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Short communication

Morphine-induced potentiation in the dentate gyrus of the hippocampus involves norepinephrine

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Abstract

We examined the role of norepinephrine in the morphine-induced potentiation in the dentate gyrus of the hippocampus in chronically implanted freely moving rats. The population spikes of the field potentials in the dentate gyrus following perforant path stimulation were recorded before and after morphine injection. We found that a single dose of morphine sulfate (5 mg/kg, i.v.) resulted in a long-lasting augmentation in the amplitudes of population spikes. When pretreated with propranolol (5 mg/kg, i.v.), a β-adrenoceptor antagonist, the morphine-induced potentiation was significantly attenuated. These results suggested that an increase in norepinephrine release in the hippocampus contributed to the morphine-induced potentiation.
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1. Introduction

Exogenous applies of opioids can induce an enhancement of the synaptic efficacy in the hippocampus (Nicoll et al., 1977; Linseman and Corrigall, 1982; Valentino and Dingledine, 1982; Corrigall, 1983; Christian et al., 1985; Wiesner et al., 1986; Neumaier et al., 1988; Mayer et al., 1994). Understanding of the neural mechanisms underlying the opioid-induced synaptic plasticity in the hippocampus may provide insights into the understanding of opioid addiction, which has been viewed as drug-induced neural plasticity (for review, see Nestler, 2001; Williams et al., 2001). Previous studies have demonstrated that an inhibition of γ-aminobutyric acid (GABA) release from hippocampal interneurons contributes to the opioid-induced synaptic plasticity in the hippocampus (Zieglgansberger et al., 1979; Madison and Nicoll, 1988; Neumaier et al., 1988; Cohen et al., 1992; Xie et al., 1992; Piguet and North, 1993; Lupica, 1995; Bramham and Sarvey, 1996). However, it is unknown whether other neurotransmitters are involved. In the present study, we examined the role of norepinephrine, an important neuromodulator, in the opioid-induced potentiation in the dentate gyrus of the hippocampus. Population spikes of the field potentials in the dentate gyrus following perforant path stimulation were recorded in chronically implanted freely moving rats. The dentate gyrus was targeted since it receives the densest noradrenergic innervation of the hippocampus which arises exclusively from the brain stem locus coeruleus (Loy et al., 1980).

2. Materials and methods

2.1. Surgery

All procedures were approved by the Institutional Animal Care and Use Committee at University of Mississippi Medical Center. For chronic implantation of electrodes, male Sprague–Dawley rats (300–400 g) were anesthetized by sodium pentobarbital (50 mg/kg, i.p.) and mounted in a stereotaxic frame. The skull was exposed, and burr holes were drilled in the skull for the placement of recording and stimulating electrodes. A bundle of multiple-wire electrode (NB LABS, Dennison, TX) was implanted into the granular cell layer of the dentate gyrus (coordinates: 2.8 mm posterior to lambda, 1.5 mm lateral to midline, 3.0–3.4 mm ventral from dura) (Paxinos and Watson, 1986). A bipolar stimulating electrode (David Kopf Instruments, SNEX-100, 10 mm) was placed into the ipsilateral medial perforant path (6.9 mm posterior to lambda, 4.0 mm lateral to midline, 2.4–3 mm ventral from dura). A biphasic current pulse (100–400 μA,

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0.1 ms per cycle) was applied to the perforant path to evoke extracellular field potentials in the dentate gyrus. The population spikes appeared as a negative potential superimposed on a broad positive potential. Placement of both stimulating and recording electrodes was adjusted during the course of the implantation procedure to obtain the optimal population spike amplitude in the dentate gyrus-perforant path. The electrodes were then secured in place with five stainless steel screws trepanned through the skull and adhered with dental acrylic. Rats were given at least a week to recover following the surgery before recording. Two days before the recording, a PE-50 catheter was implanted into femoral vein for drug injection.

2.2. Electrophysiological recordings

Electrophysiological recordings were performed as described by Seidenbecher et al. (1997) and Frey et al. (2001) with modifications. Rats were placed in a plexiglass box (35 × 35 × 35 cm) and the electrodes were connected to two flexible cables (one for recording, one for stimulation) that allow them to move freely. A biphasic current pulse (100–400 μA, 0.1 ms per cycle) was applied to the perforant path to evoke field potentials in the dentate gyrus. The field potentials were filtered by band-pass filters of 1 Hz to 6 kHz and digitized by a commercial multi-channel neuronal acquisition processor (MNAP system, Plexon, Dallas, TX). The stimulus intensity which evokes 40% of the maximum population spike amplitude (assessed by the input/output or stimulation/response curve) was used as standard for all the recordings. The amplitudes of population spikes of the field potentials in the dentate gyrus following stimulation of perforant path were recorded before and after morphine injection. The amplitude of population spike is defined as the difference between the first positive and negative deflections. Population spike recording and analysis were favored against the slope of excitatory post-synaptic potential (EPSP) because the slope of EPSP is relatively unstable in the hilar region of the dentate gyrus in freely moving rats (Seidenbecher et al., 1997; Frey et al., 2001). During baseline recording, five single responses (20-s interpulse interval) were averaged every 7 min. Once a stable baseline was obtained, a single dose of morphine sulfate (5 mg/kg) was injected through the intravenous (i.v.) line. Ten responses (20-s interpulse interval) were averaged every 15 min after morphine injection. The control group received equal volume of saline injection. To test the role of noradrenergic input in the morphine-induced potentiation, propranolol hydrochloride (5 mg/kg, i.v.), a β-adrenoceptor antagonist, was injected 10 min before morphine injection.

3. Results

A single dose of morphine sulfate (5 mg/kg, i.v.) resulted in an augmentation in the amplitude of population spikes of the evoked field potentials in the dentate gyrus-perforant path pathway. Fig. 1A shows examples of evoked field potentials recorded from dentate granule cell layer before (left panel) and 15 min after morphine injection (right panel). The time course of the morphine-induced potentiation of the population spike is shown in Fig. 1B. Data are expressed as percentage of the baseline. Morphine induced a significant increase in the amplitude of population spike with an average potentiation of 187.6 ± 10.2% (mean percentage of baseline, 15–60 min following the injection, $n = 8$, filled circles). This morphine-induced potentiation lasted for about 3 h. Saline vehicle injection did not change the evoked response ($n = 5$) (Fig. 1C, open squares). When pretreated with propranolol (5 mg/kg, i.v.), the magnitude of morphine-induced potentiation was significantly reduced (140.8 ± 10.6%, mean percentage of baseline, 15–60 min after morphine injection, $n = 4$, $P < 0.05$, One-way analysis

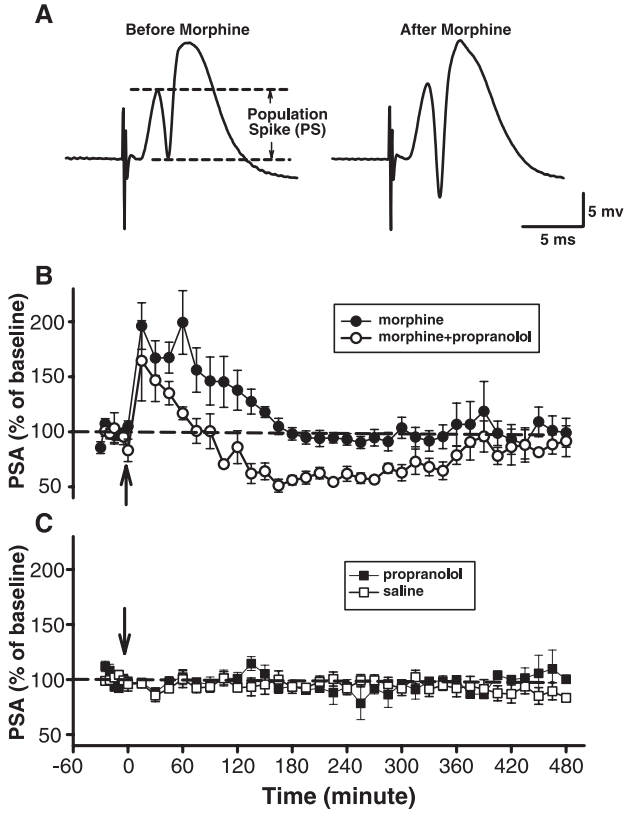

Fig. 1. Effects of morphine on the evoked field potentials (population spike) in the hippocampal dentate gyrus. (A) Representative evoked field potentials recorded before (left panel) and after morphine injection (right panel). (B) Time course of the effects of propranolol on the morphine-induced potentiation of the amplitude of population spikes (PSA). Data are expressed as percentage of the baseline. Morphine sulfate (5 mg/kg, i.v.) was injected at time 0. Propranolol was injected 10 min before morphine. Morphine alone resulted in a significant increase in the amplitude of population spikes that lasted for about 3 h ($n = 8$, filled circles). The morphine-induced potentiation was attenuated by pretreatment with propranolol ($n = 4$, open circles). (C) Neither saline ($n = 5$, open squares) nor propranolol alone ($n = 3$, filled squares) changed the baseline population spikes.

of variance and Student–Newman–Keuls test, Fig. 1B, open circles), and the reduced potentiation only lasted for about 1 h. These results suggested that an increase in norepinephrine release may contribute to the morphine-induced potentiation. Furthermore, the reduced potentiation was followed by a long-lasting depression (about 5 h). Since injection of propranolol alone had no effects on the amplitude of the population spikes ($n = 3$) (Fig. 1C, filled squares), these data suggested that morphine also has a depressive effect on the evoked field potentials which was unmasked by the pretreatment with propranolol. The depression could result from the action of some inhibitory neurotransmitters and/or neuropeptides that were co-released with norepinephrine.

4. Discussion

Norepinephrine is an important neuromodulator and has been shown to induce and facilitate synaptic plasticity in several brain areas including the hippocampus (Neuman and Harley, 1983; Lacaille and Harley, 1985; Winson and Dahl, 1985; Hopkins and Johnston, 1988; Huang and Kandel, 1996; Kirkwood et al., 1999; for review, see Bailey et al., 2000). For example, a brief application of norepinephrine induces long-lasting potentiation in the dentate gyrus of the hippocampus in the absence of tetanic stimulation (Neuman and Harley, 1983; Lacaille and Harley, 1985; Winson and Dahl, 1985). In the present study, we found that the morphine-induced long-lasting potentiation in the dentate gyrus was attenuated by the β-adrenoceptor antagonist propranolol. These results suggest that the morphine-induced potentiation may be mediated by an increase in norepinephrine release in the hippocampus. Although studies in brain slices showed that the effect of opioids on norepinephrine release is inhibitory (Werling et al., 1987), in vivo studies suggest that opioid drugs increase norepinephrine release in the brain. Roffman et al. (1974, 1975) demonstrated that systemic administration of a single dose of morphine resulted in a dose-related increase in the brain level of 3-methoxy-4-hydroxy-phenethyleneglycol sulfate, which is a major metabolite of norepinephrine in rat brain. Therefore, the morphine-induced potentiation is most likely mediated by morphine's action on other brain structures that modulate norepinephrine release in the dentate gyrus rather than by morphine's local action on norepinephrine release. One of such brain structures may be the locus coeruleus that provides the exclusive norepinephrine-containing innervation in the hippocampus (Loy et al., 1980). Recently, we found that morphine does not simply decrease the firing rate of locus coeruleus neurons as reported in earlier studies (Korf et al., 1974; Bird and Kuhar, 1977; Aghajanian, 1978; Valentino and Wehby, 1988), but that it induces long-lasting synchronous oscillatory bursts discharges in the locus coeruleus (Zhu and Zhou, 2001). The morphine-induced synchronous burst activities may influence norepinephrine release in locus coeruleus target areas. It has been demonstrated that norepinephrine release from locus coeruleus axons is enhanced by burst stimulation (Florin-Lechner et al., 1996). Furthermore, the synchronous activity in the locus coeruleus would result in a simultaneous release of neurotransmitters from many locus coeruleus axon terminals. Thus, although the overall firing rate of locus coeruleus neurons is reduced by morphine injection, as a result of temporal and spatial summation, the morphine-induced synchronous oscillatory burst activity could result in an increase in norepinephrine release in the dentate gyrus, which contributes to the morphine-induced enhancement of synaptic efficacy in this brain region.

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