Involvement of nicotinic receptor subtypes in neuropathic pain

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Several evidences suggest the relevance of the cholinergic system modulation in pain relief. Muscarinic receptor signaling is mainly involved in acute pain perception and activation of M_1 subtype muscarinic receptors induces analgesia; on the contrary, the importance of nicotinic receptors (nAChRs) is increasing in the management of neuropathic pain. Nicotine and nicotine receptor agonists have been demonstrated to exhibit antinociceptive, antihyperalgesic, and antiallodynic effects across a range of preclinical models of pain, involving peripheral and central sites of action. Moreover, a great deal of interest has developed around the possibility that specific nAChR subtypes might be involved in the neuroprotective mechanisms against neuronal damage. Experimental data largely indicate long-lasting effects of nAChR modulators that imply both an anti-hyperalgesic and a neuroprotective role, involving mainly α_7 and $\alpha_4\beta_2$ nAChR subtypes. We have recently demonstrated that the repeated administration of the α_7 agonist PNU-282987 is able to decrease pain perception in the CCI model of peripheral neuropathy. Histological studies reveal an improvement of nerve morphology evaluated as axon compactness and diameter, together with a significant preservation of myelin sheaths. Interestingly, the α_7 nAChR expression decreases dramatically in animal models of chemotherapy-induced neuropathy. In rats repeatedly treated with oxaliplatin the administration of two α_7 nAChR agonists prevented the receptor down-regulation and relieved pain. Further *ex vivo* analysis highlighted the α_7 nAChR neuroprotective effects in dorsal root ganglia and peripheral nerves preventing the oxaliplatin-induced morphological and molecular alterations. Neuroprotection paralleled with a characteristic glial activation profile.

Also the α9α10 nAChR subtype, recognized in several tissue including immune cells, has been implicated in pain relief. The most potent and selective ligand known for α9α10 nAChR is RgIA, a member of the α-4,3 family of α-conotoxin isolated from the carnivorous marine snail *Conus regius* [168]. This peptide selectively blocks α9α10 nAChRs and it is effective in reducing hypersensitivity both in model of trauma- and chemotherapy-induced neuropathic pain after single or repeated treatments. Moreover, RgIA controls the immune response of damaged nervous tissues suggesting the possibility to influence the pathophysiological process in the transition from acute to chronic pain. As described for the α7 subtypes, the modulation of α9α10 nAChRs involve not only the neuronal component but a strong impact on glial cells in the spinal cord and in pain-related brain areas exist. The pharmacological modulation of nAChR subtypes offer a contribution to the understanding of glial functions during neuropathy. Since glial cells play a role both in pain and in neuroprotection, a nAChR-dependent modulation of glial functions is suggested to distinguish rescue signals from the pathological pain-mediating pathway.