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Therapeutic potential of FGF21 in diabetes

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Abstract
FGF21, an endocrine regulator, is a member of the fibroblast growth factor family. The FGF family has 22 members in the humans. Its receptor family, i.e. FGFR has 4 members in the Homo sapiens. The family of FGF has been only found in multicellular organisms. The FGF21 has a key role in the regulation of various metabolic fundamental physiological processes such as cell differentiation, morphogenesis, proliferation etc.
FGF21 has varied importance in various metabolic pathways. It has been found that FGF21 is able to augment insulin activity in the glucose uptake and thus has an insulin-like activity in addition it has been found to have anti-obesity effects. Further, FGF 21 has been found to have lipolytic activity in adipocytes, capability to carry ketogenesis, clearance of triglycerides in hepatocytes, potential to carry torpor and signalling of hormones required for growth in hepatocytes.
Any aberrations in the FGF21 have been linked to hazardous health conditions of cancer and metabolic disorders. Various diseases such as NAFLD, Cushing's syndrome, lypodystrophye, end stage renal disease have been diagnosed with increased FGF21 serum levels. There is a wide scope of therapeutic applications considering numerous pathways that FGF21 is an integral part of and could also play as a biomarker for identification of numerous diseases.

Keywords: FGF21, PPAR, Klotho (KL) co-factor, diabetes, obesity, renal diseases, cardiovascular disorders

Introduction
A large number of integrated network of hormones control the metabolism of glucose and lipids in our body. They closely regulate the substrate consumption and energy balance in response to nutritional status. Some of the more significant hormones are insulin and glucagon secreted by the pancreas; adipokines (leptin and adiponectin) secreted by the adipose tissue; glucocorticoids by adrenal gland; glucagon-like peptide-1 and ghrelin secreted by gut-derived hormones [1-3]
The fibroblast growth factors (FGFs) superfamily plays an important role in these regulatory networks [4]. FGF15/19, FGF21 and FGF23 lack the heparin-binding property [5], and therefore can be released into the circulation to act as endocrine factors, unlike other members of the FGF superfamily. FGF15/19 controls cholesterol/bile acid synthesis [6], FGF23 modulates phosphate/vitamin D metabolism [7], and FGF21 regulates mostly glucose and lipid metabolism [8-10].
Kharitonenkov *et al.*, discovered the metabolic activity of FGF21 by administering a recombinant FGF21 in diabetic mice and dietary obese mice. It was found that FGF21 lowered blood glucose and triglyceride levels, reversed hepatic steatosis and improves insulin sensitivity [11]. Studies further prove that over-expression of FGF21 in transgenic mice results in an increased resistance to diet-induced obesity and the same in diabetic rhesus monkey results in a dramatic decline in fasting levels of blood glucose, fructosamine, insulin and glucagon, triglycerides and low-density lipoprotein cholesterol and increase of high-density lipoprotein cholesterol [9]. However, it is of importance to note that therapeutic doses of recombinant FGF21 used for these studies are substantially higher than those in physiological concentrations [12]. Since FGF21 knockout (KO) mice do not develop either hyperglycaemia or insulin resistance [13, 14], it is also possible that the therapeutic benefits of recombinant FGF21 on glucose homeostasis are only of pharmacological interest, but not of any physiological relevance.

Metabolic actions of FGF21 on its major target tissues

Hepatic FGF21 functions

FGF21 is synthesized at multiple sites but the most important one is the liver [15]. It was found that in mice, the hepatic expression and plasma levels of FGF21 are markedly elevated upon fasting, but are suppressed by re-feeding [16]. Peroxisome Proliferator Activated Receptor alpha (PPARa) is a ligand-activated transcriptional factor that controls the fasting-induced hepatic expression of FGF21, lipid metabolism and energy homeostasis [17, 18]. PPARa agonist's fenofibrates are strong inducers of FGF21 expression in both mouse livers and in human primary hepatocytes whereas both fasting and fenofibrates induced expression of FGF21 is abrogated in PPARa KO mice, suggesting that FGF21 is a key downstream target of PPARa mediating the metabolic adaptation responses to fasting/starvation, including ketogenesis, fatty acid oxidation and gluconeogenesis [19].

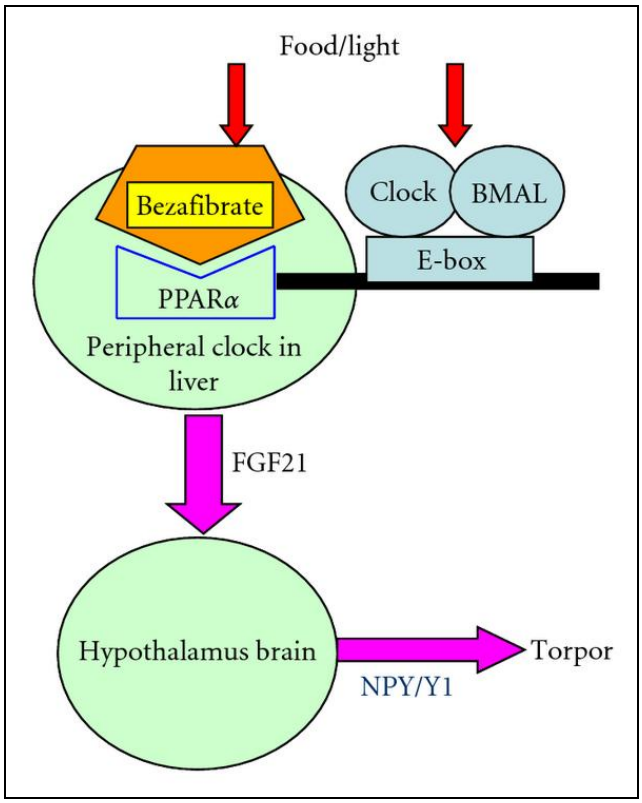
FGF21 actions in adipose tissue

In white adipocytes, FGF21 stimulates glucose uptake, modulates lipolysis, enhances mitochondrial oxidative capacity, and potentiates PPAR-γ activity [20]. It was also found to have a role in regulation of thermogenic activity of brown adipocytes [21]. The glucose uptake is stimulated in an insulin-independent manner. However unlike insulin, FGF21 has no effect on plasma membrane translocation of the glucose transporter GLUT4, but induces the expression of GLUT1 through transcriptional activation to induce glucose transportation.

FGF21 stimulates p44/42 mitogen activated protein kinase (MAPK) which in turn phosphorylates and activates the transcription factors Serum Response Factor (SRF) and E26 transformation-specific (ETS) like protein-1 (Elk-1). Elk-1binds to a highly conserved serum response element and E-26 motif to trans-activate GLUT1 gene.

Central FGF21 actions

FGF21 is considered as the missing link between the brain and the peripheral metabolic tissues [22]. The brain has a crucial part in controlling body fat content, glucose and lipid homeostasis [23]. FGF21 crosses the blood–brain barrier to enter the brain in a unidirectional and non-saturable manner [24, 25]. It was observed that in male obese rats, chronic intra-cerebroventricular infusion of recombinant FGF21 into the lateral cerebral ventricle resulted in increased food intake, energy expenditure, and hepatic insulin sensitivity [26] This proves that the metabolic effects of FGF21 are regulated also through its central actions. PPARa regulates the expression of FGF21 [27] and it works as a possible signalling peptide to transmit the signal from the liver to the brain to induce a state of decreased physiological activity as an adaptive response to conserve energy in animals characterized by a reduced body temperature and metabolic rate and is referred to as torpor [28]. Administration of the PPARa agonist bezafibrate in mice induces a time-dependent torpor-like phenomenon and simultaneously increases hepatic FGF21 production [29]. Interestingly, both transgenic expression and therapeutic administration of FGF21 stimulate torpor in mice. Likewise, intra-cerebroventricular injection of neuro-peptide Y (NPY) also reliably induces torpor-like hypothermia that resembles natural torpor in hamsters [30]. Since the PPARa agonist bezafibrate also stimulate NPY production, it has been suggested that PPARa controls torpor and circadian clock through the FGF21-NPY axis.



Source: PPAR research 2009 (2009)

Fig 1: Role of PPARα in the control of torpor through FGF21-NPY pathway.

The pancreatic actions of FGF21

Numerous studies demonstrate how different animal models have consistently exhibited the protective effects of FGF21 against various pancreatic injuries in addition to b-cell dysfunction [31]. It was observed that FGF21 KO mice are more susceptible to cerulein-induced pancreatitis (CIP), whereas FGF21 transgenic mice are resistant to develop this acute pancreatic damage [32]. The protection of FGF21 against CIP is due to its ability to activate ERK1/2 in pancreatic stellate cells. FGF21 expression can be detected in human, rat and mouse pancreatic islets as well as in rat primary b-cells and INS-1E cells [33]. Short-term administration of FGF21 reduces the plasma insulin concentrations in both healthy and db/db mice (model for diabetes, obesity and dislipidemia), whereas long-term treatment with FGF21 augments the amount of insulin per islet in db/db mice. FGF21 suppresses glucagon secretion from isolated rat islets and reduces plasma glucagon concentrations in mice.

However, FGF21 does not affect islet cell proliferation. Treatment of rat islets result in a partial protection against glucotoxicity and cytokine induced apoptosis by activation of both ERK1/2 and Akt signalling pathways [34].

In humans, plasma levels of FGF21 are elevated in patients with type-II diabetes, but are decreased in patients with type 1 diabetes and latent autoimmune diabetes [35]. Furthermore, FGF21 is functionally related to insulin secretion in man. Nevertheless, there is currently no direct evidence supporting FGF21 as a physiological regulator of FGF21 secretion. Further studies on the impact of FGF21 deficiency on b-cell size and number as well as insulin secretion profiles in a type-1 or type-2 diabetic model should help clarify the physiological roles of FGF21 in islet biology.

Several autocrine, paracrine and exocrine growth factors with metabolic action have been identified to stimulate the intake

of glucose and mitochondrial function regulation. They include neuregulins, platelet-derived growth factor, and members of the fibroblast growth factor (FGF) family, one of which is FGF21 due to its potential therapeutic actions [36].

The following paper will discuss in detail the physiological and pathophysiological significance of FGF21 and its therapeutic potential.

Review of Literature

Ranging from development to survival, fibroblast growth factors (FGFs) play diverse roles in controlling various cellular processes. Consisting of 22 members, FGFs can be classified into three broad categories There are a total of 22 FGFs found and they are classified as paracrine, intracrine, and endocrine FGFs [37] based on their mode of action.

Paracrine FGFs function as secreted local paracrine signalling molecules in multiple developmental processes, including differentiation, cell proliferation, and migration. These are FGF1~FGF10, FGF16~FGF18, FGF20, and FGF22. They bind to cell surface tyrosine kinase FGF receptors (FGFRs) [38] to mediate biological responses. Intracrine FGFs function as non-secreted signalling molecules. These are FGF11~FGF14 and they mainly play roles in neuronal functions at post-natal stages in an FGFR-independent manner [39]. Endocrine FGFs are emerging in evolution and are found in only vertebrates unlike paracrine and intracrine FGFs have been identified in both invertebrates and vertebrates. Endocrine FGFs such as FGF15/19, FGF21, and FGF23, are secreted proteins that generate a biological response in an FGFR-dependent manner. They also have a significant role in metabolism related activities at post-natal stages [40]. These hormone-like FGFs lack a conventional heparin binding domain, which allowing them to attain circulation at sites where they are abundantly present. FGF19, FGF21 and FGF23 use the Klotho co-factor proteins for binding to the (FGFRs) and its activation [41-43].

FGF15/19 play role of metabolic regulators in bile acid metabolism as metabolic regulators in bile acid metabolism and FGF23 assist in phosphate and active vitamin D metabolism. FGF21 exerts diverse pharmacological effects on glucose and lipid metabolism, ketogenesis, and growlothoth hormone signalling in hepatocytes in mice. It also physiologically regulates lipid metabolism in adipocytes and torpor.

Identification of Fgf21

The Fgf21 gene was originally identified in mice with a polymerase chain reaction (PCR) based sequencing study using human FGF15/19 as reference. The Human Fgf21 was also identified by homology-based searching in the human genome database [15]. Later, in an assay to identify novel proteins with therapeutic potential for diabetes [8], human FGF21 used a stimulator of glucose uptake in mouse 3T3-L1 adipocytes.

Structure of FGF receptor

The receptor for FGF21 comprises of two pre complex components: FGFR and KLB. KLB is an adaptor-like transmembrane molecule that binds to FGF21 directly to activate FGFR, and FGFR serves as an activity-competent subunit.

It is still not clear whether there is a preferred FGFR out of the four FGFRs (FGFR1-FGFR4) for constitution of a fully functional FGF21 receptor complex. This is because contradictory to previous beliefs that FGFR1 was the sole binding molecule, recent evidences suggest that the other three types also play a significant role. KLB facilitates as an interaction partner with many, if not all, FGFR isoforms to induce activation of FGF21 pathway in a target cell.

Mode of action of FGF21; KLB dependent signal transduction by FGF21

There have been studies that show that the presence or absence of the cofactor Klothoβ (KLB) determines the metabolic activity of FGF21. The over expression of KL or KLB can be co-related to signalling FGFs.

FGF21 initiates its action by activating FGF receptors in the presence of a co-receptor, Klothoβ [44, 45] which has been found in liver and adipose tissues but not in skeletal muscle or heart tissues. Studies have shown that FGF21 induces phosphorylation of ERK1/2 in liver and adipose tissues but not in skeletal muscle or heart. This signalling pattern suggests that lowering of glucose is a result of the metabolic actions FGF21 in peripheral tissues such as liver and adipose tissues.

There are multiple mechanisms involving transcriptional and post-translational regulation that control the activities of FGF21 action. FGF21 mediates its effects through posttranslational events without the requirement of new protein synthesis by modulation of metabolic enzyme activities through kinase- and phosphatase-mediated reactions. It is still not clear whether FGF21 signalling intersects with the insulin signalling at any point in the regulation of glucose metabolism. The ERK pathway is known to regulate gene expression and is activated by FGF21. It was found that in 3T3-L1 adipocytes, FGF21 also augments the expression of GLUT1 resulting in an increased uptake of glucose and upon addition of protein synthesis inhibitors the glucose uptake was observed to come to a halt. This observation was theorized as a transcription-mediated mechanism [46].

While most FGFs do not require any co factor for activation of the signalling pathway via FGFR dimerization, FGF21 requires a pre-requisite co-factor element Klothoβ for activation. Similar to most FGFs, FGF21 has a typical 120 amino acid β-trefoil core structure but varying at the N- and C-terminal sequences. The C-terminus of FGF21 is critical for binding to Klothoβ and the N-terminus for the efficacy of FGFR activation.

Now, unlike other FGFs, FGF21 functions in a heparin independent manner thereby allowing FGF21 to escape cell membranes which are abundant with Heparan Sulfate Proteoglycans (HSPGs) and function as an endocrine factor. It can be concluded that tissue-specific expression of Klothoβ and FGFR subtypes together define tissue selectivity of FGF21.

FGF21 requires a single pass transmembrane protein Klothoβ as a co-receptor. Klothoβ expression is restricted to a number of tissues i.e. the adipose tissue, brain, liver and pancreas resulting in their tissue selective binding to FGF21.

The receptor elements FGF21 receptor and KLB form a receptor complex and are present on the plasma membrane of the cells with FGF21 specificity. It activates in a two step process when an FGF21 molecule binds to it. First, the C-terminus of FGF21 binds to KLB inducing a conformational change in both FGF21 and FGFR. This allows the binding of the N-terminus of FGF21 to FGFR to induce the tyrosine kinase activity, thereby initiating cascade of reactions leading to cross phosphorylation, downstream signal transduction and a cellular functional response.

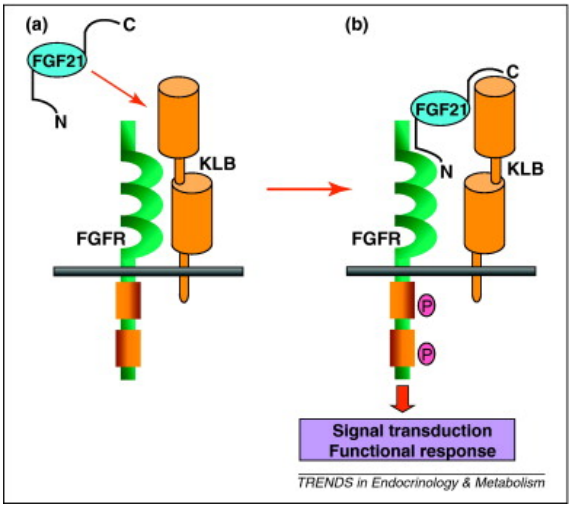
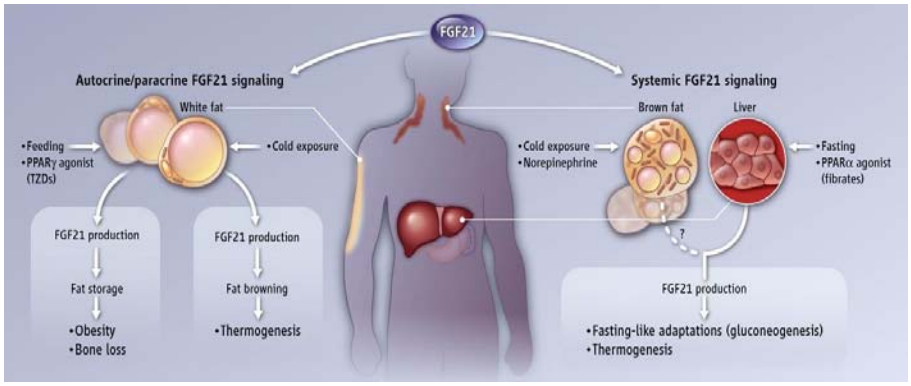


Fig 2: The proposed mechanism of FGF21 receptor activation. (a) FGFR and KLB receptor complex on the plasma membrane (b) FGF21 induces signal transduction by binding to FGFR and KLB resulting in receptor cross phosphorylation, downstream signal transduction and a cellular functional response. Source: Trends in Endocrinology & Metabolism 22.3 (2011): 81-86.



Source: Science 336.6082 (2012): 675-676.

Fig 3: Systemic and local actions of FGF21

Feeding and PPARγ agonists (such as TZDs) induce the expression of FGF21 in white adipocytes that result in improving the fat storage, gaining of fat mass and reduction of bone strength and all contribute to autocrine and paracrine effects. Fasting and PPARα agonists (such as fibrates) induce the release of FGF21 from the liver causing fasting like adaptations like gluconeogenesis.

FGF21: A biomarker for metabolic diseases

Increased levels of FGF21 have been found in non-alcoholic fatty liver disease, obesity, and diabetes [47]. It is therefore associated with adiponectin, weight, glucose, HDL cholesterol, and triglycerides [48]. In a study conducted with type II diabetes patients, elevated FGF21 levels were co related with multiple metabolic parameters such as blood glucose and lipids, blood pressure, and HbA1c, obesity, diabetes, hyperlipidemia, atherosclerosis and fatty liver disease [49, 50]. Cardiovascular morbidity and mortality can be associated with increased baseline serum levels of FGF21 levels [51] which was stronger in case of patient with higher total cholesterol levels in a Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study [52] conducted by Ong *et al*. Higher levels of serum FGF21 was associated with higher risk of coronary artery disease [53], carotid atherosclerosis, hyper-triacylglycerolaemia, hyper-insulinaemia, pericardial fat accumulation and the metabolic syndrome [54]. They found that in the FIELD study, higher plasma FGF21 levels at baseline were associated with higher risk of cardiovascular events. They also concluded that it could be a compensatory protective response to FGF21 resistance.

In case of Cushing's syndrome, a condition resulting from high cortisol levels for prolonged periods, it was observed that serum FGF21 levels are elevated [55] relative to healthy people. However it was also noticed that they do not differ largely from that of cases with obesity and type II diabetes.

Low levels of serum FGF21 is observed among patients with anorexia nervosa [56] (AN). It was observed that in mice the expression of FGF21 in liver increases upon starvation and decreases upon feeding and is therefore nutritionally regulated. In patients with restrictive type of AN, the plasma FGF21 levels are related to their nutritional status and in case of both normal weight and underweight people, it can be associated with serum levels of leptin, adiponectin, and insulin [57, 58, 27]. FGF21 levels in patients with AN are tightly regulated by nutritional treatment.

A recent study also indicates increased levels of FGF21 in case of mitochondrial diseases [59].

Role played in diabetes, CVDs, obesity and renal disorders

FGF21 has numerous beneficial effects on glucose homeostasis and lipid metabolism. FGF21 has proven to improve insulin sensitivity, glucose, and lipid homeostasis and preserves B-cell functions in diabetic animal models [10, 60, 61]. Additionally, unlike the most of the other FGFs, FGF21 is free from the proliferative and tumorigenic effects [62].

Insulin metabolism and diabetes

FGF21 induces the sequential activation of multiple transcription factors for the induction of GLUT1 to stimulate the uptake of glucose [63] in differentiated adipocytes and result in their storage as triglycerides. This pathway is additive and independent of insulin. This results in the greater clearance of glucose from the body [64, 65]. In mice, FGF21 was found to suppress hepatic glucose production, increases liver glycogen, and lowers glucagon [66]. Furthermore, FGF21 is found to preserve B-cell function and survival[67] by activation of extracellular signal-regulated kinase 1/2 and Akt signaling pathways [68-70].

Studies show that in genetically compromised diabetic rodents, FGF21 reduces plasma glucose levels to near normal levels. Also it was found that in high-fat diet-induced obese (DIO) male Wistar rats, administration of FGF21 resulted in an increase of hepatic insulin sensitivity due to increased insulin induced suppression of both hepatic glucose production and gluconeogenic gene expression indicating that the central nervous system (CNS) as a potentially important target for the beneficial effects of FGF21 as it has a non-saturable, unidirectional influx across the blood–brain barrier [25].

Among the multiple FGF receptors, FGFR1 is the main receptor molecule aiding in the FGF21 binding. A phenomenon called FGF21 resistance was observed in obese mice. The adipose tissue isolated from these mice showed that upon activation of ERK1/2, the responsiveness to FGF21 was highly impaired along with GLUT1 expression and consequent glucose uptake as a result of decreased levels of FGFR1c and Klothoβ.

Obesity

FGF21 has a downstream effector as the insulin-sensitizing adipokine adiponectin [71-73]. Studies have shown that in mice, treatments with FGF21 augmented the expression and secretion of adiponectin in adipocytes resulting in an increase in serum levels of adiponectin. To mediate the systemic effects of FGF21 on energy metabolism and insulin sensitivity, FGF21 actions are joined by adiponectin in local adipocytes to liver and skeletal muscle.

In 2010, Chui *et al.* observed in a study where obese mice were treated with FGF21 that they display both a significantly attenuated signalling response as assessed by extracellular mitogen-activated protein kinase 1 and 2 (ERK1/2) phosphorylation as well as an impaired induction of FGF21 target genes, including cFos and EGR1and were seen in both liver and fat. They had proposed that obesity is an FGF21-resistant state [12].

Fasting and feeding signals are independently controlled by FGF21 levels i.e. FGF21 levels increase with starvation and overfeeding. This observation remained consistent in both children and adults. Studies show that when judged against normal weight children, obese children show amplified levels of serum FGF21 and FFA ait is a known stimulant for FGF21. However, elevated FGF21 levels can also be correlated with high liver fat, triglycerides, insulin, homeostasis model assessment (HOMA) index, and area under the curve of glucose and lower HDL. It can easily be concluded that FGF21 can be considered as an independent marker for Metabolic Syndrome and Obesity (MetS).

Protective Role of FGF21 in Cardiovascular Disease

FGF21 is a hormone that is primarily released from the liver but it is also produced and secreted by the heart by cardiomyocytes to act as a cardiomyokine. Roberts *et al.* found that in mice with myocardial ischaemia, FGF21 was one of the cardioprotective proteins that reduced the fraction of myocardial infarcts [74]. In another study it was found that FGF21 deficient mice exhibited more cardiac hypertrophy and upon treatment with FGF21 hormone, there were direct effects on cardiac tissue to prevent the development of cardiac hypertrophy, reduce infarct damage, and attenuate the development of diabetic cardiomyopathy [75, 76]. It was observed that in neonatal mouse models, treatment using FGF21 inhibits the development of cardiac hypertrophy and the induction of pro-inflammatory pathways in the heart.

Oxidative stress and energy metabolism in many tissues, including the heart, are controlled by the transcriptional co factor PPAR co-activator-1 α (PGC1α). Hypertrophic and pro inflammatory stimuli repress the expression of PGC1α but the induction of PGC1α is related to the inhibitory action of FGF21 on cardiac hypertrophy and inflammation.

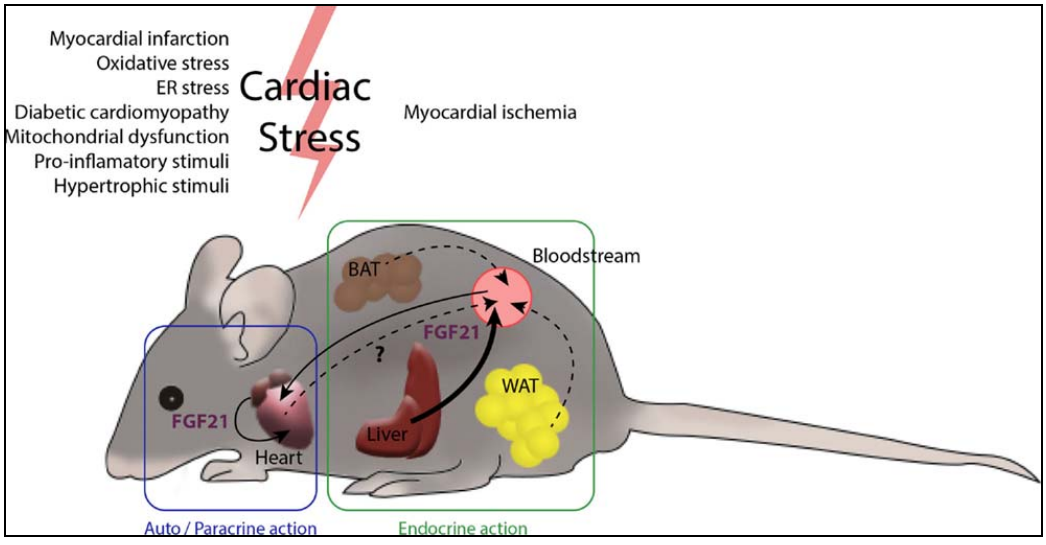


Fig 4: The heart and FGF21 inter- and intra-organ communication. After myocardial infarction, liver and white adipose tissues produce large amounts of FGF21. The heart also produces increased levels of FGF21 after cardiac hypertrophy, oxidative stress, and diabetes, among others. The endocrine actions of FGF21 released by the liver and possibly by adipose tissues, together with autocrine FGF21 originating in heart itself, may act to protect against cardiac damage. Source: Frontiers in endocrinology 6 (2015): 133.

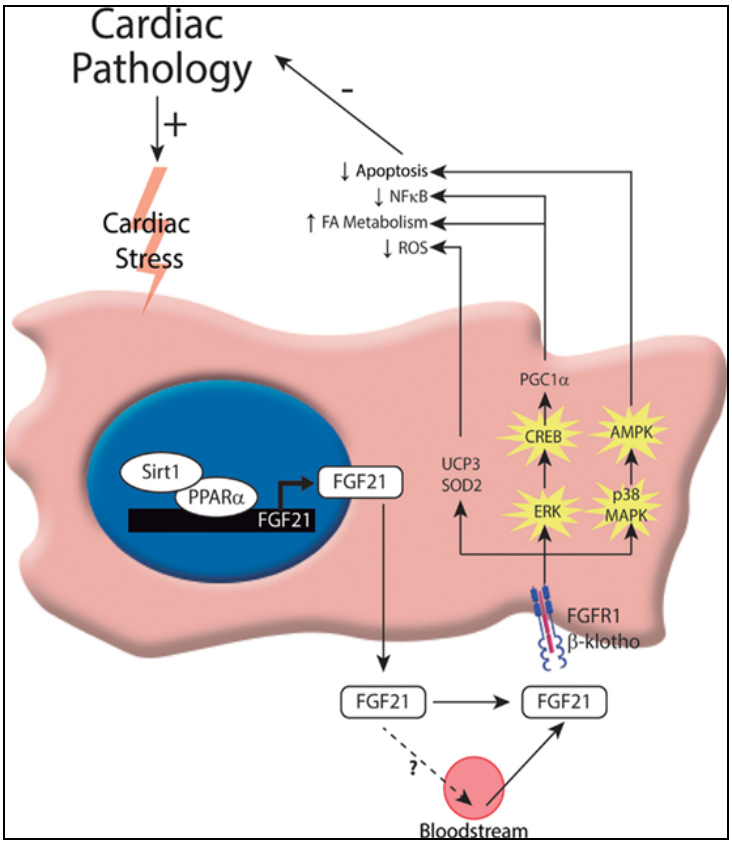


Fig 5: Intracellular mechanisms involved in the control of FGF21 production and action on the heart. In response to cardiac insults, cardiomyocytes induce the expression of FGF21. The Sirt1–PPARα pathway is the transcriptional pathway that has been implicated in governing this process. This pathway induces the expression of FGF21, which can be released by cardiac cells. Moreover, FGF21 acts on the heart, protecting it from cardiac damage. The molecular mechanisms involved in FGF21-mediated cardioprotection include activation of the FGF21 receptor, FGFR1, and the co-factor, Klothoβ, and subsequent activation of the ERK1/2 pathway. Phosphorylated CREB and p38-MAPK act through different intracellular mechanisms to exert protection against cardiac damage. Source: Frontiers in endocrinology 6 (2015): 133.

FGF21 increases the uptake of cholesterol by increasing LDL receptor. In the liver and adipose tissue, PPAR upregulates the expression of FGF21 thereby playing a significant role in regulation of glucose.

Studies have been conducted to understand the extend of the cardioprotective role of FGF21 through autocrine and endocrine pathways. FGF21 is locally generated in the heart through an autocrine manner via the Sirt1–PPARα pathway. This prevents hypertrophy, metabolic dysregulation, and activation of pro-inflammatory pathways in cardiac tissue while also acting as an anti-oxidant factor in the heart preventing the accumulation of Reactive Oxygen Species (ROS). Release of FGF21 into the extracellular space triggers the upstream signals for the activation of Sirt1 which is present upstream of FGF21, thereby working as an autocrine loop. During pregnancy, circulating levels of FGF21 in blood stream and the levels produced the cardiac cells are elevated. It could therefore be said that in the physiological setting, the endocrine and autocrine pathways are functioning.

FGF21 and renal disorders

Stien *et al*.(2009) [77] conducted a study to determine the role played by FGF21 in renal disorders and found that in the control group with Glomerular Filtration Rate (GFR) greater than 50ml/min, FGF21 is related with creatinine and GFR and in the chronic hemodialysis (CD) patients FGF21 is increased 15-fold. In comparison to the control group, there were elevated adiponectin serum levels in CD patients, thereby providing a co-relation between renal elimination and this adipokine. As adiponectin is not dialyzable, there were higher levels of it along with FGF21 after hemodialysis. As the renal failure and obesity both are FGF21 resistant states, this adipokine is upregulated, similar to in case hyperinsulinemia and hyperleptinemia as a response to obesity-associated resistance to insulin and leptin [77, 78].

Conclusion

According to a statistics report by the World Health Oraganization (WHO) diabetes has caused over 1.5 million deaths worldwide and is the 8th leading cause of death among men and women [79]. Over 41 million children under the age of 5 and 1.9 billion adults are considered obese or overweight[80]. About 31% of deaths is attributed to various cardiovascular diseases which is the number one cause of death worldwide [81]. All of this has generated an imminent need for strategizing the application of novel therapeutic agents.

FGF21 has garnered attention for its therapeutic properties ever since it was found that it acts as a regulatory molecule that lowers hyperglycemia. Since then there have been multiple studies over the decades to understand its role in obesity and associated disorders, cardiovascular diseases, renal diseases etc. FGF21 is a fibroblast growth factor which is a downstream element of PPARA that induces the activation of GLUT1 to facilitate glucose transport across the plasma membrane.

However, one downside of the application of FGF21 is its short circulating half life when administered in its native form. There have been studies to address this by using recombinant human FGF21 with polyethylene glycol

(PEGylation) as a more stable compound for treatment of type II diabetes. Also skeletal fragility poses as a side effect that limits the therapeutic scope of FGF21 usage [82, 83].

FGF21 also plays a crucial role in signal transduction between liver and brain to allow energy conservation, torpor control and regulation of circadian clock. FGF21 plays significant role against various pancreatic injuries through the regulation of insulin and glucagon and can be used as a biomarker for fatty liver disease, obesity and diabetes, coronary artery disease, carotid atherosclerosis, hyper-triacyl-glycerolaemia, hyper-insulinaemia, pericardial fat accumulation and the metabolic syndrome, Cushing's syndrome and anorexia nervosa. It can effectively be used as a therapeutic agent to treat diabetes and cardiovascular diseases due to its cardioprotective functions.

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