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Serotonergic modulation in neuropathy induced by oxaliplatin: Effect on the 5HT$_{2C}$ receptor

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ABSTRACT

Fluoxetine has been shown to be effective in clinical and experimental studies of neuropathic pain. Besides to increase serotonin levels in the synaptic cleft, fluoxetine is able to block the serotonergic 5-HT$_{2C}$ receptor subtype, which in turn has been involved in the modulation of neuropathic pain. This study investigated the effect of repeated treatments with fluoxetine on the neuropathic nociceptive response induced by oxaliplatin and the effects of both treatments on 5-HT$_{2C}$ receptor mRNA expression and protein levels in the rat spinal cord (SC), rostral ventral medulla (RVM), midbrain periaqueductal gray (PAG) and amygdala (Amy). Nociception was assessed by paw-pressure, cold plate and Von Frey tests. Fluoxetine prevented mechanical hypersensitivity and pain threshold alterations induced by oxaliplatin but did not prevent the impairment in weight gain induced by this anticancer drug. Ex vivo analysis revealed that oxaliplatin increased the 5-HT$_{2C}$ receptor mRNA expression and protein levels in the SC and PAG. Similar effects were observed in fluoxetine-treated animals but only within the PAG. While oxaliplatin decreased the 5-HT$_{2C}$ mRNA expression levels in the Amy, fluoxetine increased their protein levels in this area. Fluoxetine impaired the oxaliplatin effects on the 5-HT$_{2C}$ receptor mRNA expression in the SC and Amy and protein levels in the SC. All treatments increased of 5-HT$_{2C}$ receptor mRNA expression and protein levels in the PAG. These results suggest that the effects of fluoxetine on neuropathic pain induced by oxaliplatin are associated with quantitative changes in the 5-HT$_{2C}$ receptors located within important areas of the nociceptive system.

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1. Introduction

Previous studies have demonstrated that serotonin (5-hydroxytryptamine, 5-HT) plays a role in the control of nociceptive transmission (Heinricher et al., 2009). This monoamine increases and decreases nociceptive responses, depending on the site, cell type and subtype of the receptor it activates (Green et al., 2000; Suzuki et al., 2004). Briefly, serotonin is able to interact with 7 different classes of receptors that are differentiated into 14 subtypes (Barnes and Sharp, 1999) and the 5-HT$_{2C}$ receptor subtype has been involved in the modulation of neuropathic pain in various animal models (Nakae et al., 2013; Ren et al., 2013). Also, several studies have shown that 5-HT projections from raphe nuclei to the spinal cord modulate neuronal plasticity in response to neuropathic pain (Porreca et al., 2002).

Antidepressants belong to a group of limited pharmacological resources that can be used to treat neuropathic pain (McCleane, 2008). In this context, fluoxetine, a selective serotonin reuptake inhibitor (SSRI), has been shown to have analgesic effects in tests of neuropathic pain in rats (Pedersen et al., 2005). Clinical studies have also demonstrated that patients who suffered from neuropathic pain and displayed pain relief during treatment with escitalopram (an SSRI) had polymorphisms in their 5-HT$_{2C}$ genes, emphasizing the involvement of this serotonin receptor subtype in this clinical situation (Brasch-Andersen et al., 2011).

Besides to increase the levels of serotonin in the synaptic cleft, fluoxetine can also act as a competitive 5-HT$_{2C}$ receptor antagonist (Ni and Miledi, 1997; Palvimaki et al., 1999). Moreover, chronic treatment with SSRIs leads to 5-HT$_{2C}$ receptor desensitization (review see Artigas, 2013), suggesting that fluoxetine, as an SSRI, might modulate serotonin action at this receptor subtype.

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Oxaliplatin is an anti-neoplastic drug that is used for the treatment of advanced colorectal cancer (Kannarkat et al., 2007). Perhaps the most important dose-limiting toxicity of oxaliplatin is the induction of a neuropathic syndrome with paresthesia, dysesthesia and pain (Pasetto et al., 2006). There are few studies reporting the molecular aspects involved in neuropathic pain induced by oxaliplatin (Adelsberger et al., 2000). It has been shown that this type of neuropathy can be caused by the prolonged opening of sodium channels in peripheral nerve fibers. More recently, it was also demonstrated that peripheral nociceptive fibers were damaged by oxidative stress, which consequently resulted in sensory symptoms that were similar to those observed during oxaliplatin-induced neurotoxicity (Di Cesare Mannelli et al., 2012).

Although our group has been investigating the role of the central nervous system structures in neuropathic pain induced by oxaliplatin (Norcini et al., 2009), there has been no evidence related to the role of serotonergic neurotransmission in this condition. In the present study, we investigated the effects of chronic treatment with fluoxetine in rats treated with oxaliplatin and evaluated the possible quantitative alterations in 5-HT_{2C} receptors levels in the lumbar portion of the spinal cord and in central nervous system structures (rostral ventral medulla, midbrain periaqueductal gray and amygdala) involved in the ascending and descending pathways of the supraspinal processing of pain.

2. Materials and methods

A schematic representation of the experimental protocol can be seen in Fig. 1.

2.1. Animals

Male Sprague-Dawley rats (Harlan, Varese, Italy), weighing approximately 200–250 g at the beginning of the experimental procedures, were used for the experiments. Four animals per cage were housed at 23 ± 1 °C under a 12-h light/dark cycle; they were fed with standard laboratory diet and tap water ad libitum and experimentation began within one week of their arrival. The experimental protocol complied with the European Community guidelines for animal care (DL 116/92, the European Communities Council Directive of 24 November 1986: 86/609/EEC) and was approved by the animal subject review board of the University of Florence. The ethical policy of the University of Florence complies with the Guide for the Care and Use of Laboratory Animals of the US National Institutes of Health (NIH Publication no. 85-23, revised 1996; University of Florence assurance number: A5278-01). All efforts were made to minimize suffering and to reduce the number of animals used. Rats were randomly assigned to each experimental group and were individually habituated to handling prior to testing.

2.2. Evaluation of general toxicity.

To evaluate the effects of oxaliplatin and fluoxetine on body weight gain, all animals were weighed at 1st, 8th, 12th, 19th and 22nd days from the beginning of the pharmacological treatment.

2.3. Anticancer agent-induced neuropathy

Rats were treated with 2.4 mg/kg oxaliplatin, which was administered intraperitoneally (i.p.) for 5 consecutive days every week for 3 weeks (15 i.p. injections) (Cavaletti et al., 2001). Oxaliplatin was dissolved in a 5% glucose solution. Control animals received an equivalent volume of 5% glucose i.p.

2.4. Selective serotonin reuptake inhibitor (SSRI)

Fluoxetine was dissolved in saline at a dose of 20 mg/kg (Abdel-Salam et al., 2004) and administered subcutaneously (s.c.) for 5 consecutive days every week for 3 weeks (15 s.c. injections), concurrently with the oxaliplatin treatment. Control rats received an equal volume of saline s.c.

2.5. Paw pressure test

The pain threshold in the rats was determined with an analgesimeter (Ugo Basile, Varese, Italy), according to the method described by Leighton et al. (1988). Briefly, a constantly increasing pressure was applied to a small area of the dorsal surface of the paw using a blunt conical probe. Pressure was increased until a vocalization or a withdrawal reflex occurred. The withdrawal threshold was expressed in grams, the test was repeated three times and the mean was used as the value for each paw. Before starting experimental protocols, the pain threshold was evaluated, and rats scoring below 50 g or over 80 g were discarded. These limits assured a more precise determination of the mechanical withdrawal threshold in experiments aimed at determining the effect of treatments. Mechanical pressure application was stopped at 150 g, independent of a rat reflex. Blinded experiments were performed.

The paw pressure test was performed at 7th, 14th and 22nd days from the beginning of the pharmacological treatments (see Fig. 1).

2.6. Cold plate test

The animals were placed in a stainless box (12 cm × 20 cm × 10 cm) with a cold plate as the floor. The temperature of the cold plate was maintained at 4 ± 1 °C. Pain-related behaviors (i.e., lifting and

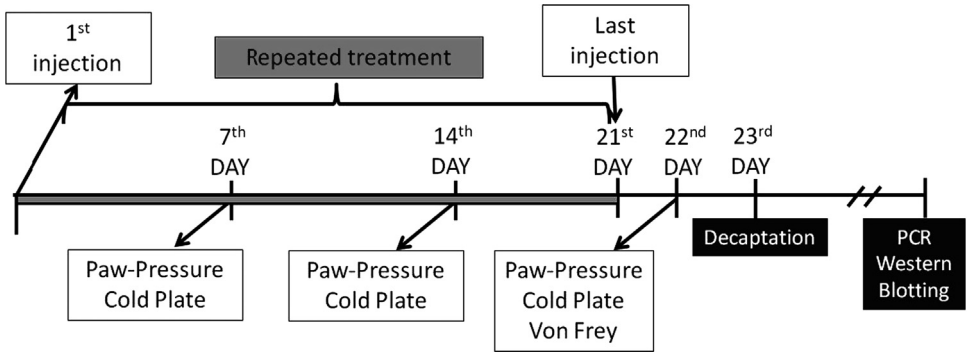

Fig. 1. Schematic representation showing the experimental protocol.

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