

Glia inhibition suppresses chemotherapy-induced neuropathic pain in the rat

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Oxaliplatin, a platinum-based chemotherapeutic agent, has become a standard treatment for advanced colorectal cancer. The dose-limiting toxicity of this compound is the development of a peripheral neuropathy. Recently, we described a characteristic glia activation profile in the presence of oxaliplatin-dependent neuropathic pain in the rat. In the present study, aimed to evaluate the glia role in neuropathy induced by oxaliplatin, we continuously infused in the rat, by intrathecal route, minocycline, a tetracycline derivative that specifically inhibits microglia, or fluorocitrate, an astrocyte metabolic inhibitor of the citric acid cycle. Both compounds were able to significantly reduce oxaliplatin-dependent pain, when evaluated as an increase on suprathreshold stimulation (hyperalgesia-related measure) or as a decrease in pain threshold (allodynia-related measure) [1]. In the dorsal horn of the lumbar spinal cord minocycline was able to reduce in a time-dependent manner the Iba1 positive cell increase evoked by the anticancer treatment. Similarly fluorocitrate-treated animals showed a decreased in GFAP-positive cell with respect to the oxaliplatin-treated group. Minocycline and fluorocitrate did not show cross-action on astrocyte and microglia, respectively. The morphometric determinations performed on the DRG neurons evidenced that oxaliplatin decreased the soma area of the medium (600-1200 μm^2) and large neurons (>1200 μm^2) as well as the incidence of eccentric nucleoli and of multinucleolated neurons were significantly increased in oxaliplatin treated rats. Neither minocycline nor fluorocitrate were able to prevent nervous tissue alteration. In summary, these data highlight the central role of glia cell in oxaliplatin-dependent neuropathic pain. On the contrary, glia inhibition does not induce neurorestorative processes suggesting the need of glia signalling modulation to obtain at the same time pain relief and neuroprotection.

References

[1] Milligan and Watkins (2009) Pathological and protective roles of glia in chronic pain. *Neuroscience Neuron-Glia Interaction* volume 10.

Key words

Neuropathy, oxaliplatin, spinal cord, DRG, minocycline, fluorocitrate.