Bv8 induces peripheral sensitization of nociceptors

D. Maftei[1], R. Lattanzi[1], V. Marconi[1], I. Fusco[1], P. Reeh[2], T. Hoffmann[2], L. Negri[1]

[1]Dept. of Physiology and Pharmacology 'Vittorio Erspamer', Sapienza University of Roma, Italy
[2]Institute of Physiology and Pathophysiology, University of Erlangen-Nuremberg, Erlangen 91054, Germany

Bv8 is a pronociceptive peptide that binds to two G-protein coupled prokineticin receptors, PKR1 and PKR2 localized in the dorsal horn of the spinal cord and dorsal root ganglia (DRG) of nociceptive neurons. In rodents, intrathecal or systemic administration of Bv8 elicits hyperalgesia with a characteristic biphasic time-course: the first peak occurs in 1 h and the second peak in 4-5 h. We have already demonstrated that the first phase of hyperalgesia is mainly attributable to a direct action of Bv8 on nociceptors through binding to PKRs (1,2) while the second phase of hyperalgesia depends on central (3) but also on peripheral sensitization.
Conversely, intraplantar injection of a very small dose (50 fmol) of Bv8 produces one peak of hyperalgesia only in the injected paw but elicites a strong hypersensitivity to various pro-algesic drugs in the time-window corresponding to the 2° hyperalgesic peak. Indeed, intraplantar sub-hyperalgesic doses of Bv8 itself (12 fmol), PGE2 (28 fmol) and capsaicin (0.33 nmol) but not bradykinin or ATP, administered 2 h after the intraplantar injection of the priming-effective dose of Bv8 (50 fmol) produce a very strong and long-lasting hyperalgesia. 4 h after the intraplantar injection of Bv8 (50 fmol) a strong neutrophil recruitment (MPO-assay) and increase in PROK2 (the mammalian Bv8 ortholog) expression levels (RT-PCR) and PGE2 content (ELISA) in the mouse paw skin is evident. Because these events comes within the time-window that corresponds to the Bv8-induced hypersensitivity (as shown before), we suppose that they may contribute to peripheral sensitization. Moreover, in isolated skin preparation, Bv8 appears to induce not only sensitization to heat but also an enhanced "sensitizability"; indeed after prolonged (90 min), pre-treatment of the receptive field with Bv8 (100 nM) the heat threshold diminishes and become even lower with stimulus repetition. Evidences supporting the notion that Bv8 can exert it's peripheral effects through direct activation of peptidergic afferents comes from immunofluorescence studies, revealing a co-localization of PROK2 with CGRP in both mouse sciatic nerve and in mouse epidermal layers of plantar skin, and from electrophysiological experiments demonstrating that Bv8 facilitates CGRP release in the skin. Indeed, using skin flaps from rat paw, in vitro, we demonstrated that simultaneous application of heat stimuli (47 °C) and high concentration of Bv8 (10, 100 and 300 nM) elevates the heat-induced CGRP release, whereas, prolonged incubation (90 min) of skin flaps with a low Bv8 concentration (5 nM) does not alter the baseline CGRP neurosecretion but significantly increases the capsaicin-induced CGRP release. Collectively these data demonstrate that Bv8 is an agent that modulates the nociceptive threshold through a peripheral sensitization of nociceptors and that this sensitization seems to be TRPV1 mediated.

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