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Research Report

Blockade of orexin type 1 receptors inhibits the development of morphine tolerance in lateral paragigantocellularis nucleus: An electrophysiological approach

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ARTICLE INFO

Article history:
Accepted 27 June 2014
Available online 8 July 2014

Keywords:
Orexin
SB-334867
Morphine
Tolerance
Extracellular in vivo single unit recording
LPGi nucleus

ABSTRACT

Repetitive administration of opioid agonists is associated with the development of tolerance to the effects of these substances and limits their application. Orexin (also known as hypocretin) is involved in morphine tolerance and dependence. The lateral paragigantocellularis nucleus (LPGi) is a key brain region implicated in the tolerance and dependence to opiates. Orexin type 1 receptor (OXR1) has been detected in LPGi nucleus. In this study the effect of OXR1 blockade was investigated on neural activity of LPGi during the development of morphine tolerance in rats. Male Wistar rats weighing 250–300 g were used in this study. To incite tolerance, morphine sulfate was injected intraperitonealy (10 mg/kg, i.p.) once a day for 6 days. A selective OXR1 antagonist (SB-334867) was microinjected into the right cerebral ventricle (10 μg/10 μl, i.c.v.) immediately before each morphine injection. On day 7, the effect of morphine (10 mg/kg, i.p.) on neural activity of LPGi was investigated using in vivo extracellular single unit recording. In this study morphine injection during 6 days led to the development of morphine tolerance in LPGi neurons which was observed as a significant decrease in responsiveness of LPGi neurons to acute morphine injection. Administration of SB-334867 before each morphine injection could reverse the responses of LPGi neurons to acute morphine injection. This study showed that OXR1 blockade by SB-334867 prevents the development of tolerance to morphine in LPGi neurons. Further studies are required to determine molecular and anatomical mediators which are thought to be involved in this phenomenon.

1. Introduction

Opioid ligands such as morphine are potent analgesics that are widely used for severe pain management (Davis et al., 2005). However, tolerance to the analgesic effect of morphine following repeated administrations interrupts the continuity of opioid therapy (Taylor and Fleming, 2001).

A growing body of evidence suggests that the lateral paragigantocellularis nucleus (LPGi), in the rostral ventral medulla (RVM), plays a pivotal role in the opiate tolerance

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http://dx.doi.org/10.1016/j.brainres.2014.06.033
0006-8993/

and dependence. LPGi provides the main excitatory input fibers to the noradrenergic locus coeruleus nucleus (LC) (Aston-Jones et al., 1986; Ennis and Aston-Jones, 1988; Ennis et al., 1992), which is a well-known structure involved in opiate dependence and withdrawal (Nestler and Aghajanian, 1997; Williams et al., 2001). During morphine withdrawal, the release of glutamate is increased in the LC nucleus (Aghajanian et al., 1994; Zhang et al., 1994) which is thought to be involved in the hyperactivity of LC neurons following withdrawal. It has also been shown that either LPGi lesions or administration of glutamate antagonists can reverse the withdrawal-induced hyperactivity of LC neurons (Rasmussen and Aghajanian, 1989; Akaoka and Aston-Jones, 1991; Rasmussen et al., 1996).

Several lines of study reported that the responses of LPGi neurons to acute morphine injection are heterogeneous. These studies have also shown that LPGi neurons become tolerant to the single dose of morphine after chronic morphine treatment (Haghparast et al., 1998; Saiepour et al., 2001; Zhu and Zhou, 2010).

Orexin (hypocretin) neuropeptides are produced exclusively in the lateral hypothalamic area (LHA) and posterior hypothalamus (PH) (de Lecea et al., 1998; Sakurai et al., 1998). There have been identified two types of orexin receptors with distinct patterns of expression throughout the brain; orexin type 1 receptor (OXR1) and orexin type 2 receptor (OXR2) (Marcus et al., 2001). Orexin receptors and orexinergic projections have also been found in the LPGi nucleus (Peyron et al., 1998; Ciriello et al., 2003).

Previous study in our laboratory has demonstrated that intracerebroventricular administration of SB-334867, a selective orexin type 1 receptor antagonist, inhibits morphine antinociceptive tolerance in rats (Ranjbar-Slamloo et al., 2012). This evidence implies that the orexinergic system is implicated in tolerance to morphine.

The present study was aimed to assess whether central administration of OXR1 antagonist can inhibit the development of morphine tolerance in LPGi neurons. To do this, the effect of orexin type 1 receptor (OXR1) blockade on neural activity of LPGi was studied during the development of morphine tolerance.

2. Results

2.1. LPGi neurons' responses to acute morphine injection

The effects of acute morphine injection on LPGi neurons' spontaneous firing rate were examined in 20 rats. All of them received i.p. morphine injection (10 mg/kg) after 15 min of baseline recording. The LPGi neurons exhibited heterogeneous responses to acute morphine treatment. Fig. 1 shows typical excitatory (A), inhibitory (B) and no effect (C) responses of LPGi neurons to acute morphine injection. Out of 20 identified LPGi neurons, 7 neurons (35%) exhibited an increase in firing rate (baseline: 10.89±1.906 spikes/s; after morphine administration: 16.09±2.634 spikes/s), 7 neurons (35%) exhibited a decrease in firing rate (baseline: 23.57±5.864 spikes/s; after morphine administration: 16.10±4.497 spikes/s) and 6 neurons (30%) exhibited no change in firing rate (baseline: 13.67±2.220 spikes/s; after morphine administration: 13.39±2.275 spikes/s).

2.2. LPGi neurons' responses to acute morphine injection in morphine treated rats

In this group, morphine was injected intraperitonealy (10 mg/kg, i.p.) once a day for 6 days. On day 7, the effect of acute morphine injection (10 mg/kg, i.p.) on neural activity of LPGi was investigated to show the development of morphine tolerance. Acute morphine injection failed to change the unit activity of the nucleus paragigantocellularis neurons (baseline: 17.24±4.173 spikes/s; after morphine administration: 17.76±4.532 spikes/s) (Fig. 2). None of the neurons react significantly to the injection of the acute morphine.

2.3. LPGi neurons' responses to acute morphine injection in vehicle-morphine treated rats

In this group, the vehicle was microinjected into the right cerebral ventricle (10 μl, i.c.v.) immediately before each morphine injection (10 mg/kg, i.p.). On day 7, the effect of acute morphine injection (10 mg/kg, i.p.) on neural activity of LPGi was investigated. Acute morphine injection had no effect on the unit activity of the LPGi neurons (baseline: 12.66±6.002 spikes/s; after morphine administration: 10.82±5.184 spikes/s) (Fig. 3). None of the neurons react significantly to the injection of the acute morphine.

2.4. LPGi neurons' responses to acute morphine injection in SB-334867-saline treated rats

In this group, SB-334867 was microinjected into the right cerebral ventricle (10 μg/10 μl) immediately before each saline injection (1 ml/kg, i.p.). Then on day 7, the effect of acute morphine injection (10 mg/kg, i.p.) on neural activity of LPGi was investigated. Acute morphine injection induced heterogeneous responses in LPGi neurons' activity (Fig. 4). Out of 16 identified LPGi neurons, 4 neurons (25%) exhibited an increase in firing rate (baseline: 5.640±2.424 spikes/s; after morphine administration: 7.130±2.206 spikes/s), 8 neurons (50%) exhibited a decrease in firing rate (baseline: 9.940±2.362 spikes/s; after morphine administration: 7.990±2.069 spikes/s) and 4 neurons (25%) exhibited no change in firing rate (baseline: 10.61±2.313 spikes/s; after morphine administration: 10.04±2.148 spikes/s).

2.5. LPGi neurons' responses to acute morphine injection in SB-334867-morphine treated rats

In this group, SB-334867 (a selective orexin type 1 receptor antagonist) was microinjected into the right cerebral ventricle (10 μg/10 μl, i.c.v) immediately before each morphine injection (10 mg/kg, i.p.). On day 7, the effect of acute morphine injection (10 mg/kg, i.p.) on neural activity of LPGi was investigated. Acute morphine injection induced heterogeneous responses in LPGi neurons' activity (Fig. 5). Out of 17 identified LPGi neurons, 5 neurons (29.4%) exhibited an increase in firing rate (baseline: 11.92±2.706 spikes/s; after morphine administration: 16.20±3.333 spikes/s), 8 neurons (47%) exhibited a decrease in firing rate (baseline: 19.58±