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The sythetic endomorphin-1 analog, CYT-1010, inhibits sensory neuropeptide release, acute neurogenic inflammation and heat injury-induced thermal hyperalgesia in rodent models

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Calcitonin gene-related peptide (CGRP) and substance P released from capsaicin-sensitive afferents induce neurogenic inflammatory and nociceptive actions. Since we have shown that the m opioid receptor agonist endomorphin-1 inhibits sensory neuropeptide outflow, the effects of its synthetic, peptidase-resistant analog, CYT-1010, was studied on CGRP release, acute neurogenic inflammation and thermal hyperalgesia. CGRP release from sensory fibres of isolated rat tracheae was evoked by electrical field stimulation and measured with radioimmunoassay. Neurogenic inflammation induced by 5% mustard oil was detected by Evans blue leakage in the rat paw skin and micrometry in the mouse ear. Mild heat injury (51˚C, 20s)-induced thermal hyperalgesia of the rat hindpaw was determined with increasing temperature water bath.Electrically-evoked CGRP release was significantly reduced by 0.5-2mM CYT-1010. Mustard oil-induced plasma extravasation and edema were decreased by i.v. pretreatment with 1-1000mg/kg CYT-1010. Heat hyperalgesia was also attenuated by CYT-1010, the action of the 1000mg/kg dose was similar to that of morphine. Dose-response correlations were not observed in either model, the greatest inhibition was 60%.This stable and highly potent EM-1 analog effectively attenuates neurogenic inflammation and thermal hyperalgesia through the inhibition of sensory neuropeptide release. Therefore, it represents a novel drug candidate for the treatment of inflammatory and pain conditions.