The potential role of fibroblast growth factor 21 in lipid metabolism and hypertension

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Abstract

Fibroblast growth factor (FGF) 21 belongs to the FGF superfamily that is involved in cell proliferation and differentiation, neural development, angiogenesis and metabolism. FGF21 requires β-Klotho as a co-receptor. Tissues involved in metabolism such as the liver, adipose tissues, skeletal muscle and pancreas express FGF21. Starvation increases hepatic expression of FGF21, which then acts centrally to increase hepatic gluconeogenesis. FGF21 also increases fatty acid oxidation. This may be relevant in cold exposure, when expression of FGF21 is induced. Chronic treatment with recombinant FGF21 reduces serum and hepatic triglyceride levels, and ameliorates fatty liver in obese mice, through the suppression of the lipogenic gene, *Srebp-1*. FGF21 reduces hepatic cholesterol production by inhibiting *Srebp-2*, a transactivator of proprotein convertase subtilisin/kexin type 9 (PCSK9). LY2045319, an FGF21 analog, reduces LDL-C and triglycerides, and increases HDL-C in obese human subjects with type 2 diabetes. FGF21 does not seem to lower blood pressure acutely. In rats fed with high-fructose water to induce mild hypertension, 4-week treatment with recombinant FGF21 led to normalization of systolic blood pressure and improved serum lipid profile. FGF receptors and β-Klotho are expressed on the nucleus tractus solitarii and nodose ganglion in the baroreflex afferent pathway. Moreover, FGF21 acts on the hypothalamus to release corticosterone and induces in adipocytes the production of adiponectin, an adipokine with anti-hypertensive activities. Therefore, FGF21 may decrease blood pressure indirectly, through its actions in the liver, brain and adipose tissues.

Introduction

Fibroblast growth factor (FGF) 21 belongs to the FGF superfamily that comprises 22 members with a wide range of biological functions, including cell proliferation and differentiation, neural development, angiogenesis and metabolism [1-3]. While the classic FGFs bind to the cell-surface tyrosine kinase FGF receptors (FGFRs) via a high-affinity interaction with heparin sulfate glycosaminoglycans (HSGAGs) and act in a paracrine or autocrine manner, FGF21 lacks the conventional heparin-binding domain. This means that it can escape from tissues rich in HSGAGs and be secreted into the bloodstream to act as an endocrine hormone [4, 5]. FGF21 requires a single-pass transmembrane glycoprotein β-Klotho as a co-receptor for binding and activation of FGFRs [6, 7]. Unlike the ubiquitous expression of FGFRs, the expression of β-Klotho is limited to a number of metabolically active tissues including liver, adipose tissues, brain and pancreas, and therefore determines the tissue selectivity of FGF21's actions [8]. Although the highest expression of FGF21 was initially identified in liver and thymus [9], later studies reported its expression in other metabolic tissues such as adipose tissues [10, 11], skeletal muscle [12] and pancreas [13, 14]. Physiologically, expression of FGF21 is induced in these tissues by various nutritional and environmental stressors to mediate adaptive metabolic responses [15]. Hepatic expression of FGF21 is dramatically induced by starvation through the activation of peroxisome proliferator-activated receptor α (PPARα) which results in an increase in circulating FGF21. Elevated serum FGF21 crosses the blood-brain barrier and acts directly on the hypothalamic neurons to stimulate the expression of corticotropin-releasing hormone, thereby induces the release of corticosterone via the hypothalamic-pituitary-adrenal (HPA) axis to increase hepatic gluconeogenesis and maintain glucose homeostasis during prolonged fasting [16]. In addition, fasting-induced hepatic FGF21 increases fatty acid oxidation and ketogenesis through the induction of peroxisome proliferator-activated receptor γ coactivator protein-1α

(PGC-1α) to provide the brain with ketone bodies as energy fuels during severe carbohydrate deficit [17]. In contrast to the induction of hepatic FGF21 by starvation and stimulation with PPARα agonists, the expression of FGF21 in white adipose tissue (WAT) is increased by feeding and stimulation with the peroxisome proliferator-activated receptor γ (PPARγ) agonist, rosiglitazone [11]. Unlike fasting-induced hepatic FGF21 that is released into the circulation and acts as an endocrine hormone, feeding-induced expression of FGF21 in WAT does not lead to an elevation in serum FGF21, but acts on WAT in a feed-forward loop to mediate the insulin-sensitizing effects of PPARγ in an autocrine manner [11]. On the other hand, FGF21 is induced by cold exposure or β_3-adrenergic receptor agonists through the cAMP-protein kinase A-p38 MAPK signaling pathway in both white and brown adipose tissues to regulate browning and adaptive thermogenic responses in mice [10, 18]. In addition to the cold-induced FGF21 expression in adipose tissues, mitochondrial dysfunction also leads to the release of FGF21 from skeletal muscle which in turn activates browning of WAT to counteract diet-induced obesity and insulin resistance in mice [12].

Pharmacologically, FGF21 has been demonstrated to have pleiotropic effects against obesity and its related metabolic diseases [15]. The first evidence was provided by a high-throughput screening for insulin-like agents that are capable of inducing glucose uptake in adipocytes [19]. Subsequent *in vivo* studies demonstrated that therapeutic administration of recombinant FGF21 protein or transgenic over-expression of FGF21 in both obese mice and diabetic monkeys leads to multiple beneficial effects, including reduction in body weight, substantial alleviation of hyperglycemia and hyperlipidemia, and protection against fatty liver diseases and insulin resistance, at least partially by improving β-cell survival and function or by increasing energy expenditure [17, 19-23]. Notably, later studies from two independent groups demonstrated that pharmacological effects of FGF21 on body weight reduction and glucose homeostasis persist in uncoupling protein 1 (UCP1)-null mice, reflecting discrete

effects of FGF21 on metabolic regulation and UCP1-dependent thermogenesis [24, 25]. However, these findings do not rule out the possible role of UCP1-independent thermogenesis in conferring the beneficial effects of FGF21 on maintenance of energy homeostasis.

Apart from extensive investigations on the metabolic activities of FGF21, recent studies show protective roles of FGF21 in the cardiovascular system [15]. Positive associations between serum levels of FGF21 and cardiovascular events in human, including coronary heart disease [26] and various types of atherosclerosis [27-29] were reported in several studies. In line with these clinical findings, serum FGF21 level is also increased with aging in apolipoprotein E-deficient ($apoE^{-/-}$) mice with spontaneous development of atherosclerosis [30]. It protects $apoE^{-/-}$ mice against atherosclerosis possibly via alleviation of vascular inflammation and hypercholesterolemia by inducing adiponectin and suppressing sterol regulatory element-binding protein (*Srebp*)-2, respectively [30]. Emerging studies started to focus on the association of FGF21 with hypertension. Surprisingly, whether there is any causal relationship between FGF21 and blood pressure has not been well investigated. This review summarizes recent clinical and animal studies in this field, and raises some plausible possibilities for the potential roles of FGF21 in hypertension.

Hypertension and Dyslipidemia

Hypertension, or raised blood pressure, is highly prevalent globally, affecting about one-third of adults [31, 32]. Although the proportion of uncontrolled hypertension has slightly dropped since 1980, the overall prevalence of hypertension increased from 600 million in 1980 to almost 1 billion in 2008 due to the growth of world population and ageing [33]. Hypertension is a major risk factor for numerous comorbidities such as coronary heart disease, ischemic and hemorrhagic stroke, heart failure, peripheral vascular disease and

chronic kidney disease, and is therefore associated with at least 7.6 million deaths per year worldwide [34, 35]. Although the exact causes of hypertension are obscure, evidence is accumulating that obesity and dyslipidemia are key risk factors for the development of hypertension [36]. In an early national survey of adults in the United States, a strong association of body mass index (BMI) with the incidence of hypertension was found [37]. In a prospective 14-year follow-up study that included over 3000 men, those in the highest quintile of total cholesterol (TC) and non-HDL-C had increased risks of developing incident hypertension by 23% and 39%, respectively; whereas, men in the highest quintile of HDL-C had 32% reduced risk of hypertension than those in the lowest quintile [38]. It was further suggested that the association between blood pressure and serum cholesterol was independent of other variables such as body weight, blood glucose and insulin levels [39]. The relationship between dyslipidemia and hypertension is also evident by the term dyslipidemic hypertension (DH), which was first described by Williams *et al.* that a higher-than-expected occurrence of extreme lipid values was observed among middle-aged men with familial hypertension [40]. In line with these findings, statins have been suggested to have an amelioratory effect on blood pressure in hypertensive patients with hypercholesterolemia [41, 42].

Emerging epidemiological evidences suggest a clinical association between serum FGF21 levels and hypertension in different ethnic groups. It was first reported by Semba *et al*. that elevated serum level of FGF21 was associated with hypertension after adjustments with multiple explanatory variables in a prospective open cohort study of community-dwelling adults in the United States [43]. The association of serum FGF21 with blood pressure has been observed in other populations, including Chinese [28, 44], Japanese [45, 46]. This is in line with an earlier study demonstrating an association of elevated serum FGF21 with increased arterial stiffness, which has been shown to have a bidirectional association with

hypertension [47], in obese women [48]. Although there is a clear correlation between serum FGF21 and blood pressure, efforts to determine if this is a causal relationship remain ongoing.

Potential Roles of FGF21 in Hypertension through Lipid Regulation

Therapeutic administration of FGF21 has been shown to alleviate dyslipidemia in obese and diabetic mice, monkeys and human patients. Chronic treatment with recombinant FGF21 reduces serum and hepatic triglyceride levels and ameliorates fatty liver in diet-induced obese mice potentially via the suppression of lipogenic gene, *Srebp-1* [20]. In addition to the regulation of *Srebp-1*, the study showed an inhibitory effect of FGF21 on *Srebp-2*, which is a master regulator of cholesterol biosynthesis by preferentially activating the transcription of key cholesterologenic genes in the liver [30] (Figure 1). FGF21 deficiency leads to increased hepatic cholesterol biosynthesis in liver and exacerbated hypercholesterolemia with a shift of apolipoprotein profiles from HDL to LDL in apoE$^{-/-}$ mice, suggesting FGF21 as a physiological suppressor of hepatic cholesterol production [49]. Intriguingly, SREBP-2 is the most important and well-established transactivator of proprotein convertase subtilisin/kexin type 9 (PCSK9) [50], which binds and targets low-density-lipoprotein (LDL) receptor (LDLR) to lysosome degradation and in turn affects LDL cholesterol (LDL-C) catabolism. Reduced serum LDL-C levels are found in mice with gene inactivation of *Pcsk9* [51]. Autosomal dominant hypercholesterolemia is found in patients with *Pcsk9* gain-of-function mutations, and can be reversed by treatment with a PCSK9 monoclonal antibody [52]. Based on these studies, FGF21 is proposed to lower serum LDL-C levels potentially via the suppression of the *Srebp-2* and *Pcsk9* [53]. Studies on the regulation of lipid metabolism by FGF21 have been extended to non-human primates. When treated with recombinant FGF21 or engineered FGF21 variants, reduction in serum triglycerides, very low-density-lipoprotein cholesterol (VLDL-C), LDL-C, with an increase in high-

density-lipoprotein cholesterol (HDL-C) was clearly observed in obese/diabetic monkeys [23, 54, 55].

Another important mechanism whereby FGF21 may influence blood pressure is through its induction of the production of adiponectin in adipocytes. Adiponectin stimulates endothelial nitric oxide synthase activity and increases the production of nitric oxide (Figure 1). In man, blood adiponectin level correlates with endothelial function [56] and blood pressure [57].

In Sprague-Dawley (SD) rats fed high-fructose water to induce mild hypertension, 4-week treatment with recombinant FGF21 led to normalization of systolic blood pressure in parallel with improved serum lipid profiles, including decreased total cholesterol and triglyceride levels in the hypertensive rats [58]. This suggests a functional role of FGF21 in ameliorating high-fructose induced hypertension possibly through its lipid lowering effects.

FGF21 and Neural Control of Blood Pressure

Despite the well-established roles of FGF21 in the regulation of lipid metabolism in both liver and adipose tissues, more recent studies have shown that FGF21 travels across the blood-brain barrier and acts centrally to regulate various functions such as female reproduction [59], glucose metabolism [16], circadian behavior [60] and energy expenditure [61] through its actions on hypothalamus. Importantly, one recent study has demonstrated the expression of all subtypes of FGFRs (FGFR1-4) and β-Klotho on the nucleus tractus solitarii (NTS) and nodose ganglion (NG) in the baroreflex afferent pathway, which plays a key role in the modulation of blood pressure [62]. Chronic intraperitoneal infusion of recombinant FGF21 exerted beneficial effects on systolic blood pressure and baroreflex sensitivity in the high fructose-drinking rats. The up-regulation in baroreflex sensitivity was associated with activation of the Akt-eNOS-NO signaling pathway in NTS and NG induced by acute

intravenous administration of FGF21, although acute FGF21 treatment did not lead to any significant change in blood pressure [62]. This may imply that the effect of FGF21 on the regulation of blood pressure may be cumulative rather than immediate.

In addition to the action on the baroreflex sensitivity, the aforementioned study demonstrated that FGF21 directly acts on the hypothalamic neurons and activates the hypothalamic-pituitary-adrenal (HPA) axis to release corticosterone [16] (Figure 1). Notably, corticosterone has been widely reported to be involved in the suppression of hypertension [63, 64]. Therefore, FGF21 may also lower blood pressure through the regulation of corticosterone.

FGF21 in Clinical Trials

Recently, the pharmacological effects of FGF21 in human have been tested in two independent clinical trials. LY2045319, an FGF21 analog has been used to treat obese human subjects with type 2 diabetes (T2D). Patients treated with the FGF21 analog have shown improved lipid profiles, including reduced LDL-C and triglycerides, and increased HDL-C when compared to patients receiving placebo [65]. Although no significant change in blood pressure was observed in obese patients treated with LY2405319, one subject was reported to develop hypotension and discontinued from the study, which may imply a role of the FGF21 analog in the reduction of blood pressure in human [65]. However, as only 38 patients were included in the above study, the effects of FGF21 on the regulation of blood pressure in humans is worthy of further investigations. More recently, another long-acting FGF21 molecule, PF-05231023, has been tested in patients with T2D and also showed efficacy in body weight reduction and improvement in circulating lipid profiles [66]. There is no evidence so far that FGF21 or its analogue lowers blood pressure in humans, but arguably, there have not been studies designed to measure small changes in blood pressure in both

normotensive and hypertensive persons. Moreover, even the blood pressure-lowering effect of established antihypertensive drugs is not always immediate, so clinical studies of antihypertensive effects should be at least 6-8 weeks in duration. It is currently unclear whether elevated serum FGF21 levels are due to the compensatory responses or the presence of FGF21 resistance, a phenomenon observed in many previous studies [67].

Conclusions

FGF21 is known to have pleiotropic effects on lipid and glucose metabolism. Emerging evidence from both clinical and rodent studies suggested potential roles of FGF21 in the pathophysiology of hypertension. Caution is needed in extrapolating experimental findings from animal models to man. Further studies are therefore needed to clarify the role of FGF21 in hypertension and to explore the use of FGF21 as a possible therapeutic target. At least, serum FGF21 is a biomarker of hypertension. Moreover, FGF21 and its analogues appear to have beneficial effects on lipid and glucose metabolism in man. The idea of one drug that can treat obesity, diabetes, dyslipidemia and hypertension all at once might have seemed impossible a few years ago, but is now a tantalizing and exciting prospect.

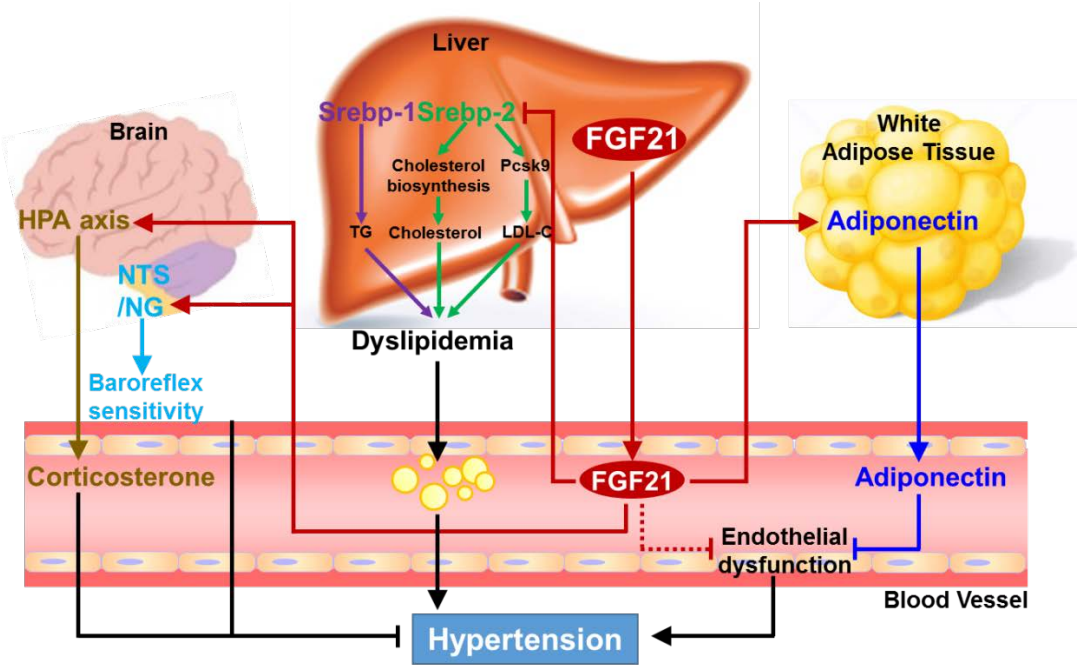

Fig.1. Potential roles of fibroblast growth factor (FGF21) in the modulation of blood pressure via the crosstalk between liver, white adipose tissue, brain and blood vessels. HPA, hypothalamic-pituitary-adrenal; LDL-C, low-density-lipoprotein cholesterol; NG, nodose ganglion; NTS, nucleus tractus solitarii; Pcsk9, proprotein convertase subtilisin/kexin type 9; Srebp, sterol regulatory element-binding protein; TG, triglyceride.

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