ANTIHYPERALGESIC AND ANTIALLODYNIC EFFECT OF PURINERGIC ANTAGONISTS IN A MOUSE MODEL OF MONONEUROPATHY: NEUROINFLAMMATORY INVOLVED MECHANISMS

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Neuropathic pain, resulting from nervous system damage, is refractory to all current pharmacological treatments and is accompanied by the release of many mediators from migrant immune and resident cells if induced by peripheral nerve damage. Neurotransmitter ATP, that activates purinoceptors, appears to play a role in pain transmission peripherally and centrally. We recently demonstrated that pyridoxal-phosphate-6-azophenyl-2',4'-disulfonic acid (PPADS), a non-selective purinoceptor antagonist, reversed in a time- and dose-related manner the nociceptive hypersensitivity in mononeuropathy induced by chronic constriction injury of C57Bl/6J male mice sciatic nerve. Many purinoceptors are involved in neuropathic pain; to investigate what receptor subtype was more involved in neuropathy, the injured mice were i.p. treated once a day for 11 days, from day 3 after nerve injury, with other purinergic antagonists, such as *iso*-PPADS, pyridoxal-phosphate-6-azophenyl-2',5'-disulfonic acid (25 mg/kg), a PPADS analogue without affinity for P2Y, and adenosine 5'-triphosphate periodate oxidized (oATP) (1 mg/kg), antagonist more selective for P2X7 subtype. Similarly to PPADS, also *iso*-PPADS in a time-related manner after 11 days of treatment abolished neuropathic pain behaviour, while oATP reduced only partially the thermal hyperalgesia, so underlying that many P2X receptor subtypes are involved in neuropathic heat hypersensitivity and only their total block caused the disappearance of painful symptoms. To understand the therapeutic significance of these results, we are studying if the pain reversing effect induced by purinergic antagonists persists after the treatment discontinuation throughout a long evaluation time and is accompanied by nerve morphometric improvement. At the same aim, mRNA of two myelin proteins P0 and PMP22 were dosed in sciatic nerve by RPA, showing that PPADS reversed the decrease in P0 expression of injured nerve. Cytokine and NO/NOS system is involved in development and maintenance of neuropathic pain. PPADS reversed, simultaneously to nociceptive hypersensitivity, the iNOS and nNOS overproduction and the proinflammatory cytokine (IL1β and IL6) overexpression in the peripheral (injured sciatic nerve and L4-L6 dorsal root ganglia, DRG, ipsilateral to lesion) and central (L4-L6 dorsal spinal cord and thalamus) nervous system steps involved in pain transmission. Immunohistochemistry studies done in DRG and spinal cord confirmed the results obtained by western blot on iNOS and nNOS content. In conclusion, purinergic antagonists could be new pharmacological alternatives for neuropathic pain relief, in the light of the current clinical need.