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The influence of AMN082, metabotropic glutamate receptor 7 (mGlu7) allosteric agonist on the acute and chronic antinociceptive effects of morphine in the tail-immersion test in mice: Comparison with mGlu5 and mGlu2/3 ligands☆

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Morphine is effective in pain therapy, but has undesired effects, including tolerance development. AMN082, a selective mGlu7 allosteric agonist, did not affect the acute morphine antinociception, but inhibited morphine tolerance in the tail immersion test in rats. The effect of AMN082 was comparable to that of the mGlu5 antagonist and mGlu2/3 agonist and was reversed by MMPIP, an mGlu7 antagonist. There is no interaction between mGlu7 and NMDA receptors in the tolerance phenomenon.

Keywords:
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ABSTRACT

Preclinical data indicated that the metabotropic glutamate receptors 5 (mGlu5) and glutamate receptors 2/3 (mGlu2/3) are involved in modulating morphine antinociception. However, little is known about the role of metabotropic glutamate receptors 7 (mGlu7) in this phenomenon. We compared the effects of AMN082 (0.1, 1 or 5 mg/kg, ip), a selective mGlu7 allosteric agonist, LY354740 (0.1, 1 or 5 mg/kg, ip), an mGlu2/3 agonist and MTEP (0.1, 1 or 5 mg/kg, ip), a selective mGlu5 antagonist, on the acute antinociceptive effect of morphine (5 mg/kg, sc) and also on the development and expression of tolerance to morphine analgesia in the tail-immersion test in mice. To determine the role of mGlu7 in morphine tolerance, and the association of the mGlu7 effect with the *N*-methyl-D-aspartate (NMDA) receptors regulation, we used MMPIP (10 mg/kg, ip), a selective mGlu7 antagonist and MK-801, a NMDA antagonist. Herein, the acute administration of AMN082, MTEP or LY354740 alone failed to evoked antinociception, and did not affect morphine (5 mg/kg, sc) antinociception. However, these ligands inhibited the development of morphine tolerance, and we indicated that MMPIP reversed the inhibitory effect of AMN082. When given together, the non-effective doses of AMN082 and MK-801 did not alter the tolerance to morphine. Thus, mGlu7, similarly to mGlu2/3 and mGlu5, are involved in the development of tolerance to the antinociceptive effects of morphine, but not in the acute morphine antinociception. Furthermore, while mGlu7 are engaged in the development of morphine tolerance, no interaction exists between mGlu7 and NMDA receptors in this phenomenon.

1. Introduction

Opioid analgesics are still the gold standard for treating acute and chronic pain [1]. Three classes of opioid receptors mediate opioid analgesia. These are mu, delta and kappa opioid receptors. The most widely used drug is the mu opioid receptor agonist, morphine. Opioid drugs produce many notable adverse effects, especially tolerance development and physical dependence, as well as respiratory depression, and other lesser side effects such as constipation, sedation, nausea and vomiting. These greatly limit their effectiveness and usage [2,3,4].

Metabotropic glutamate receptors (mGlu) are members of the G protein-coupled receptors superfamily, and until now, eight receptor subtypes (mGlu 1–8) have been identified and classified within three major groups (group I, II and III). In regard to pain modulation, the mGlu effect is shown through wide localization within the pain pathway [5]. Depending on the specific receptor subtype stimulation and its cellular, synaptic and anatomical location, pain perception can be inhibited/facilitated by mGlu activation [6]. Published data indicated that antagonists of group I mGlu (localized postsynaptically) and agonists of group II mGlu (localized presynaptically) have shown in animal pain models, some therapeutic promise [7,8]. Beyond direct analgesic effect exhibition, mGlu ligands may act as opiate analgesia

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adjuvants. For example, morphine and LY354740 (a group II mGlu agonist) co-administration inhibits morphine tolerance development in the radiant-heat source tail flick in mice [9,10]. Additionally, systemic administration of MPEP (a mGlu5 antagonist) and LY379628 (a group II mGlu agonist) have potentiated morphine's analgesic efficacy and inhibited the development of morphine tolerance in a neuropathic pain model [11,12].

Group III mGlu and group II mGlu, are mainly localized presynaptically, hence, inhibit neurotransmitter release. Regarding group III mGlu, less results are available about their engagement in nociception [13]. Thus, intrathecal administration of L-AP4, a non-selective group III agonist, was shown to reduce spontaneous nociceptive behavior in the formalin test [14]. However, the recent discovery of AMN082, a selective mGlu7 allosteric agonist [15], allows exploring the role of mGlu7 in pain perception. Earlier preclinical studies have revealed that this drug exerts antidepressant-like and anxiolytic-like effects, inhibits inflammatory pain and incision-induced hypersensitivity and also attenuates allodynia and hyperalgesia [12,16–18]. In contrast, a few studies have shown the influence of AMN082 on nociception in acute and chronic pain [17]. However, the influence of AMN082 on morphine antinociception has not been explored. Therefore, the aim of the present study was to examine: 1) the influence of mGlu7 agonist, AMN082, on acute morphine antinociception and 2) its influence on the development of tolerance to the antinociceptive effect of morphine. These effects of AMN082 were compared to the effects of MTEP, an antagonist of mGlu5 and LY354740, an agonist of mGlu2/3. To determine the engagement of mGlu7 in the effect of AMN082 on the development of morphine tolerance, a selective mGlu7 antagonist, MMPIP [18] was used. Furthermore, we sought to determine whether or not the previously described interactions [19,20] exist between mGlu7 and an *N*-methyl-D-aspartate (NMDA) receptors, especially during the development of tolerance to the antinociceptive effect of morphine.

2. Materials and methods

2.1. Animals

Male Swiss mice (HZL, Warsaw, Poland), weighing 25–30 g at the initiation of the experimental procedure, were used in our experiments. The animals were housed five per cage with standard laboratory feed (Bacutil, Motycz, Poland) and water ad libitum. Moreover, the animals were kept under a 12/12 h light/dark cycle and in a controlled temperature (22 ± 2 °C). The mice were adapted to the laboratory conditions for at least one-week prior experimentation. All behavioral studies were performed between 9:00 a.m. and 2:00 p.m. The experimental protocols and housing conditions were performed according to the National Institute of Health Guidelines for the Care and Use of Laboratory Animals, as well as the European Community Council Directive of November 2010 for Care and Use of Laboratory Animals (Directive 2010/63/EU), and were approved by the Local Ethics Committee.

2.2. Drugs and injection procedure

Morphine hydrochloride (Polfa, Kutno, Poland) was dissolved in sterile saline (0.9% NaCl) and given subcutaneously (sc). N,N′-dibenzhydrylethane-1,2-diamine dihydrochloride (AMN082), (1*S*,2*S*,5*R*,6*S*)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (LY354740) and (3-[(2-methyl-1,3-thiazol-4-yl)ethynyl])pyridinehydrochloride (MTEP) were purchased from Tocris Bioscience (Bristol, UK), dissolved in a vehicle consisting of 0.5% methylcellulose in saline, and were administered intraperitoneally (ip) at the dose of 0.1, 1 or 5 mg/kg. Morphine and all mGlu ligands were freshly prepared and were given in a volume of 10 ml/kg. Saline was administered in an equivalent volume and given sc or ip. The doses of morphine, AMN082, LY354740 and MTEP were chosen based on our previous [21–23] and published studies [17]. Because our previous studies have shown that AMN082 induced motor impairment above the dose of 5 mg/kg [22], we used all mGlu ligands at dosages not exceeding 5 mg/kg when comparing their efficacy in the acute morphine antinociception and the tolerance to the antinociceptive effects of morphine.

2.3. Tail-immersion test

The tail-immersion test was carried out as described by Janssen et al. [24]. To determine the nociceptive reaction, the animals' tails were placed in a water bath heated to 52 ± 0.5 °C with a cut-off time of 20 s to prevent tail skin tissue damage. Before the drug administration, the baseline latency (average for three measurements in seconds) for the mouse to withdraw the distal half of the tail after its immersion in water was first measured. The animals were then injected with the mGlu ligands and saline/morphine according to the experimental paradigm, and post-treatment latency responses were determined at 30 min intervals up to 180 min. The antinociceptive effects of morphine or saline with/without mGlu ligands were expressed as the percent maximum possible effect (%MPE) calculated as: MPE (%) $[(T^1 - T^0)/(20 - T^0)] \times 100$, where T^0 and T^1 are the pre-drug and post-drug latencies for tail-immersion response, respectively.

2.4. Experimental procedures

2.4.1. The effect of AMN082, LY354740 and MTEP on the acute antinociception induced by morphine in the tail-immersion test in mice

On the day of experiment, mice were randomly divided into several experimental groups (7–9 animals per group) and the baseline response latencies (average for three measurements of the baseline tail-withdrawal latency in seconds) were recorded before drug administration. Then, the animals were injected either with AMN082 (0.1, 1 or 5 mg/kg, ip), LY354740 (0.1, 1 or 5 mg/kg, ip) or MTEP (0.1, 1 or 5 mg/kg, ip) 30 min before morphine (5 mg/kg, sc) administration. The control group received vehicle/mGlu ligand (ip) and saline/morphine (sc) in the same volume and the same time point. Next, post-treatment latency responses were determined at 30 min intervals up to 180 min after saline/morphine injection. In order to assess the total analgesic effect in different groups, the area under the curve (AUC) for %MPE against the time was calculated. This analysis allows a comparison of the effects from different analgesic tests.

2.4.2. The effect of AMN082, LY354740 and MTEP on the development of tolerance to the antinociceptive effects of morphine in the tail-immersion test in mice

Tolerance to the antinociceptive effects of morphine was established based on the method described by Elhabazi et al. [25] with minor modifications. Morphine tolerance was developed by administration of morphine (5 mg/kg, sc) once daily for 7 days. The control mice received saline administration in the same volume and by the same route. To indicate the influence of mGlu ligands on the development of morphine tolerance, the animals (7 days) were treated with AMN082 (0.1, 1 or 5 mg/kg, ip), LY354740 (0.1, 1 or 5 mg/kg, ip) or MTEP (0.1, 1 or 5 mg/kg, ip), 30 min prior to morphine (5 mg/kg, sc) administration. The control groups received only the highest dose of mGlu ligands (5 mg/kg, ip) used in our study or they received saline. The tail-immersion test was performed 30 min after morphine/saline injection on day 1, 3, 5 and 7 of the experiment. The baseline latency response of mice (average of three measurements in seconds) was assessed on these days before drug administration. On day 8 of the experiment (after the baseline latency measurement), all groups of mice received a challenge injection of morphine (5 mg/kg, sc), 30 min before evaluating their pain response in the tail-immersion test.

2.4.2.1. The influence of MMPIP on the effect of AMN082. Furthermore, a separate experiment was carried out to indicate the involvement of