Antinociceptive effects of novel melatonin receptor agonists in mouse models of abdominal pain

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AIM: To characterize the antinociceptive action of the novel melatonin receptor (MT) agonists, Neu-P11 and Neu-P12 in animal models of visceral pain.

METHODS: Visceral pain was induced by intracolonic (ic) application of mustard oil or capsaicin solution or by intraperitoneal (ip) administration of acetic acid. Neu-P11, Neu-P12, or melatonin were given ip or orally and their effects on pain-induced behavioral responses were evaluated. To identify the receptors involved, the non-selective MT1/MT2 receptor antagonist luzindole, the MT2 receptor antagonist 4-P-PDOT, or the μ-opioid receptor antagonist naloxone were injected ip or intracerebroventricularly (icv) prior to the induction of pain.

RESULTS: Orally and ip administered melatonin, Neu-P11, and Neu-P12 reduced pain responses in a dose-dependent manner. Neu-P12 was more effective and displayed longer duration of action compared to melatonin. The antinociceptive effects of Neu-P11 or Neu-P12 were antagonized by ip or icv administered naloxone. Intracerebroventricularly, but not ip administration of luzindole or 4-P-PDOT blocked the antinociceptive actions of Neu-P11 or Neu-P12.

CONCLUSION: Neu-P12 produced the most potent and long-lasting antinociceptive effect. Further development of this novel compound for future treatment of abdominal pain seems promising.

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Key words: Gastrointestinal tract; Melatonin; Neu-P11; Neu-P12; Opioid; Visceral pain

Core tip: In search for new efficient therapies for the treatment of pain in the irritable bowel syndrome, the antinociceptive activity of two novel melatonin receptor agonists, Neu-P11 and Neu-P12, was characterized in a well-established mouse model of visceral pain. Neu-P12 produced a potent and long-lasting antinociceptive effect after intraperitoneal and oral administration. Further development of this novel compound for future treatment of abdominal pain seems promising.
INTRODUCTION

Melatonin is a hormone synthesized primarily in the pineal gland and in peripheral organs, including the gastrointestinal tract, bone marrow, and blood cells[1-3]. Following synthesis, melatonin is released into the bloodstream and acts as an endocrine hormone controlling biological functions with circadian rhythms, like the sleep-wake cycle. It is a lipophilic compound diffusing rapidly through biological membranes and is amongst others involved in the regulation of intestinal reflexes, metabolism, and reproduction[4]. In the pineal gland melatonin is synthesized and secreted in a circadian manner, with secretion being highest during nighttime[5].

Morris and Lutsch[6] showed that darkness and elevated levels of melatonin decrease sensitivity to pain, suggesting that the hormone may play a significant role in the modulation of pain. In the following years, several studies characterized the antinociceptive effect of melatonin in multiple animal models[7]. Melatonin receptors (MT) mediate or modulate antinociceptive effects at spinal and supraspinal levels[8]. More recently, melatonin-induced antinociception has been reported using neuropathic pain models[9].

Recent clinical trials provided evidence for a beneficial role of melatonin in gastrointestinal functional pain[10]. Double-blinded placebo-controlled clinical trials showed that melatonin reduced extra-colonic symptoms and abdominal pain in patients with irritable bowel syndrome (IBS)[11-14].

Although melatonin has been studied for the treatment of many diseases such as cancer, cardiovascular diseases, depression, seasonal affective disorder, circadian rhythm sleep disorders and insomnia, its actions are limited by rapid degradation and short half-life. Recently, two novel melatonin receptor agonists with high affinity at MT receptors and prolonged duration of action, Neu-P11 and Neu-P12, were developed[15-17]. It was shown that Neu-P11 and Neu-P12 display long half-life and oral availability and are thus promising drug candidates, which require further characterization.

In the present study, we evaluated the possible antinociceptive effects of Neu-P11 and Neu-P12 in mouse models of visceral pain and compared their effects to those of melatonin. We also aimed at characterizing the mechanism of action of Neu-P11 and Neu-P12 via identifying the receptors involved.

MATERIALS AND METHODS

Animals

Male Swiss albino CD1 mice, weighing 25-30 g were obtained from Charles River (Canada). Animals were housed at a constant temperature of 22 °C and kept at a constant photoperiod (12:12-h light-dark cycle) in saw-dust-lined plastic cages with free access to standard laboratory chow and tap water. The animal use for these studies was approved by the University of Calgary Animal Care Committee and the experiments were performed in accordance with institutional animal ethics committee guidelines that are in agreement to the guidelines established by the Canadian Council on Animal Care.

Behavioral responses to mustard oil and capsaicin solution

Behavioral pain-related responses to intracolonic (ic) administration of mustard oil (MO) and capsaicin solution were determined in the morning as described previously[18-20]. Fifteen minutes after ip injection of Neu-P11, Neu-P12, or melatonin (25 and 50 mg/kg) or 20 min after oral gavage (25, 50 and 100 mg/kg), 50 μL of MO (1% vol/vol dissolved in 70% ethanol) or capsaicin (0.3% w/v in 10% ethanol, 10% Tween 80, 80% saline) were administered into the colon of anesthetized mice using a fine catheter (external diameter 0.61 mm, 4 cm long, Minipack, Portex, Hythe, United Kingdom). Vaseline was applied to the perianal area to avoid the stimulation of somatic areas by contact with MO or capsaicin. After the administration of MO or capsaicin, the animals were placed in individual plastic cages in a quiet environment. Five minutes later, spontaneous pain-related responses: licking of the abdomen, stretching the abdomen, squashing the lower abdomen against the floor, and abdominal retractions were counted for 20 min.

Typically, the number of behaviors in MO- and capsaicin-treated mice was 60-70 and 30-40, respectively. In these conditions even slight changes in the number of behaviors, caused by either anti- or pro-nociceptive action of studied compounds, can be noticed, but simultaneously only statistically significant differences in obtained values reflect pharmacologically relevant action.

The non-selective MT1/MT2 receptor antagonist luzindole (5 mg/kg), the selective MT2 receptor antagonist 4-P-PDOT (4 mg/kg) and the opioid receptor antagonist naloxone (1 mg/kg) were administered ip 15 min prior to Neu-P11, Neu-P12 and melatonin. To study the role of MT and opioid receptors in the central nervous system, luzindole (5 μg/animal), 4-P-PDOT (10 μg/animal) or naloxone (5 μg/animal) were injected iv. Five minutes prior to the ip administration of Neu-P11, Neu-P12 and melatonin. Vehicles only were used in control experiments.

Acetic acid induced pain

The acetic acid test was performed as described recently[19-22]. Fifteen minutes after ip injection of Neu-P11, Neu-P12, or melatonin (1 and 5 mg/kg), mice received an ip injection of an acetic acid solution (0.5%, vol/vol in 0.9% NaCl). Animals were then placed individually in empty cages and after 5 min abdominal stretchings were counted for 15 min in 5 min intervals. A typical stretch was characterized by an elongation of the body and the development of tension in the abdominal muscles and...
were obtained from Tocris Bioscience (Tocris, Ellisville, Missouri, United States). Allyl isothiocyanate (mustard oil, MO) was purchased from Merck (Darmstadt, Germany). Neu-P11 and Neu-P12 were obtained from Neurim Pharmaceuticals Ltd., Israel. All drugs were dissolved in dimethyl sulfoxide and diluted in 0.9% saline to final concentrations.

**Statistical analysis**

PRISM 5.0 (GraphPad Software Inc., La Jolla, CA, United States) was used for statistical and curve-fitting analyses. One-way analysis of variance followed by Student-Newman-Keuls post hoc test was used for analysis of multiple treatment means. P values < 0.05 were considered significant. The data are expressed as mean ± SE.

**RESULTS**

**Effects of melatonin and melatonergic agonists on MO-induced pain**

As shown in Figure 1, melatonin, Neu-P11 and Neu-P12 injected ip (Figure 1A) or given orally (Figure 1B) significantly reduced the number of pain-related behaviors in the OM visceral pain sensitivity test compared to control in a dose-dependent fashion. Oral Neu-P12 was the most effective compound of all melatonin agonists in decreasing the pain behaviors.

The antinociceptive effect of Neu-P12 (ip 50 mg/kg) was observed up to 4 h after administration, the effect of Neu-P11 (ip 50 mg/kg) up to 2 h. Melatonin (ip 50 mg/kg) produced a short-lasting effect, which was observed at 15 min but disappeared at 2 h (Figure 1C).

**Effect of naloxone and melatonergic antagonists on melatonin, Neu-P11 and Neu-P12-induced effects on MO-induced pain**

The effects of melatonin, Neu-P11 and Neu-P12 on the visceral pain-related behaviors in the MO sensitivity test were blocked by the ip administration of the opioid receptor antagonist naloxone, but not by ip application of the MT1/2 receptor antagonist luzindole or the MT2 receptor antagonist naloxone, but not by ip application of the MT1/2 receptor antagonist luzindole or the MT2 antagonist 4-P-PDOT (Figure 2A). Naloxone and MT receptor antagonists administered directly to the central nervous system all effectively blocked behavioral responses in the visceral pain tests (Figure 2B).

**Effect of melatonin, Neu-P11 and Neu-P12 on capsaicin-induced pain**

Melatonin, Neu-P11 and Neu-P12 administered ip (25 mg/kg) significantly decreased the number of pain induced behaviors following ip administration of capsaicin (Figure 3A). Of all compounds tested, Neu-P12 displayed the most potent antinociceptive action.

**Effect of melatonin, Neu-P11 and Neu-P12 on the acetic acid induced pain**

Melatonin, Neu-P11 and Neu-P12 (5 mg/kg, ip) all effectively reduced the total number of visceral pain behaviors observed in the acetic acid-induced pain test. The reduction was dose-dependent, with Neu-P12 being the most effective compound at all doses tested (Figure 3B).

**Discussion**

Melatonin and its analogs showed promising antinociceptive effects in the murine models used in this study. Oral Neu-P12 was the most effective compound of all melatonin agonists in decreasing the pain behaviors. Further studies are needed to understand the mechanisms underlying these effects and to evaluate their potential clinical applications.
In our studies, the two novel non-selective MT1/MT2 melatonergic agonists used, Neu-P11 and Neu-P12, produced a potent antinociceptive effect comparable to that of melatonin and this effect holds true in three different models of visceral pain. The in vivo experiments indicated that Neu-P12 is the most effective drug with the longest duration of action.

We showed that the antinociceptive effects of melatonin, Neu-P11 and Neu-P12 were blocked by the icv administration of a MT2 receptor antagonist 4-P-PDOT, as well as icv and ip injection of naloxone, suggesting a crucial role of central MT2 and opioid receptors, as well peripheral opioid receptors. The involvement of MT2 and opioid receptors in the antinociceptive effects of melatonin was earlier suggested by Ambriz-Tututi and Granados-Soto in models studying other forms of pain, who showed that intrathecal luzindole and 4-P-PDOT and intrathecal or subcutaneous naltrexone blocked the effect of melatonin on tactile allodynia in neuropathic rats[23]. Another study revealed that the antihyperalgesic effect of melatonin on nociceptin-induced hyperalgesia in mice was significantly antagonized by the icv administration of luzindole[24].

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chapters 4 and 5. Neurons containing melatonin in their axon terminals innervate target tissues such as bone marrow and perhaps the gastrointestinal tract. Melatonin in the gut, in turn, acts on enteric nerves to inhibit gastric acid secretion and motility. Such actions help modulate the hormone's effects on other systems, including the immune system and the pituitary gland.

The possible mechanisms by which melatonin works include mediation of the hypothalamic-pituitary-adrenal axis, which is linked to the circadian rhythm of melatonin release and the experience of pain.

In summary, melatonin has several potential applications in medicine, including its use as a treatment for gastrointestinal motility disorders, insomnia, and other conditions associated with abnormal circadian rhythms. Further research is needed to fully understand the mechanisms by which melatonin works and to develop new therapeutic applications for this hormone.
In summary, melatonin, and its agonists Neu-P11, and Neu-P12 decreased visceral abdominal pain-related behaviors in mice. The antinociceptive action of the melatoninergic agonists was mediated by central and peripheral opioid receptors, as well as central MT2 receptors. All analgesic effects were seen following oral application, an attribute that allows oral treatment if further developed for clinical use.

Neu-P12, which displayed the most significant analgesic effect and the longest duration of antinociceptive action and Neu-P11 have the potential to become future drugs for the treatment of pain in abdominal diseases including, but not limited to, IBS and ulcerative colitis.

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