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Antinociceptive effect of three common analgesic drugs on peripheral neuropathy induced by paclitaxel in rats

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ABSTRACT

Nowadays, there are no validated drugs to control the neuropathic pain induced by paclitaxel, one of the most effective antineoplastic drugs.
The aim was to study the involvement of opioid and NMDA receptor on established paclitaxel-induced pain, testing three common analgesics drugs morphine, ketamine and methadone.
Animals received four intraperitoneal (i.p.) injections on alternate days of paclitaxel (1 mg/kg). Three weeks later, animals showed a mechanical and heat allodynia/hyperalgesia. Morphine (1, 2.5, 5 and 10 mg/kg) abolished the reduction in the mechanical and thermal withdrawal thresholds in a dose dependent manner. This effect was blocked by naloxone. Only highest dose of ketamine (50 mg/kg) was able to increase the mechanical and thermal threshold and returned to basal values. Subanalgesic doses of morphine (1 mg/kg) and ketamine (12.5 mg/kg) produced an additive effect on heat hyperalgesia reaching an antinociceptive effect. This combination did not induce any change on tactile allodynia. Methadone (2.5 and 5 mg/kg) produced an analgesic effect that was completely antagonized by naloxone in both tests.
Our results confirm that: the activation of opioids receptor produced analgesia; the blockade of NMDA receptors produce antinociception but at high doses with motor impairments and low doses of ketamine enhancing the effect of opioids.

1. Introduction

Neuropathic pain is one of the main side effects that follow the administration of a wide number of anti-tumoral agents such as paclitaxel (Rowinsky et al., 1990). Nowadays, there is no effective treatment to prevent or reverse this chemotherapy-induced neuropathy (Quasthoff and Hartung, 2002). The mechanism(s) responsible for the pain syndrome are quite unknown (Polomano et al., 2001). Animals treated with paclitaxel present spontaneous discharge in A- and C-fibers (Xiao and Bennett, 2008) and a mitochondrial dysfunction and this could be the origin of the neuropathic pain (Flatters and Bennett, 2006).

To date, using animal models of chemotherapy-induced nerve damage potential therapeutic drugs have been tested. Flatters and Bennett (2004) reported that ethosuximide but not morphine and MK-801 reversed paclitaxel-induced painful neuropathy. Many drugs like cannabinoid (Pascual et al., 2005), gabapentin (Matsumoto et al., 2006), thalidomide and minocycline (Cata et al., 2008), neurotropin (Kawashiri et al., 2009) and acetyl-L-carnitine (Flatters et al., 2006) have been successful reducing hyperalgesia induced by paclitaxel. In 2008, Xiao et al., tramadol, topiramate, amitriptyline, baclofen and oxcarbazepine were tested as potential analgesics on this peripheral neuropathy. To date had not tested ketamine or its combination with opioids for the treatment of neuropathy induced by paclitaxel.

Morphine is a well known opioid receptor agonist with analgesic properties. Animal models (Obara et al., 2007) and controlled patient trials (Eisenberg et al., 2005) suggest that μ-opioid receptor agonists are effective at attenuating neuropathic pain. However, side effects suppose substantial barriers to their clinical use (Andersen et al., 2004; Clare et al., 2006). There are more evidences suggesting that opioids are effective relieving neuropathic pain of primarily peripheral origin (Przewlocki and Przewlocka, 2005) than central neuropathic pain (Rowbotham et al., 2003).

Many evidences suggest that NMDA receptors play an important role in the generation of central sensitization and in the development and maintenance of chronic pain (Chizh and Headley, 2005; Eide, 2000). It is known that the NMDA receptor and its associated transduction pathway do not play a significant role in acute pain but only in the development and maintenance of chronic pain, where noxious inputs are tonically active and generate hyperexcitability in pain-transmitting neurons of the spinal cord dorsal horn (Haley et al., 1990). Strong pain stimuli activate NMDA receptors and produce hyperexcitability of dorsal root neurons. This could induce central sensitization, wind-up phenomenon, and pain memory. It has been reported that animals with paclitaxel-induced hyperalgesia has altered discharges of spinal wide dynamic range neurons and down-regulation of glutamate transporter expression in rats (Cata et al., 2006).

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