Morpho-functional evaluation of the activity of stereoisomers of the antioxidant alpha-lipoic (tioctic) acid in a model of compressive neuropathy

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Peripheral neuropathy is characterized by myelin suffering and axonal degeneration. Treatment of these disorders is still problematical, lacking relevant information about their etiology and pathophysiology. It has been suggested that excessive oxidative stress may have a relevant role in the development of these neurological disorders. The purpose of the present study was to assess if compression of sciatic nerve, induced by loose ligation of it, is accompanied by an increased oxidative stress and if this type of nerve damage is sensitive to treatment with the antioxidant alpha-lipoic acid (ALA). Loose ligation of the right sciatic nerve was performed in spontaneously hypertensive rats (SHR), used as a model of exaggerated oxidative stress, and normotensive Wistar-Kyoto rats (WKY) used as a reference group. Animals with sciatic nerve ligation were left untreated or were intraperitoneally treated for 14 days with racemic-ALA (25 and 50 mg/Kg/day), (R+)-ALA(25 mg/Kg/day), (S-)-ALA (25 mg/Kg/day) and pregabalin (50 mg/Kg/day).

At the end of experiments analgesic effect elicited by different treatments was assessed by paw-pressure test. Plasma malondialdehyde (MDA) and oxidative status of protein were evaluated as markers of oxidative stress. Azan-Mallory and osmic acid staining were used for assessing sciatic nerve microanatomy. Phosphorylated 200-kDa neurofilament (NFP) and myelin basic like-protein (MBP) immunoreactivity were studied by quantitative immunohistochemistry as markers of axon and myelin sheaths status. Oxidative stress was more pronounced in SHR and WKY with ligated sciatic nerve compared to untreated rats. Treatment with (R+)-ALA and with 50 mg/Kg/day racemic-ALA and to a lesser extent with the lower dose of racemic ALA or with pregabalin countered the increase of MDA. (S-)-ALA did not change MDA levels. ALA (50 mg/Kg/day) or (R+)-ALA treatment increased the nociceptive threshold in the right paw, comparable with that of pregabalin. (S-)-ALA did not modify the nociceptive threshold of right paw. Microanatomical analysis revealed that treatment with (R+)-ALA or with the higher dose of racemic-ALA countered nerve injury. The above data indicate an increased oxidative stress in this animal model of compressive neuropathy. The observation of a reduced oxidative stress and of a neuroprotective activity elicited primarily by (R+)-ALA suggests that the naturally occurring stereoisomer of ALA may represent an optimal approach for treating peripheral neuropathies characterized by excessive oxidative stress.

Key words
Peripheral nerve; chronic constriction injury; neurorestoration; morphology; oxidative stress