Neuroscience Letters 614 (2016) 49–54

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Research paper

The antinociceptive effects of a δ-opioid receptor agonist in mice with painful diabetic neuropathy: Involvement of heme oxygenase 1

Sílvia Castany[1], Mireia Carcolé[1], Sergi Leánez, Olga Pol*

Grup de Neurofarmacologia Molecular, Institut d'Investigació Biomèdica Sant Pau & Institut de Neurociències, Universitat Autònoma de Barcelona, Barcelona, Spain

HIGHLIGHTS

- STZ-induced type 1 diabetic mice develop allodynia and hyperalgesia.
- DPDPE inhibited painful diabetic neuropathy.
- CORM-2 and CoPP treatments enhance the antinociceptive effects of DOR agonists.
- Heme oxygenase 1 participates in the analgesic effects of DPDPE during diabetes.

ARTICLE INFO

Article history:
Received 26 November 2015
Received in revised form
20 December 2015
Accepted 29 December 2015
Available online 4 January 2016

Keywords:
Analgesia
Diabetes
Pain
Opioid receptors
Heme oxygenases
Carbon monoxide

ABSTRACT

Diabetic neuropathy is poorly controlled by classical analgesics and the research of new therapeutic alternatives is indispensable. Our aim is to investigate if treatment with a carbon monoxide-releasing molecule (tricarbonyldichlororuthenium(II) dimer; CORM-2) or an inducible heme oxygenase (HO-1) inducer (cobalt protoporphyrin IX; CoPP) could enhance the antinociceptive effects produced by a δ-opioid receptor (DOR) agonist in mice with painful diabetic neuropathy.

In diabetic mice induced by streptozotocin (STZ) injection, the antiallodynic and antihyperalgesic effects produced by the subcutaneous administration of a DOR agonist ([D-Pen(2),D-Pen(5)]-Enkephalin; DPDPE) and the reversion of its effects with the administration of an HO-1 inhibitor (tin protoporphyrin IX; SnPP) were evaluated. Moreover, the antinociceptive effects produced by the intraperitoneal administration of 10 mg/kg of CORM-2 or CoPP, alone or combined, with a subanalgesic dose of DPDPE were also assessed.

Our results demonstrated that the subcutaneous administration of DPDPE inhibited the mechanical and thermal allodynia as well as the thermal hyperalgesia induced by diabetes in a dose-dependent manner. Moreover, while the antinociceptive effects produced by a low dose of DPDPE were enhanced by CORM-2 or CoPP co-treatments, the inhibitory effects produced by a high dose of DPDPE were completely reversed by the administration of an HO-1 inhibitor, SnPP, indicating the involvement of HO-1 in the antinociceptive effects produced by this DOR agonist during diabetic neuropathic pain in mice. In conclusion, this study shows that the administration of CORM-2 or CoPP combined with a DOR agonist could be an interesting strategy for the treatment of painful diabetic neuropathy.

1. Introduction

Painful neuropathy is one of the most common complications of diabetes mellitus, occurring in nearly 40% of people with type 1 diabetes, and remains an important clinical problem due to its resistance to classical analgesic drugs, such us morphine [1,2]. This loss in morphine antinociceptive efficacy was described in diabetic animals following the systemic, spinal and supraspinal administration of this μ-opioid receptor (MOR) agonist, accompanied by numerous undesirable effects that severely limit its effectiveness [3–6]. There-

Abbreviations: CoPP, cobalt protoporphyrin IX; CORM-2, tricarbonyldichlororuthenium(II) dimer; DOR, δ-opioid receptor; DPDPE, [D-Pen(2),D-Pen(5)]-Enkephalin; HO-1, inducible heme oxygenase; MOR, μ-opioid receptor; SnPP, tin protoporphyrin IX; STZ, streptozotocin.

* Corresponding author at: Grup de Neurofarmacologia Molecular, Institut de Neurociències, Facultat de Medicina, M2-115, Universitat Autònoma de Barcelona, 08193 Bellaterra, Barcelona, Spain. Fax: +34 935 811 573.
E-mail address: opol@santpau.es (O. Pol).
[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.neulet.2015.12.059
0304-3940/

fore, the investigation of new alternatives for alleviating painful diabetic neuropathy is indispensable.

In the few studies concerning the role played by δ-opioid receptors (DOR) on the development of type 1 diabetes in animals, everyone agrees that there are no changes in the expression of DOR and/or it could even increase [7,8]. These studies also revealed that the intracerebroventricular or intrathecal administration of DOR agonists as well as the continuous dorsal root ganglia activation of DOR inhibited the nociceptive responses induced by diabetes in rodents [7–10]. Nonetheless the role played by the systemic administration of DOR agonists in these animals has not been assessed. Therefore, our objective is to evaluate the antinociceptive effects produced by the subcutaneous administration of a specific DOR agonist ([D-Pen(2),D-Pen(5)]-Enkephalin; DPDPE) in diabetic mice.

Previous studies demonstrated that treatment with a carbon monoxide-releasing molecule (tricarbonyldichlororuthenium(II) dimer; CORM-2) or the heme oxygenase 1 (HO-1)-inducer compound, cobalt protoporphyrin IX (CoPP), enhanced the analgesic effects of morphine during acute and chronic pain [11–13] as well as those produced by DOR agonists in inflammatory pain [14]. But the effect produced by these treatments on the antinociceptive actions of DPDPE during painful diabetic neuropathy remains unknown. Therefore, in a model of streptozotocin (STZ)-induced diabetic neuropathy, we evaluated: (1) the antiallodynic and antihyperalgesic effects produced by the subcutaneous administration of different doses of DPDPE; (2) the antinociceptive effects of DPDPE in CORM-2 or CoPP diabetic treated mice and (3) the reversion of DPDPE antinociceptive effects with the HO-1 inhibitor, tin protoporphyrin IX (SnPP).

2. Material and methods

2.1. Animals

Experiments were performed in six to eight weeks old male C57BL/6 mice acquired from Harlan Laboratories (Barcelona, Spain). Mice weighing 22–25 g were housed under 12-h/12-h light/dark conditions in a room with controlled temperature (22° C) and humidity (66%). Animals had free access to food and water and were used after 6 days of acclimatization to housing conditions. All experiments were conducted between 9:00 AM and 5:00 PM and carried out according to the animals guidelines of the European Communities Council (86/609/ECC, 90/679/ECC; 98/81/CEE, 2003/65/EC, and Commission Recommendation 2007/526/EC) and approved by the local Ethical Committee of our Institution (Comissió d'Etica en l'Experimentació Animal i Humana de la Universitat Autònoma de Barcelona). All efforts were made to minimize animal suffering and to reduce the number of animals used.

2.2. Induction of diabetic neuropathy

Diabetes was induced by the intraperitoneal administration of five consecutive daily injections of 55 mg/kg of STZ (Sigma–Aldrich, St. Louis, MO) freshly prepared in citrate buffer (0.1 M, pH 4.5) [15]. Control animals receive an equal volume of citrate buffer alone (naïve). Animals were fasted prior to first administration of STZ and were allowed to feed again after injection. At 21 days after the injection of STZ, the tail vein blood glucose levels were measured to confirm hyperglycemia by using a glucometer (OneTouch® UltraMini®). The development of mechanical allodynia, thermal hyperalgesia and thermal allodynia was evaluated by using the von Frey filaments, plantar and cold plate tests, respectively. All animals were tested in each paradigm before and at 21 days after STZ injection.

2.3. Nociceptive behavioral tests

Mechanical allodynia was quantified by measuring the hind paw withdrawal response to von Frey filament stimulation. In brief, animals were placed in methacrylate cylinders (20 cm high × 9 cm diameter) with a wire grid bottom through which the von Frey filaments (North Coast Medical, Inc., San Jose, CA) with a bending force in the range of 0.008–3.5 g were applied by using a modified version of the up–down paradigm reported by Chaplan et al. [16]. The filament of 3.0 g was used as a cut-off and the strength of the next filament was decreased or increased according to the response. The threshold of response was calculated from the sequence of filament strength used during the up–down procedure by using an Excel program (Microsoft Iberia SRL, Barcelona, Spain) that includes curve fitting of the data. Both hind paws were tested. Animals were allowed to habituate for 1 h before testing to allow an appropriate behavioral immobility.

Thermal hyperalgesia was assessed as reported by Hargreaves et al. [17]. Paw withdrawal latency in response to radiant heat was measured using the plantar test apparatus (Ugo Basile, Varese, Italy). Briefly, mice were placed in methacrylate cylinders (20 cm high × 9 cm diameter) positioned on a glass surface. The heat source was positioned under the plantar surface of paw and activated with a light beam intensity. A cut-off time of 12 s was used to prevent tissue damage. The mean paw withdrawal latencies from both hind paws were determined from the average of three separate trials, taken at 5 min intervals to prevent thermal sensitization and behavioral disturbances. Animals were habituated to the environment for 1 h before the experiment to become quiet and to allow testing.

Thermal allodynia to cold stimulus was assessed by using the hot/cold-plate analgesia meter (Ugo Basile), previously described by Bennett and Xie [18]. The number of elevations of each hind paw was recorded in the mice exposed to the cold plate (4 ± 0.5 °C) for 5 min.

2.4. Experimental procedure

At first, we assessed the painful diabetic neuropathy induced by STZ. After baseline measurements established in the following sequence: von Frey filaments, plantar and cold plate tests, diabetes was induced and animals were again tested in each paradigm at day 21 after STZ injection ($n = 8$ animals per group). Basal glucose levels from the tail blood were measured. Mice treated with an equal volume of citrate buffer (naïve) were used as controls ($n = 8$ animals per group). All the following experiments were performed at 21 days after STZ injection when diabetic neuropathy was confirmed.

In a second set of experiments, we evaluated the mechanical antiallodynic, thermal antihyperalgesic and thermal antiallodynic effects of the subcutaneous administration of different doses of DPDPE (0.5, 1, 3 and 5 mg/kg) or vehicle in STZ-injected animals ($n = 6$ animals per dose).

In a third set of experiments, the antiallodynic and antihyperalgesic effects produced by the intraperitoneal administration of 10 mg/kg of CORM-2 or CoPP alone or combined with the subcutaneous administration of 0.5 mg/kg of DPDPE in STZ-injected mice were evaluated ($n = 6$ animals per group). The antinociceptive effects produced by the intraperitoneal administration of 10 mg/kg of SnPP alone or combined with the subcutaneous administration of 5 mg/kg of DPDPE in STZ-injected animals ($n = 6$ animals per group) we also assessed.

The doses of CORM-2, CoPP and SnPP were selected in accordance to previous pilot studies performed in this model and those used in other works [11,12]. The doses of DPDPE were chosen from the dose-response curves performed in this study, as the ones that produced a minimal or maximal antinociceptive effect in STZ-injected mice.