# 298 GPR81 antagonist to treat Metabolic Diseases such as obesity

## Asset Overview

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| **Product Type** | Small molecule |
| **Indication** | Metabolic disease including obesity |
| **Current Stage** | Lead optimization |
| **Target(MoA)** | GPR81 (G-protein coupled lactate receptor) |
| **Brief Description** | G protein-coupled receptor 81 (GPR81), known as hydroxycarboxylic acid receptor 1 (HCA1), is expressed in adipocytes and mediates antilipolytic effects through inhibition of adenylyl cyclase. The primary endogenous agonist of GPR81 is lactic acid (and its conjugate base, lactate). Lactate is an important metabolic intermediate released by skeletal muscle and other organs including the adipose tissue, which converts glucose into lactate under the influence of insulin. Lactate is produced from glucose by adipose tissue and is involved in the antilipolytic effect of insulin, providing a new link between fat and carbohydrate metabolism. |
| **Organization** | Lead Discovery Center |

## Differentiation

□ **GPR81 is a validated target for the treatment of metabolic disorder**

- GPR81 is predominantly expressed in adipocytes unlike related receptors such as GPR109A and GPR 109B which show a high degree of homology to GPR 81. L-lactate at physiological concentration leads to the inhibition of lipolysis in adipocytes after binding to GPR81
- Using GPR81-deficient mice, they demonstrate that GPR81 is not involved in the regulation of lipolysis during intensive exercise. However, insulin-induced inhibition of lipolysis and insulin-induced decrease in adipocyte cAMP levels were strongly reduced in mice lacking GPR81
- Synthetic agonists of GPR81 showed significant cardiovascular adverse effect in animals
- However, GPR81 antagonists have a clear application toward metabolic disorders such as obesity. Also, GPR81/LepR knock-out mice are leaner than wild type mice on a hypercaloric diet

□ **2 antagonistic hit classes identified for GRP81 inhibition**

- Due to the restricted and specific expression in adipose tissue, GPR81 is a highly interesting obesity drug target
- HTS conducted using compound libraries (~440,000 compounds) as well as an available compound collection from AstraZeneca (~250,000 compounds). 2 antagonistic hit classes were identified based on IC50 values. Assay cascade for hit validation was established

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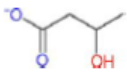
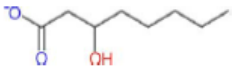
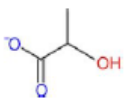
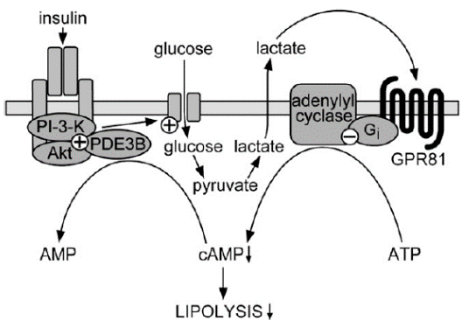
## Key Data

### EC50 values (mM) of acids acting on GPR109A, GPR109B and GPR81

| | Structure | GPR109A | GPR109B | GPR81 |
|---|---|---|---|---|
| 3-hydroxy-butyrate |  | 770 | >25,000 | Inactive |
| 3-hydroxy-octanoate |  | Inactive | 8 | Inactive |
| 2-hydroxy-propanoate (lactate) |  | Inactive | Inactive | 1500, 3000 |

EC50 values (mM) and structures of endogenous hydroxy-carboxylic acids acting on GPR109A, GPR109B and GPR81. EC50 values are determined by ligand-induced GTPgS binding.

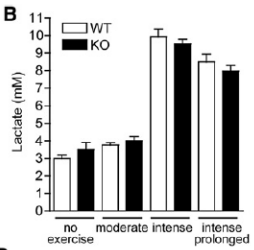
### Effect of GPR81 on Lipolysis during Intensive Exercise

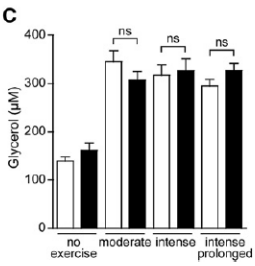


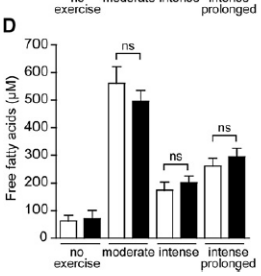

Model of the Mechanisms Underlying Insulin-Induced Inhibition of Adipocyte Lipolysis via PDE3B-Mediated cAMP Degradation and Lactate/GPR81-Dependent Inhibition of cAMP Formation

A

| exercise | speed (m/min) | duration (min) |
|---|---|---|
| moderate | 20 | 10 |
| intense | 21 | 2 |
| | 30 | 2 |
| | 40-45 | 1 |
| intense prolonged | 21 | 5 |
| | 30 | 2 |
| | 35 | 2 |
| | 40-42 | 1 |




(A) Speed and duration of the different treadmill exercise programs. (B–D) Lactate (B), glycerol (C), or free fatty acid plasma concentrations (D) were determined in wild-type (WT) or GPR81-deficient mice (KO) before (no exercise) and after the indicated treadmill exercise programs.

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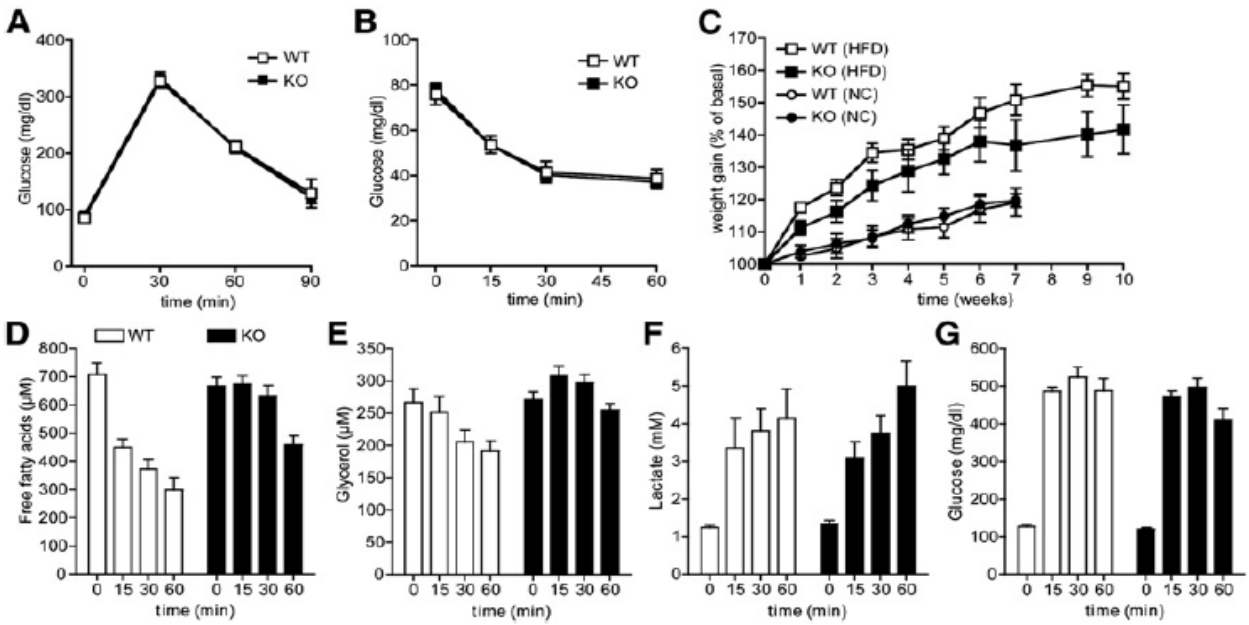
## Role of GPR81 in Metabolic Regulation




(A) Wild-type (WT) or GPR81-deficient mice (KO) were fasted overnight and injected i.p. with 3 mg/g glucose. Thereafter, plasma glucose levels were determined at the indicated time points. (B) Wild-type (WT) or GPR81-deficient mice (KO) were fasted overnight and injected i.p. with 0.75 mU/g insulin, and plasma glucose levels were determined at the indicated time points. (C) Wild-type (WT) or GPR81-deficient mice (KO) were fed a high-fat diet (HFD) or normal chow (NC). The gain in body weight was expressed as percentage of initial body weight. (D–G) Overnight fasted wild-type (WT) and GPR81-deficient mice (KO) were injected i.p. with 3 mg/g glucose, and plasma levels of free fatty acids (D), glycerol (E), lactate (F), and glucose (G) were determined at the indicated time points.

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## Intellectual Property

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|---|---|
| Patent No. | |
| Application Date | |
| Status | |
| Country | |

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