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FGF21 and the Second Coming of PPARγ

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Abstract

Peptide hormone fibroblast growth factor-21 (FGF21) has insulin-mimetic properties. Dutchak et al. now suggest that FGF21 also acts in an autocrine fashion in adipocytes and is required to mediate effects of the PPARγ agonist class of antidiabetic drugs. Does this new property improve FGF21's fledgling clinical prospects or endorse a clinical resuscitation of PPARγ agonists?

The search for peptides with insulin-like metabolic properties harks back to the unmet need for insulin sensitizers to treat diabetes and obesity. Among fibroblast growth factors (FGFs), FGF21 is conspicuous by its failure to bind heparin, a feature that effectively turns it from paracrine growth factor into bona fide hormone. A study in this issue of *Cell* by Dutchak et al. (2012) shows that FGF21 sensitizes adipocytes to the actions of peroxisome proliferator-activated receptor γ (PPARγ) and is required to achieve the full effects of PPARγ ligands of the thiazolidinedione (TZD) class of antidiabetic drugs. TZDs function as PPARγ agonists and until recently were the second-most prescribed group of oral insulin sensitizers. In an unexpected twist, Dutchak et al. link the mechanism of FGF21 sensitization to PPARγ sumoylation, raising the question of whether the latter—or germane posttranslational modifications—can be leveraged to more effectively employ TZDs for the treatment of metabolic diseases.

Circulating FGF21 is hepatic in origin and shows limited circadian variations, except under prolonged fasting (Badman et al., 2007). In humans, plasma FGF21 levels vary considerably among individuals, are elevated in insulin-resistant diabetics, and are decreased by administration of TZDs. However, pharmacological administration of FGF21 results in multiple metabolic benefits: it lowers glycemia by promoting peripheral utilization and decreasing hepatic production of glucose; it lowers triglycerides and total as well as LDL cholesterol; it decreases liver fat and body weight; and it promotes β cell growth (Wente et al., 2006). It should be pointed out that the pharmacology and the physiology of FGF21 are somewhat discordant, and that not all pharmacological effects can be ascribed to the endogenous peptide.

The broad-based metabolic effects of FGF21 on glucose and lipid metabolism likely reflect its dual regulation by PPARα in liver (Inagaki et al., 2007) and by PPARγ in adipocytes (Muise et al., 2008; Wang et al., 2008). The study by Dutchak et al. provides insight into this dual regulation by showing that liver- but not adipocyte-derived FGF21 is stimulated by PPARα ligands. Conversely, TZDs—or feeding—promote FGF21 production in adipocytes but not in liver, effectively establishing a closed loop in which adipocyte-derived FGF21 acts in an autocrine fashion to amplify the effects of PPARγ activation without changes to systemic FGF21 levels (Figure 1). The regulation of FGF21 in the fed state raises an

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interesting physiological question, as FGF21 has thus far been considered a “fasting” or “starvation” signal. Why would the same hormone be induced by fasting in one organ and by feeding in another? One potential explanation is that the autocrine function of FGF21 in adipocytes has evolved to buffer this cell type against drops in liver-derived FGF21, suggesting an “adipostat”-like role for FGF21. For example, as proposed by the authors, FGF21 might be involved in regulating futile energy cycling by way of the glycerol/fatty acid cycle (Reshef et al., 2003).

A striking aspect of Dutchak et al. is the impaired response to TZDs in mice lacking FGF21. However, we should focus on the fact that TZDs retain some therapeutic properties in FGF21 knockout mice, such as the ability to lower plasma insulin and triglyceride levels, as well as hepatic fat—even as the detrimental effects of these drugs on body weight and fluid balance are lost. This finding suggests that the detrimental effects require an intact TZD-FGF21 autocrine loop (Figure 1). This cannot be easily reconciled with a strictly autocrine mechanism, in that the effects of TZDs on fluid balance are thought to arise as a consequence of PPARγ activation in tissues other than adipose, but the boundaries between cell-autonomous and -nonautonomous functions of PPARγ are necessarily blurred. On balance, the therapeutic profile of TZDs in FGF21 knockout mice suggests that the key to avoiding the dreaded side effects of these compounds is to settle for lower metabolic benefits.

A more enigmatic aspect of Dutchak et al. is the proposed association of PPARγ sumoylation with TZD action. In macrophages, TZDs induce PPARγ Lys395 sumoylation to repress inflammatory genes, and this modification has been linked to the beneficial anti-inflammatory actions of TZDs (Pascual et al., 2005). Dutchak et al. show that in adipose tissue, TZDs have the opposite effect to decrease PPARγ Lys107 sumoylation, and that this effect is lost in FGF21 knockout mice. The mechanism of the rise of PPARγ Lys107 sumoylation in FGF21-deficient fat cells and the apparent paradox of the differential effects of TZDs on PPARγ sumoylation on different sites and different cell types deserve further investigation. Among the questions that will have to be addressed are whether these modifications are tissue-specific, and whether they are interdependent. In addition, much remains to be discovered with regard to the integration of PPARγ sumoylation on different sites with other posttranslational modifications, especially phosphorylation (Choi et al., 2010).

But the elephant in the room is whether any answer to these questions can change the pharmaceutical industry’s gun-shy stance in this area, what with growing regulatory concerns and assorted liabilities left in the wake of current TZDs. Ideally, one would want to design a PPARγ ligand endowed with TZDs’ metabolic effects and shorn of its cardiovascular, oncogenic, and bone loss comorbidities. The question raised by Dutchak et al. in this regard is whether acting on PPARγ’s posttranslational modification might provide an alternative approach to reach that goal.

Finally, do the present findings affect the prospects of clinical development of FGF21 and related biologicals? Probably not, for several reasons: first, the broad metabolic benefits of FGF21 make it uniquely attractive; second, none of the reported liabilities of TZDs have thus far been reported in the FGF21 clinical trial literature; and third, the effects of *endogenous* FGF21 to mediate the actions of TZDs don’t necessarily portend its ability to do so when administered pharmacologically, as there appears to be a dichotomy between the effects of the endogenous peptide and pharmacological administration of the recombinant peptide. Even so, further studies of this fascinating class of hormones are likely to reveal aspects of integrated metabolism that can be used to develop new treatments for diabetes and obesity.

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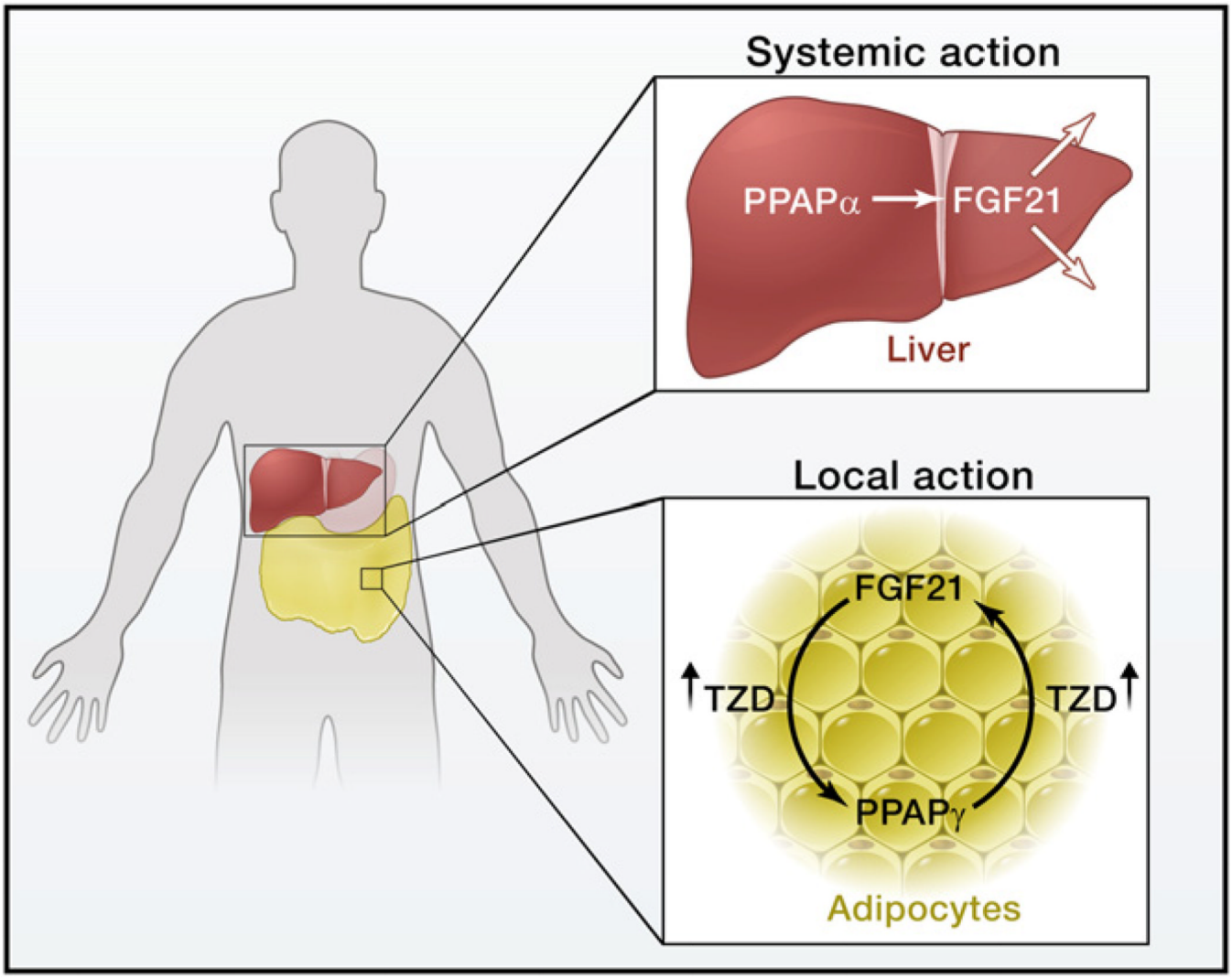

Figure 1. Representative Diagram of the Proposed Mechanism of FGF21 Action

Liver is the primary source of circulating FGF21, and hepatic synthesis is driven by PPARα activation. In addition, adipocytes are a secondary source of FGF21. But unlike hepatocytes, adipocytes make FGF21 in response to PPARγ agonists (TZDs) or feeding. Plasma levels of FGF21 don't change significantly following PPARγ activation, indicating that adipocyte-derived FGF21 acts locally. Its main role appears to be to potentiate the effects of PPARγ activation on adipocyte differentiation and gene expression. Nonetheless, systemic actions of PPARγ agonists are also impaired by the loss of FGF21.