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An in vivo study on oxaliplatin-induced neuropathic pain: the protective effects of antioxidant compounds

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Oxaliplatin is the standard treatment for advanced colorectal cancer, but its dose-limiting toxicity is the development of a neuropathic syndrome. Several neuromodulatory agents and antioxidants have demonstrated some activity in the acute treatment of this acute neuropathy, whereas the therapeutic effect on oxaliplatin's cumulative neurotoxicity are still lacking. Of particular interest is the in vivo oxaliplatin-induced oxidative damage.

In a rat model of painful oxaliplatin-induced neuropathy (2.4 mgkg-1 intraperitoneally, daily injected for 21 days), we are describing a pattern of molecular and morphological alterations of both the peripheral and the central nervous system.

In the present study an important component of oxidative stress has been evidenced in the plasma of oxaliplatin-treated rats at day 21th of treatment. Protein oxidation was highlighted by an increase in carbonylated protein levels, whereas the lipoperoxidation was evidenced by an increment of malonyldialdehyde levels. Finally, enhanced levels of 8-OH-2-dG were measured as indicative of DNA oxidation. The same pattern of protein, lipid and DNA oxidation was revealed also in the sciatic nerve, and in the spinal cord.

The activity of two well known antioxidant compounds, silibinin and alpha-tocopherol, was evaluated in the oxaliplatin model following acute and chronic administration. At day 21th of oxaliplatin treatment, when neuropathy was evident, both silibinin and alpha-tocopherol administered as single p. os dose of 100 mgkg-1 were ineffective on pain threshold. Chronic administration of 100 mgkg-1 silibinin or α-tocopherol p. os once a day, starting from the first day of oxaliplatin injection until the 21th, partially prevented mechanical hyperalgesia evaluated by paw-pressure test. Moreover, mechanical (evaluated by Von Frey test) and thermal allodynia (evaluated by cold plate) were significantly reduced. Antioxidants were also able to improve motor coordination (Rota-rod test). The antineuropathic effect of both molecules improved by about 50% oxaliplatin-induced behavioural alterations.

Since silibinin and alpha-tocopherol repeated treatments significantly reduced the oxidative state of the plasma and the nervous system of oxaliplatin-treated rats, it is allowed to think that a relationship between the antihyperalgesic and the antioxidant effect exists.

Starting from this evidence, we consider oxidative stress as an important target in oxaliplatin-dependent neuropathy and the research of fully active antioxidant compounds as an attractive therapeutic perspective.

Keywords: neuropathy, oxaliplatin, antioxidant compounds