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Cortical dendritic alterations induced by repeated oxaliplatin administration

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Background. Oxaliplatin (OHP), a commonly used chemotherapy agent, is well known for inducing peripheral neurotoxicity. This condition manifests as acute, cold-triggered symptoms like paresthesias and muscle cramps, along with long-term sensory disturbances, particularly in the hands and feet. Although OHP does not penetrate the blood-brain barrier, many patients undergoing treatment report experiencing cognitive difficulties – often referred to as "chemo-fog." These cognitive issues are usually temporary but can persist in more severe cases. Until now, no animal model has effectively mirrored both the peripheral and central nervous system effects of OHP-induced neurotoxicity. This study aims to fill that gap.

Methods. Adult male Balb/c mice (10 weeks old) received intravenous injections of oxaliplatin (7 mg/kg) once a week for eight weeks, while control animals were administered saline. After the treatment period, behavioral and neurophysiological evaluations were performed. Tissue samples were collected from the caudal nerves, footpad skin, and brain. Histological examination of the caudal nerves and skin biopsies was conducted to confirm peripheral neuropathy. Brain tissue was processed using Golgi-Cox staining, and morphometric analysis of layer V pyramidal neurons of the somatosensory cortex and the pre-frontal cortex was carried out with Neurolucida software (Microbrightfield Inc.).

Results. As anticipated, OHP treatment resulted in mild axonopathy within the caudal nerves and a marked reduction in intraepidermal nerve fiber density, both of which correlated with consistent behavioral and neurophysiological alterations. In the cortex, pyramidal neurons in both investigated areas from OHP-treated mice showed a significant decrease in the average length and branching (number of nodes) of basal dendrites. Moreover, the morphological distribution of dendritic spine in different types – mushroom, thin, filopodia, and stubby – was significantly altered in OHP-treated animals compared to controls, with a shift towards more immature types than mushroom.

Conclusions. Our findings reveal that chronic OHP administration, using a regimen known to induce peripheral neurotoxicity, also leads to pronounced morphological alterations in cortical dendritic structures. Although OHP does not directly interact with central neurons, the mechanisms driving these changes remain unclear and merit further investigation. Notably, similar dendritic abnormalities are observed in various neurodegenerative conditions, such as AD, suggesting that these structural disruptions may contribute to the cognitive deficits commonly referred to as chemo-fog. Further studies are needed to assess whether such changes occur in other brain regions and to better understand their broader implications.

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Keywords: Golgi staining, oxaliplatin, cortical changes.