Metabolic Regulation by Fibroblast Growth Factor 21

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Fibroblast growth factor 21 (FGF21) is a secreted hormone that can beneficially regulate glucose and lipid homeostasis. Through a reverse endocrinology approach, we uncovered that FGF21 expression is transcriptionally regulated by the peroxisome proliferator activated-receptor alpha (PPARa) in liver. PPARa is a member of the nuclear hormone receptor superfamily that is physiologically activated by increased fatty acid mobilization to liver during fasting, and regulates the genetic program whereby lipids are converted to ketone bodies through a process known as ketogenesis. Here, I show the effects of FGF21 as a fasting hormone that is expressed in liver and contributes to the regulation of adipose tissue and hepatic ketogenesis during the fasted state. Using in vitro and in vivo methods to investigate the effects of FGF21, a model whereby FGF21 stimulates lipolysis in adipose tissue was generated. Intriguingly, using our FGF21 transgenic mice, I observed the expression of many genes involved in lipogenesis was highly induced in adipose tissue in an FGF21-dependent manner. Moreover, many of these lipogenic genes were found to be down-regulated in adipose of the FGF21 knockout mouse. The inhibition of lipogenic genes in adipose tissue was associated with increased SUMOylation of PPARg protein in this tissue. Using a feeding-fasting paradigm, I found that FGF21 expression in the liver and adipose tissue was rhythmic, peaking in liver prior to feeding and peaking in the adipose after feeding. Furthermore, the induction of FGF21 by PPARg ligands suggested a unique function for this protein in adipose, independent from its role in the fasted state. To assess the contribution of FGF21 to the anti-diabetic properties of PPARg agonists (ie. thiazolidinediones), diet-induced obese wild type and Fgf21-/- mice were treated with the TZD rosiglitazone. Rosiglitazone produced a significant increase in adipose FGF21 expression, but decreased hepatic FGF21 mRNA and circulating FGF21 protein. These data suggest that FGF21 functions as an autocrine factor within adipose tissue. Moreover, the therapeutic effects of rosiglitazone as an insulin sensitizer were lost in the Fgf21-/- mouse, as assessed by glucose and insulin tolerance tests. Several other effects of rosiglitazone were lost in the Fgf21-/- mice, including increased adipose mass, edema, and PPARg target gene expression in the adipose. These data indicated that PPARg can control the expression of FGF21, which functions as a feed-forward mechanism to stimulate PPARg target genes and PPARg dependent physiology. Since PPARg can be modified by SUMO on two different sites on the protein, in vitro experiments were performed to show that PPARg is SUMOylated at Lysine-107, a previously identified negative regulator of its transcriptional activity. Importantly, I found that treatment of Fgf21-/- adipocytes with FGF21 reduced the amount of SUMOylated PPARg, thereby allowing it to be it an active state. Collectively, these data reveal that FGF21 has two independent roles in regulating metabolism in vivo: as a hepatic endocrine hormone that is induced during the fasting response through PPARa, and as an adipose autocrine/paracrine factor that is induced in a feed-forward loop to stimulate PPARg activity.