The beta3-adrenoceptor agonist GW427353 (Solabegron) decreases excitability of human enteric neurons via release of somatostatin.

Abstract:

BACKGROUND & AIMS: beta3 Adrenoceptor (beta3-AR) is expressed on adipocytes and enteric neurons. GW427353 is a human selective beta3-AR agonist with visceral analgesic effects. Some of its effects may involve release of somatostatin (SST) and actions on enteric neurons. The aim of this study was to investigate the mode of action of GW427353 in human submucous neurons. METHODS: Voltage sensitive dye imaging was used to record from human submucous neurons. SST release from human primary adipocytes was measured with enzyme-linked immunoabsorbent assay. Immunohistochemistry was used to detect adiponectin, beta3-AR, SST, SST2 receptors, tyrosine hydroxylase (TH), and protein gene product 9.5. RESULTS: Confocal imaging showed cytoplasmic beta3-AR labeling in somata of submucous neurons and nerve varicosities. GW427353 had no direct postsynaptic actions but decreased fast synaptic input to submucous neurons. Tissue perfusion with GW427353 reduced nicotine-evoked neuronal spike frequency, an effect prevented by the beta3-AR antagonist SR-59230 and the SST2-receptor antagonist CYN154806 and mimicked by the SST2 receptor agonist octreotide. Adipocytes expressed adiponectin, beta3-AR, and SST. TH-positive fibers were in close proximity to adipocytes. Submucous
neurons expressed SST2 receptors. Human primary adipocytes released SST in response to GW427353 in a concentration-dependent manner, an effect abolished by SR-59230. CONCLUSIONS: Inhibitory action of GW427353 involves release of SST which stimulates inhibitory SST2 receptors on human submucous neurons. Adipocytes are a potential source for SST. beta3-AR activation may be a promising approach to reduce enteric neuron hyperexcitability. The action of GW427353 may be the neurophysiologic correlate of its beneficial effect in patients with irritable bowel syndrome.