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Lithium prevents and attenuates paclitaxel-induced neuropathic pain

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Neuropathic pain induced by a commonly used chemotherapy-drug paclitaxel (taxol) is a major toxicity responsible in clinics that force patients to discontinue this otherwise life-saving treatment. Glycogen synthase kinase 3β (GSK3β) is a powerful regulator of neuroinflammation in many neurologic diseases. In this study, the role of GSK3β in the development and maintenance of taxol-induced neuropathic pain in a rat model induced by i.p. injection of taxol (2 mg/kg) on 4 alternative days (accumulated doses 8 mg/kg) was investigated. Ten days post the first taxol injection, using western blots, we found that expression of phosphorylated GSK3β (the inactive form of GSK3β) in the spinal dorsal horn was reduced while total GSK3β protein expression remained unchanged, indicating an increased activity of GSK3β. This was concomitantly associated by downregulation of glial glutamate transporter 1 (GLT-1) protein expression, activation of astrocytes (increased expression of GFAP) in the same region, and mechanical allodynia in the rats. Next, we treated the rats with the GSK3β inhibitor, lithium chloride (LiCl, 2 mg/kg/day, s.c. injection, starting immediately prior to the first taxol injection and then daily for 10 days). This treatment prevented the development of mechanical allodynia induced by taxol and suppressed GSK3β activities (an increased expression of phosphorylated GSK3β) in the spinal dorsal horn. At the same time, the taxol-induced downregulation of GLT-1 protein expression and activation of astrocytes were also significantly ameliorated. Finally, we determined if LiCl can reverse the taxol-induced allodynia. Ten days after the first taxol injection, LiCl (2 mg/kg/day, s.c.) was applied to rats with allodynia for another 10 days. This treatment attenuated the existing allodynia. Meanwhile, in the spinal dorsal horn, the taxol induced increased GSK3β activities and GFAP protein expressions were suppressed; GLT-1 protein expression was improved. Together, our data indicate that an increase of GSK3β activities is a key event related to the down-regulation of glial glutamate transporter expression in the spinal dorsal horn, and the development and maintenance of neuropathic pain induced by taxol. Further, inhibition of GSK3β activity with lithium is an effective approach to prevent and attenuate paclitaxel-induced neuropathic pain.

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