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"ROLE OF FIBROBLAST GROWTH FACTOR (FGF21) IN DIABETES"

ASHISH KAKKAR

RAJIV ACADEMY FOR PHARMACY
(AFFILIATED TO U.P.TECHNICAL UNIVERSITY, LUCKNOW)
MATHURA, U.P.

ASHISH KAKKAR
ashishkakkar001@gmail.com
RAJIV ACADEMY FOR PHARMACY (AFFILIATED TO U.P.TECHNICAL UNIVERSITY, LUCKNOW) MATHURA, U.P.

ABSTRACT

FGFs have diverse roles in regulating cell proliferation, migration and differentiation. Their actions are dependent on their ability to bind and activate a family of cell surface receptors with intrinsic protein tyrosine kinase activity. These receptors possess an extracellular cytoplasmic ligand-binding domain that has three immunoglobulin-like (Ig-like) regions, a hydrophobic transmembrane domain, and a discontinuous intracellular tyrosine kinase domain exhibiting a short intervening sequence. FGF-21 also improves the lipoprotein profiles by decreasing LDL-cholesterol and total cholesterol, and increasing HDL cholesterol. FGF-21 transgenic mice exhibit similar metabolic characteristics, namely reduced adiposity and resistance to diet-induced metabolic disturbances.

KEY WORDS

Fibroblast,diabetes,lipoprotein.

INTRODUCTION

Fibroblast growth factors (FGFs) make up a large family of polypeptide growth factors that are found in organisms ranging from nematodes to humans. In vertebrates, the 22 members of the FGF family range in molecular mass from 17 to 34 kDa and share 13-71% amino acid identity. Between vertebrate species, FGFs are highly conserved in both gene structure and amino-acid sequence. FGFs have a high affinity for heparan sulfate proteoglycans and require heparan sulfate to activate one of four cellsurface FGF receptors. During embryonic development, FGFs have diverse roles in regulating cell proliferation, migration and differentiation. In the adult organism, FGFs are homeostatic factors and function in tissue repair and response to injury [1].

The fibroblast growth factor (FGF) 1 family presently consists of at least 20 different members, including the well characterized acidic FGF (aFGF or FGF-1) and basic FGF (bFGF or FGF-2). These heparin-binding polypeptides are mitogenic and angiogenic, and are involved in cell differentiation and tissue development and repair [2]. Their actions are dependent on their ability to bind and activate a family of cell surface receptors with intrinsic protein tyrosine kinase activity [3]. These receptors possess an extracellular cytoplasmic ligand-binding domain that has three immunoglobulin-like (Ig-like) regions, a hydrophobic transmembrane domain, and a discontinuous intracellular tyrosine kinase domain exhibiting a short intervening sequence [4].

FGF 21

Fibroblast growth factor-21 (FGF-21), which is a member of the fibroblast growth factor (FGF) super family, has recently been described to play important roles in controlling glucose and lipid metabolism [5]. Therapeutic administration of FGF-21 in rodents and non-human primates exerts metabolic control by protecting the animals from diet-induced obesity, and by lowering fasting plasma glucose, triglycerides, insulin and glucagon levels in diabetic animal models [6]. FGF-21 also improves the lipoprotein profiles by decreasing LDL-cholesterol and total cholesterol, and increasing HDL cholesterol. FGF-21 transgenic mice exhibit similar metabolic characteristics, namely reduced adiposity and resistance to diet-induced metabolic disturbances [7].

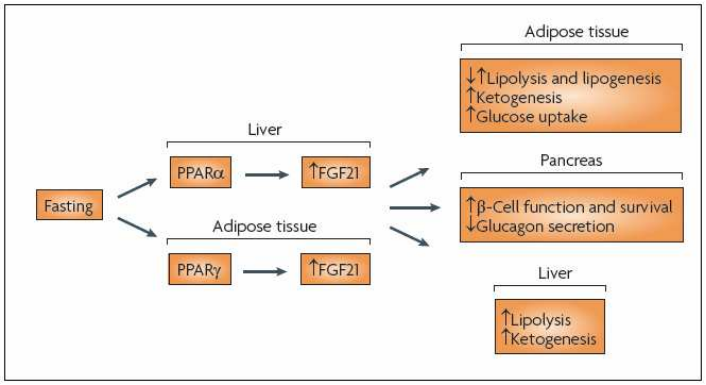

Fig. 1

FGF21 mediates the fasting response and is regulated by peroxisome proliferator-activated receptor-α (PPARα) and PPARγ in liver and adipose tissue, respectively. The biology of FGF21 in model systems and humans is still being elucidated, but among its many functions are increasing glucose uptake in adipose tissue, improving β-cell function, inhibiting glucagon secretion, increasing ketogenesis and regulating lipolysis and lipogenesis in a complex manner. FGF21 is expressed in liver, adipose and pancreatic tissue. It acts primarily on adipose tissue [8].

Pernille Hojman et al. found that insulin stimulates the expression of FGF-21 in human skeletal muscle and induces an increase in circulating FGF-21 levels. In addition to the acute effect of insulin on muscular FGF-21 expression, they found a positive correlation between fasting insulin on the one hand and muscle FGF-21 mRNA, and plasma FGF-21 in individuals with a wide range of insulin sensitivity. This was in particular reflected in the acute in vivo insulin infusion study, where unstimulated young muscles in most cases did not express FGF-21 at detectable levels. Moreover, they found a correlational relationship between muscle FGF-21 expression and age, but they did not find associations between plasma FGF-21 and age [9].

The finding that muscular FGF-21 expression is regulated by insulin is in accordance with a recent report from Izumiya et al [10], who found that insulin induced FGF-21 expression in murine muscle cells. Thus, the pathway for regulation for FGF-21 in muscles seems completely different from regulation of FGF-21 expression in liver, where FGF-21 is highly expressed. Several animal studies have focused on the regulation of FGF-21 in liver [11]. Here FGF-21 is controlled by PPAR-alpha, and PPAR-alpha agonists have been shown to mimic the induction of FGF-21. The liver expression of FGF-21 is closely associated with fasting/fed transition in mice as PPAR-alpha and thus FGF-21 is induced by fasting [12]. In the muscles, however, FGF-21 expression seems to by regulated by the insulin/Akt-signaling pathway.

Pernille Hojman et al. were not able to determine any correlation between muscle FGF-21 mRNA and plasma FGF-21, even though both correlated with fasting insulin. This indicates that muscle tissue is not the primary source of FGF-21 during chronic hyperinsulinemia. Previous studies have shown that plasma FGF-21 correlated significantly with FGF-21 expression in adipose tissue, suggesting that the adipose tissue might be the primary source of plasma FGF-21 in humans [13]. Thus FGF- 21 expression in muscles may have a paracrine role in the muscle tissue. Insulin stimulates muscular expression of FGF-21 and increases plasma-FGF-21. Moreover, muscular FGF-21 expression is associated with hyperinsulinemia. This suggests that FGF-21 expression in muscles is regulated by insulin.

Role of FGF-21 in Diabetes

FGF-21 It is a liver-derived polypeptide that appears to have considerable potential for the treatment of diabetes mellitus [14,15]. In a recent paper, FGF-21 was found to act as an adipocyte-specific inducer of glucose uptake and to lower plasma triglyceride (TG) levels over an extended period [15]. Notably, the effect is not immediate, and it is independent of insulin. FGF-21 effects on glucose uptake are additive, not synergistic with insulin. Moreover, unlike insulin, adipocyte responses to FGF-21 required exposure over a number of hours. The actual mechanism involved is unclear, but could involve a number of points along the glucose metabolic pathway (Figure 2).

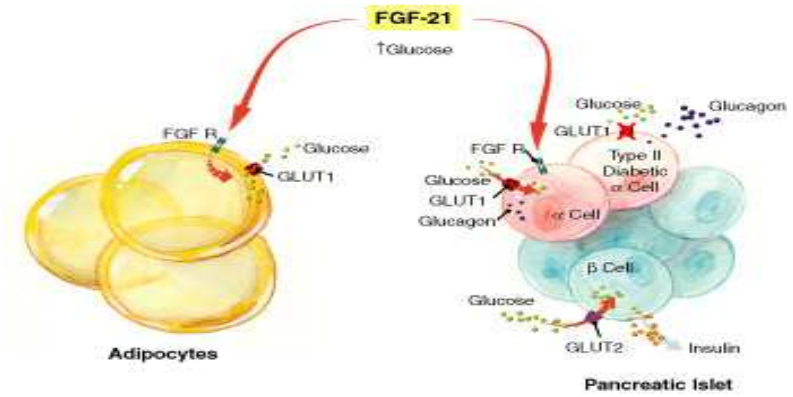

Fig 2

Potential targets for FGF-21-mediated glucose uptake: FGF-21 may stimulate glucose uptake into adipocytes via FGF R modulation of adipocyte GLUT1. In addition, FGF-21 may enhance glucose uptake into glucagon-secreting pancreatic a-cells. In type II diabetics, this could have the effect of increasing insulin sensitivity by suppressing glucagon release, decreasing circulating glucose, and lowering the amount of insulin production required by the pancreatic ß-cells.

Normally, dietary glucose is absorbed into the intestinal vasculature and quickly encounters ß-cells of the pancreatic islets. Rodent ß-cells express GLUT2, a member of the SLC2 family of glucose and polyol transporters [16,17]. GLUT2 is unusual in that it is constitutively expressed on the cell surface and allows almost free diffusion of its target, glucose. Thus, any increase in extracellular glucose will be reflected by an almost immediate proportional increase in intracellular glucose. All rises in intracellular glucose are quickly followed by insulin release. The release is biphasic, peaking after three minutes, declining somewhat, and rising again after ten minutes for the duration of the glycemic episode [18]. Released insulin encounters insulin receptors expressed on the principal targets of insulin such as muscle and fat. The first wave of insulin activates plasma membrane GLUT4 receptors, opening channels for glucose influx. The second and continuing wave of insulin induces GLUT4 translocation from internal vesicles to the plasma membrane, increasing the influx of glucose.10 Insulin resistance is a hallmark of type II diabetes, and is characterized by an inability to efficiently transport glucose into muscle and (white) fat. Approximately 75-90% of dietary glucose goes into muscle fibers, while 10% of plasma glucose is taken up by adipocytes [18,20]. GLUT4 is reportedly poorly expressed on muscle and fat in diabetes [17,19]. This reduction could lead to hyperglycemia, since the “funnel” for glucose deposition would be reduced. GLUT4 would seem to be a possible target for FGF-21, an agent that causes glucose uptake.

Although it is tempting to speculate that FGF-21 might exert its glucose uptake effects via GLUT4, this doesn’t appear to be the case. Remarkably enough, FGF-21 seems to impact another GLUT transporter, GLUT1. GLUT1 activity seems to be independent of insulin action (at least on monocytes), and it is reported to be the predominant GLUT on human ß-cells (in contrast to rodent). FGF-21 is hypothesized to impact GLUT1 on adipocytes, but not skeletal muscle. The effect is probably indirect, as some isoform of FGF R1 and/or FGF R2 is likely to be the receptor for FGF-21 [15]. Although GLUT1 is a glucose transporter, it is unclear what effect FGF-21 could have on facilitated adipocyte glucose transport. Glucose entry into adipocytes generally results in its storage as TG. In the liver, plasma-derived glucose can be broken down to acetyl-CoA, and then reassembled from acetyl-CoA, two carbons at a time, into 16- and 18-carbon fatty acids. These can then be transported to the adipocyte via very low density lipoprotein (VLDL) where they are bound to glucose-derived, 3-carbon glycerol to

form TG. In theory, this should result in increased TG stores and, by inference, enlarged adipocytes. However, FGF-21 transgenic mice, in which the human protein is over-expressed in the liver, exhibit, white adipocytes that are smaller than normal. If FGF-21 does facilitate glucose influx, perhaps it does so on an expanded white adipocyte mass. Alternatively, adipocyte glucose may be metabolized and not used for fat storage.

FGF-21 has also been proposed to impact glucagon metabolism. In the fasting state, glucose levels are variable, maintained at a basal level by the opposing effects of insulin and glucagon. Glucagon is a hormone released by pancreatic islet a-cells in response to low glucose. It acts on its receptor, expressed by hepatocytes, to induce glucose release. Normally, after a meal, glucose levels are high, prompting insulin release and glucagon shutdown. In type II diabetes, however, glucagon would appear to be inappropriately expressed after a meal, promoting higher glucose levels than would otherwise be warranted [21]. GLUT1 appears to be the glucose transporter in a-cells [22,23]. In theory, a defective GLUT1 transporter in an environment of normo- or hyperglycemia could incorrectly signal hypoglycemia, with subsequent glucagon release. This would create abnormally high circulating glucose levels, and put pressure on the insulin-producing cells to release more insulin to correct the hyperglycemia (figure 2). A reduction in glucagon and plasma glucose could potentially lead to improved insulin sensitivity. If FGF-21 acts on GLUT1, it may be at the level of the a-cell. The insulin tyrosine kinase receptor is known to directly down regulate GLUT2 activity on hepatocytes, and a somewhat analogous situation may occur with tyrosine kinase FGF receptor(s) [24].

CONCLUSION

Fibroblast growth factor family FGFs are highly conserved in both gene structure and amino-acid sequence. FGFs have a high affinity for heparan sulfate proteoglycans and require heparan sulfate to activate one of four cellsurface FGF receptors. Mainly FGF 21 has shown great role in treatment of diabetes. Hence in the end I conclude with proposing FGF 21 as a potential target for fighting against diabetes mellitus.

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