Prostanoid system is involved in Bv8-induced nociception

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Bv8, Prokineticin 1 (PK1 or EG-VEGF) and Prokineticin 2 (PK2 or mammalian-Bv8) make up a new family of chemokines involved in different biological activity such as: circadian rhythms, neurogenesis, angiogenesis, haematopoiesis and pain sensitization [1]. These chemokines activate two G-protein linked receptors: prokineticin receptor 1 (PKR1) and prokineticin receptor 2 (PKR2), encoded within distinct chromosomes in both mouse and human, and sharing about 85% amino acid identity [2]. PKR1 is widely distributed in the periphery, including the gastrointestinal system, blood system and dorsal root ganglion (DRG) neurons, whereas PKR2 is the main receptor in the adult brain localized in hypothalamus, olfactory ventricular regions and limbic system [3]. Multiple signaling pathways are activated by PKRs. The activation of PKRs stimulates calcium mobilization, phosphoinositol turnover, and activation of Akt kinase and mitogen-activated protein kinase (MAPK) [4]. In dorsal root ganglion neurons, PKRs induced $[Ca^{++}]i$ mobilization and protein kinase C- ε (PKC-ε) translocation [5]. In rats and mice, activation of PKRs by Bv8 induces sensitization to heat, protons and capsaicin. Several *in vitro* and *in vivo* data sustain a co-operativity between PKRs and TRPV1. However blocking the TRPV1 pathway, strongly reduces but does not abolish Bv8-induced hyperalgesia.

Here we demonstrated that Bv8-induced nociceptive sensitization was abolished by the COX-1/2 inhibitor indomethacin (10 ng), the COX-1 inhibitor SC560 (2 ng), the prostaglandin EP1 receptor antagonist SC51322 (2 μg) and the PKA inhibitors WIPTIDE (10 μg) and H89 (10 μg) suggesting an involvement of PGs which activate EP1 receptor and its downstream effector PKA. The COX-2 inhibitor, NS392 was ineffective. Accordingly, COX-1 null but not COX-2 null mice were 20 times less responsive to Bv8-induced nociceptive sensitization than wild-type mice.

In vitro, about 18% of Bv8 responding DRG neurons were COX-1 positive (and small sized probably those expressing PKR1). Moreover, the PGE2 level in the culture medium was significantly increased in 10 minutes after the application of Bv8 50 nM. In mouse paw skin, i.pl. injection of Bv8 (0.5 and 5 ng) dose-dependently increased PGE2 level, that reached maximum in 4 h after injection.

Conclusions: activation of the COX-1 pathway in nociceptors contributes to sensitization induced by activation of PKR1. The later increased level of PGE2 in the skin probably depends on neurogenic inflammation and on COX-2 activation.

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