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# Endocrinization of FGF1 produces a neomorphic and potent insulin sensitizer

**Jae Myoung Suh**[1,†], **Johan W. Jonker**[3,†], **Maryam Ahmadian**[1], **Regina Goetz**[6], **Denise Lackey**[5], **Olivia Osborn**[5], **Zifeng Huang**[6], **Weilin Liu**[3], **Eiji Yoshihara**[1], **Theo van Dijk**[3], **Rick Havinga**[3], **Weiwei Fan**[1], **Yun-Qiang Yin**[1], **Ruth T. Yu**[1], **Christopher Liddle**[4], **Annette R. Atkins**[1], **Jerrold M. Olefsky**[5], **Moosa Mohammadi**[6], **Michael Downes**[1,*], and **Ronald M. Evans**[1,2,*]

[1]GeneExpression Laboratory, Salk Institute for Biological Studies, La Jolla, California, USA [2]Howard Hughes Medical Institute, Salk Institute for Biological Studies, La Jolla, California, USA [3]Center for Liver, Digestive and Metabolic Diseases, Departments of Pediatrics and Laboratory Medicine, University of Groningen, University Medical Center Groningen, Hanzeplein 1, 9713 GZ Groningen, The Netherlands [4]The Storr Liver Unit, Westmead Millennium Institute and University of Sydney, Westmead Hospital, Westmead, New South Wales 2145, Australia [5]Department of Medicine, Division of Endocrinology and Metabolism, University of California at San Diego, La Jolla, California 92093, USA [6]Department of Pharmacology, New York University School of Medicine, New York, New York 10016, USA

## Abstract

FGF1 is an autocrine/paracrine regulator whose binding to heparan sulfate proteoglycans effectively precludes its circulation [1,2]. Though known as a mitogenic factor, FGF1 knockout mice develop insulin resistance when stressed by a high fat diet, suggesting a potential role in nutrient homeostasis [3,4]. Here we show that parenteral delivery of a single dose of recombinant FGF1 (rFGF1) results in potent, insulin-dependent glucose lowering in diabetic mice that is dose-dependent, but does not lead to hypoglycemia. Chronic pharmacological rFGF1 treatment increases insulin-dependent glucose uptake in skeletal muscle and suppresses hepatic glucose production to achieve whole-body insulin sensitization. The sustained glucose lowering and insulin sensitization attributed to rFGF1 are not accompanied by the side effects of weight gain, liver steatosis and bone loss associated with current insulin sensitizing therapies. Furthermore, we demonstrate that the glucose lowering activity of FGF1 can be dissociated from its mitogenic



*Correspondence and requests for materials should be addressed to R.M.E. (evans@salk.edu) or M.D. (downes@salk.edu).
†These authors contributed equally to this work

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# FGF1 and FGF19 reverse diabetes by suppression of the hypothalamic–pituitary–adrenal axis

Rachel J. Perry[1,2,3], Sangwon Lee[2,4], Lie Ma[2,4], Dongyan Zhang[1], Joseph Schlessinger[2,4] & Gerald I. Shulman[1,2,3]

Fibroblast growth factor-1 (FGF1) and FGF19 have been shown to improve glucose metabolism in diabetic rodents, but how this occurs is unknown. Here to investigate the mechanism of action of these growth factors, we perform intracerebroventricular (ICV) injections of recombinant FGF1 or FGF19 in an awake rat model of type 1 diabetes (T1D) and measure rates of whole-body lipolysis, hepatic acetyl CoA content, pyruvate carboxylase activity and hepatic glucose production. We show that ICV injection of FGF19 or FGF1 leads to a ~60% reduction in hepatic glucose production, hepatic acetyl CoA content and whole-body lipolysis, which results from decreases in plasma ACTH and corticosterone concentrations. These effects are abrogated by an intra-arterial infusion of corticosterone. Taken together these studies identify suppression of the HPA axis and ensuing reductions in hepatic acetyl CoA content as a common mechanism responsible for mediating the acute, insulin-independent, glucose-lowering effects of FGF1 and FGF19 in rodents with poorly controlled T1D.

[1] Howard Hughes Medical Institute, Yale University School of Medicine, New Haven, Connecticut 06536-8012, USA. [2] Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut 06536-8012, USA. [3] Department of Cellular & Molecular Physiology, Yale University School of Medicine, New Haven, Connecticut 06536-8012, USA. [4] Department of Pharmacology, Yale University School of Medicine, New Haven, Connecticut, USA. Correspondence and requests for materials should be addressed to G.I.S. (email: gerald.shulman@yale.edu).

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# Autocrine FGF1 signaling promotes glucose uptake in adipocytes

Vera J. M. Nies[a,1], Dicky Struik[a,1], Sihao Liu[b], Weilin Liu[a], Janine K. Kruit[a], Michael Downes[b], Tim van Zutphen[a], Henkjan J. Verkade[a], Ronald M. Evans[b,2], and Johan W. Jonker[a,2]

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**Fibroblast growth factor 1 (FGF1) is an autocrine growth factor released from adipose tissue during over-nutrition or fasting to feeding transition. While local actions underlie the majority of FGF1's anti-diabetic functions, the molecular mechanisms downstream of adipose FGF receptor signaling are unclear. We investigated the effects of FGF1 on glucose uptake and its underlying mechanism in murine 3T3-L1 adipocytes and in ex vivo adipose explants from mice. FGF1 increased glucose uptake in 3T3-L1 adipocytes and epididymal WAT (eWAT) and inguinal WAT (iWAT). Conversely, glucose uptake was reduced in eWAT and iWAT of FGF1 knockout mice. We show that FGF1 acutely increased adipocyte glucose uptake via activation of the insulin-sensitive glucose transporter GLUT4, involving dynamic crosstalk between the MEK1/2 and Akt signaling proteins. Prolonged exposure to FGF1 stimulated adipocyte glucose uptake by MEK1/2-dependent transcription of the basal glucose transporter GLUT1. We have thus identified an alternative pathway to stimulate glucose uptake in adipocytes, independent from insulin, which could open new avenues for treating patients with type 2 diabetes.**

FGF1 | glucose metabolism | adipocytes | insulin | fibroblast growth factors

## Significance

Fibroblast growth factor 1 (FGF1) is released by white adipose tissue (WAT) in response to feeding or over-nutrition and plays a role in WAT remodeling and metabolic homeostasis. In addition, pharmacological administration of recombinant FGF1 improves glucose balance in diabetic mouse models by activating signaling in WAT. Autocrine effects on adipocyte function may thus play a role in the metabolic effects of FGF1. Here, we investigated the direct effects of FGF1 on adipocyte function. Our work establishes an FGF1-dependent autocrine pathway, independent of insulin, that controls glucose uptake in adipocytes.

Excessive nutrient intake and a sedentary lifestyle have resulted in a pandemic of obesity and related chronic metabolic diseases, including type 2 diabetes (T2D), nonalcoholic fatty liver disease (NAFLD), cardiovascular disease (CVD), and certain types of cancer (1). A critical player in the pathophysiology of these obesity-related diseases is the nuclear receptor peroxisome proliferator-activated receptor γ (PPARγ), a lipid sensor and master regulator of adipocyte differentiation and fat storage, and the molecular target of the thiazolidinedione (TZD) class of insulin-sensitizing drugs (2, 3).

We have previously identified fibroblast growth factor 1 (FGF1) as a downstream target of PPARγ and demonstrated that this growth factor is essential for white adipose tissue (WAT) expansion and glycemic control during energy excess (4). Activation of PPARγ by high-fat diet feeding or TZD treatment induces the local release of FGF1 in WAT (4), where it is thought to function as an autocrine or paracrine factor (5, 6). Mice deficient in FGF1 become severely insulin resistant upon high-fat diet feeding and display aberrant WAT architecture characterized by increased inflammation and fibrosis (4). In subsequent studies, we also demonstrated that pharmacological treatment of diabetic mouse models with recombinant FGF1 has potent glucose-lowering, insulin-sensitizing, and anti-steatotic effects. The effects of systemically administered FGF1 on insulin sensitivity and blood glucose levels are at least partly dependent on FGFR1 signaling in the WAT (7). However, besides adipose, FGF1 has also been shown to regulate glucose homeostasis via interactions with other organs, including the hypothalamus and pancreas (8–11).

In the current study, we investigated the direct effect of FGF1 on mature adipocyte function independent of interactions with other organs. To this end, we used ex vivo and in vitro adipose models. We show that FGF1 stimulates glucose uptake in eWAT and iWAT in an autocrine manner. Mechanistically, we show that FGF1 has distinct acute and prolonged effects on adipocyte glucose uptake. Acute FGF1-stimulated adipocyte glucose uptake is dependent on MEK1/2 and Akt crosstalk and activation of GLUT4. Chronic FGF1-stimulated adipocyte glucose uptake is mediated through MEK1/2-dependent transcriptional up-regulation of GLUT1. Together, we have identified an FGF1-dependent autocrine pathway that is distinct from insulin action to stimulate glucose uptake in adipocytes.

## Results

**FGF1 Stimulates Glucose Uptake in Adipose Tissue.** Glucose uptake in the adipose tissue contributes to systemic glucose homeostasis (12–14). We found that FGF1

Author affiliations: [a]Laboratory of Pediatrics, Section of Molecular Metabolism and Nutrition, University of Groningen, University Medical Center Groningen, 9713 GZ Groningen, The Netherlands; and [b]Gene Expression Laboratory, Salk Institute for Biological Studies, La Jolla, CA 92037

Author contributions: V.J.M.N., D.S., S.L., T.v.Z., and J.W.J. designed research; V.J.M.N., D.S., S.L., and J.K.K. performed research; V.J.M.N., D.S., S.L., W.L., J.K.K., M.D., H.J.V., R.M.E., and J.W.J. analyzed data; and V.J.M.N., D.S., and J.W.J. wrote the paper.

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The authors declare no competing interest.



[1]V.J.M.N. and D.S. contributed equally to this work.

[2]To whom correspondence may be addressed. Email: j.w.jonker@umcg.nl or evans@salk.edu.

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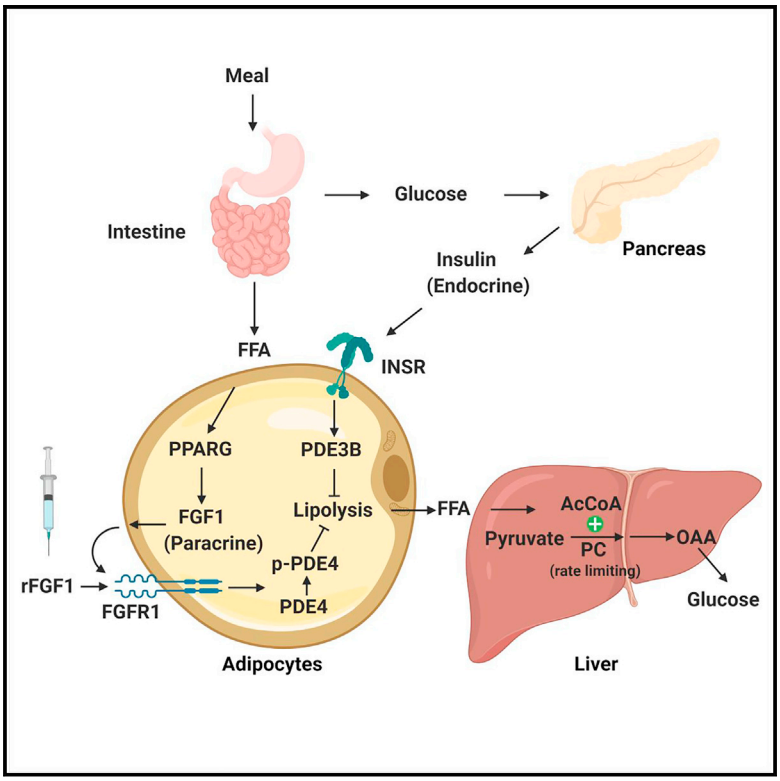
Article

# FGF1 and insulin control lipolysis by convergent pathways

## Graphical abstract




## Highlights

- FGF1-FGFR1 signaling suppresses adipose lipolysis to curb hepatic glucose production
- FGF1 suppresses lipolysis by inhibiting cAMP/PKA axis via PDE4D-S44 phosphorylation
- Overexpression of PDE4D in the adipose tissue of diabetic mice corrects hyperglycemia
- FGF1/PDE4D antilipolytic pathway is responsive to fed/fast states

## Authors

Gencer Sancar, Sihao Liu, Emanuel Gasser, ..., Johan W. Jonker, Michael Downes, Ronald M. Evans

## Correspondence

downes@salk.edu (M.D.), evans@salk.edu (R.M.E.)

## In brief

Sancar et al. demonstrate that FGF1 acutely lowers hepatic glucose production by suppressing adipose lipolysis. While insulin suppresses lipolysis via adipose PDE3B, FGF1 is dependent on PDE4D, allowing the FGF1/PDE4D pathway to remain functional under insulin resistance. This paracrine FGF1/PDE4D pathway is responsive to feeding in the adipose tissue.

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# FGF1 and insulin control lipolysis by convergent pathways

Gencer Sancar,[1] Sihao Liu,[1] Emanuel Gasser,[1] Jacqueline G. Alvarez,[1] Christopher Moutos,[1] Kyeongkyu Kim,[1] Tim van Zutphen,[3] Yuhao Wang,[1] Timothy F. Huddy,[1] Brittany Ross,[1] Yang Dai,[1] David Zepeda,[1] Brett Collins,[1] Emma Tilley,[1] Matthew J. Kolar,[2] Ruth T. Yu,[1] Annette R. Atkins,[1] Theo H. van Dijk,[3] Alan Saghatelian,[2] Johan W. Jonker,[3] Michael Downes,[1,*] and Ronald M. Evans[1,4,*]

[1]Gene Expression Laboratory, Salk Institute for Biological Studies, La Jolla, CA 92037, USA

[2]Clayton Foundation Laboratories for Peptide Biology, Salk Institute for Biological Studies, La Jolla, CA 92037, USA

[3]Section of Molecular Metabolism and Nutrition, Department of Pediatrics, University of Groningen, University Medical Center Groningen, 9713 GZ, Groningen, the Netherlands

[4]Lead contact

*Correspondence: downes@salk.edu (M.D.), evans@salk.edu (R.M.E.)

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## SUMMARY

Inexorable increases in insulin resistance, lipolysis, and hepatic glucose production (HGP) are hallmarks of type 2 diabetes. Previously, we showed that peripheral delivery of exogenous fibroblast growth factor 1 (FGF1) has robust anti-diabetic effects mediated by the adipose FGF receptor (FGFR) 1. However, its mechanism of action is not known. Here, we report that FGF1 acutely lowers HGP by suppressing adipose lipolysis. On a molecular level, FGF1 inhibits the cAMP-protein kinase A axis by activating phosphodiesterase 4D (PDE4D), which separates it mechanistically from the inhibitory actions of insulin via PDE3B. We identify Ser44 as an FGF1-induced regulatory phosphorylation site in PDE4D that is modulated by the feed-fast cycle. These findings establish the FGF1/PDE4 pathway as an alternate regulator of the adipose-HGP axis and identify FGF1 as an unrecognized regulator of fatty acid homeostasis.

## INTRODUCTION

Chronic hyperglycemia and dyslipidemia are hallmarks of type 2 diabetes mellitus (T2DM) attributed to the failure of insulin to appropriately suppress hepatic glucose production and adipose lipolysis. Moreover, unregulated lipolysis leads to the aberrant accumulation of free fatty acids (FFAs) in peripheral metabolic tissues including liver, muscle, and pancreatic islets, further exacerbating disease severity (Saponaro et al., 2015; Sears and Perry, 2015). Physiologically, adipose lipolysis is regulated, in part, by opposing hormonal stimuli that control cAMP levels and protein kinase A (PKA) activity (Bartness et al., 2014; Duncan et al., 2007). Pro-lipolytic hormones (e.g., glucagon, growth hormone, thyroid hormone, cortisol, catecholamines) elevate cellular cAMP levels to drive PKA phosphorylation of key lipolytic proteins including perilipin and hormone-sensitive lipase (HSL). Conversely, insulin discovered 100 years ago remains the only known anti-lipolytic hormone, acting via phosphodiesterase 3B (PDE3B) to suppress cAMP levels and inhibit PKA activity (Kitamura et al., 1999; Strålfors and Honnor, 1989; Choi et al., 2006). Phosphodiesterases (PDEs) catalyze the conversion of cAMP to AMP. To date, 11 PDE families (PDE1-PDE11), each encompassing multiple isoforms, have been described (Azevedo et al., 2014). In adipose tissue in particular, different PDE4 isoforms have been implicated in the regulation of the cAMP/PKA pathway; however, their contributions to lipolysis are not known (Baeza-Raja et al., 2016; Grønning et al., 2006; Zhang et al., 2009). Notably, half of the PDE activity in adipocytes is attributed to PDE4A-D, where the isoform-specific N-terminal domains regulate protein-protein interactions and subcellular localizations (Houslay and Adams, 2003; Choi et al., 2006). Consistent with this, PDE4 inhibitors enhance lipolysis, particularly when PDE3 activity is inhibited (DiPilato et al., 2015; Grønning et al., 2006; Kraynik et al., 2013; Snyder et al., 2005). Mice deficient in PDE4A, PDE4B, and PDE4D genes were previously generated (Jin and Conti, 2002; Jin et al., 2005; Jin et al., 1999). Loss of PDE4A and PDE4B in adipocytes led to increased cAMP levels without affecting lipolysis (Grønning et al., 2006; Zhang et al., 2009). In contrast, adipocyte PDE4D expression is induced by insulin and synthetic catecholamines, and lower PDE4D levels are associated with increased β-adrenergic signaling, implicating a potential role in lipolysis (Jang et al., 2020; Oknianska et al., 2007).

Fibroblast growth factor 1 (FGF1) has an established role in adaptive adipose remodeling (Jonker et al., 2012; Wang et al., 2020). Mice lacking FGF1 develop a more aggressive diabetic phenotype in response to a dietary challenge (high-fat diet, HFD) that is, in part, attributed to a failure to appropriately remodel adipose tissue. FGF1 expression in adipose tissue is controlled by PPARγ and is robustly induced in the fed state

# GLUCOSTATIC MECHANISM OF REGULATION OF FOOD INTAKE*

Jean Mayer, Ph.D., D.Sc.

BOSTON

The regulation of energy intake is fundamental to all homeostatic mechanisms. Yet this basic process has received less attention than many of the physiologic regulations that it makes possible.

Before this century, three theories were advanced to account for the phenomenon of hunger. The theories of peripheral origin (Haller, Erasmus, Darwin, Johannes Müller and Weber) held that the taking of food resulted from the stimulation either of all afferent nerves by some change in the tissues or of a strictly local group of sensory nerves, mainly in the stomach. The theory of central origin (Magendie, Tidewald and Milne-Edwards) postulated that a hunger center was sensitive to a starvation state of the blood. The theories of general sensation (Roux and Michael Foster) considered that the hunger center of the blood was stimulated not only by the hunger state of the blood but also indirectly by afferent impulses from all organs of the body.

After Cannon and Washburn, as well as Carlson, had shown that epigastric sensations of "hunger pain" coincided with waves of contractions of the empty stomach, Carlson[1] suggested that hypoglycemia, mediated by its effect on the stomach, might be responsible for inducing these hunger sensations. Although hunger pangs are found in most persons, the idea that the sensations elicited by stomach contractions due to hypo-

Scott and his collaborators[4] were unable to correlate spontaneous fluctuations of blood sugar levels with a desire for food. The existence of diabetic hyperphagia and of the phenomenon of hunger diabetes also presented seemingly insurmountable difficulties. Even the increase in spontaneous intake due to insulin-induced hypoglycemia was held by some authors to be of no general significance because of the abnormal "unphysiologic" circumstances in which the organism was placed.[5]

The demonstration by Hetherington and Ranson[6] that destruction of parts of the medioventral nuclei of the hypothalamus leads to obesity and the work of Anand and Brobeck[7] showing that more lateral lesions cause anorexia reopened the problem of the nature of the physiologic mechanism of the regulation of food intake.

Experimental work on rats, mice, dogs and human subjects culminated in the proposal of a "glucostatic mechanism" of regulation of food intake.[8-10] The initial reasoning was as follows: the regulation of food intake proceeds by relatively frequent partaking of food (meals). It appears improbable that hypothalamic centers are sensitive to decrease of the body content in fat or protein — during the short interval between meals, this decrease is proportionally very small. On the other