

Poster presentation

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The role of cGMP and PKG-I in spinal nociceptive processing

Achim Schmidtko^{*1}, Irmgard Tegeder¹, Ellen Niederberger¹,
Franz Hofmann², Peter Ruth³ and Gerd Geisslinger¹

Address: ¹Pharmazentrum Frankfurt/ZAFES, Institut für Klinische Pharmakologie, Johann Wolfgang Goethe-Universität, Frankfurt am Main, Germany, ²Institut für Pharmakologie und Toxikologie, Technische Universität München, Germany and ³Pharmakologie und Toxikologie, Pharmazeutisches Institut, Universität Tübingen, Germany

Email: Achim Schmidtko* - Schmidtko@em.uni-frankfurt.de

* Corresponding author

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Background

Persistent stimulation of nociceptors results in sensitization of nociceptive sensory neurons, which is associated with hyperalgesia and allodynia. The release of NO and subsequent synthesis of cGMP in the spinal cord are involved in this process. cGMP-dependent protein kinase I (PKG-I) has been suggested to act as a downstream target of cGMP, but its exact role in nociception hadn't been characterized yet. To further evaluate the NO/cGMP/PKG-I pathway in nociception we assessed the effects of PKG-I inhibitor and activator in the rat formalin assay and analyzed the nociceptive behavior of PKG-I^{-/-} mice.

Results

The PKG-I-inhibitor, Rp-8-Br-cGMPS (0.1 – 0.5 μmol i.t.), reduced the nociceptive behaviour of rats in the formalin assay [1]. In contrast, administration of a high dose (2.5 μmol i.t.) of the cGMP analogue, 8-Br-cGMP, caused hyperalgesia. However, low doses of the same drug (0.1 – 0.25 μmol i.t.) unexpectedly reduced the nociceptive behaviour, revealing dose-dependent contrary effects of 8-Br-cGMP. The antinociceptive effects of 'low-dose' 8-Br-cGMP are obviously independent of PKG-I activation, since co-administration with the PKG-I inhibitor, Rp-8-Br-cGMPS, failed to antagonize antinociception [2]. To further assess the role of PKG-I in nociception, we studied the behaviour of PKG-I^{-/-} mice. PKG-I deficiency was associated with reduced nociceptive behaviour in the formalin assay and reduced mechanical hyperalgesia during zymosan-induced paw inflammation. A high dose of 8-Br-cGMP (250 nmol i.t.) caused mechanical allodynia only in PKG-I^{+/+} mice, indicating that the presence of PKG-I was essential for this pronociceptive effect. In contrast,

administration of 'low-dose' 8-Br-cGMP (25 nmol i.t.) reduced the nociceptive behaviour in both PKG-I^{+/+} and PKG-I^{-/-} mice, supporting the hypothesis that the antinociceptive effects of 8-Br-cGMP are independent of PKG-I activation [3].

Conclusions

Our data suggest that in the spinal cord, high concentrations of cGMP cause hyperalgesia through activation of PKG-I, whereas low concentrations of cGMP reveal antinociceptive effects via a PKG-I-independent mechanism.

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