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The analgesic agent tapentadol inhibits calcitonin gene-related peptide release from isolated rat brainstem via a serotonergic mechanism

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Abstract

In this study we tested the hypothesis that tapentadol inhibits GGRP release from the rat brainstem through a mechanism mediated by the inhibition of NA reuptake; as a second alternative hypothesis, we investigated whether tapentadol inhibits GGRP release via the inhibition of 5-HT reuptake.

Rat brainstems were explanted and incubated in short-term experiments. CGRP released in the incubation medium was taken as a marker of CGRP release from the central terminals of trigeminal neurons within the brainstem. CGRP levels were measured by radioimmunoassay under basal conditions or in the presence of tapentadol; NA, 5-HT, clonidine, yohimbine and ondansetron were used as pharmacological tools to investigate the action mechanism of tapentadol.

The α2-antagonist yohimbine failed to counteract the effects of tapentadol. Moreover, neither NA nor the α2-agonist clonidine per se inhibited K(+)-stimulated CGRP release, thereby indicating that the effects of tapentadol are nor mediated through the block of NA reuptake. Further experiments showed that 5-HT and tramadol, which inhibits both NA and 5-HT reuptake, significantly reduced K(+)-stimulated CGRP release. Moreover, the 5-HT3 antagonist ondansetron was able to counteract the effects of tapentadol in this system.

This study provided pharmacological evidence that tapentadol inhibits stimulated CGRP release from the rat brainstem in vitro through a mechanism involving an increase in 5-HT levels in the system and the subsequent activation of 5-HT3 receptors.

5-hydroxytryptamine; Brainstem; Calcitonin gene-related peptide; Ondansetron; Rat; Tapentadol.

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