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Neuroactive steroids allopregnanolone and pregnenolone efficiently counteract bortezomib-evoked painful/sensory symptoms in a rat model

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Chemotherapy-induced peripheral neuropathy (CIPN) is a disabling condition resulting from antineoplastic treatment which may diminish following dose reduction or discontinuation of chemotherapeutics administration. The proteasome inhibitor bortezomib (BTZ) can cause painful peripheral neuropathy (BIPN), a set of sensory-related symptoms with a negative impact on cancer survivors' quality of life. Although reducing pain is often a main focus of BIPN treatment, remarkably few analgesics have been tested. A growing number of reports suggests that CIPN can be attenuated by the concomitant use of neuroactive steroids (NAS), cholesterol derivatives with proven neuroprotective effects in different *in vivo* models of peripheral neuropathy. Therefore, here we tested the analgesic effect of two NAS, allopregnanolone (ALLO) and pregnenolone (PREG), in a rodent model of BIPN. Female Wistar rats were intravenously treated with BTZ (0.2 mg/kg, 3qwx4) then a co-administration of BTZ with subcutaneous administration of ALLO (3mg/kg/every 2 days) or PREG (6mg/kg/every 2 days) were performed for another 4 weeks. Moreover, we tested the effect of ALLO and PREG on BTZ-induced neurotoxicity taking advantage of a battery of behavioral and neurophysiological tests, tracking their progress for 4 additional weeks of follow-up. In addition, we assessed the severity of peripheral axonopathy performing a morphological evaluation of myelinated peripheral nerves and intraepidermal small unmyelinated fibers.

As expected, treatment with BTZ for 8 weeks resulted in a clear manifestation of neuropathic symptoms, with a significant development of mechanical allodynia and thermal hyperalgesia. Therefore, a significant decrease in both sensory action potential (SAP) amplitude and sensory conduction velocity of caudal nerve, as well as a reduction in SAP of digital nerve were reported.

At the end of treatment, although neither drug showed recovery from the damage observed in the caudal nerve, a significant protection of ALLO and PREG was observed in SAP of the digital nerve. Interestingly, ALLO ameliorated both mechanical allodynia and hyperalgesia exhibited by BTZ- treated animals after 8 weeks of treatment, while PREG showed a protective effect only on thermal sensitivity thresholds. In addition, loss of IENF and significant degeneration of myelinated axons in BTZ-treated distal caudal nerves were also observed. Finally, most nerve abnormalities observed during the treatment with BTZ spontaneously recovered after drug withdrawal. Taken together, our results suggest that since NAS counteracted painful symptoms including allodynia and hyperalgesia induced by BTZ, they could be used to alleviate BIPN neurotoxic manifestations, as well as partially contrast the neurotoxic effects on digital nerves. Further studies are still needed to shed more light on the specific mechanisms of action of NAS.

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Keywords: CIPN, bortezomib, axonopathy, allopregnanolone, pregnenolone, mechanical allodynia, thermal hyperalgesia.