Somatostatin receptor subtype-4 is a promising drug target on neurons for treatment of pain, anxiety, depression and cognitive disorders

Neuropeptide somatostatin acts on G-protein-coupled receptors of two groups SRIF1 (sst2, sst3, sst5) and SRIF2 (sst1, sst4). Agonists of SRIF1 receptors are in the therapy of endocrine and gastrointestinal abnormalities. Role of SRIF2 receptors is however remained out of the focus of interest. We have revealed that from one group of capsaicin-sensitive TRPV1-expressing nociceptors, somatostatin is released in response to stimulation which elicits potent systemic antinociceptive and anti-inflammatory responses by activation sst4 receptors. The stable heptapeptide analogue of somatostatin TT-232, an sst4 agonist without endocrine (SRIF1) side effects has a potent antinociceptive action both on acute and neuropathic pain models (Seltzer, diabetic mechanical allodynia). The non-peptide sst4 superagonist (J-2156) has also pronounced antinociceptive/anti-inflammatory effects in various tests whose effects are absent in sst4 gene-deleted mice. In the sst4 knockout mice hyperalgesia, chronic (CFA) and acute arthritis are more pronounced than that of the controls. Somatostatinergic systems in brain form both long-projecting neurons and short interneurons associated with mainly sst2 receptors. Sst4 receptors are dominantly expressed in the neocortex, hippocampus CA1, olfactory bulb and that of mRNA also in neurons of the amygdala and hypothalamus. Sstr4(-/-) mice showed increased anxiety in the elevated plus maze and forced swim tests while opposite results were found after injection of sst4 agonist J-2156 (100μg/kg i.p.). Sst4 agonism enhanced the stress-responsiveness of neurons of several brain regions (C-Fos) and sst4 LacZ immunoreactivity was in the cortex, hippocampus and amygdala. In the T-maze test on SAMP8 mice treatment with the sst4 agonist NNC 26-9100 enhanced learning and memory and it induced decline of Aβ (x-42) levels of the brain. Intra-hippocampal injection of the sst4 agonist L-803,087 enhanced cue-based memory formation but impaired place memory formation. The morphological and behavioral results using selective sst4 agonists and Sstr4(-/-) mice provide promising perspectives for this receptor as drug target for treating neuropathic and inflammatory pain as well as anxiety, depression, memory disorders and Alzheimer disease.

Biography
Janos szolcsanyi is a professor emeritus and a former head of the department of pharmacology of the University Of Pecs, Hungary. He is also a guest professor at Heidelberg, Chapel Hill UNC, USA, a visiting scientist and consultant in several universities and drug firms.

Notes: