PROSTANOID SYSTEM IS INVOLVED IN Bv8-INDUCED NOCICEPTION

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The recently discovered prokine ticin receptors, PKR1 and PKR2, and their activation by peptides belonging to the Bv8-EG-VEGF-Prokine ticin family (PKs), suggest a novel mechanism of peripheral nociceptor activation and sensitization. In rats and mice activation of PKRs by Bv8 sensitezed to the actions of noxious heat, protons and capsaicin. Several in vitro and in vivo data susta in a co-operativity between PKRs and TRPV1 in Bv8 induced hyperalgesia. However blocking the TRPV1 pathway, strongly reduces but does not abolish Bv8-induced hyperalgesia.

Here we demonstrated that Bv8-induced nocic eptive sesnsitization 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 that activation of the EP1 receptor and its downstream effector PKA by prostaglandins partecipate to the nociceptor sensitization. The COX2 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.

Paw skin levels of PGE2, significantly increased 4 h after intraplantar injection of 0.5 ng Bv8(109.4±42, vs 30.61±10 pg/mg tissue). After an higher dose (5 ng Bv8) skin levels of PGE2 were already increased 1 h after the injection (85±30, vs 50±11 pg/mg tissue) and peacked 4 h after the injection (119±45 pg/mg tissue).

Recent observations support an interaction between Bv8 and the eicosanoid system: the heat nociceptive response (hot-plate test) of mice to intraplantar injection of the threshold dose of PGE2 (10 ng) increased tremendously when mice were preinjected with 0.5 ng Bv8. Hence, PGE2 released by Bv8 could, in turn, sensitize cutaneous nociceptors.