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Effect of age on metabolomic changes in a model of paclitaxel-induced neurotoxicity

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Chemotherapy-induced peripheral neuropathy (CIPN) is one of the most common dose-limiting side-effects of paclitaxel (PTX) treatment. Many age-related changes have been hypothesized to underlie susceptibility to damage or impaired regeneration/repair after nerve injury. The results of these studies, however, are inconclusive and other targets, which might be used as potential biomarkers of nerve impairment, need to be investigated.

Twenty-four young (2 months of age) and 24 adult (9 months of age) Wistar male rats were randomized to either paclitaxel (PTX) treatment (10 mg/kg i.v. once/week for 4 weeks) or vehicle administration. Neurophysiological and behavioral tests were performed to investigate nerve damage at baseline, after 4 weeks and the 2-week follow-up period. Skin biopsies from sacrificed animals were examined for intraepidermal nerve fiber (IENF) density assessment. Blood and liver samples were collected for targeted metabolomics analysis using Ultra-Performance Liquid Chromatography-Mass Spectrometry (UPLC-MS/MS).

At the end of treatment, the neurophysiological studies revealed a reduction in sensory nerve action potential amplitude ($p < 0.05$) in the caudal nerve of young PTX-treated animals, and in both the digital and caudal nerve of adult treated animals ($p < 0.05$). Behavioral tests revealed a significant decrease in the mechanical threshold in young PTX-treated animals ($p < 0.001$), while adult treated rats showed no significant difference in mechanical threshold compared to controls. Concerning IENF assessment, both young and adult PTX-rats had reduced IENF density ($p < 0.0001$), which persisted at the end of follow-up. Targeted metabolomics analysis showed significant differences in the plasma metabolite profiles between PTX-treated animals developing peripheral neuropathy and age-matched controls, with triglycerides, diglycerides, acylcarnitines, carnosine, long chain ceramides, sphingolipids, and bile acids playing a major role in the response to PTX administration.

Our study identifies for the first time multiple related metabolic axes involved in paclitaxel-induced peripheral neuropathy, and suggests age-related differences in CIPN manifestations and in the metabolic profile.