Tapentadol modulates Calcitonin Gene-Related Peptide release from rat brainstem. Comparison with Morphine and Reboxetine.

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We have recently characterized an *in vitro* experimental model involving organotypic cultures of rat brainstem and the measurement of *calcitonin gene-related peptide* (CGRP) released in the incubation medium. CGRP is considered the main neuromediator of trigeminal signaling and pain transmission. Brainstems release sizable amounts of CGRP under basal conditions, which can be increased by depolarizing stimuli mimicking a condition of pain transmission activation. CGRP released from the tissue can be taken as a marker of peptide release from trigeminal nerve terminals projecting at level of the brainstem. Thus, this model can be used to investigate the pre-synaptic regulation of pain transmission at the level of brainstem. We have successfully used this model to study both the pathophysiology of pain transmission and the effects of drugs and endogenous agents with putative anti-nociceptive activity.
Tapentadol is a recently approved analgesic drug with a dual mechanism of action: mu-opioid agonist and inhibitor of norepinephrine reuptake, with minimal effects on serotonin transmission. Preclinical evidence suggests a synergistic interaction between these two effects. This study was aimed to investigate the effects of tapentadol in our model. Preliminary experiments were carried out with morphine and reboxetine, attempting to dissect the single effects of the opioid and noradrenergic components of tapendaol action. These drugs showed a different pharmacological profile when tested under basal conditions or after stimulation of CGRP release: *i*) morphine inhibited both basal and KCl-induced CGRP secretion, while having no effect on capsaicin-stimulated CGRP release; *ii*) reboxetine was able to reduce the secretion of peptide either after capsaicin or after stimulation by high K^+ concentrations, but it had no effect whatsoever on basal CGRP release. In this setting, tapentadol did not modify basal CGRP secretion, whereas it was able to inhibit the increase in CGRP release induced by different stimuli, including capsaicin. Thus, the profile of tapentadol activity at the brainstem level resembles more that of a noradrenergic reuptake inhibitor rather than that of an opioid agonist.