

IMPAIRED NOCICEPTION IN MICE LACKING THE PROKINETICIN RECEPTOR 2 (PKR2)

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Bv8, prokineticin-2 (PK2) and EG-VEGF or prokineticin-1 (PK1), are naturally occurring peptide agonists of two G-protein coupled receptors, PKR1 and PKR2. PKR2 is expressed in many nuclei of central nervous system, and both PKR1 and PKR2 are present in dorsal root ganglion (DRG). In rats and mice intrathecal (i.t.) and intraplantar (i.pl.) injections of Bv8 and PK2 always decreased the nociceptive threshold to thermal and mechanical stimuli. In rats, i.t. injection of PK1 produced mechanical hyperalgesia at low doses (10 ng) but produced weak analgesia at high doses (700 ng). We demonstrated that Bv8/PK2-induced hyperalgesia depends on peripheral activation of PKR1: indeed PKR1-null mice are 30-100 times less sensitive to Bv8-induced thermal hyperalgesia, moreover they display impaired nociception and inflammatory pain sensation (1). Here we evaluate the pain behaviour of PKR2-null mice. They display slightly reduced sensitivity to Bv8-induced thermal hyperalgesia respect to WT-mice. Like PKR1-null mice, they exhibited longer tail withdrawal from hot water (21.2 ± 0.96 sec) and hot-plate escape (20.2 ± 0.74 sec) latency than WT controls (9.9 ± 0.31 sec, 10.1 ± 0.34 sec) at temperature range from 46 to 48°C. Capsaicine-induced paw licking (23 ± 1.9 , vs 74 ± 5.2 sec) and acetic acid-induced abdominal stretching (20.1 ± 2.1 , vs 44.8 ± 3.6) were significantly attenuated in PKR2-null mice. They were also less sensitive than WT-mice to inflammatory pain (CFA). These results seem to indicate, for PKR2, a role similar to that of PKR1 in thermal, chemical and inflammatory nociception. However after s.c. administration of 1% formalin into the hindpaw, PKR2-null mice showed significantly increased early phase response to formalin respect to WT mice. On the contrary, PKR1-null mice exhibited significantly reduced early and late phase response, indicating that peripheral PKR2 reduce the formalin-induced pain response. I.pl. injection of 10 ng PK1 in WT and in PKR2-null mice significantly decreased (-50%) the paw-withdrawal latency from hot water, whereas the same dose in PKR1-null mice increased (+ 46%) the paw-withdrawal latency. These data suggest different roles of PKR1 or PKR2 in nociception: the presence or activation of PKR2 seems to reduce pain perception.

(1) Negri L, Lattanzi R, Giannini E, Colucci M, Margheriti F, Melchiorri P, Vellani V, Tian H, De Felice M, Porreca F. (2006) *J Neurosci.* 26:6716-6727.