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Research report

Dopaminergic modulation of neuropathic pain: Analgesia in rats by a D2-type receptor agonist

Nuria Cobacho[a], José Luis de la Calle[b], Carlos Luis Paíno[a,*]

[a] Service of Neurobiology-Research, IRYCIS, Hospital Ramón y Cajal, Carretera de Colmenar km 9, 28034 Madrid, Spain
[b] Pain Unit, Hospital Ramón y Cajal, Carretera de Colmenar km 9, 28034 Madrid, Spain

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ABSTRACT

Experimental studies have shown that dopaminergic mechanisms can modulate both nociception and chronic pain perception, but such property is not exploited pharmacologically at the clinical level. We have previously shown that levodopa produces D2-receptor-mediated antiallodynic effects in rats with peripheral mononeuropathy. Here, we test the effects of a D2-type receptor (D2R) agonist, quinpirole, on neuropathic pain in rats. Allodynic responses to cooling and light touch were measured in the hind limbs of rats with chronic constriction injury of one sciatic nerve. Single intraperitoneal injection of quinpirole (1 mg/kg) totally inhibited cold and tactile allodynic responses for over 3 and 48 h, respectively. At that dose, quinpirole had no effect on nocifensive responses to heat. Lumbar intrathecal injection of quinpirole produced short-term inhibition of the responses to cold and tactile stimuli, suggesting that spinal mechanisms may contribute to the antiallodynic activity of quinpirole. Chronic subcutaneous infusion of quinpirole by implanted Alzet pumps (0.025 mg/kg·day) provided a slowly progressing inhibition of cold and tactile allodynic responses, which re-emerged after the pumps were removed. These experiments show the involvement of dopaminergic systems in the modulation of chronic allodynias and provide experimental support for proposing the use of D2R agonists for neuropathic pain relief.

1. Introduction

Painful peripheral neuropathies can be caused by traumatic, metabolic, infectious, oncologic, toxic, drug-related or hereditary conditions (see Baron et al., 2010 for a recent review). Lesion of afferent pathways is the common requirement in all these conditions for development of neuropathic pain. This algesic state is characterized by dysesthesias, spontaneous pain and/or evoked pain to mechanical and thermal stimuli classified as hyperalgesias (increased sensitivity to pain) and allodynias (pain caused by normally innocuous stimuli).

Despite the considerable progress made in characterizing the biological changes underlying afferent pathway lesions, the pathophysiological mechanisms that explain why or how neuropathic pain states are produced remain in the field of hypothesis. Partial nerve lesions leading to neuropathic pain course with ectopic nerve activity, increased expression in the nerve of Na^+ and Ca^{2+} channels, α-adrenergic receptors and TRPV1 receptors, changes of the terminal field of afferent fibers in spinal cord, increased numbers of spinal microglia and central sensitization correlated with pre- and postsynaptic changes in opioid or glutamate receptors, and alterations of GABAergic interneurons and the descending modulatory system. Such diversity of peripheral and central changes after afferent lesions is sufficient to explain the wide variability of symptoms and pain characteristics among different patients. It may also explain why there is no single treatment that works for all conditions. Antidepressants, anticonvulsants, opioids, NMDA antagonists, cannabinoids and topical drugs are used with variable effectiveness to treat neuropathic pain (Finnerup et al., 2005; Vranken, 2009; Wong et al., 2007) and, still, almost half of the patients do not obtain analgesic benefits, and the ones that do may experience residual pain. Additionally, adverse effects may preclude the use of some treatments in some patients (see Selph et al., 2011 for updated review). Combined therapy using two or more drugs can be a clinically meaningful strategy for achieving more satisfactory pain relief and for reducing doses and side effects (Baron et al., 2009; Dworkin et al., 2010; Gatti et al., 2009; Gilron et al., 2005, 2009; Hanna et al., 2008).

Antidepressants, either tricyclic or serotonin–noradrenaline reuptake inhibitors, are often considered as first-line treatment

* Corresponding author at: Servicio de Neurobiología-Investigación, Hospital Ramón y Cajal, Carretera de Colmenar km 9, 28034 Madrid, Spain.
Tel.: +34 913368385; fax: +34 913369016.
E-mail addresses: carlos.paino@hrc.es, carlos.paino@yahoo.com (C.L. Paíno).

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for several neuropathic pain conditions. Their mechanism does not appear to rely on their mood-enhancing properties but rather on the modulatory action of monoamines on nociceptive circuits (Millan, 2002; Rojas-Corrales et al., 2003; Yaksh et al., 1995; Yaksh and Wilson, 1979; Yokogawa et al., 2002). Spinal projections of both brainstem serotonergic and noradrenergic neurons are known to mediate antinociception (Bardin et al., 2000; Fleetwood-Walker et al., 1985; Yaksh et al., 1995; Yaksh and Wilson, 1979). Dopaminergic terminals in spinal cord have also been shown to modulate nociceptive transmission (Barasi and Duggal, 1985; Fleetwood-Walker et al., 1988; Gao et al., 2001; Jensen and Yaksh, 1984; Lapirot et al., 2011; Munro, 2007; Tamae et al., 2005; Taniguchi et al., 2011) and to enhance antinociception mediated by other monoamines (Munro, 2007). Additionally, there are multiple evidences that pain perception can be controlled by supraspinal dopaminergic pathways (reviewed in Potvin et al., 2009; Wood, 2008). In spite of that, the use of dopaminergic drugs for pain control in the clinics remains unexplored with a few exceptions. In animal experiments of acute pain, the enhancement of dopaminergic activity by levodopa has been shown to inhibit nociception (Paalzow, 1992; Shimizu et al., 2004). We have shown that levodopa administration relieves cold and tactile allodynia in a rat model of neuropathic pain and at least part of the analgesic action takes place in the spinal cord and involves dopaminergic D2-type receptors (D2R) (Cobacho et al., 2010).

The present study has been undertaken to test the effect of a selective D2R agonist, quinpirole, on neuropathic pain symptoms produced by chronic constriction of sciatic nerve in rats. As shown below, single doses of quinpirole produced inhibition of allodynic responses to cold and tactile stimuli lasting more that 3 h, while chronic subcutaneous infusion of quinpirole for 1 week provided a slowly progressing improvement of symptoms. These experiments provide support for considering the use of D2R agonists in difficult-to-control pain symptoms associated to chronic peripheral neuropathies.

2. Methods

2.1. Animals

Adult male Sprague–Dawley rats weighing 250–300 g at the beginning of the experiments were used for the present study. The experimental procedures followed the ethical guidelines of the International Association for the Study of Pain (IASP) for the investigations of experimental pain in conscious animals (Zimmermann, 1983) and were approved by the Ramón y Cajal Hospital Animal Welfare Ethic Committee. The rats were bred in the Ramón y Cajal Hospital animal premises and fresh male breeders from Charles River (France) were introduced to the colony every 4–5 months. The animals were housed in groups of 3 with food and water *ad lib.* and maintained at 24 °C room temperature under a 12-h light/12-h dark schedule. The behavioral tests were started at the 3rd hour of the light period.

2.2. Animal models and surgical procedures

2.2.1. Rat model of neuropathic pain

A peripheral mononeuropathy was produced in young adult rats by the chronic constriction injury (CCI) method developed by Bennett and Xie (1988) with little variations. Briefly, the left sciatic nerve was exposed by blunt dissection of muscle and four loose ligatures, 1 mm apart, were done with 6/0 silk. The ligatures barely compressed the nerve so that blood circulation was maintained. The muscles were repositioned with one resorbable stitch and the skin was closed with staples that were withdrawn 7 days later. In our experience, using this procedure, the animals typically show signs of neuropathic pain by the first week after CCI and maintain stabilized signs for more than 3 weeks thereafter. These signs include tactile and cold allodynia and heat hyperalgesia.

2.2.2. Acute treatments

Single injections of 1 mg/kg quinpirole were delivered by intraperitoneal (i.p.) route. Pain tests for tactile and cold allodynia were performed previously to the treatment and at 20 min, 90 min, 180 min, 24 h and 48 h after injection.

2.2.3. Direct lumbar puncture

Intrathecal injections were performed by a direct lumbar puncture method between L3 and L4 vertebrae as we have described in detail elsewhere (Cobacho et al., 2010; De la Calle and Paino, 2002). In animals under isoflurane anesthesia, a 25G × 1 in. neonatal lumbar puncture needle (Becton-Dickinson, ref. 405243) was advanced into the subarachnoidal space and 35–40 μl of CSF was allowed to flow out into the needle cup. This liquid was withdrawn and replaced by 20 μl of quinpirole hydrochloride dissolved in Hank's balanced salt solution to deliver doses of 0, 10 or 50 nmol subarachnoidally. An empty 1 ml syringe was then fitted to the needle (Vaseline was applied around the open end of the syringe to easy this step) and the treatment solution was slowly pushed into the intrathecal space, under visual control, by a small bolus of air. The needle was then withdrawn and the time was recorded. The animal was transferred to the test cage, where it woke up and moved normally in less than 10 min.

2.2.4. Chronic quinpirole infusion

Alzet osmotic minipumps (model 2ML1, delivering 10 μl/h for at least 7 days) were loaded with filter-sterilized quinpirole hydrochloride (0.8 mg/ml in sterile water) and kept submerged in isoosmolar saline solution at 37 °C for approximately 2 h to initiate a steady flow delivering an approximate dose of 0.025 mg/kg of body weight each hour, which is 0.6 mg/kg per day. The pumps (or sham pumps, made of sterile sealed plastic bulbs of equal size, for controls) were subcutaneously implanted between the scapulae, under brief isoflurane anesthesia, through a 15 mm incision in the skin. The incision was closed with two skin staples. After completing the 7th day tests, the rats were anesthetized again and the pumps (or sham pumps) were removed through the still-unhealed incision. To check that the rats were receiving the intended rate of infusion at 7 days, all the removed pumps were fitted to the tip of a 20G Abbocath catheter and incubated in sterile saline solution at 37 °C for 16 additional hours. The infused liquid was collected from the catheter cups. In all cases, at least 20 μl of liquid was recovered from the catheter cup, thus indicating that the drug was actually flowing at the moment of the last test. Additionally, pooled recovered liquids from two testing experimental series of animals were i.p. injected (1 mg/kg) to CCI-rats that had served as controls to check that the drug was still active after 7 days in water solution. Both animals showed a drastic inhibition of the allodynic responses to cold and tactile stimuli, following identical time courses (not shown) as the ones described below for the experiments of i.p. quinpirole injections. We considered thus that quinpirole was pharmacologically active and infusing at the time when the 7th day tests were performed.

2.3. Pain tests

Rats were tested for both tactile and cold allodynia. Basal measurements were performed before any surgery, so as to discard animals that showed to be hyper-reactive to the tests. Post-CCI measurements were performed at 14 days after surgery and only rats showing either a tactile withdrawal response below 4 g or a