Oxaliplatin-induced neuropathy: glial activation in spinal cord and brain

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Neuropathic pain is an unpleasant, abnormal signalling associated with injury or malfunction in the peripheral or central nervous system (CNS). It has been increasingly recognized that glial cells play a critical role in the induction and maintenance of persistent pain. These cells dynamically modulate the function of neurons under both physiological and pathological conditions.

Numerous models of neuropathic pain have indicated that microglia can influence development of this phenomenon, e.g. partial sciatic nerve ligation, spinal nerve ligation and spinal cord injury. Despite these numerous studies, little is known about chemotherapy-based animal models of neuropathic pain. Aim of our study was to better characterized the neuropathy elicited by oxaliplatin treatment.

In a rat model of painful oxaliplatin-induced neuropathy (2,4 mg kg\textsuperscript{-1} intraperitoneally, daily injected for 21 days), we investigated the influence of this drug on neuropathic pain symptoms and the pattern of activation of microglia and astrocytes in CNS.

Our results showed that all rats with oxaliplatin treatment developed mechanical hyperalgesia, mechanical allodynia, cold allodynia and motor coordination impairment.

To examine whether oxaliplatin induced glia reaction in the spinal cord, we observed changes in the expression of Iba-1 and GFAP, markers of reactive gliosis and proliferation of microglia and astrocytes, respectively. Iba-1 expression in the dorsal horn of the spinal cord was increased after 21 days treatment compared with the naive condition, suggesting that oxaliplatin treatment induced a microglia activation. Nevertheless, the ramified morphology of this cell type showed the typical resting conformation. Increased GFAP immunoreactivity after treatment was seen in expansion of cell body size, thickening of the processes and labelling intensity, compared with naive animals, suggesting prolonged hyperactivation of astrocytes after injury. Thus Iba-1 and GFAP enhanced expressions were also used as a specific functional marker in the brain. The pattern of enhanced expression paralleled that of spinal cord and the brain regions mainly involved in the hyperactivation were the cingulate gyrus, putamen, thalamus, periaqueductal grey matter, middle forebrain and cerebellum.

Consistent with our findings, many studies suggest that spinal microglia hyperactivation is required for the initiation, but not the maintenance of injury-induced hyperalgesia, whereas the prolonged activation of astrocytes plays an important role in maintaining neuropathic pain.

Key words
Neuropathic pain, oxaliplatin, glia, central nervous system