Collaboration Opportunity

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Antagonists of the G-protein Coupled Lactate Receptor GPR81

Project Partners

1) MPI for Heart and Lung Research, Department Pharmacology, Bad Nauheim, Prof. Dr. S. Offermanns
2) LDC GmbH, Dortmund

Project Aim

The primary aim of this project is to identify specific antagonists of the GPR81 receptor (HCA_1) with drug-like properties. GPR81, a previously deorphanized G-protein coupled receptor (GPCR), functions as the receptor for L-lactate. After binding to GPR81, L-lactate at physiological concentrations leads to the inhibition of lipolysis in adipocytes. Related receptors, GPR109A and GPR109B, show a high degree of homology to GPR81 and are expressed in various tissues, whereas GPR81 is predominantly expressed in adipocytes. This specific expression pattern turns GPR81 into a promising drug target. Surprisingly, synthetic agonists of GPR81 showed significant cardiovascular adverse effects whereas GPR81 antagonists have a clear application potential for metabolic disorders such as obesity.
Two series of GPR81 antagonists identified by High Throughput Screening (HTS) and hit validation have been progressed to chemical optimization, which produced even a third chemical series. The goal is to develop antagonists of GPR81 which demonstrate proof-of-concept in therapeutic animal models.

Status

GPR81 is a validated target: GPR81/LepR knock-out mice are leaner than wild type mice on hypercaloric diet; otherwise GPR81-/- mice show no adverse phenotype

- Primary assay developed (cellular CHO-based chAMPion/GPR81 assay)
- HTS conducted using LDC´s and HDC´s compound libraries (~440.000 compounds) as well as an available compound collection from AstraZeneca (~250.000 compounds)
- Primary hits confirmed, IC50 values determined, 2 antagonistic hit classes identified
- Assay cascade for hit validation established: GPR81 cAMP GloSensor assay, GPR81 cAMP HTRF assay, lipolysis assay using human preadipocytes, Ca^{2+} release assay, selectivity assay using GPR109A, proliferation assays
- Hit-to-lead optimization program started on two hit classes including medicinal chemistry (MedChem)
- Initial SAR of two hit classes elucidated, of which individual hits show dose-dependent activity in the above mentioned cellular assays although not yet in the lipolysis assay (hit-to-lead optimization ongoing)
- Based on the pharmacophores, a third hit class was identified and confirmed
- ADMET properties determined

Ongoing Work/Next Steps

- MedChem-based hit-to-lead (H2L) optimization
- Transfer of functional lipolysis assay with human preadipocytes from Lonza, measuring free fatty acids (FFA)
- PK/Tox profile for oral administration
- *In vivo* efficacy in preclinical animal model(s) → nomination of lead series and licensing activities

Scientific Background

In humans, the three major regulators for lipolysis are catecholamines, natriuretic peptides and insulin, from which insulin predominates as antilipolytic hormone, limiting the release of fatty acids. Besides insulin, several antilipolytic GPCRs have been described, which are negatively coupled to adenylate cyclase via inhibitory G-proteins. The three recently deorphanized GPCRs, GPR81, GPR109A and GPR109B, are characterized by a high degree of homology and form the new subgroup of hydroxy-carboxylic acid receptors (HCAs) within the large GPCR family, since their physiological endogenous ligands were all identified as hydroxyl-carboxylic acids: 3-hydroxy-butyrate was identified as the endogenous ligand of GPR109A, 3-hydroxy-octanoate as the ligand of GPR109B and 2-hydroxy-propanoate (L-lactate) as the ligand of GPR81, respectively. Activation of these HCAs by their ligands induces signaling to G_i proteins and inhibition of cAMP production. Depending on the metabolic state of the organism, the plasma concentrations of these endogenous metabolites vary to a considerable degree, resulting in the activation of the respective receptor and inhibition of lipolysis. Therefore, it is suggested that the receptors in an autocrine manner function as metabolic sensors for the fine tuning of the regulation of trigyceride storage in adipose tissue. There is convincing evidence for the involvement of GPR81 and lactate in the antilipolytic action of insulin.

The three GPCRs, GPR109A, GPR109B and GPR81, are expressed in adipocytes. Expression of GPR109A and B is additionally found in various immune cells, including epidermal Langerhans cells, which explains the well known side effects of niacin treatment, which is an agonist of GPR109A. In addition, GPR109A is expressed in the retinal pigment epithelium as well as in intestinal epithelium. Due to the restricted and specific expression in adipose tissue, GPR81 is a highly interesting obesity drug target.

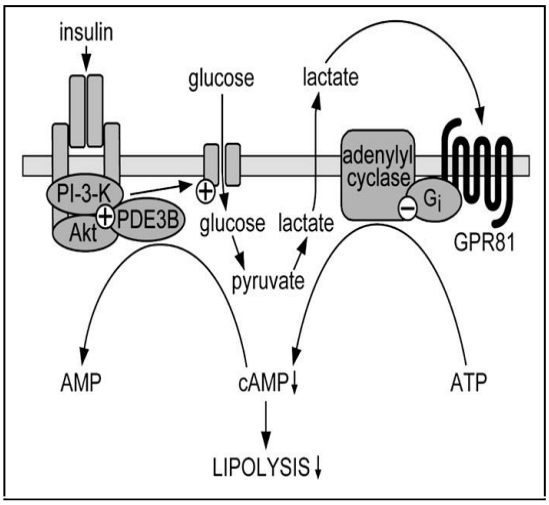

Figure 1. Antilipolysis by Insulin involves Lactate/GPR81
Model of the mechanism: Insulin-induced inhibition of adipocyte lipolysis via PDE3B-mediated cAMP degradation and lactate/GPR81-dependent inhibition of cAMP formation

Further Reading

Ahmed K. et al. (2010) An Autocrine Lactate Loop Mediates Insulin-Dependent Inhibition of Lipolysis through GPR81. Cell Metab. 11, 311-319.
Ahmed K. et al. (2009) GPR109A, GPR109B and GPR81, a Family of Hydroxy-carboxylic acid Receptors. Trends Pharmacol Sci. 30, 557-562.
Langin D. (2010) Adipose tissue lipolysis revisited (again!): lactate involvement in insulin antilipolytic action. Cell Metab. 11, 242-243.

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