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 influence of opioids and NMDA receptor antagonists established paclitaxel-induced pain in rats. Animals received four intraperitoneal (i.p.) injections of alternate days of paclitaxel (1 mg/kg). Three weeks later, animals showed a mechanical and heat allosynia hypersensitivity. Morphine (0.25, 0.5 and 1 mg/kg) attenuated the mechanical and thermal thresholds in a dose-dependent manner when compared to control groups. This effect was enhanced by naloxone (0.3 mg/kg), only highest dose of ketamine (50 mg/kg) was able to increase the mechanical abnormal threshold. Subcutaneous doses of morphine (0.5 mg/kg) and ketamine (12.5 mg/kg) produced an additive effect on heat hyperalgesia reaching an antinociceptive effect. This combination can help reducing any change on tail flick latency. Methadone (0.25 and 0.5 mg/kg) produced an antinociceptive effect that was completely antagonized by naloxone in both tests. Our results confirm the usefulness of opioids receptor production analysis, the blockade of NMDA receptor produce antinociceptive effect, high doses with motor impairment and low doses of ketamine enhancing the effect of opioids.

Keywords: Animal model; Neuropathic pain; Paclitaxel; Ketamine; Opioids

1. Introduction

Neuropathic pain is one of the main side effects that follows the administration of a number of anti-tumoral agents such as paclitaxel (Kosmalsy et al., 1994). Nowadays, there is no effective treatment to prevent or reverse this chemotherapy-induced neuropathy (Quesada and Hartung, 2002). The mechanisms responsible for these syndromes are quite unknown (Finnane et al., 2000). Animals treated with paclitaxel present spontaneous discharge in the spinal cord and benzodiazepine administration and this could be the origin of the neuropathic pain (Kottke-Marchant et al., 2000). Today, using animal models of the neuropathic-induced nerve damage potential therapeutic drugs have been studied. Hartung and Zipfel (2004) reported that diazepam and diazepam misses several weeks of sensory and motor deficit. Diazenediol and methyleneglycol (Garcia et al., 2006) employed for the treatment of peripheral neuropathy in rats. Today, there is no conclusion on the combination of opioids for the treatment of neuropathy induced by paclitaxel.

Morphine is a well known opioid receptor agonist with analgesic properties. Animal models (Kumar et al., 2007) and clinical applications (Gibson et al., 2000) suggest that opioid receptor agonists are effective in attenuating neuropathic pain. However, side effects such as respiratory depression, sedation and vomiting have been reported. These side effects suggest that opioids are not effective in the relief of neuropathic pain of mainly peripheral origin (Pak and Finnerup, 2001) than central neuropathic pain (Rotherham et al., 2000).

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 (Chilcote and Kendle, 2005; Fink, 2005). It is known that the NMDA receptor and its associated transduction pathway play a significant role in pain states but only in the development and maintenance of chronic pain, where nociceptive neurons are tonically active and generate hyperexcitability in pain-relevant neurons of the spinal cord dorsal horn (Balcany et al., 1990). Strong pain stimuli activate NMDA receptors and produce hyperexcitability of dorsal horn 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 decreased regulation of glutamate transporter expression in rats (Cato et al., 2005).

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