# Neuroprotective effects of the α9α10 nAChR selective antagonist (RgIA): a new possible strategy against neuropathy

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Chronic pain is a major health problem, affecting millions of people worldwide and causing substantial disability and a significant deterioration in quality of life. Although neuropathic pain is a complex phenomenon, there are few available types of drugs.
Commonly used medications, such as NSAIDs, opioids, and antidepressants, are often characterized by limited therapeutic outcomes and serious side effects. Novel therapeutic strategies are necessary to obtain molecules that combine analgesic with neuroprotective properties.
The involvement of nicotinic acetylcholine receptors (nAChRs) in pain was suggested by a number of experimental observations. While nAChRs agonists were intensively studied, new data suggest a role for selective antagonists. In particular, the efficacy of α9α10 nAChR antagonists as pain relievers is emerging. α-Conotoxins, and in particular RgIA, a selective antagonist of α9α10, produce anti-nociceptive effects in both acute and chronic pain models (1-2).
To evaluate the neuroprotective properties of RgIA, the anti-neuropathic profile of this α9α10 antagonist was studied in the chronic constriction injury (CCI) model of neuropathic pain by behavioral and morphological measures.
Acute intramuscular administration of RgIA, 2 and 10 nmol, 14 days after ligation was able to reduce mechanical hypersensitivity, to increase pain threshold to non-noxious stimuli, and to normalize hind limb weight bearing alterations. The chronic administration of 2 and 10 nmol RgIA once a day for 14 days, was able to reduce the pain perception in all behavioral tests (Paw-Pressure, Von Frey, Incapacitance). Histological analysis of sciatic nerves highlighted that CCI causes edema, inflammatory infiltrate, decreases the axons' compactness and diameter, together with a loss of myelin sheath and a decrease in the number of fibers. Morphological evaluations showed that 2 and 10 nmol RgIA treatments were able to increase the mean axon diameter, myelin thickness and the number of fibers. Both dosages significantly prevented edema formation and the number of inflammatory infiltrate cells. In particular, a decrease of CD86+ macrophage number was observed. In dorsal root ganglia, RgIA significantly reduced the inflammatory infiltrate, but exerted only a mild effect on the neuron area alteration induced by CCI.
To evaluate the α9α10 antagonist effect on Central Nervous System the glia activation profile was examined in lumbar spinal cord sections by immunohistochemistry. In the dorsal horn of CCI animals, microglia as well as astrocyte cell number were increased ipsilaterally. Repeated treatments with 2 or 10 nmol RgIA reduced glia cell activation.
These data strongly evidence the neuroprotective properties of RgIA and suggest a possible use of α9α10 nAChR antagonists as disease modifying agents.

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2. Vincler M. et al. 2006 Molecular mechanism for analgesia involving specific antagonism of α9α10 nicotinic acetylcholine receptors. PNAS; 103(47): 17880-178