Antihyperalgesic actions of synthetic somatostatin receptor agonists in chronic mouse models of meniscectomy-evoked joint damage and Oxaliplatin-induced sensory polyneuropathy

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Background and aims: The inhibitory effects of somatostatin on hormone production and tumour cell proliferation are well known, but its potent anti-inflammatory and anti-nociceptive actions have also been shown. Our group provided evidence that the analgesic effects in inflammatory pain models are predominantly mediated by the somatostatin receptor subtype 4 and 1 (sst_4, sst_1) expressed on capsaicin-sensitive primary sensory neurons and pain-related brain regions. Therefore, we aimed at investigating the role of these receptors in joint damage- and neuropathy-induced chronic mechanical hyperalgesia using gene-deleted mice and synthetic agonists.

Methods: In both models sst_4 gene-deficient ($sst_4^{-/-}$) mice generated on the C57Bl/6 background and their wildtype counterparts ($sst_4^{+/+}$) were used (males and females; n=6-8/group). Joint destruction-related chronic pain was evoked by removing the medial meniscus in ketamin-xylazine anaesthesia under an operation microscope. Then the wound was closed and the mice were tested for 80 days. The mechanonociceptive threshold of the paw was measured by dynamic plantar aesthesiometry, the mediolateral knee diameter with a digital thickness gage caliper before and twice a week after the procedure. Toxic polyneuropathy was induced by a single oxaliplatin injection (3 mg/kg, i.p.). Mechanonociception was assessed by aesthesiometry, whereas motor coordination with the accelerating rotarod device before and twice a week during 40 days. The general condition and the body weight were also regularly examined. The effects of the heptapeptide $sst_{1/4}$ agonist TT-232 and the peptidomimetic compound J-2156 were tested 10 min after acute administrations (100 microg/kg i.p.).

Results: In both the $sst_4^{-/-}$ and $sst_4^{+/+}$ groups, meniscectomy induced a 60-70% drop of the mechanonociceptive threshold 3 days later, which was due to the operative procedure. This hyperalgesia gradually decreased, and the thresholds returned to the preoperative values 50 days after the intervention. The mediolateral knee diameter increased by 20-30% during the whole study. On days 17-21, when the decrease of the mechanonociceptive threshold was remarkable, TT-232 and J-2156 administered acutely evoked significant anti-hyperalgesic actions in both mice. Oxaliplatin resulted in a 35% mechanical hyperalgesia 3 days following the injection, which was stably maintained during the 40 days of the study. Motor function impairment, weight and hair loss, or visible signs of distress were not observed. These provided evidence for the sensory nature of the polyneuropathy without major systemic toxicity. There was no difference in any parameters between $sst_4^{-/-}$ and $sst_4^{+/+}$ mice. However, acute administration of TT-232 significantly decreased hyperalgesia and J-2156 converted it to hypoalgesia in both groups.

Conclusion: A single oxaliplatin injection is appropriate to induce sensory polyneuropathy without severe systemic toxicity and motor impairment, therefore, neuropathic hyperalgesia can be reliably investigated in this mouse model. Although endogenous activation of sst_4 receptors plays a predominant role in neither joint damage-evoked nor neuropathic chronic mechanical hyperalgesia, exogenous agonists have potent inhibitory effects in both models. Since these agents similarly inhibited hyperalgesia in case of lacking the sst_4 receptor, sst_1 is likely to mediate these anti-hyperalgesic effects.

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