IJAE
Vol. 117, n. 2 (Supplement): 57, 2012
ITALIAN JOURNAL OF ANATOMY AND EMBRYOLOGY

Involvement of Alpha7 nAChR downregulation in rat oxaliplatin-induced neuropathy

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Oxaliplatin, unlike other platinum derivatives, does not result in significant renal impairment or ototoxicity, and it has only mild hematological and gastrointestinal toxicity. On the other hand the limiting side effect is its neurotoxicity that acts as bases for a neuropathic syndrome. A tangled panel of symptoms may be disabling for these patients, adversely affecting activities of daily living and thereby quality of life.

In a rat model of painful oxaliplatin-induced neuropathy, we are describing a pattern of molecular and morphological alterations of both the peripheral and the central nervous system. Among them an important activation of the glial component has been evidenced. Alpha7 nAChR is widely expressed throughout the CNS. It has been described in neurons, microglia and astrocytes, where it seems to play a modulatory role. Moreover, alpha7 nAChR stimulation induces antihyperalgesic and neuroprotective effects in trauma-induced neuropathy.

Aimed to study the pathophysiological mechanism of the chemotherapy-dependent neuropathy, the role of the alpha7 nAChR was investigated in the rat model of oxaliplatin-induced neuropathy (2.4 mgkg-1 intraperitoneally, daily injected for 21 days).

At day 21th, when neuropathic pain is well established, alpha7 nAChR protein level expression was dramatically decreased both in the peripheral and in the central nervous system. The repeated treatment with the alpha7 nAChR agonist PNU-282987 (30 mgkg-1 p. os, daily administered for 21 days, starting from the first oxaliplatin injection) was able to prevent mechanical hyperalgesia (evaluated by Paw pressure test). Moreover, mechanical (evaluated by Von Frey test) and thermal allodynia (evaluated by Cold Plate test) were significantly reduced. Repeated treatment with PNU-282987 was also able to improve motor coordination (evaluated by Rota-rod test).

Western blot analysis revealed that the repeated treatment with the agonist prevented the decrease of alpha7 protein level in a significative manner. Further ex vivo analysis of the nervous system showed a PNU-282987 neuroprotective effect: in morphological terms, in the dorsal root ganglia, and in the peripheral nerve and in the spinal cord as indicated by molecular parameters.

These results strongly suggest the pivotal role of alpha7 nAChR in the neuroprotection during neuropathy.

Keywords: Neuropathic pain, immune system, nicotinic receptor, glia.

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