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FGF-21 – can it be a promising agent in the treatment of type 2 diabetes?

FGF-21 – czy może być obiecującym lekiem w terapii cukrzycy typu 2?

Diabetes, especially type 2 diabetes, which is strongly connected with visceral obesity and insulin resistance, has become an increasing global health problem in recent years. The perception of adipose tissue as a reservoir of fatty acids has been replaced over the last years by the assumption that adipose tissue plays a vital role in lipid and glucose metabolism and produces a large number of hormones and cytokines, which generate insulin resistance [12]. Visceral obesity aggravates insulin resistance and there has been much interest in the possible role of adipose tissue adipocytokines. It is well known that adipocytes produce and secrete a variety of biologically active mediators (adipocytokines), which are thought to contribute to the development of insulin resistance, type 2 diabetes, and cardiovascular disease.

BIOLOGICAL ACTION OF FIBROBLAST GROWTH FACTOR 21

Fibroblast growth factors (FGFs) are hormonal factors with various biological functions. Human FGF family includes 22 members that are divided into seven subfamilies based on structure and sequence identity. While most of FGFs act as local regulators of cell growth and differentiation, recent studies indicated that FGF19 subfamily members including FGF15/19, FGF21 and FGF23, sharing approximately 30% amino acid sequence homology, exert important metabolic effects by an endocrine fashion [17]. Fibroblast growth factor 21 (FGF-21) a member of FGF 19 subfamily, is newly discovered adipocytokine with potent antidiabetic properties [15]. FGF 21 is believed to be a metabolic regulator, which in animal models has been shown to improve glucose metabolism and insulin sensitivity.

Full length FGF-21 molecule consisting of 209 amino acids was cloned in 2000 and mapped to chromosome 19. A mature FGF-21 built of 181 amino acid has recently emerged as an important metabolic regulator of glucose and lipid metabolism. FGF-21 exerts its metabolic effect via FGFRs in heparin deficient way, but with the use of cofactor, β Klotho [4,7,11]. Restricted expression of β Klotho limits FGF-21 action primarily to liver, pancreas, and adipose tissue [9]. FGF-21 is mainly expressed in hepatocytes and in the pancreas, but also originates from adipose and muscle, where it is regulated by the peroxisome proliferators-activated receptors, PPARγ and PPARα [14]. FGF-21 stimulates glucose uptake in differentiated mouse 3T3-L1 cells and human adipocytes [8]. What is important, this effect on glucose uptake is insulin independent. It has been reported that in isolated

pancreatic islets, FGF-21 also suppressed glucose-mediated glucagon release and stimulated insulin secretion, which may suggest direct protecting from glucolipotoxicity effect on pancreatic α and β cells [15]. Interestingly, FGF21, unlike classical FGFs, has not been reported to induce proliferation and to be a mitogenic factor. This phenomenon creates chances for this adipokine to be an attractive therapeutic agent for type 2 diabetes.

FGF-21 has been reported as a major metabolic regulator of glucose and lipid homeostasis and obesity. Kharitonenkov et al. demonstrated that in transgenic mice with overexpresion of FGF-21 a lean, insulin-sensitive phenotype was observed. FGF-21 transgenic mice have improved metabolic profiles: reduced glucose, insulin, cholesterol and triglyceride levels, insulin sensitivity and resistance to diet-induced and age-induced weight gain and fat accumulation [8, 6]. Moreover, contrary to these observations, the lack of FGF-21 led to increased body weight, development of fatty liver disease, impaired glucose tolerance and increased insulin resistance. The data suggest that FGF-21 is also involved in regulation of ketogenesis, fatty acid oxidation and adaptive response to starvation [1]. The research of many others, such as Coskun T et al. and Hu J et al. shows that when administered to animals, this adipocytokine promotes improved and sustained glucose and lipid control, reduced insulin resistance, preservation of β-cell mass and function, correction of obesity [3,16]. On the basis of the results obtained from the studies, we can suppose that FGF-21 action in animal models is not associated with serious side-effects of hypoglycemia, edema, liver toxicity, adiposity, mitogenicity, lipodystrophy or excessive weight loss, even at suprapharmacologic doses [5, 10].

However, very little is known about changes of serum FGF-21 levels in humans. The results of the studies conducted in humans reveal that FGF-21 is increased in subjects with diabetes, obesity and lipids disorders [18,2]. It has been observed that FGF-21 concentrations correlate with reduced insulin sensitivity, HDL-cholesterol, increased adiposity, blood glucose, insulin, triglicerides and components of the metabolic syndrome. It may suggest the compensatory mechanism of the observed changes or tissue resistance to FGF-21. Stein et al. demonstrated a statistically significant relation of this adipocytokine to renal function [13]. They found that circulatory levels of FGF-21 were > 15-fold higher in patients with chronic kidney diseases maintained on hemodialisys in comparison to the control group. On the basis of the results obtained from the studies, we can suppose that this adipocytokine is eliminated by renal route. It can be also concluded that serum creatinine or other markers of renal function should always be included in studies concerning FGF-21 physiology. The physiological significance of increased FGF-21 concentrations in renal failure requires further investigations.

IS THE TREATMENT OF TYPE 2 DIABETES POSSIBLE WITH THE USE OF FGF-21?

Insulin resistance, which accompanies type 2 diabetes, is a main target for therapy. It was proved that FGF-21 improves tissue sensitivity to insulin and exerts beneficial effects on glucose and lipid metabolism. Is FGF-21 a good therapeutic option for diabetes, lipid disorders and obesity? The data seem to be very encouraging. Kharitonenkov et al. evaluated FGF-21 bioactivity in diabetic nonhuman primates [10]. After six weeks of administration of FGF-21 to diabetic rhesus monkeys, a significant decline in fasting plasma glucose, fructosamine, triglycerides, insulin, and glucagons was observed. What is important especially on the safety purposes, hypoglycemia and cell proliferation was not observed at any point during the study. FGF-21 administration also led to significant amelioration of lipoprotein profiles, including lowering of low-density lipoprotein cholesterol and raising of high-density lipoprotein cholesterol. These findings support the development of FGF-21 for the treatment of diabetes and other metabolic diseases. The therapy using FGF-21 as a drug, increasing insulin sensitivity in peripheral tissues, may contribute to lowering the risk of metabolic disease with insulin

resistance. Taking the above observations into consideration, the possibility of using a synthetic form of FGF-21 can be an effective and causal therapy for civilization-related diseases.

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SUMMARY

Diabetes type 2 has become an increasing global health problem in recent years and cardiovascular complications are the leading cause of death in this group of patients. Insulin resistance, which mainly concerns adipose tissue, skeletal muscles and the liver, is a dominant phenomenon in the pathogenesis of type 2 diabetes and other metabolic disorders. Overwhelming evidence that diabetes increases mortality and deteriorates the quality of life supports the importance of searching new markers of insulin resistance which may be a potential target for the therapy. Fibroblast growth factor 21 (FGF-21) is newly discovered, a unique member of the FGF family that functions as an endocrine hormone. It has been reported as a potent metabolic regulator, which in animal models has been shown to improve glucose metabolism and insulin sensitivity. FGF-21 acts as an activator of glucose uptake on adipocytes, protects animals from diet-induced obesity when overexpressed in transgenic mice, it lowers blood glucose and improves lipids profile when therapeutically administered to diabetic rodents. The most recent scientific research suggests that FGF-21 improving insulin sensitivity, may be a novel and attractive drug candidate for the treatment of cardiovascular diseases, especially obesity and type 2 diabetes. However, further investigations are required to determine whether the unique metabolic effects of FGF-21 shown in rodents and primates are also present in humans.

STRESZCZENIE

W ostatnich latach cukrzyca typu 2 stanowi narastający problem zdrowotny na całym świecie, a wiodącą przyczyną zgonu w tej grupie pacjentów są powikłania sercowo-naczyniowe. W patogenezie cukrzycy typu 2 i innych schorzeń metabolicznych główną rolę odgrywa insulinooporność, która dotyczy zwłaszcza tkanki tłuszczowej, mięśni szkieletowych oraz wątroby. Niezliczona ilość dowodów naukowych świadczących o tym, że cukrzyca zwiększa śmiertelność i pogarsza jakość życia, wskazuje na zasadność prowadzenia badań nad poszukiwaniem nowych markerów insulinooporności, mogących być potencjalnymi celami stosowanej terapii. Czynnik wzrostu fibroblastów 21 (FGF-21) jest nowo odkrytą adipokiną należącą do rodziny FGF, o szczególnych właściwościach, wykazującą działanie hormonalne. Na podstawie badań na modelach zwierzęcych dowiedziono, że FGF-21 wywiera silne działanie insulinouwrażliwiające oraz poprawia metabolizm glukozy. U transgenicznych myszy z nadekspresją genu FGF-21 stwierdzono, iż związek ten zwiększa wychwyt glukozy przez adipocyty oraz zapobiega otyłości indukowanej dietą. W badaniach eksperymentalnych przeprowadzonych u gryzoni z doświadczalnie wyindukowaną cukrzycą udowodniono, że podanie FGF-21 obniża ciśnienie krwi oraz poprawia profil lipidowy. Najnowsze wyniki badań sugerują, że FGF-21 poprawiając insulinowrażliwość, może być nowym, atrakcyjnym lekiem w terapii schorzeń sercowo-naczyniowych, zwłaszcza otyłości i cukrzycy typu 2. Jednakże istnieje konieczność prowadzenia dalszych badań mających na celu wyjaśnienie, czy właściwości FGF-21 obserwowane u gryzoni i naczelnych zostaną potwierdzone u ludzi.