Paclitaxel-induced neuropathic pain: Unravelling the underlying mechanisms at the central nervous system

J. Ribeiro, J.T. Costa-Pereira, C.P.R. Xavier, I. Martins
1 Department of Biomedicine – Unidade de Biologia Experimental, Faculdade de Medicina da Universidade do Porto, Portugal
2 ISC – Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Portugal
3 IBMC - Instituto de Biologia Celular e Molecular, Universidade do Porto, Portugal
E-mail address: jribeiro504@gmail.com (J. Ribeiro).

Aim: Here we studied the effects of the cytostatic paclitaxel on: (i) the development of nociceptive and aversive behaviors; (ii) noxious-evoked-activation of spinal dorsal horn neurons and (iii) on descending noradrenergic modulation, which is the main spinal nociceptive inhibitory system.

Introduction: Chemotherapeutic drugs are widely used for cancer treatment but they also cause numerous deleterious side effects. Chemotherapy-induced neuropathy (CIN) is one of the most common side effects. The mechanisms underlying CIN are starting to be uncovered namely the alterations induced by cytostatics at the peripheral nervous system but the effects of these drugs at the central nervous system are still poorly studied.

Methods: Male Wistar rats were injected with paclitaxel (Taxol, 2.0 mg/kg) or the vehicle solution dimethyl sulfoxide on four alternate days. Nociceptive and aversive behaviors were assessed by the von Frey and conditioned place aversion (CPA) tests, respectively. Noxious-evoked-activation of spinal dorsal neurons was achieved at one month after CIN by evaluating the expression of c-fos expression upon cold stimulation. To study the descending noradrenergic pain modulation we assessed the effects of the α2-adrenoceptor antagonist clonidine at 1 and 10 μg administered intrathecally, on the von Frey test. We further assessed the expression of the α2-adrenoceptor and dopamine-β-hydroxylase (DBH), a noradrenaline biosynthetic enzyme expressed in noradrenergic fibers, at the spinal dorsal horn.

Results: Paclitaxel induced mechanical allodynia and aversive behaviors. c-fos and DBH expression were increased in paclitaxel-treated animals while α2-adrenoceptor expression remained unaltered. Clonidine induced antinociception at both doses with more pronounced effects in paclitaxel-treated animals.

Conclusion: Paclitaxel-treated animals showed neuropathic-like-behaviors and increased spinal neuronal activation. It remains to ascertain if DHB upregulation results in increased spinal noradrenaline levels, but the increase of α2-AR antinociceptive potency in paclitaxel-treated animals indicates the recruitment of descending inhibition probably as a buffer to increased spinal sensitization.