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Human GPR43/FFAR2: identification of novel promising agonists

GPR43, or free fatty acid receptor (FFAR) 2, is a GPCR activated by short-chain fatty acids (SCFA) released from the gut microbiome. The receptor is highly expressed in neutrophils, and agonists are desired to treat inflammatory diseases. GPR43 couples to Gq and Gi proteins. Pertussis toxin decreased the potency of acetate in stimulating calcium transients, but did not affect the signal window. Thereby, calcium signals seem to be transmitted by Gq, however, may involve additional regulation by Gi. Following compound screening in a calcium assay, the specificity of hits was tested using control cells. Hits were confirmed using inositol phosphate (IP1) as a readout, which is like calcium regulated by Gq and phospholipase C. Seven GPR43 agonists were confirmed on native receptors in a calcium assay using human primary neutrophils. Five agonists were inactive at human GPR41 in a calcium assay with promiscuous Galpha15, and therefore highly selective. All novel agonists revealed much lower or no activities at mouse GPR43 when assessing calcium transients, whereas the pharmacology of SCFA was comparable between human and mouse GPR43. Hence, the putatively small orthosteric binding pocket for SCFA seems to be more conserved across species than the (supposedly allosteric) binding pocket/s of novel agonists. This work was supported by the Novartis Institutes for BioMedical Research (NIBR).