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NOCICEPTOR SENSITIZATION BY THE SECRETORY PROTEIN Bv8

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The small protein Bv8, isolated from amphibian skin, belongs to a novel family of secretory proteins whose orthologs have been conserved throughout evolution, from invertebrates to humans. In this study we investigated the effects of systemic, intrapaw and intrathecal injections of Bv8 on the sensitivity of rat cutaneous nociceptors to thermal and mechanical stimuli. When injected intravenously or subcutaneously (from 6 to 25 pmol/kg) in rats, Bv8 produced an intense and long-lasting sensitization of skin nociceptors to mechanical (pressure) and thermal stimuli. Bv8-induced hyperalgesia showed a characteristic biphasic time-course and lasted four hours. Topically delivered into one rat paw, 50 fmol of Bv8 decreased by 50% the nociceptive threshold to pressure of the injected paw without affecting the threshold in the contralateral paw. Intrathecally delivered Bv8 (60 fmol) produced nociceptive sensitization to pressure and thermal stimuli applied to rat paw and tail. Both the intrathecal and peripheral Bv8-induced nociceptor sensitization were blocked by coadministration of pertussis toxin (1 ng) and prevented by inhibitors of RAS-, ERK-, AKT-, COS-, NOS-signaling pathways and by EP1 prostaglandin receptor antagonists. These data suggest that Bv8, possibly through binding to a PTX sensitive G protein coupled receptor, results in RAS-dependent activation of ERK-, AKT-, COS-, NOS-signaling pathways, leading to prostaglandin- nitric oxide-mediated nociceptor sensitization.