Somatostatin receptor subtype 4 is a promising drug target for the treatment of neuropathic pain, neurogenic inflammation, anxiety and depression

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We have provided evidence that the inhibitory neuropeptide somatostatin is released from the activated capsaicin-sensitive peptidergic sensory nerves, and mediate analgesic and anti-inflammatory actions via its subtype 4 (sst4) Gi-protein-coupled receptor. Although the native peptide cannot be therapeutically used due to its short half-life and broad range of endocrine actions via its sst2, sst3, sst5 receptors, small molecule sst4 agonists might be promising candidates, as novel analgesic and anti-inflammatory drugs.

We investigated the expression pattern of sst4 in the brain using LacZ immunohistochemistry, as well as inflammatory and pain processes mediated by different mechanisms of neurogenic and neuropathic origins using sst4 gene-deleted mice and synthetic agonists. Special emphasis was put on chronic disease models mimicking unmet medical needs.

Sst4 is present in several brain areas involved in pain and mood regulation, such as neocortical areas, hippocampus, amygdala and the dorsal spinal root. Sst4-deficient mice showed increased inflammation in arthritis and airway inflammation, enhanced nocifensive behaviors, inflammatory and neuropathic hyperalgesia, anxiety and depression-like behaviors, as well as had greater susceptibility to chronic variable stress. Neuronal activation patterns were different in stress- and pain-related brain regions of wildtype and sst4-deficient mice both under acute and chronic stress/pain conditions suggesting that the central actions are mediated by sst4-dependent modulation of neuronal plasticity and sensitization.

The synthetic heptapeptide sst4/sst1 agonist TT-232 and the selective non-peptide sst4 superagonist J-2156, but not the sst2,3,5 agonist octreotide, inhibited non-neurogenic and neurogenic inflammation and pain behaviors both in acute models and chronic diabetic neuropathy, traumatic nerve injury and arthritis. Our 66 patented, orally active small molecule sst4 agonists were screened by in silico receptor binding models, competitive binding and G-protein activation assays in primary sensory neurons and sst4-expressing cell lines. In vivo testing of the 3 most promising candidates revealed that they all inhibited neurogenic inflammation, neuropathic hyperalgesia, anxiety and depression-like behaviors in 50-500 migrog/kg oral dose range, and one had sedative effect after the highest dose.

Our results provide evidence that sst4 is a good target for treating neurogenic inflammation, neuropathic pain, anxiety and depression. Our small molecule agonists are promising drug candidates for drug development.