Bv8/Prokineticin2 in pain transmission

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Bv8 (Prokineticin 2, PK2) is a cytokine-like molecule expressed mainly by inflammatory leucocytes and behaves as a main pain player. It belongs to a family of small proteins identified in several species from reptiles to mammals characterized by a conserved N-terminal sequence and five disulfide bridges. In mammals they bind two closely related family A G-protein coupled receptors (PKR1 and PKR2) localized in all regions of the nervous system related with pain, particularly in the dorsal horn of the spinal cord and in DRG nociceptive neurons also expressing TRPV1 and TRPA1 suggesting a cooperative interaction in nociceptor sensitization. PKRs are also present on granulocytes, macrophages and endothelial cells. In neuronal cells they are coupled to Gq and activates both MAPK and PI3K. Computational analysis suggest an identical TM-bundle binding site for hPKR1 and hPKR2 so that small-molecule antagonists are not likely to easily differentiate between the subtypes. Our group synthesized triazine-guanidine derivatives that appear very promising in controlling acute and persistent pain. Myeloid cells and testis express two mRNA transcripts of PK2, one coding for the canonical PK2, homologue to the amphibian Bv8 and the other for an inactive elongated form, PK2L, which may be cleaved giving rise to a smaller peptide PK2ß, which retains selective affinity for PKR1. In the nervous system we found only the PK2 mRNA and PK2 is present in some DRG neurons also expressing TRPV1. Peripheral administration of the mammalian PK2 or Bv8 in rodents induced hyperalgesia and allodynia in WT mice, whereas nociceptor activation was impaired in PKR1- or PKR2-KO mice. Moreover Bv8, increasing CGRP and SP expression and release, induces long-lasting sensitization of nociceptors resulting in enhanced responses to evoking stimuli, including Bv8 itself or capsaicin, so providing a basis for long-lasting hypersensitivity that may result in conditions of tissue injury. A common mechanisms of inflammatory and neuroparhic pain is the spinal activation of MAPK and PI3K: Bv8 induced hyperalgesia was inhibited in dose-dependent manner by i.t. pretreatment with ERK (PD98059) or PI3K (wortmanin, LY294002) inhibitors. We have shown that the inflammation produced by paw injection of CFA is highly correlated with an overexpression of PK2 in the granulocytes that infiltrate the inflamed tissue and are responsible for inflammation-associated hyperalgesia. In mouse models of neuropathic pain, the chronic constriction injury of the sciatic nerve(CCI) and the spared nerve injury(SNI) a clear activation of the Bv8/PK system takes place starting in the nerve, where PK2 was already increased at 3 dpi (day after injury) associated with infiltrating granulocytes/ macrophages and Schwann cells (SC), and moves towards the centre where PK2 is significantly increasd at 6 dpi, and showed a constant tendency to increase up to 17 dpi. In the spinal cord, at 10 dpi, high PK2 immunoflurescence is associate with activated astrocytes and presynaptic terminals suggestsing that PROK2 may be transported to the central endings where it induces central sensitization leading to microgliosis, astrocytosis, production of proinflammatory cytokines, and activation of neurons of the superficial layers of spinal cord overexpressing the PKR2. One-week therapeutic treatment with Bv8-antagonists reduces allodynia and thermal hyperalgesia, reduces PK2 overexpression at peripheral and spinal levels, inhibits the PK2-driven glial and microglial activation, reverses the spinal cord specific nociceptive neuron sensitization, Moreover switching off the PROK2 production and signalling significantly decreases the burden of proinflammatory cytokines in the lesioned nerve and in spinal cord and prompts an anti-inflammatory repair program. Our data demonstrate that reducing Bv8 levels in damaged tissues or antagonizing PKRs might be an innovative strategy to control persistent, invalidating pain.