig. 2. Characterization of morphine-induced PS facilitation. (A) PS amplitudes immediately before (pre) and 10 min after (post) 10 μM morphine application are plotted in each case tested ($N = 11$). $^{**}P < 0.01$: paired t-test. (B) Concentration dependency of the effect of morphine. The ordinate is expressed as a percentage of changes in PS amplitudes to the baseline responses before morphine application. Each value represents the mean ± S.E.M. of four to 17 slices.

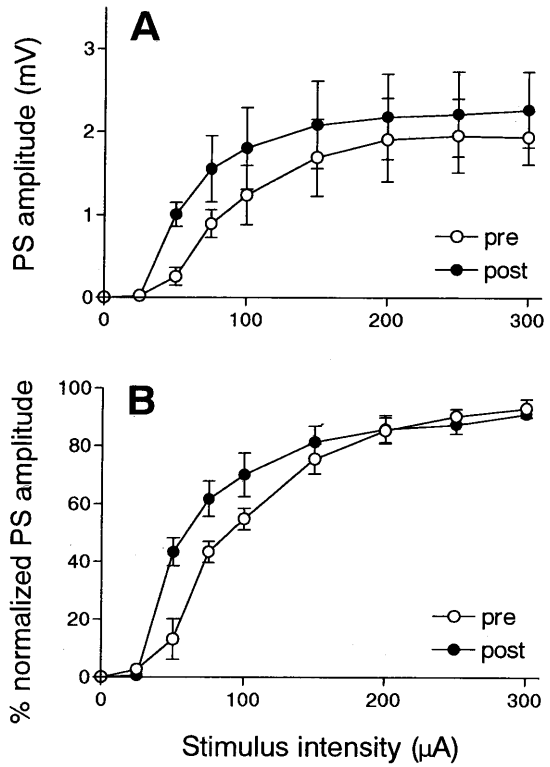

Fig. 3. I/O profile of the effect of morphine. Responses were measured immediately before (○, pre) and 10 min after (●, post) application of 10 μM morphine. (A) PS amplitudes evoked by test stimulation of increasing stimulus intensities are plotted. (B) Data in the panel (A) are expressed as a percentage to the maximal responses. Each value represents the mean ± S.E.M. of six cases.

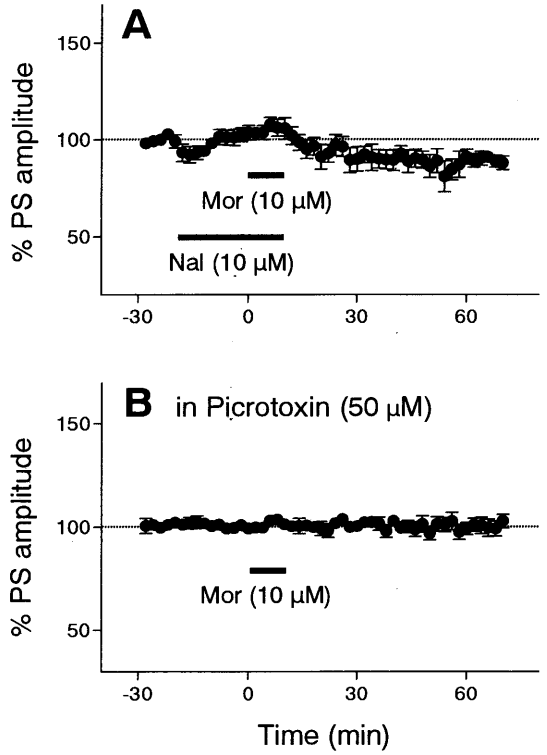

Fig. 5. Pharmacological studies on the effect of morphine (Mor) on PS amplitude. (A) The effect of naloxone (Nal), a μ opioid receptor antagonist, on morphine-induced facilitation of PS amplitude ($N = 7$). Naloxone (10 μM) and morphine (10 μM) were applied from −20 to 10 min and from 0 to 10 min, respectively. (B) The effect of picrotoxin, a $GABA_A$ receptor antagonist, on morphine-induced facilitation of PS amplitude ($N = 7$). Morphine 10 μM was applied from 0 to 10 min in ACSF containing 50 μM picrotoxin. Each value represents the mean ± S.E.M. of N cases.

3.2. Effect of morphine on LTP induction

After perfusion (10 min) with morphine (10 μM), tetanic stimulation was applied to induce LTP in the presence of morphine. Immediately after the tetanic stimulation, morphine was washed out. Compared with control group in which LTP was induced in the absence of morphine, the degree of LTP in the morphine-treated group was enlarged in a concentration-dependent manner (Fig. 6A, Ba). However, because morphine alone shifted the baseline upper (Fig. 1B), the possibility that such pre-existence of baseline increment altered the extent of LTP could not be ruled out. Particularly, because morphine-induced PS augmentation means that the same intensity of the LPP stimulation caused more synaptic activations in the dentate granule cells, the tetanic stimulation in the morphine-treated slices may have higher efficacy to induce LTP than that in intact slices. Therefore, in order to exclude the effect of morphine on baseline responses, PS amplitudes immediately before tetanic stimulation were subtracted from the LTP magnitudes. As a result of this manipulation, no effect of morphine on LTP was observed (Fig. 6Bb). Thus, the facilitatory effect of morphine on LTP was interrogatively suspected. To clarify this point, PS amplitude was adjusted in the presence of morphine to the basal level by reducing the stimulus intensity (Fig. 7). Under these conditions, LTP was no more enhanced by morphine. Therefore, we concluded that morphine enhanced neurotransmission but not LTP in the dentate gyrus.

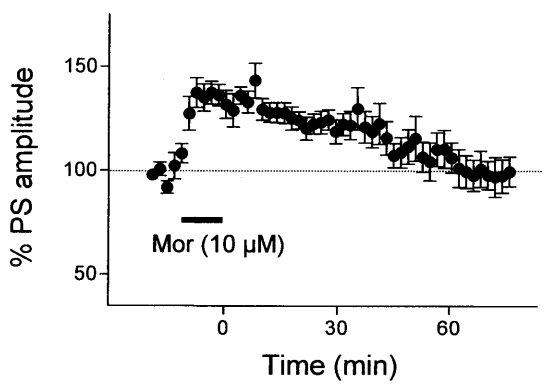

Fig. 4. Reversible morphine-induced PS augmentation. Morphine (Mor) (10 μM) was applied for 10 min (0–10 min). Each value represents the mean ± S.E.M. of seven cases.

4. Discussion

Although morphine perfusion did not change fEPSP, the same perfusion significantly increased PS in the dentate granule cells. The PS potentiation appeared reversible and displayed a time- and concentration-dependent manner, which was completely prevented by co-application of naloxone. These suggest that morphine-induced facilitation is the pharmacological action mediated by μ opioid receptor activation. Incidentally, in the present study, 10 μM morphine significantly enhanced the neurotransmission. This concentration is compatible with the dose of morphine that can alter the behavior of animals, which is generally known to be ≈2–15 μM in the brain.

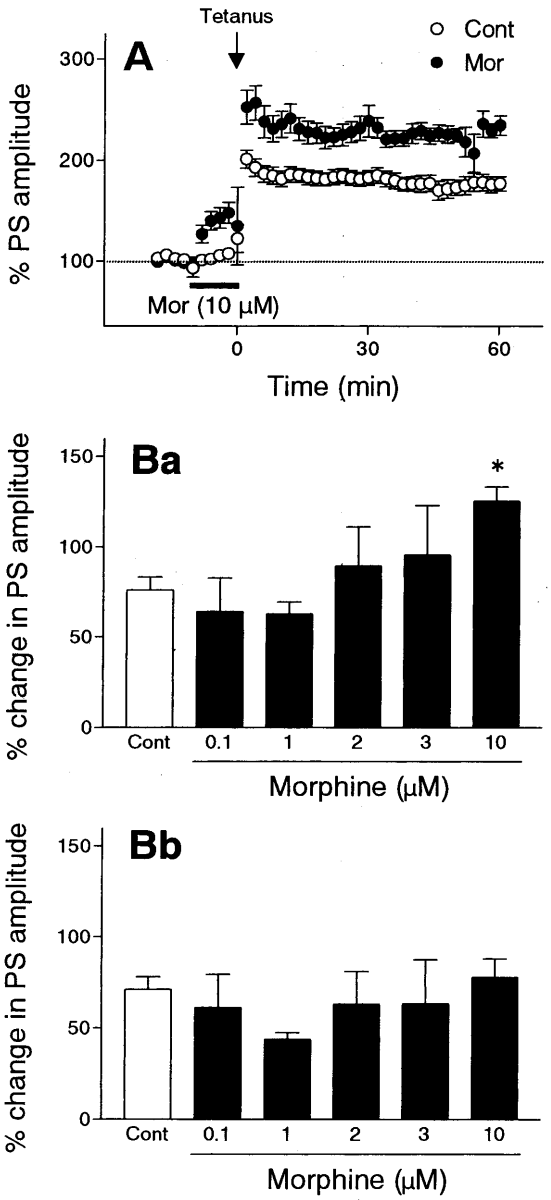

Fig. 6. Effects of morphine on LTP. (A) Time course of LTP induced in the absence (○, $N = 17$) or presence (●, $N = 7$) of 10 μM morphine (Mor). Tetanic stimulation consisting of 100 pulses at 100 Hz was applied at time 0 in order to induce LTP (Tetanus). Data represent the means ± S.E.M. of N cases. (B) Concentration dependency of the effect of morphine on LTP. (Ba) The magnitudes of LTP (the average of changes in PS amplitude from 30 to 60 min) are expressed as a percentage to the baseline responses before morphine application. Each bar represents the mean ± S.E.M. of four to 17 cases. (Bb) LTP magnitudes are expressed as a percentage to the responses immediately prior to the tetanic stimulation; values 10 min after morphine perfusion are subtracted from LTP magnitudes of the panel (Ba). $^*P < 0.05$ versus the control (Cont): Tukey–Kramer multiple range comparisons test following one-way analysis of variance (ANOVA).

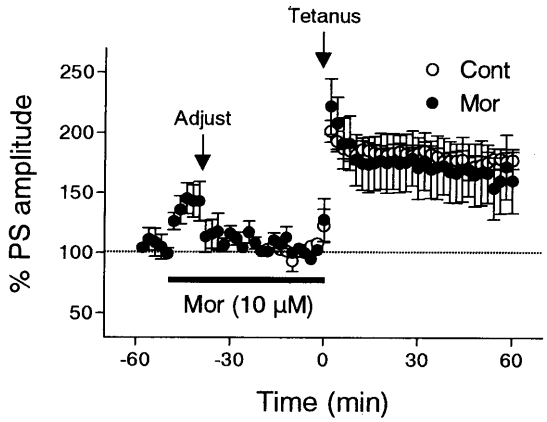

Fig. 7. Effects of baseline adjustment on the actions of morphine on LTP. After morphine perfusion (10 min), test stimulation intensity was reduced (Adjust) so that PS amplitude was approximately the same as baseline response before morphine perfusion, and then tetanic stimulation (Tetanus) was applied 40 min after the adjustment (Mor) (●, $N = 7$). To promote a comparison, the time course of intact LTP (the same data as Fig. 6A) is superimposed as ○ (Cont, $N = 17$). Each value represents the mean ± S.E.M. of N cases.

The result that morphine augmented PS without affecting fEPSP means that the granule cells exposed to morphine produced more action potentials in response to the same degree of excitatory inputs, suggesting that morphine changes the threshold for action potentials. Generally, the initiation of action potentials is strictly regulated by GABAergic innervations onto and near the cell body. From this viewpoint, we tested the effect of morphine using disinhibited hippocampal slices, which are almost free from GABAergic influences. In the slices, morphine showed no effect. This is suggestive of the involvement of inhibitory interneurons in the facilitatory effect of morphine. This idea is further supported by previous reports, showing that μ opioid agonists hyperpolarize GABAergic interneurons (Madison and Nicoll, 1988) and decrease GABA release from the interneurons (Cohen et al., 1992). Therefore, morphine may indirectly augment excitatory synaptic transmission through the disinhibition of GABAergic inputs. Indeed, several feedback neurocircuitry systems have been identified in the dentate gyrus.

The mossy fibers from the dentate granule cells bifurcate in the hilus and make excitatory synapses on hilar polymorphic cells including mossy cells (Ribak et al., 1985; Scharfman et al., 1990). Mossy cells, the most common cells in the hilus, make synapses with granule cell dendrites in the inner one-third (or commissural zone) of the molecular layer of the dentate gyrus (Buckmaster et al., 1992). Scharfman et al. (1990) suggest that the mossy cells make both excitatory and inhibitory contacts onto interneurons as well. Furthermore, Ribak and Seress (1983) reported the feedback inhibitory mechanism through GABAergic basket cells, which receive the inputs from mossy fiber collaterals. Their electron microscopic data showed that the inhibitory fashion of the basket cells is very similar to that of cortical local circuit neurons. Electrophysiological studies also indicated that stimulation of the mossy fibers invokes GABAergic recurrent activation possibly via basket cells (Hetherington et al., 1994). According to these reports, the facilitatory effect of morphine might be explained by the inhibition of these inhibitory recurrent pathways in the dentate gyrus.

Although the effect of morphine on basal synaptic transmission was reversible, PS amplitude following tetanic stimulation, i.e. after LTP induction, did not decline, even after the withdrawal of morphine. These two phenomena appear controversial. However, in the slices that had not received the adjustment of stimulus intensity (Fig. 6), the tetanic stimulation with the same stimulus intensity might efficiently induce LTP through higher activation of the LPP-dentate granule cell synapse because the synaptic function per se was enhanced by morphine. On the other hand, the slices in which the stimulus intensity was adjusted to the baseline level received longer treatment with morphine, i.e. for 50 min (Fig. 7). The long-term exposure to morphine may produce irreversible effects. Thus, prospective decline in PS amplitude following the withdrawal of morphine might not be observed. Another possible explanation is that the effect of morphine may become irreversible and stable by application of tetanic stimulation. Therefore, tetanus-potentiated PS amplitude might not decay even in the absence of morphine.

Our data that morphine did not affect LTP induction apparently contrast to previous reports indicating that μ receptor agonists facilitated LTP (Xie and Lewis, 1991; Bramham and Sarvey, 1996). The discrepancy may be due to differences in experimental conditions, including the drugs used. For example, we examined LTP of PS while these previous studies measured LTP of fEPSP. Therefore, we should compare the effect of morphine on LTP of both PS and fEPSP. However, another possibility can be raised. In the previous studies, synthetic opioidergic agents, such as [*N*-MePhe^3-D-Pro^4]morphiception, 7-benzylidenenaltrexone and a peptide CTAP were used for their experiments, whereas morphine, originally a natural product, was used in the present study. Indeed, Mayer et al. (1994) indicated that electrophysiological effect of morphine was not always consistent with that of other synthetic opioids, such as [D-Ala^2-*N*-MePhe^4-Gly-ol]enkephalin in the dentate gyrus of anesthetized rats. Furthermore, Whistler et al. (1999) showed that synthetic μ opioid receptor agonists induced receptor-G protein uncoupling, whereas a highly addictive opiate drug, such as morphine, did not elicit the G protein release, strongly suggesting functional dissociation of μ opioid receptor signaling. Therefore, it is probable that morphine and other drugs exert different effects, even if they act on the same μ opioid receptor.

In conclusion, we have shown the following: (1) morphine reversibly increases PS amplitude in a time- and concentration-dependent manner, but not fEPSP slope, in the dentate granule cells; (2) morphine-induced excitation may be due to disinhibition through GABAergic interneurons; and (3) morphine do not enhance LTP. This is the first report to clarify the in vitro effects of exogenous opioid morphine on the electrophysiology of the dentate gyrus in detail. The results provide the hypothesis that opioids might regulate hippocampal neurotransmission through the recurrent feedback circuits. Further investigation would make clear the problems that remain obscure above and thereby, provide a novel understanding of the role of opioids in neurocircuitry of the hippocampus.

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