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BRIEF ARTICLE

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

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Abstract

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 Neu-P12 for future treatment of abdominal pain seems promising.

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.

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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 blood stream 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 ℃ and kept at a constant photoperiod (12:12-h light-dark cycle) in sawdust-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 *icv*. 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[19-21]. 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

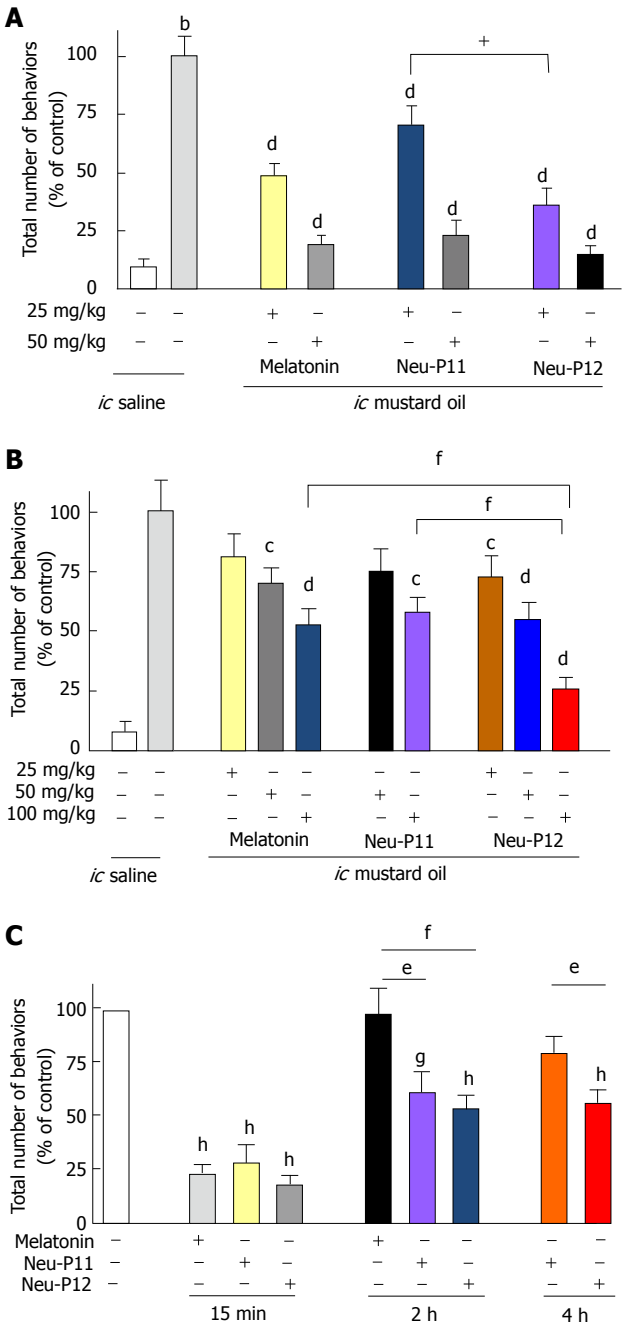

Figure 1 Effects of melatonin and melatonergic agonists on mustard oil-induced pain. A: *Ip* melatonin, Neu-P11, and Neu-P12 (all 25 and 50 mg/kg) reduced the number of pain-related behaviors in the mustard oil (MO) sensitivity test 15 min after drug administration; B: Oral melatonin, Neu-P11 and Neu-P12 (all 25 mg/kg, 50 mg/kg and 100 mg/kg) decreased the number of pain-related behaviors in the MO sensitivity test 20 min after drug administration; C: Effect of ip injected melatonin, Neu-P11 and Neu-P12 (all at 50 mg/kg) on the number of pain-related behaviors in the MO sensitivity test at 15 min, 2 and 4 h after drug administration. Data are mean ± SE (n = 6-10). $^{b}P < 0.01$ *vs* MO; $^{c}P < 0.05$, $^{d}P < 0.01$ *vs* vehicle + MO; $^{e}P < 0.05$, $^{f}P < 0.01$ *vs* drug; $^{g}P < 0.05$, $^{h}P < 0.01$ *vs* control.

hind paws. Vehicle was used in control experiments. Typically, the number of behaviors in acetic acid solution-treated mice was 30-40.

Drugs

Melatonin, luzindole, 4-P-PDOT, naloxone and capsaicin 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-depended 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 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 *ic* 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 be-

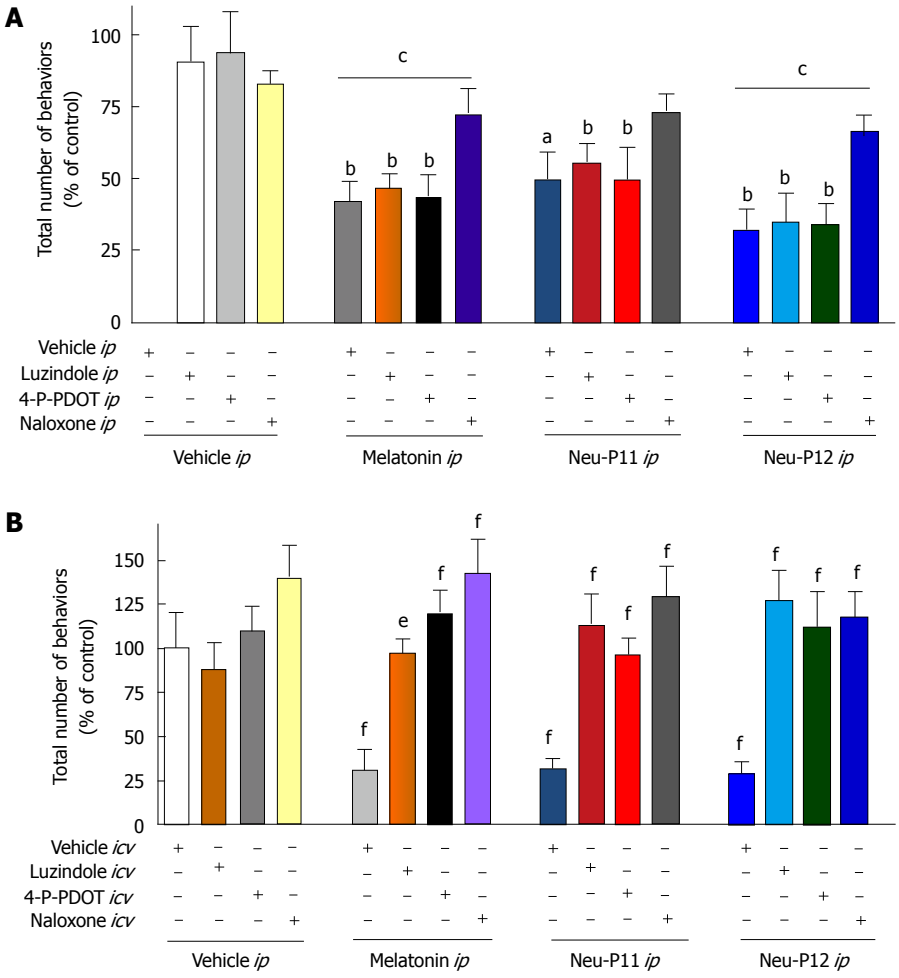

Figure 2 Effect of naloxone and melatonergic antagonists on melatonin, Neu-P11 and Neu-P12-induced effects on mustard oil-induced pain. A: Effects of antagonists: *ip* naloxone (1 mg/kg), but not luzindole (5 mg/kg) or 4-P-PDOT (4 mg/kg) blocked the effects of melatonin, Neu-P11, and Neu-P12 (all at 25 mg/kg, *ip*) on the number of pain-related behaviors in the mustard oil sensitivity test 15 min after drug administration; B: *Icv* naloxone (5 μg/animal), luzindole (5 μg/animal) and 4-P-PDOT (10 μg/animal) blocked the effects of melatonin, Neu-P11 and Neu-P12 (all at 25 mg/kg, *ip*) in the mustard oil sensitivity test 15 min after drug administration. Data are mean ± SE (n = 6-10). $^{a}P < 0.05$, $^{b}P < 0.01$ *vs* control; $^{c}P < 0.05$ *vs* drugs + vehicle; $^{e}P < 0.05$, $^{f}P < 0.01$ *vs* vehicle *icv* + drugs *ip*.

haviors induced by the *ip* injection of acetic acid (Figure 3B). Neu-P12 displayed the most potent antinociceptive effect.

DISCUSSION

In this study we showed that *ip* and oral administration of melatonin, Neu-P11 and Neu-P12 produced a potent antinociceptive effect in different animal models of visceral pain of abdominal origin. The analgesic action of all compounds was mediated by central and peripheral opioid and central, but not peripheral, MT receptors.

Melatonin significantly and dose-dependently decreased the total number of pain-related behaviors induced by OM, capsaicin and acetic acid solution in mice. This observation is in line with earlier reports suggesting a role of melatonin and MT receptors in pain signaling. It was shown by others that intrathecal co-administration of low doses of melatonin and morphine attenuated mechanical and thermal hyperalgesia in acute postoperative pain model in rats, suggesting that melatonin acts as a neuromodulator in the spinal cord[22].

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*. admin-

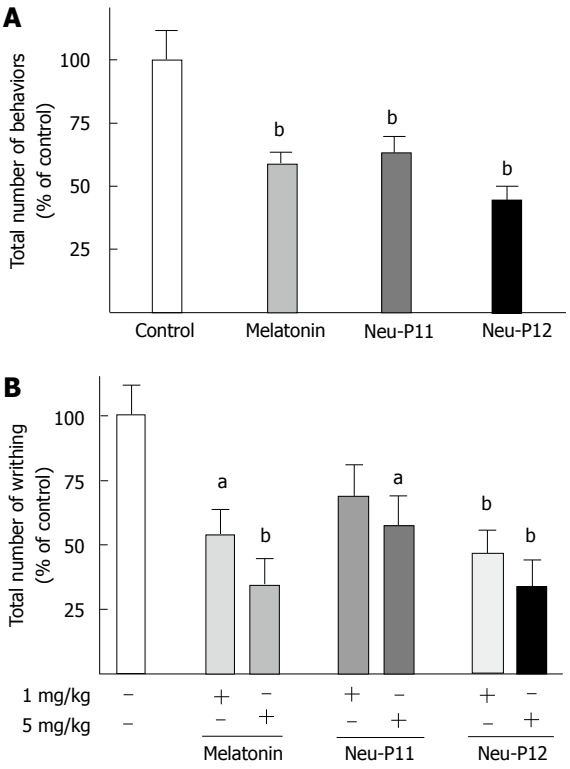

Figure 3 Melatonin, Neu-P11 and Neu-P12 decreased the number of pain-related behaviors. A: Melatonin, Neu-P11 and Neu-P12 (all at 25 mg/kg, *ip*) decreased the number of pain-related behaviors in the capsaicin-induced visceral pain test 15 min after drug administration; B: Melatonin, Neu-P11 and Neu-P12 (all 5 at mg/kg, *ip*) decreased the number of pain-related behaviors in the writhing test 15 min after drug administration. Data are mean ± SE (n = 6-10). $^{a}P < 0.05$, $^{b}P < 0.01$ *vs* control.

istration of luzindole or naloxone[24]. Similar results were recently reported by Mickle *et al*[25] suggesting that melatonin attenuates post-inflammatory hypersensitivity through a supra-spinal process linked to the central opioidergic system.

The involvement of opioid receptors in the antinociceptive effects of melatonin and melatonergic agonists observed in our study is an interesting, and complex phenomenon. Earlier receptor binding experiments confirmed the presence of mu- and delta-, but not kappa-opioid bind sites in bovine pinealocyte membranes[26]. (D-Ala^2, N-MePhe^4, Gly-ol)-enkephalin and (D-Pen^2, D-Pen^5)-enkephalin, which are mu- and delta-selective opioid receptor agonists, respectively, enhanced melatonin synthesis in pineal cultures by a naloxone-reversible manner[27,28] and acute administration of morphine induced melatonin release from rat pineal glands[29]. Despite these findings, there is no clear evidence for a melatonin-opioid system interaction or melatonergic ligand binding to opioid receptors. We might suggest a possible involvement of delta-opioid receptors in the antinociceptive activity of melatonin, as it was shown that its antihyperalgesic effect was partially inhibited by the selective delta opioid receptor antagonists, naltrexone and naltrindole, but not by a selective kappa opioid receptor antagonist 5'-guanidinonaltrindole[7]. Another possible explanation is that melatonin may interfere with the neural mechanisms involved in the development of tolerance to a delta-opioid agonist analgesia *via* its receptor[30]. Recently Wang reported that co-activating delta-opioid receptor and melatonin receptor could induce much longer analgesia by deltorphin-5-methoxytryptamine chimeric opioid peptides[31].

Some reports suggest that the interaction between melatonergic and opioidergic system may be explained at a molecular level. Melatonin may regulate changes in pain threshold by modulating fluctuations in opioid receptor expression and the release of beta-endorphin from pituitary gland[32-34]. It can be also suggested that melatonin, similarly to opioids, may modify K^+ and Ca^{2+} ion channel function[35,36]. Furthermore, melatonin and opioid receptors are coupled to G_i proteins and may share the Gi-mediated intracellular pathways[27,37].

Rapid elimination of melatonin from the circulation is a major obstacle in its potential use in clinical treatment. The reported half-life of melatonin in blood is approximately 20-30 min[38-40]. However, administration of higher doses of melatonin induces a nocturnal decrease in body temperature and may desensitizes its receptors[41,42]. A possible solution to overcome limited melatonin bioavailability is by developing formulations with prolonged-release or the design of synthetic melatonergic agonists with prolonged action. A controlled-release melatonin formulation (Circadin®) has recently been approved in the European Union and other countries for the treatment of insomnia in patients aged 55 years and older[43].

Neu-P11, one of the novel melatonergic agonists used in our study was shown to be a melatonin agonist, serotonin 5-HT-1A and 5-HT-1D agonist and serotonin 5-HT2B antagonist[44]. Sleep promoting, anti-diabetic, antihypertensive, analgesic, anti-neurodegenerative, anxiolytic and antidepressant effects of Neu-P11 have been demonstrated in a series of relevant animal models[15,16]. The pharmacological actions of Neu-P12, which is a close derivative of Neu-P11, have not been fully studied yet. In the present study we report that both Neu-P12 and Neu-P11 display potent antinociceptive effects and have longer duration of action compared to melatonin and might thus become potential analgesics for future use in clinical treatment of visceral pain of abdominal origin. From our experience Neu-P12 has the longest duration of action and may thus be the most promising compound fur further development. It is finally important to mention that the effects are seen following *ip* or oral application as especially the oral activity is a good prerequisite for future human use as oral application seems the most favorable delivery pathway.

Since melatonin receptors are also involved in the regulation of gastrointestinal motility, drugs targeting these receptors might be useful in the treatment of motility disorders where increased motility is a problem as in diarrhea or IBS. Thus, the effects of melatonin and its agonists on gastrointestinal motility worth additional research.

In summary melatonin, and its agonists Neu-P11, and Neu-P12 decreased visceral abdominal pain-related behaviors in mice. The antinociceptive action of the melatonergic 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.

COMMENTS

Background

Melatonin was reported to attenuate pain in animals and in patients with irritable bowel syndrome. However, due to low metabolic stability, it is rapidly degraded in physiological conditions.

Research frontiers

The aim was to characterize the antinociceptive action of the novel melatonin receptor agonists, Neu-P11 and Neu-P12 in animal models of visceral pain and to compare their effects to that of melatonin.

Innovations and breakthroughs

Orally and intraperitoneally 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 naloxone. Centrally, but not intraperitoneally administration of melatonin receptor antagonists, luzindole or 4-P-PDOT blocked the antinociceptive actions of Neu-P11 or Neu-P12.

Applications

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.

Terminology

Metabolic stability, resistance to degradation and attenuation of pharmacological action by various physiological factors, mainly enzymes. Irritable bowel syndrome, gastrointestinal disease characterized by motility disorders and abdominal pain.

Peer review

The authors used the percentage of control (numbers of pain-related behaviors) instead of true numbers. An interesting study and the discussion is well-done.

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