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CHEMOTHERAPY-INDUCED REMODELING OF CORTICAL PYRAMIDAL NEURONS: MORPHOLOGICAL EFFECTS OF OXALIPLATIN AND PACLITAXEL

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Chemotherapy-induced neurotoxicity represents a limitation in cancer treatment, often leading to long-lasting sensory and cognitive disturbances. Oxaliplatin (OHP) and Paclitaxel (PTX) are two commonly used agents known for inducing peripheral neuropathy, yet growing evidence suggests they may also affect central neuronal circuits. This study investigates the impact of these drugs on cortical pyramidal neurons, aiming to identify structural correlates of chemotherapy-related cognitive impairment. Adult male Balb/c mice received intravenous injections of OHP (7 mg/kg/week, 8 weeks) and PTX at three different doses (5-7,5-10 mg/kg, 8 weeks), compared to vehicle-treated controls. Golgi-Cox staining was performed on brain tissue, and morphometric analyses were carried out on layer V pyramidal neurons in the somatosensory and prefrontal cortices using Neurolucida software. At the end of OHP treatment (T1), both cortical areas displayed reduced average dendritic length and branching, with preserved dendrite number. Spine density was maintained in the somatosensory cortex but shifted toward immature types, while the prefrontal cortex exhibited a reduction in spine number and mature (mushroom-type) forms. After 4 weeks of follow-up (T2), decrease in dendritic complexity and persistent spine immaturity were evident in both regions. Ongoing analyses on PTX-treated animals aim to define the dose-dependent effects of this drug on cortical morphology. Preliminary observations suggest similar trends in dendritic and spine alterations, potentially with distinct regional or dose-related patterns. Overall, these findings indicate that both OHP and PTX induce structural remodeling of cortical pyramidal neurons, providing morphological evidence for central neurotoxicity associated with chemotherapy.

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THERAPEUTIC VERSUS PREVENTIVE ADMINISTRATION OF NEUROACTIVE STEROIDS TO TREAT BORTEZOMIB-INDUCED PAINFUL NEUROPATHY

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Chemotherapy-induced peripheral neuropathy (CIPN) is a disabling condition resulting from antineoplastic treatment. The proteasome inhibitor bortezomib (BTZ) can cause painful peripheral neuropathy (BIPN) 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 suggest that CIPN can be attenuated by the concomitant use of neuroactive steroids (NAS), cholesterol derivatives with proven neuroprotective effects in several *in vivo* models of peripheral neuropathy. However, an important factor in the development of neuroprotective intervention is whether to adopt a therapeutic or a preventive approach. Therefore, we tested the analgesic effect of two NAS, allopregnanolone (ALLO) and pregnenolone (PREG), in two rodent models of BIPN. Female Wistar rats were intravenously treated with BTZ (0.2 mg/kg, 3qw) for 4 weeks. To study the therapeutic effect, co-administrations of BTZ and ALLO (3 mg/kg/every 2 days) or PREG (6 mg/kg/every 2 days) were performed subcutaneously for another 4 weeks. Instead, in the preventive schedule, ALLO or PREG were co-administered for 4 weeks with BTZ from the beginning of the study. Here, we tested the protective effects of the two NAS using a battery of behavioral and neurophysiological tests as well as morphological and morphometrical analyses of myelinated nerves and intraepidermal small unmyelinated fibers (IENF) densities. Treatment with BTZ induced significant mechanical allodynia and thermal hyperalgesia, as well as a reduction of sensory action potential amplitude in peripheral nerves already at 4 weeks, with severe neuropathic symptoms at 8 weeks. NAS administration alleviated BTZ-induced behavioral alterations and partially prevented neurophysiological symptoms. In addition, BTZ treatment induced a significant loss of both myelinated and unmyelinated fibers in the caudal nerves and skin, respectively. A protective effect was observed after NAS treatment on IENF. Taken together, our results suggest that since NAS counteracted painful symptoms induced by BTZ, they could be used to alleviate BIPN neurotoxic manifestations. Moreover, having knowledge of the precise timing of therapeutic intervention is paramount to boost any neuroprotective treatment efficacy.

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