Peripheral nerve injury induced neuropathy and neuropathic pain: role of a new player

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A new pronociceptive chemokine called mammalian-Bv8 or Prokineticin 2 (PK2) can lower pain threshold and modulate immune responses. PK2 is highly up-regulated in inflamed tissues and was demonstrated to be a major determinant in triggering inflammatory pain [1]. In rodents it activates two G-protein coupled receptors: prokineticin receptor 1 (PKR1) and 2 (PKR2) localized in the brain, dorsal root ganglia (DRG), granulocytes, macrophages and endothelial cells as well as in several other organs [2]. We have already demonstrated that the pharmacological blocking of the PKRs is a winning strategy in inflammatory pain treatment [3].

Aim: we evaluated the presence of PK/PKRs in sensory neurons, their role in neuropathy induced by CCI of the sciatic nerve, a model which combines nerve compression with an epineurial inflammation and the effectiveness of a PKR antagonist, PC1, in controlling neuropathic pain.

Methods: CCI of the sciatic nerve was induced in mice [4]. Thermal hyperalgesia (Plantar test), mechanical (Dynamic Aestesiomether) and tactile (Von Frey filaments) allodynia were assessed. From day 3 to day 9 after surgery, a group of mice (n=5) received PC1 (150 μg/kg, s.c., twice a day) and another group received saline s.c. Ten days after surgery the mice were sacrificed and DRG, sciatic nerve and plantar skin were collected to evaluate PK2/PKRs mRNA and protein levels by RT-PCR and immunohistochemical studies. Moreover, the levels of the proinflammatory cytokine IL-1 and the anti-inflammatory cytokine IL-10 were evaluated by ELISA.

Results: in our hands all mice developed thermal hyperalgesia and mechanical allodynia from day 1 and tactile allodynia from day 12 after surgery, on the lesion side, while sham-operated mice did not. CCI induced a clear activation of the PK2/PKRs system in the peripheral nervous system (PNS) compared with the controls mice. The levels of the endogenous agonist, PK2, and of the receptor PKR2 appeared significantly increased in the CCI sciatic nerve and DRG, whereas PKR1 level was increased only in the damaged nerve associated with the infiltrating cells and the activated Schwann cells. After CCI the level of the proinflammatory cytokine IL-1 was also increased, whereas the level of the anti-inflammatory cytokine IL-10 was decreased.

Repeated administrations of PC1 from day 3 to day 9 after surgery significantly reduced the development of thermal hyperalgesia and mechanical allodynia and prevented the development of tactile allodynia.

PC1 treatment reduced PK2 expression in the injured nerve and DRG, leaving the PKR1 and PKR2 levels unchanged. PC1 treatment restored also the physiological level of the pro-inflammatory cytokine IL-1 and increased the production of the anti-inflammatory cytokine IL-10 in the sciatic nerve.

CCI of the sciatic nerve caused partial denervation and significant epidermal thinning in the injured paw. In PC1 treated animals the epidermal thinning was significantly reduced compared to saline treated mice.

Conclusion:our data demonstrate that blocking Bv8/PK system might be a successful strategy in preventing / reducing the inflammation of peripheral sensory nerve and neuropathic pain.

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4. Bennett et al. (1988). *Pain,* 33:87.