FGF21 as a mediator of adaptive responses to stress and metabolic benefits of anti-diabetic drugs

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Abstract

Most hormones secreted from specific organs of the body in response to diverse stimuli contribute to the homeostasis of the whole organism. Fibroblast growth factor 21 (FGF21), a hormone induced by a variety of environmental or metabolic stimuli, plays a crucial role in the adaptive response to these stressful conditions. In addition to its role as a stress hormone, FGF21 appears to function as a mediator of the therapeutic effects of currently available drugs and those under development for treatment of metabolic diseases. In this review, we highlight molecular mechanisms and the functional importance of FGF21 induction in response to diverse stress conditions such as changes of nutritional status, cold exposure, and exercise. In addition, we describe recent findings regarding the role of FGF21 in the pathogenesis and treatment of diabetes associated with obesity, liver diseases, pancreatitis, muscle atrophy, atherosclerosis, cardiac hypertrophy, and diabetic nephropathy. Finally, we discuss the current understanding of the actions of FGF21 as a crucial regulator mediating beneficial metabolic effects of therapeutic agents such as metformin, glucagon/glucagon-like peptide 1 analogues, thiazolidinedione, sirtuin 1 activators, and lipoic acid.

Key Words
- FGF21
- stress
- adaptation
- metabolic disease
- energy metabolism

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Introduction

All known organisms have the capability to maintain homeostasis in response to environmental challenges. The ability to modify gene expression is a fundamental organismal mechanism of adaptation to environmental stimuli. In particular, hormones secreted from specific organs are important mediators of these adaptive responses through autocrine, paracrine, and endocrine actions. For example, insulin and glucagon are well-known adaptive hormones that control whole-body glucose balance in response to changes in nutritional status. Emerging evidence has suggested that fibroblast growth factor 21 (FGF21) could also be an endocrine hormone contributing to the metabolic homeostasis. The FGF21 gene was cloned as the 21st member of the FGF family by Dr Nobuyuki Itoh's group in 2000 (Nishimura *et al.* 2000), and its biological function was first identified as a potent enhancer of glucose uptake by Dr Alexei Kharitonenkov's group at Lilly Research Laboratories in 2005 (Kharitonenkov *et al.* 2005). After this discovery, FGF21 has gained considerable attention as a key regulator in the maintenance of energy homeostasis and as a promising therapeutic molecule for the treatment of obesity and type 2 diabetes (T2D).

Numerous studies have suggested that FGF21 plays a crucial role in the control of glucose and lipid energy balance in response to changes of nutritional status, such

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as starvation and feeding (Badman *et al*. 2007, Inagaki *et al*. 2007, Coskun *et al*. 2008, Potthoff *et al*. 2009). FGF21 is also important in the maintenance of body temperature by enhancing thermogenesis in response to cold exposure (Fisher *et al*. 2012, Lee *et al*. 2014*a*). In addition, FGF21 participates in the pathogenesis and treatment of various diseases such as diabetes associated with obesity, liver diseases, muscle atrophy, cardiovascular diseases, and kidney injury. Intriguingly, FGF21 can mediate the therapeutic benefits of several anti-diabetic compounds such as metformin, glucagon/glucagon-like peptide 1 (GLP1) analogues, thiazolidinedione (TZD), and sirtuin 1 (Sirt1) activators. Here, we highlight recent insights regarding the role of FGF21 as an adaptive hormone in response to various physiological or pathological conditions and as a mediator of the beneficial metabolic effects of several therapeutic agents (Fig. 1).

The role of stress-induced FGF21 in physiological conditions

FGF21 and nutritional status

FGF21 expression is regulated by nutritional status, and changes in the FGF21 level are important for adaption to changes of the nutritional balance such as deprivation or oversupply of macronutrients and changes of amino acid composition (Kim & Lee 2014). Alteration of FGF21 expression in response to nutritional alteration was first reported in 2007 (Badman *et al*. 2007, Inagaki *et al*. 2007). In starved mice, FGF21 is induced in the liver, contributing to metabolic adaptation to the fasting state by enhancing ketogenesis and β-oxidation in the liver. An increase of serum FGF21 level after fasting has been also observed in healthy human individuals (Galman *et al*. 2008). Fasting-induced hepatic FGF21 expression is mediated by the peroxisome proliferator-activated receptor alpha (PPARα; Badman *et al*. 2007, Inagaki *et al*. 2007), CREBH (Lee *et al*. 2011, Kim *et al*. 2014*a*), and Sirt1 (Li *et al*. 2014). Increased FGF21 also plays an important role in the regulation of fasting glucose levels by enhancing gluconeogenesis via upregulation of the hepatic PPARγ coactivator 1 alpha (PGC1α; Potthoff *et al*. 2009). Indeed, a recent study has shown that FGF21, produced in the fasted liver, enters into the brain and activates hypothalamic–pituitary–adrenal axis, leading to the enhancement of hepatic PGC1α expression and gluconeogenesis (Liang *et al*. 2014). These results suggest that FGF21 coordinates an adaptive response to fasting via liver–brain axis.

In addition to its role in fasting, FGF21 has been reported to enhance insulin-stimulated glucose uptake under acute refeeding conditions (Markan *et al*. 2014). The serum FGF21 level was increased during the early stage of refeeding in mice, when the insulin level was also elevated. Importantly, liver-specific *Fgf21* knockout ($Fgf21^{\Delta hep}$) mice exhibited reduced serum FGF21 levels in both fasting and early refeeding and displayed aggravation of fasting-induced glucose intolerance, whereas these findings were not observed in adipose tissue-specific *Fgf21* knockout ($Fgf21^{\Delta Ad}$) mice (Markan *et al*. 2014). These results suggest that the liver, but not adipose tissue, is a primary organ producing FGF21 during fasting and acute refeeding and that FGF21 acts as an insulin sensitizer to enhance insulin-stimulated glucose uptake during the early refeeding period. In addition to complete nutrient deprivation, a 50% food restriction causing malnutrition has been reported to increase serum FGF21 levels in mice (Kubicky *et al*. 2012). *Fgf21* knockout ($Fgf21^{-/-}$) mice were resistant to malnutrition-induced reduction of bone growth (Kubicky *et al*. 2012), suggesting that FGF21 is an important regulator of skeletal homeostasis as well as liver and adipose tissue. In contrast to malnutrition, caloric restriction without malnutrition did not result in FGF21 induction in mouse or human subjects (Zhang *et al*. 2012, Kim *et al*. 2013*a*, Lips *et al*. 2014). Moreover, caloric restriction-induced metabolic changes were not different between $Fgf21^{-/-}$ and $Fgf21^{+/+}$ mice (Kim *et al*. 2013*a*), suggesting that FGF21 does not mediate the effects of caloric restriction on energy metabolism.

An increasing body of evidence suggests that FGF21 expression is regulated by changes in specific macronutrients. After feeding a ketogenic diet with low carbohydrates and high fat, mimicking a fasting state, FGF21 was induced in the liver of mice in an PPARα-dependent manner; consequently, increased FGF21 contributes to the enhancement of β-oxidation and ketogenesis caused by a ketogenic diet (Badman *et al*. 2007). In parallel, ketogenic diet-fed $Fgf21^{-/-}$ mice showed impaired adaptation to ketosis (Badman *et al*. 2009). A protein-restricted (low protein) diet has been also reported to increase hepatic FGF21 expression in mice through general control nonderepressible 2- and PPARα-dependent pathways. An increase in serum FGF21 levels was also observed in human subjects after a low protein diet (Laeger *et al*. 2014). The effects of a low protein diet on the enhancement of energy expenditure and decrease of fat mass were partially diminished in $Fgf21^{-/-}$ mice compared to control mice, suggesting the importance of FGF21 induction in whole-body adaption to low protein

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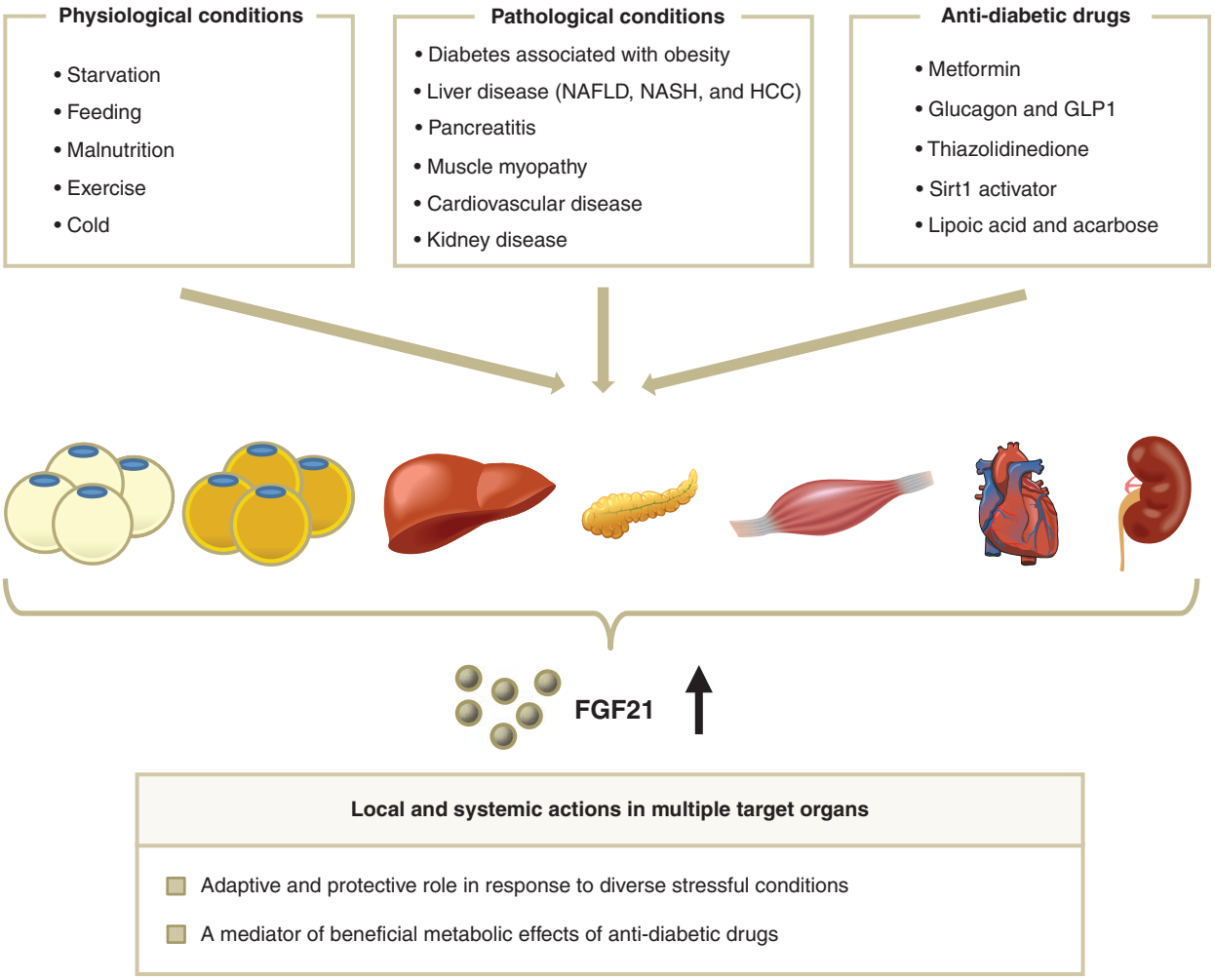

Figure 1
Functional role of fibroblast growth factor 21 (FGF21) secreted from multiple organs in response to diverse stresses or stimuli. FGF21 expression is induced in multiple major organs, including white/brown adipose tissue, liver, pancreas, skeletal muscle, heart, and kidney, in various physiological and pathological conditions. FGF21 levels are also increased by several anti-diabetic drugs or compounds. Consequently, elevated FGF21 plays an adaptive role in response to diverse stressful conditions and acts a mediator of beneficial metabolic effects of anti-diabetic drugs through local and systemic actions in target organs. NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; HCC, hepatocellular carcinoma; GLP1, glucagon-like peptide 1.

intake (Laeger *et al.* 2014). Intriguingly, the serum FGF21 level and hepatic FGF21 expression were not increased in mice with a 50% reduction in food intake without changes of protein intake (Laeger *et al.* 2014). Furthermore, FGF21 induction in mice fed a ketogenic diet was not attenuated by carbohydrate supplements (Laeger *et al.* 2014), implying that the increase in FGF21 during food restriction and the ketogenic diet appears to be primarily driven by low protein intake rather than by reduced carbohydrate intake. A high-fat diet (HFD) has been also reported to cause hepatic FGF21 induction in mice (Muise *et al.* 2008, Fisher *et al.* 2010). In this process, free fatty acids appear to stimulate FGF21 gene expression in PPARα-dependent (Mai *et al.* 2009) or -independent pathways (Tanaka *et al.* 2015). Collectively, these results indicate that the induction of FGF21 in response to changes in macronutrient ingestion is important for metabolic adaption.

In addition to changes in the quantities of macronutrients, changes of amino acid composition in proteins and monosaccharide composition in carbohydrates influence FGF21 expression. Methionine restriction (approximately a 75–80% decrease of methionine intake) has been reported to extend the lifespan and lead to decreased

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fat mass and improved insulin sensitivity in rodents, probably by enhancing β-oxidation (Orentreich *et al.* 1993, Hasek *et al.* 2010). Importantly, methionine-restricted mice showed increases in the hepatic FGF21 expression and serum FGF21 level, accompanied by attenuation of obesity- or age-related insulin resistance (Ables *et al.* 2012, Lees *et al.* 2014). These results suggest that FGF21 may mediate beneficial metabolic effects of methionine restriction. However, metabolic effects of methionine restriction in *Fgf21*$^{-/-}$ mice remain to be determined. Complete deprivation of a specific amino acid also affects FGF21 gene expression. Several studies have suggested that FGF21 was induced by the eukaryotic translation initiation factor 2 alpha (eIF2α)–activating transcription factor 4 (ATF4)-dependent pathway in the liver but not in adipose tissue or skeletal muscle of mice fed a leucine-deficient diet (De Sousa-Coelho *et al.* 2013, Kim *et al.* 2013*a*). Importantly, the enhanced glucose tolerance and reduced fat mass observed in WT mice fed a leucine-deficient diet were not shown in *Fgf21*$^{-/-}$ mice, suggesting that hepatic FGF21 acts as a critical mediator of the changes in whole-body energy metabolism in response to amino acid deficiency (De Sousa-Coelho *et al.* 2013, Kim *et al.* 2013*a*). Saccharides also influence FGF21 gene expression. In line with FGF21 induction in the livers during refeeding of mice (Markan *et al.* 2014), glucose was shown to directly induce FGF21 gene expression in hepatocytes *in vitro* through activation of the carbohydrate response element binding protein (Iizuka *et al.* 2009, Uebanso *et al.* 2011). A recent study has shown that fructose ingestion also acutely increased circulating FGF21 levels in humans (Dushay *et al.* 2015), suggesting that FGF21 may play a role in the metabolism of fructose or other monosaccharides, as well as glucose. A fundamental physiological role of FGF21 in individual carbohydrate metabolism remains to be clarified.

FGF21, cold exposure, and exercise

Heat production is important in the maintenance of body temperature in response to cold exposure. Thermogenesis in brown adipose tissue (BAT) is a critical component of heat production. Emerging evidence has suggested that white adipose tissue (WAT) browning, conversion of WAT- to BAT-like tissues, participates in the regulation of the body temperature (Harms & Seale 2013). It has been reported that FGF21 is induced in BAT and WAT of mice and humans in an adaptive response to cold exposure (Fisher *et al.* 2012, Lee *et al.* 2014*a*), and thermogenic stimuli such as norepinephrine induce FGF21 gene expression in BAT via activation of the p38α–ATF2 axis (Hondares *et al.* 2011). Importantly, *Fgf21*$^{-/-}$ mice had decreased core temperatures after cold exposure compared to control mice, due to an impaired browning (Fisher *et al.* 2012). Thyroid hormones (THs), another thermogenic inducer, have been also reported to increase FGF21 gene expression in adipose tissue (Adams *et al.* 2010). However, the effect of TH on energy expenditure was not different between *Fgf21*$^{-/-}$ and *Fgf21*$^{+/+}$ mice (Domouzoglou *et al.* 2014), suggesting that FGF21 regulates adaptive thermogenesis in cold environments but not that after TH treatment.

In addition to cold exposure, acute or chronic exercise has been reported to increase circulating FGF21 levels in mice and humans (Cuevas-Ramos *et al.* 2012, Kim *et al.* 2013*b*). While contradictory data have been reported (Lee *et al.* 2014*a*), FGF21 might act as a mediator of the metabolic improvement by exercise. Consistently, recent data showed that enhancement of glucose tolerance by exercise was diminished in *Fgf21*$^{-/-}$ mice. Furthermore, exercise-induced AMP-activated protein kinase (AMPK) activation was markedly reduced in the skeletal muscle of *Fgf21*$^{-/-}$ mice compared to control mice, suggesting that FGF21 mediates the beneficial effects of exercise on glucose intolerance (Loyd *et al.* 2014). Thus, all of these studies indicate that FGF21 is a crucial player in the physiological adaption to cold and exercise.

The role of stress-induced FGF21 in pathological conditions

FGF21 and diabetes associated with obesity

FGF21 levels are paradoxically increased in the serum of obese diabetic mice or human subjects with T2D and obesity (Chavez *et al.* 2009, Fisher *et al.* 2010). This increase of serum FGF21 in obesity is probably due to the upregulation of FGF21 gene expression in the liver and adipose tissue (Fisher *et al.* 2010). While the liver rather than adipose tissue primarily produces FGF21 during fasting (Markan *et al.* 2014), it is unclear which of the liver or adipose tissue is the main producer of FGF21 in obesity. Considering the pharmacotherapeutic effects of FGF21, obesity-mediated FGF21 induction may be an adaptive mechanism to metabolic derangement associated with obesity. In line with this notion, HFD-fed *Fgf21*$^{-/-}$ mice showed aggravated glucose intolerance compared to HFD-fed *Fgf21*$^{+/+}$ mice (Assini *et al.* 2015), although other investigators reported no difference of glucose intolerance between in *Fgf21*$^{-/-}$ mice and *Fgf21*$^{+/+}$

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mice fed HFD (Fisher *et al.* 2010, Adams *et al.* 2013*a*). In parallel, leptin-deficient *ob*/*ob* mice exhibited aggravated glucose intolerance and insulin resistance when *Fgf21* was genetically disrupted (Kim *et al.* 2015). Thus, FGF21 may act as a compensatory signal to mitigate metabolic stresses due to obesity.

In obesity, FGF21 signaling has been reported to be impaired in major metabolic organs, including pancreatic islets, liver, and WAT (Fisher *et al.* 2010, So *et al.* 2013). Based on these findings, we speculate that obesity-related endogenous FGF21 induction alone is not sufficient to overcome impaired FGF21 signaling or FGF21 resistance. Administration of exogenous FGF21 and FGF21 mimetics improves glucose tolerance or insulin sensitivity in diabetic rodents and monkeys (Coskun *et al.* 2008, Xu *et al.* 2009, Wu *et al.* 2011, Foltz *et al.* 2012). Two recent papers have shown that an engineered FGF21 variant (LY2405319) ameliorates metabolic parameters in obese human subjects with T2D as well as diabetic monkeys (Adams *et al.* 2013*b*, Gaich *et al.* 2013). Especially, LY2405319-received T2D subjects showed a significant decrease of body weight and fasting insulin levels and the improvement of dyslipidemia including reduced LDL cholesterol and increased HDL cholesterol levels compared to placebo-treated subjects (Gaich *et al.* 2013). The glucose lowering effect of LY2405319 was also observed, while statistical significance was marginal (Gaich *et al.* 2013).

These pharmacological effects of FGF21 and its mimetics are attributable to the action on various metabolic target organs, such as adipose tissue, brain, liver, and pancreatic β cells (Owen *et al.* 2015). Several studies have shown that FGF21 enhances insulin-induced glucose uptake and thermogenesis in adipose tissue (Kharitonenkov *et al.* 2005, Xu *et al.* 2009). In obese mice with whole-body deletion of *β-klotho*, a co-receptor for FGF21, the metabolic effects of FGF21 such as enhancement of energy expenditure or glucose tolerance and decrease of fat mass were diminished (Adams *et al.* 2012). Notably, these beneficial effects of FGF21 were also reduced in obese mice lacking *β-klotho* in adipose tissue or the brain (Ding *et al.* 2012, Owen *et al.* 2014). Furthermore, hepatic FGF21 actions such as alleviation of steatosis and suppression of hepatic glucose production were less pronounced in these mice, suggesting indirect FGF21 action on the liver. These findings suggest that both adipose tissue and the brain are major targets of systemic actions of FGF21 in metabolic improvement, although direct repressive effects of FGF21 on gluconeogenesis and lipogenesis in the liver have also been reported (Zhang *et al.* 2011, Kong *et al.* 2013). The importance of FGF21 action in adipose tissue has been also inferred from reduction of FGF21-mediated metabolic improvement in adiponectin knockout ($Adipoq^{-/-}$) mice (Holland *et al.* 2013, Lin *et al.* 2013).

Additionally, FGF21 increases insulin content in pancreatic β cells and partially protects islets from glucolipotoxicity and cytokine-induced apoptosis (Wente *et al.* 2006). Chow-fed $Fgf21^{-/-}$ mice showed impaired glucose-stimulated insulin secretion (GSIS), probably due to a lack of FGF21 action-inhibiting growth hormone (GH) signaling in β cells, and also displayed insulin resistance due to the increased GH signaling in insulin target tissues (So *et al.* 2015). Given that GH reportedly induces FGF21 gene expression (Chen *et al.* 2011, Yu *et al.* 2012), endogenous FGF21 induction may be a compensatory mechanism to alleviate insulin resistance induced by chronic GH treatment. In contrast, we have observed no difference in GSIS or insulin levels in the $Fgf21^{-/-}$ mouse strain (Kim *et al.* 2015). Further study is needed to evaluate the effect of endogenous FGF21 on the pancreatic islet function. Taken together, these results suggest that FGF21 acts as a therapeutic agent for the treatment of T2D associated with obesity via its pleiotropic actions in diverse metabolic organs.

Several studies have suggested that FGF21 exerts its metabolic beneficial effects through the regulation of other hormones. As previously described, FGF21 increases the production of insulin and adiponectin in pancreatic β cells and adipose tissue respectively (Wente *et al.* 2006, Holland *et al.* 2013, Lin *et al.* 2013). It has been also reported that FGF21 reduces circulating glucagon levels in obese mice (Kharitonenkov *et al.* 2005). Given the role of glucagon in the aggravation of hyperglycemia through enhancing hepatic glucose production, glucagon could be a mediator for *in vivo* effect of FGF21. In addition, FGF21 is able to exert therapeutic effects in an insulin-dependent manner. While the effect of FGF21 on glucose lowering was still preserved in liver-specific insulin receptor knockout mice, the suppressive effects of FGF21 on circulating cholesterol and hepatic triglycerides were diminished in these mice (Emanuelli *et al.* 2014). These results suggest that FGF21 ameliorates hyperglycemia independent of insulin action in the liver of obese mice but affects hepatic lipid metabolism in an insulin-dependent manner. Given the metabolic action of insulin in various tissues, investigations on the relationship between FGF21 and insulin signaling in adipose tissue and the brain will also be of interest.

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FGF21 and liver disease

FGF21 is implicated in various liver diseases such as nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), and liver cancer. Several studies have suggested that FGF21 was increased in the serum and liver of human subjects with NAFLD, and its level was correlated with hepatic triacylglycerol (TG) content (Dushay *et al.* 2010, Li *et al.* 2010). Molecular mechanisms underlying FGF21 induction in NAFLD have been recently identified (Jiang *et al.* 2014, Kim *et al.* 2015). Endoplasmic reticulum (ER) stress, which is implicated in the development and progression of NAFLD, appears to be responsible for FGF21 induction. Increased gene expression of both ER stress markers and FGF21 was observed in the livers of mice with steatosis or in those of human subjects with NAFLD (Jiang *et al.* 2014, Kim *et al.* 2015). Moreover, ER stressors are able to directly induce FGF21 gene expression in hepatocytes *in vitro* and in mouse livers *in vivo*. Consistently, ER stress-induced hepatic FGF21 expression was diminished in mice with the deletion of the inositol-requiring 1 alpha (*Ire1α*) gene (Jiang *et al.* 2014) or with Ser51Ala mutation of the *Eif2α* gene in the liver (Kim *et al.* 2015). These results suggest that the IRE1α-X-box binding protein 1 axis or the eIF2α–ATF4 axis is an important signaling pathway in ER stress-induced FGF21 expression. Furthermore, chemical-induced increases of ER stress marker gene expression and lipid accumulation in the livers of mice were reduced by recombinant FGF21 administration (Jiang *et al.* 2014) and in the livers of tetracycline-inducible *Fgf21* transgenic mice (Kim *et al.* 2015). *Fgf21*$^{-/-}$ *ob*/*ob* mice also had an increased expression of ER stress marker genes and aggravated liver injury compared to *Fgf21*$^{+/+}$ *ob*/*ob* mice (Kim *et al.* 2015). Taken together, these results suggest that FGF21 plays a role in the adaptive response to ER stress induced by a pharmacological ER stressor or NAFLD.

In addition to NAFLD, FGF21 participates in the development and progression of NASH induced by a methionine–choline deficient (MCD) diet (Fisher *et al.* 2014). In mice fed an MCD diet, the serum FGF21 level was elevated, probably due to an increase in FGF21 expression in the liver but not in other organs. *Fgf21*$^{-/-}$ mice fed the MCD diet showed increased progressive steatohepatitis and hepatic fibrosis compared to control mice. Furthermore, *Fgf21*$^{-/-}$ mice showed aggravated hepatic peroxidative damage, probably due to the elevation of free fatty acids caused by reduced activity of acyl CoA synthetases, which convert long-chain fatty acids to acyl CoAs. Another *Fgf21*$^{-/-}$ mouse strain also displayed increased lipid accumulation and ER stress response after an MCD diet (Tanaka *et al.* 2015). Indeed, FGF21 administration or FGF21 overexpression ameliorated MCD diet-induced metabolic derangements (Fisher *et al.* 2014). Thus, FGF21 induction in NASH may be a physiologic adaptation to hepatic stress responses, and FGF21 may be a promising therapeutic agent for the treatment of NAFLD or NASH.

NAFLD and NASH are risk factors for the development and progression of hepatocellular carcinoma (HCC; Michelotti *et al.* 2013). It has been reported that hepatic FGF21 expression was increased in diethylnitrosamine (DEN)-induced liver tumors and in livers of humans with HCC (Yang *et al.* 2013). Furthermore, *Fgf21* transgenic mice showed a delayed appearance of DEN-induced liver tumors, although the incidence and burden of HCC were similar between *Fgf21* transgenic and control mice (Huang *et al.* 2006). These findings suggest that FGF21 induction may be an adaptive mechanism to protect or delay the development and progression of liver cancer. Notably, an *Fgf21* transgenic mouse strain in this study did not show reduced body weight, in contrast to other *Fgf21* transgenic mouse strains. This discrepancy is probably due to a difference in mouse background (FVB vs C57BL/6) or a difference in serum FGF21 concentration between mouse strains. Further studies are needed to evaluate the fundamental role of FGF21 in hepatic carcinogenesis.

Liver is a primary organ to detoxify diverse toxic chemicals. It has been reported that FGF21 expression is increased depending on the aryl hydrocarbon receptor in the liver of mice after administration of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), a highly toxic and carcinogenic chemical (Cheng *et al.* 2014). *Fgf21*$^{-/-}$ mice were susceptible to TCDD-induced mortality compared to control mice (Cheng *et al.* 2014), suggesting that FGF21 induction may be a protective signal against toxin-induced injury. It remains to be determined whether FGF21 regulates activity and expression of the detoxification enzyme or whether this action exerts a protective effect against toxin-induced injury.

FGF21 and pancreatitis

It has been reported that FGF21 is expressed in pancreatic acinar and islet cells (Wente *et al.* 2006, Johnson *et al.* 2009). Several studies have shown that FGF21 modulates the development and progression of pancreatitis, a known risk factor for pancreatic cancer (Johnson *et al.* 2009, 2014). In mice with cerulein-induced acute pancreatitis, FGF21 expression was increased in acinar cells but not in islet cells. Importantly, pancreatic inflammation and fibrosis were increased in *Fgf21*$^{-/-}$ mice compared to control mice

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and, conversely, were decreased in *Fgf21* transgenic mice (Johnson *et al*. 2009). Furthermore, FGF21 expression was markedly reduced in acinar cells of *Mist1* knockout mice showing early events of pancreatitis such as the premature activation of digestive enzymes and acinar disorganization (Johnson *et al*. 2014). These results suggest that FGF21 induction may be an adaptive mechanism to protect the development and progression of pancreatitis. Given the protective role of FGF21 in pancreatitis, it will be of interest to study whether FGF21 exerts anti-cancer activity in the progression of pancreatic cancer.

FGF21 and muscle disease

Emerging evidence has suggested that FGF21 is expressed in skeletal muscle and that its expression is upregulated under muscle stress conditions, such as atrophy or myopathy (Izumiya *et al*. 2008, Tyynismaa *et al*. 2010). In transgenic mice expressing a mutant form of mitochondrial helicase *Twinkle* or muscle-specific cytochrome *c* oxidase 10 (*Cox10*) knockout mice showing impairment of the mitochondrial respiratory chain and myopathy, skeletal muscle FGF21 expression was upregulated along with serum FGF21 levels (Tyynismaa *et al*. 2010). Moreover, serum FGF21 levels were increased in human subjects with mitochondrial respiratory chain deficiencies (Suomalainen *et al*. 2011), suggesting that FGF21 is a biomarker of muscle-manifesting mitochondrial respiratory chain disorders. Skeletal muscle-specific autophagy knockout mice showing muscle atrophy also exhibited increased muscular FGF21 induction, probably due to aggravated mitochondrial stress caused by autophagy deficiency (Kim *et al*. 2013*a*). Furthermore, it has been reported that several mitochondrial stressors, such as mitochondrial complex inhibitors, directly induce FGF21 expression via the eIF2α–ATF4 pathway (Kim *et al*. 2013*a*). Notably, all of these mice had reduced fat mass, probably due to increased energy expenditure and fatty acid catabolism induced by FGF21. Based on a report showing the beneficial effect of FGF21 on mitochondrial respiratory capacity (Chau *et al*. 2010), we speculate that FGF21 acts as an adaptive regulator counteracting muscle stress imposed by mitochondrial dysfunction or autophagy deficiency. Further studies are necessary to prove the protective role of FGF21 in the diseases associated with mitochondrial dysfunction.

FGF21 and cardiovascular disease

Accumulating evidence has suggested that FGF21 can modulate the development of coronary artery disease (CAD) and atherosclerosis. It has been reported that FGF21 was increased in the serum of human subjects with CAD and carotid artery plaques, and increased FGF21 levels were associated with adverse lipid profiles in CAD subjects (Lin *et al*. 2010, Chow *et al*. 2013). A recent study has shown that the serum FGF21 level was also increased in atherosclerosis-prone apolipoprotein E knockout ($Apoe^{-/-}$) mice fed an atherogenic diet (Wu *et al*. 2014). FGF21 administration improved atherogenic diet-induced dyslipidemia and vascular atherosclerotic lesions in $Apoe^{-/-}$ mice, probably by mitigating ER stress, a contributing factor in the pathogenesis of atherosclerosis (Wu *et al*. 2014). In addition, FGF21 treatment improved aggravated lipid profiles in atherosclerotic rats through its antioxidant effects (Zhu *et al*. 2014). The enhancement of cellular cholesterol efflux from macrophage-derived foam cells by FGF21 may also contribute to the improvement of atherosclerosis (Lin *et al*. 2014). Taken together, these findings suggest that FGF21 plays an adaptive and protective role in response to atherogenic stress, although further studies are needed to validate these findings.

Cardiokines, which are secreted from the heart in response to various cardiac stresses, play an important role in the maintenance of normal cardiac function through autocrine, paracrine, or endocrine mechanisms (Shimano *et al*. 2012). It has been reported that FGF21 expression was induced through a Sirt1–PPARα-dependent mechanism in the hearts of mice under various cardiac stress conditions such as isoproterenol/phenylephrine infusion, coronary artery ligation-induced myocardial infarction (ischemia), or transverse aortic constriction (Planavila *et al*. 2013). In addition, FGF21 expression was increased in the hearts of human subjects with dilated cardiomyopathy or advanced heart failure (Planavila *et al*. 2015). However, the source of FGF21 in these conditions is controversial, because another study showed FGF21 induction in the liver and adipose tissue but not in the ischemic myocardium of mice (Liu *et al*. 2013). Importantly, stress-induced cardiac hypertrophy was increased in $Fgf21^{-/-}$ mice, while exogenous FGF21 administration ameliorated cardiac hypertrophy in these mice (Liu *et al*. 2013, Planavila *et al*. 2013). These results suggest that cardiac stress-induced FGF21 expression is a compensatory signal to protect against cardiac failure or cardiac dysfunction. Several mechanisms of improved stress-induced cardiac hypertrophy by FGF21 have been suggested. A role for the FGF receptor 1/β-klotho/protein kinase B (PKB/AKT) pathway in this process has been suggested in an *in vivo* study employing the strategy of siRNA administration to the anterior ventricular wall (Liu *et al*. 2013). In addition,

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i.m. injection of the adenovirus expressing FGF21 increased serum adiponectin levels and attenuated cardiac hypertrophy in mice with experimental myocardial infarction (Joki *et al.* 2015). Notably, FGF21-mediated cardiac protection was diminished in *Adipoq*$^{-/-}$ mice, indicating that adiponectin mediates the beneficial effects of FGF21 on cardiac function. Enhancement of the antioxidant capacity via upregulation of antioxidant enzyme gene expression may contribute to the protective effects of FGF21 (Planavila *et al.* 2015). These results collectively suggest that FGF21 may be a pharmacological agent for treatment of myocardial injury.

FGF21 and kidney disease

It has been reported that serum FGF21 levels were increased in subjects with acute or chronic kidney diseases (Stein *et al.* 2009, Hindricks *et al.* 2014), and circulating FGF21 was elevated in proportion to the severity of kidney diseases (Lin *et al.* 2011). Increasingly, studies have suggested that FGF21 elicits protective effects against the progression of diabetic nephropathy, a leading cause of chronic renal failure (Kim *et al.* 2013*c*, Zhang *et al.* 2013*a*). FGF21 administration prevented renal lipid accumulation, oxidative stress, inflammation, and fibrosis in mice after treatment of excessive fatty acids or streptozotocin (Zhang *et al.* 2013*a*) and in leptin receptor-deficient *db*/*db* mice with diabetic nephropathy (Kim *et al.* 2013*c*). Conversely, *Fgf21*$^{-/-}$ mice exhibited more aggravated lipotoxicity and renal damage compared to the control mice (Zhang *et al.* 2013*a*). These findings suggest that FGF21 induction is an adaptive mechanism to protect against renal injury in diabetic conditions and that FGF21 is a potential therapeutic agent for the treatment of diabetic nephropathy.

The role of FGF21 in pharmacologic agent-induced metabolic benefits

A growing body of evidence suggests that several pharmacologic agents that are currently available or are being developed for the treatment of metabolic diseases have a potential to induce FGF21. Here, we will review the functional role and molecular mechanisms of FGF21 induction by anti-diabetic drugs.

Metformin and FGF21

Metformin is a first-line agent for patients with T2D, according to the guidelines of the European Association for the Study of Diabetes and the American Diabetes Association. Metformin likely exerts its glucose-lowering effect through inhibition of glucose absorption in the intestine, suppression of gluconeogenesis in the liver, and enhancement of insulin actions in the liver, adipose tissue, or skeletal muscle (Foretz *et al.* 2014). The changes of composition or alterations of microbial metabolism in the gut microbiota are also involved in the beneficial metabolic effects of metformin (Cabreiro *et al.* 2013, Shin *et al.* 2014). The effect of metformin on suppression of gluconeogenesis has been reported to be dependent on AMPK, which functions as a conserved cellular energy sensor in an adaptive response to diverse energy stress conditions (Shaw *et al.* 2005, He *et al.* 2009). Metformin-induced AMPK activation causes a decrease in the transcription of hepatic gluconeogenic enzyme genes, which depends on diverse factors such as CREB-regulated transcription coactivator 2 (He *et al.* 2009) and the small heterodimer partner (Kim *et al.* 2008). Metformin also improves hepatic lipid homeostasis by enhancing β-oxidation and suppressing lipogenesis in the liver via AMPK-mediated phosphorylation of acetyl CoA carboxylase (Fullerton *et al.* 2013). However, metformin is also able to suppress hepatic glucose production by altering the energy charge in an AMPK-independent manner without affecting gluconeogenic gene expression (Foretz *et al.* 2010). These effects are mediated by a reduced ATP level or an increased AMP/ATP ratio via partial inhibition of mitochondrial respiratory-chain complex I (Foretz *et al.* 2010, Miller *et al.* 2013).

Secretory proteins (or hormones) derived from major metabolic organs such as adipose tissue, muscle, and liver play a key role in the maintenance of energy homeostasis (Ouchi *et al.* 2011, Pedersen & Febbraio 2012, Stefan & Haring 2013). These secretory proteins may be involved in beneficial metabolic effects of metformin. Metformin treatment increased serum GLP1 levels in human subjects with or without T2D (Mannucci *et al.* 2004), as well as in obese diabetic mice (Kim *et al.* 2014*b*). In addition, metformin has been reported to induce FGF21 expression in hepatocytes through an AMPK-dependent pathway (Nygaard *et al.* 2012). We have observed that metformin causes FGF21 upregulation, which is dependent on the eIF2α–ATF4 axis but not on AMPK (Kim *et al.* 2013*d*). Moreover, serum FGF21 levels in human subjects with T2D were shown to increase after 6 months of metformin treatment (Kim *et al.* 2013*d*). Hence, FGF21 induction by metformin may contribute to its metabolic effects. However, it has been also reported that the administration of metformin to human subjects with T2D for 1 week led

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to decreased serum FGF21 levels (Zhang *et al*. 2013*b*). Serum FGF21 levels in HIV-infected subjects treated with metformin for 12 months were not significantly different from those in the placebo group (Srinivasa *et al*. 2015). These discrepancies could be attributable to differences in patient selection, experimental analyses, or duration of metformin treatment. Since the numbers of human subjects studied were small, large-scale studies are needed to evaluate the role of FGF21 induction in the therapeutic effects of metformin.

Glucagon, GLP1, and FGF21

Glucagon secreted from pancreatic islet α cells is a well-known counterregulatory hormone that maintains glucose homeostasis by increasing gluconeogenesis and glycogenolysis in response to fasting or hypoglycemia. Hyperglucagonemia is observed in the early phase of insulin resistance/T2D and contributes to hyperglycemia by increasing the rate of hepatic glucose output and enhancing glycogen breakdown (Unger & Cherrington 2012). Lipid metabolism and energy expenditure are also regulated by glucagon or glucagon agonism. Some studies have shown that glucagon decreased the levels of plasma TG and cholesterol in rats with or without hyperlipidemia (Eaton 1973). Glucagon also promotes lipolysis by activating hormone-sensitive lipase in white adipocytes (Slavin *et al*. 1994), enhances β oxidation, and suppresses lipogenesis in hepatocytes (Prip-Buus *et al*. 1990). In addition, glucagon has been reported to increase energy expenditure in mice or human subjects, probably by stimulating oxygen consumption and heat production in BAT (Doi & Kuroshima 1982, Tan *et al*. 2013). Thus, glucagon-induced beneficial effects on dyslipidemia and obesity make it an attractive therapeutic agent for treatment of metabolic disease, despite its potential ability to increase blood glucose level.

Intriguingly, glucagon and glucagon agonists have been reported to induce hepatic FGF21 gene expression, leading to the increase of serum FGF21 levels in mice and healthy human volunteers (Arafat *et al*. 2013, Habegger *et al*. 2013). The effects of glucagon agonism inducing body weight loss, hypocholesterolemia, and increased energy expenditure were lower in *Fgf21*$^{-/-}$ mice than in control mice (Habegger *et al*. 2013). Given that FGF21 reduces fat mass or serum cholesterol levels and enhances thermogenesis, FGF21 may act as a mediator of metabolic improvement by glucagon. A recent paper has shown that glucagon stimulates hepatic FGF21 secretion via PKA and Epac (exchange protein directly activated by cAMP)-dependent pathways without change of FGF21 mRNA expression (Cyphert *et al*. 2014), suggesting that glucagon increases FGF21 levels through post-translational mechanisms as well as transcriptional mechanisms.

GLP1, a proglucagon-derived peptide hormone, is secreted from L cells of the intestine in response to nutrients. GLP1 plays a key role in the control of glucose homeostasis by enhancing insulin release and suppressing glucagon secretion (Meier 2012). GLP1 also inhibits gastric emptying and induces satiety, which contributes to the suppression of food intake (Meier 2012). Five GLP1 receptor agonists (liraglutide, exenatide, lixisenatide, albiglutide and dulaglutide) are currently being used for the treatment of T2D. Intriguingly, GLP1 analogues also stimulate FGF21 expression, similar to glucagon or glucagon agonists. Treatment with liraglutide, a derivative of human GLP1 with a fatty acid chain, induced FGF21 gene expression in the liver but not in adipose tissue of *KK-A*^{y} mice (Nonogaki *et al*. 2014); consequently, serum FGF21 levels were increased in liraglutide-treated *KK-A*^{y} mice showing amelioration of hyperglycemia and obesity. Moreover, treatment with exendin-4 (the naturally occurring form of exenatide) for 10 weeks increased hepatic FGF21 gene expression in HFD-fed mice compared to control HFD-fed mice (Lee *et al*. 2014*b*). Dissimilar results regarding the effect of exendin-4 on FGF21 expression have also been reported. Hepatic FGF21 expression and serum FGF21 levels were decreased in HFD-fed mice treated with exendin-4 for 4 weeks compared to saline treatment (Samson *et al*. 2011). Consistent with this result, the addition of exenatide reduced FGF21 levels in T2D subjects undergoing pioglitazone treatment (Samson *et al*. 2011). Furthermore, a decrease in hepatic FGF21 levels was correlated with reduction in hepatic TG content and liver weight in HFD-fed mice after exendin-4 treatment, implying that reduction of FGF21 due to exendin-4 may be secondary to reduced lipid accumulation. Further studies are needed to evaluate the relationship between FGF21 induction and metabolic benefits by GLP1 analogues.

Combined glucagon/GLP1 dual agonists that retain the anti-hyperglycemic potential of GLP1 while avoiding the hyperglycemic effects of pure glucagon are being evaluated in clinical trials. The glucagon/GLP1 dual agonist is an attractive therapeutic agent as an anti-obesity drug as well as an anti-diabetic drug, due to the lipolytic and thermogenic properties of glucagon (Sadry & Drucker 2013). Glucagon/GLP1 dual agonists also increased hepatic FGF21 expression and improved obesity-induced metabolic deterioration in mice, similar to glucagon or

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GLP1 agonists (Pocai *et al*. 2009). However, the role of FGF21 in glucagon/GLP1 dual agonism remains to be determined.

PPARγ agonist (TZD) and FGF21

TZD, a PPARγ agonist, is an anti-diabetic drug used for the treatment of T2D. TZD has been reported to enhance glucose uptake in adipose tissue or skeletal muscle and inhibit gluconeogenesis in the liver by reinforcing insulin action (Soccio *et al*. 2014). In addition to its role as an insulin sensitizer, TZD directly converts macrophage polarity from pro-inflammatory M1 to anti-inflammatory M2 type (Bouhlel *et al*. 2007) or indirectly via lipid partitioning (Prieur *et al*. 2011), probably leading to attenuation of obesity-induced adipose inflammation and insulin resistance. TZD may also elicit beneficial metabolic effects by regulating the levels or actions of hormones. Treatment with TZD caused an increase in serum adiponectin levels in obese mice and consequently improved obesity-induced glucose intolerance (Nawrocki *et al*. 2006). The effectiveness of TZD was diminished in obese *Adipoq*$^{-/-}$ mice, suggesting that adiponectin is an important contributor to TZD-mediated improvement of whole-body glucose metabolism (Nawrocki *et al*. 2006). In addition, TZD has been reported to increase FGF21 gene expression in adipose tissue, but not in the liver, through activation of PPARγ and, consequently, serum FGF21 levels are higher in TZD-treated mice compared to control mice (Muise *et al*. 2008). These results suggest a possible role of FGF21 in the anti-diabetic actions of TZD. In line with this assumption, obese *Fgf21*$^{-/-}$ mice were refractory to the metabolic effects of TZD (Dutchak *et al*. 2012). Notably, these effects of TZD are associated with the local action of FGF21 in adipose tissue but not with the systemic action. Adipose-derived FGF21 induction by TZD suppresses sumoylation of PPARγ and consequently enhances PPARγ activity in adipose tissue, probably contributing to anti-diabetic effects of TZD (Dutchak *et al*. 2012). However, another paper reported that *Fgf21*$^{-/-}$ mice exhibited metabolic responses to TZD similar to those of *Fgf21*$^{+/+}$ mice (Adams *et al*. 2013*a*). Furthermore, PPARγ sumoylation in adipose tissue did not differ between the two groups after TZD treatment (Adams *et al*. 2013*a*). There is no clear explanation for these discrepancies, which might be attributable to the differences in knockout mouse strains or experimental procedures. Further studies are required to understand the relationship between FGF21 and PPARγ in TZD-induced pharmacologic actions. Given that both TZD and FGF21 induce browning of WAT (Vernochet *et al*. 2009, Petrovic *et al*. 2010, Fisher *et al*. 2012), it will also be interesting to study the role of FGF21 in TZD-induced browning.

Sirt1 activators and FGF21

Sirt1, an NAD-dependent deacetylase, is an important regulator of cellular or whole-body energy metabolism through the modulation of acetylation/deacetylation of histones or non-histone proteins. Sirt1 gain- or loss-of-function studies in the whole-body or in specific organs have suggested that Sirt1 is a promising therapeutic target for the treatment of insulin resistance and T2D (Boutant & Canto 2014). Pharmacologic studies have suggested that several Sirt1 activators have therapeutic efficacy in T2D associated with obesity. Resveratrol, a natural polyphenol product derived from grapes, is a well-known Sirt1 activator that improves metabolic profiles in obese mice (Baur *et al*. 2006, Lagouge *et al*. 2006) and human subjects with obesity or T2D (Timmers *et al*. 2011). SRT1720, a synthetic small molecule activator of Sirt1, improves insulin sensitivity and glucose tolerance (Milne *et al*. 2007). Sirt1-mediated regulation of glucose and lipid homeostasis may be elicited by various mechanisms, including an increase of PGC1α-mediated β oxidation and mitochondrial biogenesis (Feige *et al*. 2008), suppression of sterol regulatory element-binding protein 1c-mediated fatty acid synthesis (Ponugoti *et al*. 2010), reduction of nuclear factor-kappa B-mediated macrophage inflammation (Schug *et al*. 2010), or enhancement of PPARγ-mediated browning (Qiang *et al*. 2012). In addition, Sirt1-mediated changes in the levels of certain hormones may contribute to its beneficial metabolic action. Sirt1 induces adiponectin gene expression through deacetylation of forkhead box O1 (Qiao & Shao 2006), which may help improve glucose tolerance and insulin sensitivity. Additionally, it has been reported that Sirt1 increases insulin secretion through the suppression of transcription of uncoupling protein 2 (Bordone *et al*. 2006). Resveratrol has been also reported to enhance insulin release from pancreatic β cells (Vetterli *et al*. 2011). A recent paper reported that Sirt1 or its activators (resveratrol and SRT1720) induced FGF21 gene expression in the liver of mice and that liver-specific *Sirt1* knockout (*Sirt1*$^{\Delta hep}$) mice had a reduced hepatic expression and serum level of FGF21 compared to control mice in response to fasting (Li *et al*. 2014). Importantly, *Sirt1*$^{\Delta hep}$ mice exhibited reduced ketogenesis and increased hepatic lipid accumulation in fasting conditions; this was rescued by adenovirus-mediated hepatic FGF21 overexpression

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(Li *et al*. 2014). These results suggest that Sirt1-mediated FGF21 induction plays an important role in the adaptive metabolic response to fasting. Furthermore, Sirt1 may participate in GLP1 receptor agonist-induced FGF21 expression in hepatocytes (Lee *et al*. 2014*b*). Further studies will be necessary to elucidate the role of FGF21 in the metabolic improvement by Sirt1 activators.

Other pharmacological compounds and FGF21

A growing body of evidence suggests that other therapeutic reagents influence FGF21 gene expression. Lipoic acid, also known as thioctic acid, is an octanoic acid-derived organosulfur compound that is naturally synthesized in small amounts in the body (Shay *et al*. 2009). Lipoic acid plays an important role in the maintenance of mitochondrial respiratory capacity as a cofactor that covalently binds to mitochondrial complex enzymes (Shay *et al*. 2009). Numerous studies have suggested that lipoic acid supplements improved glucose intolerance and insulin sensitivity in mice and human subjects (Jacob *et al*. 1999). In Germany, lipoic acid is medically approved for the treatment of adult-onset T2D and diabetic complications such as diabetic neuropathy. Lipoic acid has been reported to regulate glucose and lipid metabolism by modulating the activity of Sirt1 or AMPK (Park *et al*. 2008, Yang *et al*. 2014). Importantly, lipoic acid has been also reported to induce FGF21 expression in hepatocytes and in the livers of mice, probably via upregulation of CREBH (Bae *et al*. 2014). However, a biological role of FGF21 in lipoic acid-induced metabolic improvement remains to be determined. Acarbose, an α-glycoside hydrolase inhibitor that is being used as an anti-diabetic drug, has been reported to increase serum FGF21 levels in aged mice (Harrison *et al*. 2014). Given the effects of acarbose on the enhancement of the life-span and improvement of metabolic derangement (Harrison *et al*. 2014), these findings suggest that acarbose may elicit its metabolic actions through FGF21. This issue awaits further investigation.

Conclusions

Numerous studies have suggested that FGF21 is a promising therapeutic agent for the treatment of obesity-related insulin resistance due to its multiple actions on diverse metabolic target organs. In addition to the metabolic effects of FGF21, we discussed the importance of FGF21 induction in several disease conditions such as muscle atrophy, liver injury, cardiovascular disease, and renal injury. FGF21 may also play a protective role against glutamate-induced neuronal excitotoxicity (Leng *et al*. 2015) or chemical-induced testicular injury (Jiang *et al*. 2013). Chronic FGF21 overexpression has been reported to extend the life-span in mice, probably through a mechanism involving suppression of the GH/insulin-like growth factor 1 signaling pathway (Zhang *et al*. 2012). Despite diverse beneficial effects of FGF21, it may have side effects such as growth retardation (Inagaki *et al*. 2008), bone loss (Wei *et al*. 2012), and female infertility (Owen *et al*. 2013). Further studies are needed to evaluate the legitimate therapeutic role of FGF21 or its mimetics in several diseases, which will provide new strategies to develop novel agents without adverse effects. In addition, further work on the elucidation of uncharacterized downstream effectors of FGF21 in specific organs will help develop promising drug targets capable of mimicking the beneficial effects of FGF21.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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