EFFECTS OF PALMITOYLETHANOLAMIDE (PEA) IN CISPLATIN-INDUCED PERIPHERAL NEUROPATHY IN MICE

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Chemotherapy-induced peripheral neuropathy (CIPN) is a common major dose-limiting side effect of anti-tumour treatment. As a result of this dose reduction, delay and withdrawal may lead to decreased chemotherapy efficacy. Moreover, this neuropathy is often painful and may significantly interfere with a patient's quality of life among cancer survivors. There is high unmet need of neuroprotective agents able to decrease the neurotoxicity associated with cytotoxic agents by providing protection for healthy tissue without compromising anti-tumour efficacy and preventing the development of neuropathic pain. PEA, an endogenous fatty acid amide, is a congener of the endocannabinoid anandamide that belongs to a class of lipid mediators, the superfamily of N-acylethanolamines. PEA has shown efficacy in many different preclinical animal models for chronic and neuropathic pain, and most importantly is effective in reducing pain in man in various clinical trials in a variety of pain states. PEA has recently been reported to restore myelinated-fibre function in patients with chemotherapy-induced painful neuropathy. These results prompted us to verify the effects of PEA in cisplatin-induced peripheral neuropathy in mice. To this end, cisplatin (4 mg/kg, twice a week, i.p) and PEA (10 mg/kg, daily, per os) were administered for a 4 weeks-period. To evaluate the effect of PEA on cisplatin-induced nociceptive thresholds alterations, thermal and mechanical threshold sensitivities were determined and sensory/motor and sensory nerve conduction velocities (NCVs) were determined stimulating respectively the caudal and the digital nerves to verify the ability of PEA to contrast cisplatin-induced nerve functional activity impairment.

Results demonstrate that PEA completely counteracted cisplatin-induced decrease of thermal thresholds and partially abolished cisplatin-induced mechanical allodinia. Moreover, cisplatin treatment caused significant reductions in caudal and digital NCVs compared to controls (-15.1% and -15.3%, respectively) while PEA chronic treatment only partially prevented the NCVs impairment (-9.6% and -9.2%, respectively). Similar results, ~~although not statistically significant,~~ were obtained in ~~the digital NCV and caudal~~the caudal and digital amplitudes. ~~These neurophysiological results indicate that the most distal caudal nerve has a higher sensitivity in detecting CIPN than the digital nerve.~~

The data obtained confirm that PEA elicits antihyperalgic and antiallodynic effects in peripheral neuropathies and reveal that these effects are only slightly paralleled by an improvement of NCV. Although a broader study is necessary to understand the mechanisms involved in PEA effects, these data suggest that the acylethanolamide could have beneficial effects on peripheral neuropathy induced by chemotherapeutic agents.