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Dehidropeptidase-1: A promising target to prevent oxaliplatin-induced peripheral neuropathy

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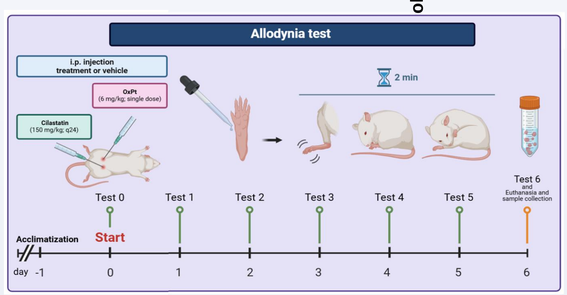
Introduction

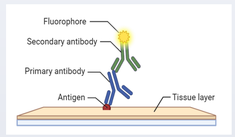
Oxaliplatin, like other anticancer drugs, accumulate in the dorsal root ganglia (DRG) and nerve terminals resulting in neuronal body, axonal or myelin injury (1). Oxaliplatin induced neurotoxicity is produced by its direct cytotoxic effect through DNA-damage and by the induction of an inflammatory response in DRGs and spinal cord (2).

Dehydropeptidase-1 (DPEP1) hydrolyses different dipeptides, including glutathione (GSH), which is an active enzyme in the inactivation and excretion of toxic substances (3). Cilastatin, a DPEP1-inhibitor, has shown effectivity in preventing cisplatin nephrotoxicity in rats (4). Based on these facts, we hypothesized that, if DPEP1 is involved in oxaliplatin induced neuro-inflammation, DPEP1-inhibitors could be used prevent neurotoxicity. In this study we searched for the expression of DPEP1 in DRG in the early stages of oxaliplatin toxicity.

Methods

According to the current legal regulation, oxaliplatin-induced neuropathy was established in 10 male Wistar rats while other 8 intreated rats were used as controls. After euthanasia on the 6th day, lumbar DRGs and the sciatic nerve were removed and processed for immunofluorescence staining and confocal microscopy. For immunohistochemistry (IHC), anti-DPEP1 polyclonal antibodies were developed in our laboratory and commercial primary antibodies to characterize neurons (MAP2), glial cells (GFAP), endothelial cells (CD31) and inflammation (TNF-α, IL-6) were used to define its cellular and subcellular expression.





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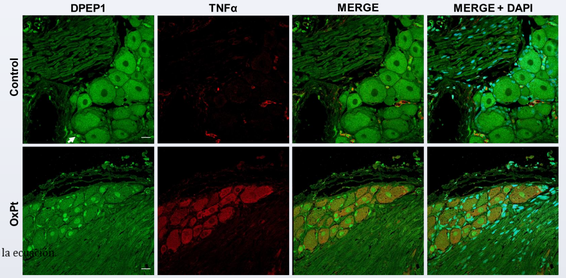

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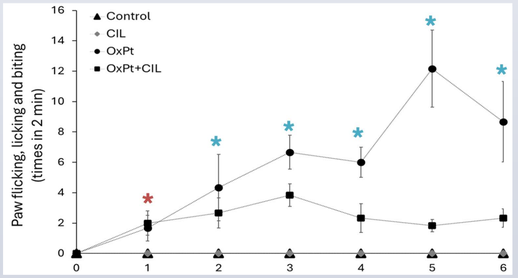
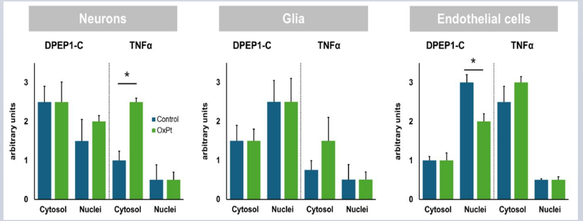
Effect of treatment with placebo, cilastatin oxaliplatin and oxaliplatin + cilastatin on allodynia

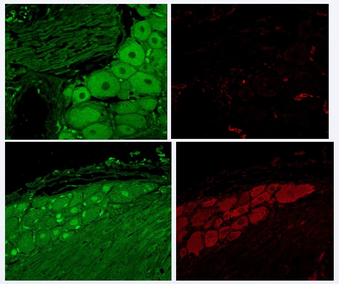




Quantification of DPEP1 and TNFα expression

Results

DPEP1 expression was present in neurons, glia and endothelial cells of DRG. An increase in DPEP1 was found in neuron´s nuclei after oxaliplatin treatment. As expected, high intensity expression of inflammatory markers was observed in endothelial cells, axons and cells surrounding neural fibers after oxaliplatin treatment.



Top: DPEP1 and TNFα expression (control) Bottom: DPE1 and TNFα expression (Oxaliplatin-treated)

Discussion

DPEP1 is expressed in neurons, glia and endothelial cells of DRG and oxaliplatin treatment in rats induced high grade of inflammation in DRG. These facts open the possibility to think that DPEP1 could be involved in oxaliplatin induced neuropathy and that its inhibition could have therapeutic effects.

References

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2. Curr Neuropharmacol. 2019; 17(2): 18 – 96
3. Clin Cancer Res. 2006;12(10):3050–6