Proceedings of the British Pharmacological Society at http://www.pA2online.org/abstracts/Vol10Issue2abst034P.pdf

Hyperalgesia is mediated by hemokinin-1 in acute and chronic inflammation and neuropathy models of the mouse

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Background: The preprotachykinin C (TAC4) gene and its products, hemokinins in mice and endokinins in humans, were discovered in 2000. Hemokinin-1 (HK-1) is not only expressed in several peripheral tissues, but also in the central nervous system, where its regional distribution is similar to that of substance P (SP) derived from the preprotachykinin A (TAC1) gene. HK-1 exhibits structural homology with SP, therefore, they have immunological cross-reactions. HK-1 has a remarkable selectivity and potency for the neurokinin 1 (NK1) receptor similarly to SP, but based on a range of distinct actions, an own HK receptor has also been proposed. In vivo data suggested that HK-1 also might participate in inflammatory and pain processes. Therefore, we aimed to investigate the role of HK-1 in hyperalgesia induced by acute neurogenic inflammation, adjuvant induced chronic arthritis and traumatic mononeuropathy with the help of gene-deleted mice. **Methods**: Male TAC4 gene-deficient ($TAC4^{-/-}$) mice and their C57Bl/6 wildtype counterparts were used (n=6-16/group). Acute neurogenic inflammation of the paw was evoked by the ultrapotent Transient Receptor Potential Vanilloid 1 (TRPV1) receptor agonist resiniferatoxin (RTX; 20 µl, 0.03 µg/ml i.pl.). Noxious heat threshold was measured with the increasing temperature hot plate before and 5, 10, 15 and 20 min following RTX-injection. The mechanonociceptive threshold was determined with the dynamic plantar aesthesiometer prior to the induction of inflammation and 2, 4, 6 and 24 h afterwards. Chronic joint inflammation was elicited by Complete Freund's Adjuvant (CFA; 50 µl, 1 mg/ml i.pl.) injection. The mechanonociceptive threshold was determined by aesthesiometry and paw volume was measured with plethysmometry before, and three times a week during a 21-day experimental period. Traumatic mononeuropathy was induced by tight ligation of 1/2-1/3 of the right sciatic nerve in deep anaesthesia. 7-19 days after nerve ligation the mechanonociceptive threshold of the hindpaws and motor coordination were measured by aesthesiometry and accelerating rotarod, respectively. **Results**: In wildtype mice RTX induced an approximately 8˚C drop of the thermonociceptive threshold showing the development of thermal allodynia in the early phase due to the sensitization of the peripheral nerve terminals by the released inflammatory mediators. Mechanical hyperalgesia including central sensitization processes at the spinal cord level occurred 2 h after the injection and lasted for 24 h. In $TAC4^{-/-}$ mice the early thermal allodynia and the later developing mechanical hyperalgesia were significantly diminished compared to the wildtypes. Adjuvant-induced 30-40% mechanical hyperalgesia was also markedly attenuated in TAC4 gene-deleted mice, while oedema was not altered. Sciatic nerve ligation resulted in a 45-50% decrease of the mechanonociceptive threshold in wildtypes 7-19 days after the operation, while the motor performance was not affected. This neuropathic hyperalgesia was also significantly smaller in $TAC4^{-/-}$ animals. **Conclusions**: HK-1 plays a predominant role in acute inflammatory thermal allodynia, as well as mechanical hyperalgesia under inflammatory and neuropathic conditions. It is likely to act on the peripheral sensory nerve terminals and also in the spinal cord central sensitization occurs. Identification of its target and mechanisms of action opens new perspectives to develop novel analgesics. **Funding**: SROP-4.2.1.B-10/2/KONV-2010-0002, SROP-4.2.2.B-10/1/2010-0029