GDF15 Restricts Energy Intake on a Ketogenic Diet in Mice

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# Abstract

# Introduction

Ketogenic or low carbohydrate diets, often accompanied by an increase in dietary fat are increasingly common in the population with 16% of Americans reporting that they are on a carbohydrate restricted diet (1). Several randomized controlled trials have demonstrated weight loss, improved glycemic control, and reduced energy intake (reviewed in 2–4). For those individuals who lose weight on a LCHF diet, there is broad agreement that much of this effect is due to energy restriction with either modest or insignificant changes in energy expenditure (5,6). A recent meta-analysis showed decreased hunger and increased satiety on LCHF diets, though the hormonal mediators of this increased satiation remain unclear (7).

GDF15 is a hormone and emerging drug target that signals through GFRAL receptors in the hindbrain to reduce food intake. In humans, elevations of this hormone are associated with pregnancy-related nausea and cancer-associated cachexia (8–11). Elevations in GDF15 suppress appetite in a GFRAL-dependent manner. In terms of specific macronutrients, GDF15 causes a reduction in lipid consumption, and not other macronutrients (12). GDF15 is generated in many tissues in response to a variety of stressors but the integrated stress response has emerged as an important pathway controlling GDF15 production (13,14). Prior studies have implicated the hepatic integrated stress response to ketogenic diets (13,15,16). In this study we investigate the role of GDF15 in moderating energy intake, body composition and insulin sensitivity on a ketogenic diet.

# Methods

# Results

GDF15 Is Induced on Mice Fed a Ketogenic Diet

Induction of Hepatic GDF15 by the Integrated Stress Response

Ablation of GDF15 Results in Weight Gain and Increased Energy Intake on a Ketogenic Diet

# Discussion

In this study, the observed increases in GDF15 are relatively modest, but similar increases in GDF15 in humans are associated with pregnancy-related outcomes such as pre-eclampsia, nausea, gestational diabetes and miscarriage (8,17–19). This is also the approximate magnitude of exercise-associated elevations in GDF15 (20–24)

There are mixed data on the effects of hypercaloric diets in *Gdf15* or *Gfral* knockout mice with some papers showing hyperphagia and weight gain (25–28), but several others showing no effect (12,29,30) potentially representing strain, timing or background differences. As such, it is plausible that GDF15 is only physiologically relevant when elevated, but when signaling is absent (especially from birth) it is either dispensable or made to seem so by other adaptations. It is also plausible that other hormones which affect LCHF-dependent feeding changes may partially or completely compensate in the absence of GDF15.

# Author Contributions

# Acknowledgements

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# Figure/Table Legends