

Highlighted Papers

Natriuretic Peptide-Induced Catecholamine Release From Cardiac Sympathetic Neurons

Cardiac sympathetic overstimulation is characteristic of advanced heart failure, which was recently found not to be improved by the administration of recombinant brain natriuretic peptide (BNP; nesiritide), despite the predicated beneficial effects of natriuretic peptides. It is possible that the lack of improvement was related to a proadrenergic effect of natriuretic peptides. The purpose of the present study was to search for novel means to prevent the proadrenergic effects of natriuretic peptides. The findings show that activation of neuronal H₃- and H₄-receptors inhibits the release of catecholamines elicited by BNP in cardiac synaptosomes and differentiated PC12 cells. Selective H₃- and H₄-receptor agonists each synergized with a protein kinase G (PKG) inhibitor and with a phosphodiesterase 3 (PDE3) activator in attenuating BNP-induced norepinephrine release from cardiac sympathetic nerve endings. This indicates that PKG inhibition and PDE3 stimulation are pivotal for the H₃- and H₄-receptor-mediated attenuation of BNP-induced catecholamine release. Because excessive catecholamine release is likely to offset the desirable effects of natriuretic peptides, these findings suggest a novel means to alleviate their adverse effects and to improve their therapeutic potential.

See article at *J Pharmacol Exp Ther* 2012, **343**:568-577.

GPR35 Antagonists Display High Species Ortholog Selectivity

GPR35 is a poorly characterized member of the rhodopsin-like class A subfamily of G protein-coupled receptors (GPCRs), which has attracted attention as a possible therapeutic target in conditions ranging from diabetes and cardiovascular disease to inflammation and pain. Substantial selectivity in potency of a number of GPR35 agonists has previously been demonstrated between human and rat orthologs of this G protein coupled receptor hindering its understanding. A further limitation in efforts to understand the function of GPR35 is that until recently, no antagonists had been described. This study investigated whether the difference in potency across species was also observed with the GPR35 antagonists methyl-5-[(*tert*-butylcarbamothioylhydrazinylidene)methyl]-1-(2,4-difluorophenyl)pyrazole-4-carboxylate (CID-2745687) and 2-hydroxy-4-[4-(5*Z*)-5-[(*E*)-2-methyl-3-phenylprop-2-enylidene]-4-oxo-2-sulfanylidene-1,3-thiazolidin-3-yl]butanoylamino)benzoic acid (ML-145). Both CID-2745687 and ML-145 competitively inhibited effects of two agonists, cromolyn disodium and zaprinast, at human GPR35. By contrast, neither ML-145 nor CID-2745687 was able to effectively antagonize effects of either zaprinast or cromolyn disodium in either rodent ortholog of GPR35. These results demonstrate that marked species selectivity of ligands at GPR35 is not restricted to agonists and that considerable care is required to select appropriate ligands to explore the function of GPR35 in nonhuman cells and tissue.

See article at *J Pharmacol Exp Ther* 2012, **343**:683-695.

Strontium Is a Biased Agonist of the Calcium-Sensing Receptor

The calcium-sensing receptor (CaSR)-specific allosteric modulator cinacalcet has revolutionized treatment of secondary hyperparathyroidism in patients with chronic kidney disease. However, its application is limited to patients with end-stage renal disease because of hypocalcemic side effects presumably caused by CaSR-mediated calcitonin secretion from thyroid parafollicular C-cells. These hypocalcemic side effects might be reduced by compounds that bias the signaling of CaSR leading to similar therapeutic effects as cinacalcet without stimulating calcitonin secretion. The present study used rat medullary thyroid carcinoma 6-23 cells as a model of thyroid parafollicular C-cells. Concentration-response experiments were conducted investigating the effects of two CaSR agonists (calcium and strontium) to activate different signaling entities. Interestingly, the potency of strontium-stimulated calcitonin secretion was elevated compared with calcium. The enhanced potency of strontium-mediated calcitonin secretion was caused by a different signaling pattern than that produced by calcium. The results suggest that calcitonin secretion can be affected by CaSR-stimulated signaling bias, which may be used to develop novel drugs for treatment of secondary hyperparathyroidism.

See article at *J Pharmacol Exp Ther* 2012, **343**:638-649.

Differential Effects of Selexipag and Prostacyclin Analogs in Rat Pulmonary Artery

ACT-333679[[4-[(5,6-diphenylpyrazin-2-yl)(isopropyl)amino]butoxy]acetic acid] is the main metabolite of the selective prostacyclin (PGI₂) receptor (IP receptor) agonist selexipag. The goal of this study was to determine the influence of IP receptor selectivity on vasorelaxant efficacy of ACT-333679 and the PGI₂ analog treprostinil in pulmonary artery under conditions associated with pulmonary arterial hypertension. Selexipag and ACT-333679 evoked full relaxation of pulmonary artery from control and monocrotaline-induced pulmonary arterial hypertensive (MCT-PAH) rats, and ACT-333679 relaxed normal pulmonary artery contracted with either endothelin-1 (ET-1) or phenylephrine. In contrast, treprostinil evoked weaker relaxation of control pulmonary artery and failed to induce relaxation of pulmonary artery from MCT-PAH rats. Treprostinil did not evoke relaxation of normal pulmonary artery contracted with either ET-1 or phenylephrine. ACT-333679 did not evoke direct contraction of rat pulmonary artery, whereas treprostinil evoked concentration-dependent contraction that was inhibited by an EP3 receptor antagonist. These data demonstrate that the relaxant efficacy of the selective IP receptor agonist selexipag and its metabolite ACT-333679 is not modified under conditions associated with pulmonary arterial hypertension, whereas relaxation to treprostinil may be reduced.

See article at *J Pharmacol Exp Ther* 2012, **343**:547-555.