Antinociceptive activity of the PKR antagonist, PC1, by different routes of administration

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The small protein Bv8 (an amphibian secreted protein) and its mammalian homologues Prokineticin 1 (PK1) and 2 (PK2) belong to a new family of chemokines identified a decade ago and linked to several biological effects including pain sensitization. These chemokines, in mammals activate two closely related G-protein coupled receptors (prokineticin receptor 1 and 2, PKR1 and PKR2) expressed in regions of the nervous system associated with pain: DRG, the outers layers of the dorsal horn of the spinal cord and peripheral terminals of nociceptor. In rats, activation of PKRs by Bv8 produces nociceptive sensitization to mechanical and thermal stimuli. Very low doses of Bv8 (50 fmol) injected by intraplantar (i.pl.) route induces a decrease in the nociceptive threshold of the injected paw that lasts 2-3 h, leaving threshold in the contralateral paw unchanged. The same dose of Bv8 injected by intrathecal (i.t) route or higher doses by subcutaneous (s.c.) route, induces systemic hyperalgesia with a characteristic biphasic time-course. The first phase depends on direct action on nociceptors, because it resembles that produced by i.pl. injection; the second phase may depend by central and/or peripheral sensitization [1].
Hence PKRs represent potential targets for novel antinociceptive drugs. Recently, a triazine derivative compound, named PC1 was designed and synthesized. Binding experiments indicated that PC1 binds to PKRs with an affinity 30 times higher for PKR1 than for PKR2 [2].

Aim of this work was to study the ability of PC1, administered by different routes in rats, to antagonize the Bv8-induced mechanical hyperalgesia (Randall-Selitto test).

The monophasic hyperalgesia induced by intraplantar injection of 50 fmol Bv8 was abolished by local i.pl. or i.t. preinjection of 15 pmol PC1, or by a systemic s.c. dose of 22 nmol/kg of PC1.
The biphasic hyperalgesia induced by intrathecal injection of 50 fmol Bv8 was abolished by intrathecal pre-injection of 15 pmol PC1. Conversely, the same dose of 15 pmol of PC1 by i.pl. route, was able to abolish only the first phase (when injected 5 min before Bv8) or second phase (when injected 150 min after Bv8).
Both the first and second phase of hyperalgesia induced by i.t. injection of Bv8 were abolished by systemic s.c. injection of 22 nmol/kg of PC1.
The biphasic hyperalgesia induced by s.c. injection of Bv8 (25 pmol/kg) was abolished by intrathecal pre-injection of 15 pmol PC1 and by s.c. injection of 22 nmol/kg of PC1.

These findings confirm that the PC1 antihyperalgesic effect depends on blocking of peripheral and central PKRs. PC1, after peripheral administration, may reach the CNS.

[1] Negri et al. (2002). Br. J. Pharmacol, 137: 1147-1154.
[2] Balboni et al. (2008). *J Med Chem,* 51:7635-7639.