PARTNERING WITH SCIENCE:
New Hope for the Effective Treatment of Type 2 Diabetes

ABSTRACT

Research scientists are exploring new physiological pathways and new therapeutics to regulate glucose in people living with type 2 diabetes. Studies have shown that fibroblast growth factor 21 (FGF-21) has the ability to regulate blood glucose levels; however, these effects are temporary. In another promising development, activation of the fibroblast growth factor receptor-1 (FGFR-1) using a specifically designed antibody has shown to be effective in regulating glucose and is capable of long residence times in the blood. Scientists are also exploring the role of FGF-1, another member of the FGF family, in fat remodeling and glucose regulation. It is possible that the regulation of blood glucose levels by FGF-1 might actually involve regulation of a neural pathway (as opposed to a systemic metabolic pathway). People living with diabetes can have hope that scientists are close to developing novel therapeutics to regulate glucose over an extended period of time.
INTRODUCTION

Hope. In the case of serious disease, it is an essential element for a favorable outcome in medical treatment. Such hope emerges from patient confidence in the knowledge and skill of their physician, and the technology and medicine at their disposal. In the case of type 2 diabetes, there have been exciting new developments in the understanding of glucose regulation and insulin sensitization that appear to involve entirely new physiological mechanisms – thus, opening the door to entirely novel therapeutic approaches to the effective treatment of this disease.

FGF-21 AND GLUCOSE REGULATION

In 2005, Dr. Alexei Kharitonenkov at Eli Lilly & Co. published a research report showing that fibroblast growth factor 21 (FGF-21) reduced plasma glucose and triglycerides to near normal levels when administered subcutaneously to two types of mice with diabetes [1]. This result identified FGF-21 as a previously unknown and potent regulator of glucose uptake. FGF-21 is a member of the FGF family of proteins – recognized primarily for their ability to stimulate different types of cells to divide and grow. The ability of FGF-21 to regulate blood glucose levels was therefore unexpected. Regular dosing appeared to be necessary because the pharmacokinetic profile of FGF-21 showed that it was rapidly cleared after an injection, and therefore, the glucose lowering effects were only temporary (lasting 24 hours).

ANTIBODY ACTIVATION OF FGF RECEPTOR-1

In 2011, a report was published by Dr. Junichiro Sonoda at Genentech, Inc. which showed that an antibody designed to stimulate one of the known receptors for fibroblast growth factors could temporarily lower blood glucose in mice that had type 2 diabetes [2]. Briefly, FGF-21 was assumed to exert its function via its ability to stimulate one or more receptors of the FGF family of proteins (FGFR). These scientists hypothesized that a molecule able to stimulate the appropriate FGFR could mimic the action of FGF-21. Furthermore, if such a novel molecule also had a long half-life in the body, then its effects would be much longer lasting than those of FGF-21. These scientists focused their attention upon designing a monoclonal antibody able to activate FGF receptor-1 (FGFR-1), one of the major receptors for the FGF family of proteins. The antibody they designed not only recognized and bound to FGFR-1, but also activated it (much like FGF-21 would do when it binds). Antibodies are known to be capable of long residence times in the blood (and can be further modified for this property). Thus, they identified another means by which to pursue a novel and potentially effective therapeutic to treat type 2 diabetes.

FGF-1 IN FAT REMODELING AND GLUCOSE REGULATION

During 2012-2016, Dr. Ronald Evans at the Salk Institute published a series of papers showing that another member of the FGF family, FGF-1, had a very potent activity related to fat remodeling and glucose regulation [3-5]. This was another unexpected result, since previous studies of FGF-1 knockout mice (genetically modified mice with inactive FGF-1 genes) identified no physiological effect. In other words, mice with no trace of FGF-1 developed normally and also had no identifiable health problem as adults. Thus, prior to this report, it was felt that FGF-1 was non-essential in the body (presumably due to other members of the FGF family being able to compensate for any important activity of FGF-1). What Evans and colleagues showed was that mice that lacked FGF-1 were unable to correctly adjust the extent of their fat tissue when placed on an alternating diet of high fat (which normally requires increasing/decreasing of fat tissue). Furthermore, these researchers showed that in addition to regulation of fat tissue in response to caloric intake, FGF-1 also regulated blood glucose levels. They showed that subcutaneous injection of FGF-1 lowered blood glucose levels in mice with diabetes – producing normal levels for a potentially longer period of time than FGF-21.

Such results naturally lead to an urgent need to understand FGF-1’s mechanism of action (since it appeared to be novel). A recent 2016 research report published in Nature Medicine by Michael Schwartz at the University of Washington provides critical insight into understanding the mechanism of action of FGF-1 in controlling blood glucose levels [6]. In this report, a remission of diabetes in mice, sustained over a period of several weeks, was achieved after injection of FGF-1 into the ventricles of the brain. This result suggests that the regulation of blood glucose levels by FGF-1 might actually involve regulation of a neural pathway (as opposed to a systemic metabolic pathway); thus, attention is focusing
up upon a previously unknown role of FGF-1 in neurological regulation of metabolism. Schwartz’s paper concludes with a statement that effective delivery of therapeutic doses of FGF-1, for sustained regulation of blood glucose, might be possible via an intranasal spray (since most people do not like having injections into their brain).

FGF-1 PROTEIN STABILIZATION

For the past 22 years at Florida State University (FSU), research in my laboratory has utilized FGF-1 as a model protein to understand principles of protein folding, evolution, and design. Over this period we have generated a number of stabilized and “hyperactive” variants of the FGF-1 protein. It turns out that such variants are of keen interest to drug companies wanting to develop FGF-1 as a therapeutic agent. In practical terms, FGF-1 is a poor choice of a protein to develop as a practical drug – mainly because it has extremely poor stability and tends to aggregate and degrade. We have a number of variants of FGF-1 that are substantially stabilized. We also performed a pharmacokinetic study of FGF-1 in 2012 that showed how to design variants with significantly increased mean residence time in the body [7]. Additionally, from a commercialization standpoint, FGF-1 is in the public domain and cannot be patented. Thus, resources spent to develop it as a drug can potentially be immediately circumvented by a competing generic form. In the absence of patent protection (i.e. without “a composition of matter” patent) no investor will commit to drug development. Fortunately, the variants of FGF-1 that we have developed are patentable. FSU has been issued a number of patents for these variants, and has also successfully licensed this intellectual property to interested commercial partners. Additionally, we recently published a 2016 report on a mutant FGF-1 that might serve as a lead compound in the novel treatment of type 2 diabetes [8].

CONCLUSION

Patients with type 2 diabetes can have evidenced-based hope that research scientists are in the process of elucidating an entirely new physiological pathway of glucose regulation, and that novel therapeutics to regulate this pathway are being developed. Such therapeutics offer the potential regulation of normal glucose levels over a hitherto unrealized extended period of time.

CONFLICT OF INTEREST DISCLOSURES

The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr. Blaber reports grants from Trefoil Therapeutics, outside the submitted work; In addition, Dr. Blaber has a patent U.S. Patent Application 61/149,823 pending. No other disclosures were reported.

REFERENCES:


