Perspective of FGF-21, a new metabolic regulator in neurocontrol of circulation and pathological process of hypertension

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Increasing evidence has demonstrated that the fibroblast growth factor-21 (FGF-21) plays a crucial role in metabolic disorders, such as obesity, diabetes, and metabolic syndrome, and the secondary hypertension is the most common complication for these metabolic disorders. Intriguingly, several lines of evidence point out the potential involvement of FGF21 in not only secondary but also primary hypertension. However, the underlying molecular and cellular mechanisms are remained unknown. In this short and perspective review, we highlight the potential connection between the FGF-21 and hypertension by several direct and indirect evidences based upon the current literatures and our preliminary observation. Additionally, the current evidence also indicates the limitation of Myalept, a leptin-like medication approved by FDA at 2014, that has been used for the treatment of systemic metabolism disorder of adipose tissue. Taken all these data together, the FGF-21, a new metabolic regulator, would be a promising linkage factor between metabolic and circulatory systems and potential drug target for both metabolic disorders and hypertension. Journal of Nature and Science, 1(5):e93, 2015

FGF-21 | metabolic disorder | hypertension | baroreflex

Hypertension and metabolic disorders

Hypertension or high blood pressure, sometimes called arterial hypertension, is a chronic medical condition, in which the blood pressure in the arteries is elevated. As of year 2000, nearly one billion people or ~26% of the adult population of the world had suffered from hypertension and it was common in both developed (333 million) and undeveloped (639 million) countries (1). In Europe, the hypertension occurs in about 30-45% of people as of year 2013 (2), whereas, it occurs in about 44% (34-76%) of the population, the highest rates of hypertension in the world (3). Hypertension is more common in men (4). Importantly, hypertension is one of the most common complications in the patients with metabolic disorders, such as obesity, insulin resistant (type 2 diabetes mellitus, T2DM), and metabolic syndrome (MS). Increasing evidence has demonstrated that the Leptin, the peptide hormone encoded by obesity gene (Ob), plays critical roles in metabolic process. Myalept (5), a leptin-like medication approved by FDA at 2014, has been used for the treatment of systemic metabolism disorder of adipose tissue, which is usually accompanied with deficiency of leptin, diabetes, and Hypertriglyceridemia. The evidence has demonstrated that leptin impairs cardiovagal baroreflex function at the level of the solitary tract nucleus (6), leading to the upregulation of sympathetic drive and increase in artey blood pressure as the result. From the theratical point of view, leptin-like medication should not be applied for the patients with matabolic disorder with hypertension. Hence, it currently becomes the key point for translational science and interdiscipline linking circulatory and matabolic systems all over the world seeking the linkage factor between two systems and this linkage factor would be a new and promising generation of biological agent to be suitable for those patients with primary and secondary hypertension, and matabolic disorder with hypertension as well.

New matabolic regulator FGF-21 and hypertension

Fibroblast growth factor 21 (FGF-21) is recently identified a cytokine belong to FGF superfamily, which is expressed in numerous tissues, circulating levels of FGF-21 are derived specifically from the liver in mice (7). When the body is in a state of starvation stress, the circulating level of FGF-21 is dramatically increased; therefore, the FGF-21 is also termed as the hunger factor. The secrretion of FGF-21 is controlled by the peroxisome proliferator-activated receptors (PPARs) and its agonist, Fenofibrate, is currently used for lipid-lowering agents (8). The studies have confirmed that the FGF-21 possesses potent pharmacological effects on glycometabolism, lipometabolism, and insulin sensitivity in metabolic tissues (9), and all these biological activities of FGF-21 have to be achieved by forming a complex (9-11) with single-transmembrane protein β-Klotho that functions as a co-receptor for FGF-21, leading to the activation of MAPK and Akt signal transduction pathway, PPARy as well as downstream factor (12, 13). The FGF-21 is closely associated with numerous metabolic disorders; on the one hand, the expression of FGF-21 is significantly elevated (14, 15) in the patients with obesity, T2DM, metabolic syndrome, and nonalcoholic fatty liver diseases, on the other hand, a large body of investigations with cellular levels or using animal models have demonstrated that the FGF-21 has a significant metabolic protective effects (12, 16) and this phenomenon has been termed as the FGF-21-resistant, well similar to insulin-resistant like mechanism, i.e., the expression of FGF-21 receptor in the liver is extremely downregulated and the overall function deficiency for FGF-21 is occurred, which leads to the increase in the secretion of FGF-21 (from the liver and the serum level of FGF-21 as the consequence (17)).

The FGF-21 plays a key regulatory role in metabolic processes and it has well been documented that the hypertension is one of the most important complications for the metabolic disorders; however, it is still a blank if FGF-21 directly contributes to the etiology and pathophysiology of hypertension, due mainly to the modulation of neurocontrol of blood pressure and circulation, i.e., the baroreflex afferent function. Through a large number of data analysis with current published records, we have a reason to believe that there is a key basis for the existence of close contact between FGF-21 and hypertension (Figure 1). Firstly, the line of direct evidence includes that the increased serum level of FGF-21 could exist independently upon the patients with primary hypertension (primary HTN) or coronary heart diseases complicated with hypertension (CHD-HTN) (18, 19); in addition, the serum level of FGF-21 is significantly elevated in those patients with obesity accompanied with hypertension (obesity-HTN) compared with the obesity without hypertension (14), furthermore, intraperitoneal administration of FGF-21 shows a hypotensive action to a certain extent in rodents with hypertension and insulin-resistant (HTN-IR) (20). These lines of direct evidence strongly suggest that there is a potential association between FGF-21 and hypertension and this action may be independent upon the metabolic effect of FGF-21. Secondly, several line of indirect evidence also imply the close connection between FGF-21 and hypertension, for example, a starvation diet for the weight-loss and metabolic medication, such as Fenofibrate possesses a remarkable hypotensive effects in the patients with obesity and diabetes (T2DM) (21, 22), in the meanwhile, the...
stimulation with hunger stress and Fenofibrate could result in the dramatically serum elevation of FGF-21 (8). These observations presumably hint that the FGF-21 would be key linkage effectors connecting the starvation diet for weight-loss or metabolic medication with hypotensive action. Thus, we hypothesize that FGF-21 could be a key player in pathophysiological progress and the neurocontrol of blood pressure and circulation, whereas, the potential targets for FGF-21 and underlying mechanisms remain uninvestigated.

FGF-21 injection

Serum FGF21 level ↑

HTN-IR rats

primary HTN +

CHD-HTN +

Obesity-HTN +

Hypotensive effects

FGF21 secretion

Fenofibrate

Obesity / T2DM

Figure 1. The key evidences of FGF-21 association with hypertension.

Figure 2. Relative mRNA expressions of FGF-21 and FGFRs-Klb in difference organs of rats.

FGF-21 has a close association with the etiology of hypertension and blood pressure regulation, but the specific target and mechanisms are not elucidated yet. Due to the significant morbidity and mortality of hypertension as the primary disease condition or as the complication with the cardiovascular and metabolic disorders, it would always be an important scientific question that needs to be answered urgently and precisely.

FGF-21 and potential interests for the gender difference in hypertension

From the translational scientific point of view, this is a very important and complicated question that needs further clarification for both the bedside and bench although it has been digging deeply from all aspects for couple of decades. It has widely accepted that the incidence for the primary hypertension or obesity complicated with hypertension is more common in males compared with age-matched females (27, 28). Whereas, the normal blood pressure and the prevalence of hypertension tend to be lower in females than those in age-matched males, and these differences seems disappeared when females reach the postmenopausal period (29).

Over the past 15 years and due largely to the establishment of intact nodose ganglion slice preparation in rats (30, 31), studies have undergone a significant progress in the baroreflex afferent functions and the finding of low-threshold and sex-specific myelinated Ah-type baroreceptor neurons (BRNs) (32) in NG would be a milestone for better understanding the sexual dimorphism of neurocontrol of circulation (33-39), except for the traditionally and afferent-specifically classified myelinated A- and unmyelinated C-types (30, 40-46) in rats. The most importantly, the physiological function of Ah-type BRNs is tightly dependent upon the female hormone, 17β-estradiol (17β-E2) (34, 37, 47) and likely to contribute to the gender-based difference in the etiology of hypertension and blood pressure regulation under the physiological condition. Compared with myelinated A- and unmyelinated C-type neurons, the higher neuroexcitability characterized by Ah-type BRNs might be attributed at least to the specific or relatively higher expression of voltage-gated Na+ channels (Nav1.7, Nav1.8, and Nav1.9), hyperpolarization-activated cation channel (HCN1), and large-conductance Ca2+-activated K+ channel (KCa1.1) (36, 38, 43, 48-51) and chemosensitive to certain neurotransmitters (50) or chemicals (44) as well.
Figure 3. FGF-21: The future interdisciplinary focuses of basic research and clinical application.

Figure 4: The research proposals regarding FGF-21 as the linkage factor crossover metabolic, neuronal and circulation systems.
Interestingly, the study has shown that the FGF-21’s function is also associated with 17β-E2 and plays crucial roles in female neuro-endocrinology and reproduction (24). Owing to the apparent gender difference in hypertension of either primary or secondary to metabolic disorder such as the obesity, we have a strong reason to hypothesize that, based upon the current published information combined with our preliminary data, the FGF-21 may influence the electrophysiological remodeling of low-threshold and sex-specific myelinated Ah-type BRNs by specifically functional expression and distribution of FGFRs in the first- and second-order baroreceptor neurons within the baroreflex afferent pathway, and contribute to the sexual dimorphism in pathophysiological progress of the primary and secondary hypertension.

The signal and molecular effects of FGF-21 on neurons

The biological effects of FGF-21 are mediated by FRS2 (FGF receptors substrate 2) of cell membrane tyrosine kinase receptors, FGFRs, required with the single transmembrane protein Klb (9). As the FGFR1-4 and Klb expressed on NG and NTS (Figure 2), the neuronal signals and ion channels effects of FGF-21 are attractive. The obvious signals activated by FGF-21 on metabolic, neuronal and heart tissues, including phosphorylation of PI3K/Akt (phosphatidylinositol 3-kinase/Akt), ERK1/2 (extracellular signal-regulated kinase) and AMPK (AMP-activated protein kinase) pathways (12, 13, 51) and so on. The nitric oxide (NO) and NOS (nitric oxide synthase) signal pathway plays significant role in central cardiovascular regulation and modulates the baroreflex in the NTS of rats (39), and it was well known that both ERK and Akt are upstream factors of NOS phosphorylation (52, 53), therefore, the NOS/NO pathway on NTS neurons is the potential downstream signal of FGF-21. The BRNs housed in nodose ganglia is the primary afferent neurons for the signal transduction of blood pressure. The neuroexcitability of BRNs and baroreceptor reflex sensitivity (BRS) based on ion channels (Na’, K’ channels e.g.) play important roles in neurocontrol of blood pressure regulation. According to our previous report , Na’ channels (voltage-gate Na’ channels Nav1.7, Nav1.8, and Nav1.9) functionally expressed on NG (53), while it was reported the ERK signal pathway can activated the tetrodotoxin (TTX)-sensitive Na’1.7 channel directly by phosphorylation (at loop I of Nav1.7, L1) (54). Collectively, the potential of molecular basis for signal transduction of blood pressure control of FGF-21 exists in both NG and NTS (Figure 3).

FGF-21: the future interdisciplinary focus of basic research and clinical application

FGF-21 plays important roles in the metabolic liver and adipose tissues, and other organs or tissues where expressed FGFRs-Klb, especially the central and peripheral nervous systems, and the relationship between FGF-21 and hypertension is noticeable (Figure 1), while the effects and mechanisms of FGF-21 working on hypertension processes remains unclear. Therefore, we propose that FGF-21 is a potential target for blood pressure regulation in this review simply because nodose ganglia / BRNs and NTS, where are the central parts of the autonomic control and baroreflex afferent pathway for blood pressure control, also expressed abundant FGFRs-Klb (Figure 2). Additionally, metabolic, neuronal and circulatory diseases, as well as sexual hormone estrogen related gender modulations are all linked by the effects of FGF-21. Attractively, there still have three key directions of this hot linkage filed needed to be investigated in future (Figure 4): firstly, the effects of FGF-21 on blood pressure control via its receptors distributed on BRNs in NG and NTS , and the changes in FGF-21 functions during hypertension processes; Secondly, the mechanisms behind FGF-21 regulating blood pressure through the baroreflex afferent pathway, ion channels or molecular modulation, and the downstream signal pathways activations of FGF-21 receptors on baroreceptor neurons; finally, the interactions of FGF-21 and estrogen, the effects of FGF-21 on low-threshold and sex-specific subpopulation of Ah-BRNs, and how they relate to gender difference in incidence of hypertension. Consequently, this review proposes future research directions of FGF-21 on pathophysiological processes of hypertension, and provides new theoretical basis and strategies for the clinical management of primary and secondary hypertension associated with metabolic diseases such as obesity, T2DM, and metabolic syndrome, and gender-related hypertension.

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7. Markan KR, Naber MC, Ameka MK, Anderegg MD, Mangelsdorf DJ, Klib (9). As the FGFR1-4 and Klb expressed on NG and NTS (Figure 3).
15. Sembra RD, Grazia C, Straif J, Sun K, Schumack DA, Ferrucci L. Elevated serum fibroblast growth factor 21 is associated with...


