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Poster presentation

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

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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 inhibiton and activaton 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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References

1. Schmidtko A, Ruth P, Geisslinger G, Tegeder I: **Inhibition of cyclic guanosine 5'-monophosphate-dependent protein kinase I (PKG-I) in lumbar spinal cord reduces formalin-induced hyperalgesia and PKG upregulation.** *Nitric Oxide* 2003, **8:**89-94.
2. Tegeder I, Schmidtko A, Niederberger E, Ruth P, Geisslinger G: **Dual effects of spinally delivered 8-bromo-cyclic guanosine monophosphate (8-bromo-cGMP) in formalin-induced nociception in rats.** *Neurosci Lett* 2002, **332:**146-150.
3. Tegeder I, Del Turco D, Schmidtko A, Sausbier M, Feil R, Hofmann F, Deller T, Ruth P, Geisslinger G: **Reduced inflammatory hyperalgesia with preservation of acute thermal nociception in mice lacking cGMP-dependent protein kinase-I.** *Proc Natl Acad Sci U S A* 2004, **101:**3253-3257.