REPORTS

The Analgesic Activity of Neo-Kyotorphin: A Newly Identified Pentapeptide from Bovine Brain.

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Received: March 15, 1983; accepted April 21, 1983.

Abstract: Analgesic effects of a novel pentapeptide from bovine brain, termed neo-kyotorphin (Thr-Ser-Lys-Tyr-Arg), were determined in mice after intracisternal injection. Neo-kyotorphin showed a dose-dependent analgesia with an ED50 value of 195 nmol/mouse. This effect was not blocked by naloxone pretreatment.

We have recently identified a novel analgesic pentapeptide, Thr-Ser-Lys-Tyr-Arg, from bovine brain (1). As this peptide is structurally related to the analgesic dipeptide kyotorphin (Tyr-Arg), we termed it neo-kyotorphin. In this report, we describe the analgesic activity induced by neo-kyotorphin in comparison with that of kyotorphin. Further details of the purification and the identification of neo-kyotorphin are reported elsewhere (2).

The analgesic activity of neo-kyotorphin was examined in dd-K mice (14–17 g), according to the intracisternal injection method previously reported (3). Synthetically prepared neo-kyotorphin was dissolved in distilled water and injected intracisternally with a J-shaped needle in volumes of 10 µl. Following the injection, the mice were evaluated for responsiveness to noxious stimuli with the tail-pinch method, using a hemostatic forceps with a constant pressure of 200 g. In control trials, all the mice tested bit the forceps within 2 sec. Analgesia was considered positive when the mouse did not bite within 6 sec after administration of the stimulus. The results are expressed as the percentage of mice showing analgesia.

Intracisternally administered neo-kyotorphin produced dose-dependent analgesic effects, in the range of 100–400 nmol/mouse (Fig.1). The analgesic effect reached a maximum within 5 min after injection and lasted for 15–60 min. When a large dose (400 nmol) of neo-kyotorphin was given, a transient clonic convulsion was induced in some of the mice within 30 sec of the injection. We have previously observed that a high dose of enkephalins or endorphins also cause such a convulsion (3). The ED50 value of the analgesic effect of neo-kyotorphin was 195 nmol/mouse with 95% confidence limits of 92–413 nmol/mouse. Therefore, its analgesic activity is lower than that of Met-enkephalin (ED50 = 146 nmol/mouse), and approximately equal that of Leu-enkephalin (ED50 = 223 nmol/mouse) (3). Moreover, neo-kyotorphin is approximately 5.6 times less potent than kyotorphin (ED50 = 34.7 nmol/mouse) in the analgesic activity (4).

Naloxone hydrochloride (0.5 mg/kg, s.c.), administered 5 min prior to the injection of 400 nmol neo-kyotorphin, failed to antagonize its analgesic effect. Neo-kyotorphin did not inhibit the electrically induced contraction of longitudinal muscle of the guinea pig ileum even at a dose of 133 µM. These findings suggest that neo-kyotorphin produced analgesia by neither acting directly through the opiate receptor nor by releasing enkephalins. Also, it seems unlikely that kyotorphin, a Met-enkephalin releaser, mediates the neo-kyotorphin-induced analgesia. Neo-kyotorphin may be classified as a non-opioid analgesic peptide, like neurotensin (5) and bombesin (6).

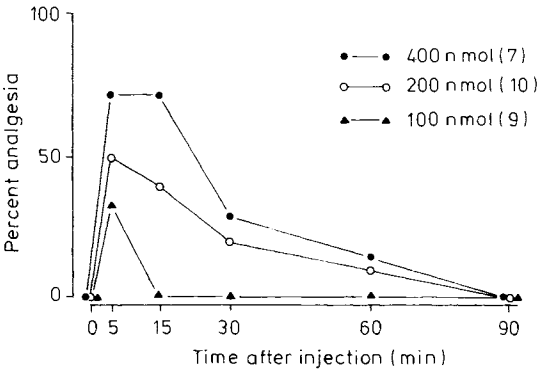

Fig. 1. Analgesic effects of neo-kyotorphin intracisternally injected into mice. The doses are shown in the figure, and numbers in parentheses indicate the number of mice used.

Acknowledgement

We thank M. Ohara for assistance in preparing the manuscript.

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