Howard Hughes Medical Institute

Published as: *Nat Rev Endocrinol*. 2017 October ; 13(10): 599–609.

FGF1 — a new weapon to control type 2 diabetes mellitus

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Abstract

A hypercaloric diet combined with a sedentary lifestyle is a major risk factor in the development of insulin resistance, type 2 diabetes mellitus (T2DM) and associated co-morbidities. Standard treatment for T2DM begins with lifestyle modification, and includes oral medications and insulin therapy to compensate for progressive β-cell failure. Current pharmaceutical options for T2DM, however, are limited in that they do not maintain stable, durable glucose control without the need for treatment intensification. Furthermore, each medication is associated with adverse effects ranging from hypoglycaemia to weight gain or bone loss. Unexpectedly, FGF1 and its low mitogenic variants have emerged as potentially safe candidates in restoring euglycaemia, without causing overt adverse effects. In particular, a single peripheral injection of FGF1 can lower glucose to normal levels in hours without the risk of hypoglycaemia. Similarly, a single intracerebroventricular injection of FGF1 can induce long-lasting remission of the diabetic phenotype. This Review discusses potential mechanisms by which centrally administered FGF1

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Author contributions

E.G. and C.P.M. contributed equally to this article. E.G., C.P.M., M.D. and R.M.E. researched data for the article and wrote the manuscript. All authors contributed to discussion of the content and reviewed and/or edited the manuscript before submission.

Competing interests statement

M.D. and R.M.E are co-inventors of mutated FGF1 proteins and methods of their use **(US Patent No. 8,906,854)** and might be entitled to royalties.

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Subject ontology terms

Health sciences/Endocrinology/Endocrine system and metabolic diseases/Diabetes/Type 2 diabetes
[URI/692/163/2743/137/773]
Health sciences/Anatomy/Nervous system/Central nervous system
[URI/692/698/1688/1366]
Health sciences/Anatomy/Nervous system/Peripheral nervous system
[URI/692/698/1688/1959]
Health sciences/Medical research/Experimental models of disease
[URI/692/308/1426]
Health sciences/Health care/Therapeutics/Hormonal therapies
[URI/692/700/565/238]

improves central glucose-sensing and peripheral glucose uptake in a sustained fashion. Specifically, we explore the potential crosstalk between FGF1 and glucose-sensing neuronal circuits, hypothalamic neural stem cells and synaptic plasticity. Finally, we highlight therapeutic considerations of FGF1 and compare its metabolic actions to FGF15/FGF19 and FGF21.

Graphical abstract

FGF1 has recently emerged as a potentially safe candidate to restore euglycaemia in type 2 diabetes mellitus. In this Review, Ronald Evans and colleagues discuss possible mechanisms by which central injection of FGF1 can improve central glucose sensing and peripheral glucose uptake, the neuronal circuits involved and therapeutic considerations for translating these findings in rodents to the clinic.

Introduction

Type 2 diabetes mellitus (T2DM) affects over 400 million adults worldwide (~9% of the adult population), a number almost double that seen in 1980[1,2]. The estimated $825 billion spent globally each year in direct expenses related to the management of T2DM will only increase, as the prevalence of the disease is expected to continue to rise in coming decades[3]. The current pharmacological paradigm of T2DM management involves sequential attempts at normoglycaemia with oral agents, which often culminate in the need for patients to be placed on insulin to approach glycaemic control. An increasing number of new drugs and drug classes have become available to manage the disease; however, despite initial promise, each option remains burdened by a combination of adverse effects and lack of long-term efficacy[4,5]. In all, the disease has largely remained a chronic and progressive condition. Although stem-cell-derived β-cell replacement could possibly cure diabetes mellitus, successful metrics have not been met. With no widely effective treatment, let alone cure, available and rates of the disease continuing to rise alongside costs, the toll of T2DM seems unyielding.

In this regard, fibroblast growth factor 1 (FGF1) has emerged as a promising solution to the diabetes dilemma. Although FGF1 is considered to be a well-established component of processes such as embryonic development, wound healing, neurogenesis and angiogenesis, the whole-body *Fgf1* knockout mouse shows no deficiency in any of these processes[6,7]. Indeed, only in 2014 was FGF1 shown to be a metabolic hormone crucial for the management of nutrient stress, glycaemic control and insulin sensitivity[8]. *Fgf1* knockout mice develop marked hyperglycaemia and insulin resistance when challenged with a high-fat diet. In *ob/ob* and *db/db* mice or diet-induced obesity (DIO) models, peripheral delivery of a single dose of recombinant FGF1 (rFGF1) can normalize blood glucose levels within hours, without inducing hypoglycaemia[8]. Chronic treatment similarly achieved sustained glucose lowering, with insulin sensitization observed within 3 weeks of initiating therapy[8]; no desensitization to the effects of FGF1 was observed. This work brought FGF1 to the forefront as a potential new therapeutic approach for insulin sensitization and the treatment of T2DM.

Following on from these original findings, a single central injection of rFGF1 in mice rendered diabetic by DIO and low-dose streptozotocin (STZ) was shown to induce normoglycaemia for up to 18 weeks post-injection[9]. Long-lasting glucose-lowering effects were also observed after a single central injection of rFGF1 in leptin-deficient *ob/ob* and leptin-receptor-deficient *db/db* (on a BKS background) mice, as well as in leptin-receptor-deficient Zucker diabetic fatty rats (ZDF)[9]. This central effect was associated with increased hepatic glycogen content and was independent of weight loss, reduced food intake, increased insulin sensitivity or increased insulin levels (FIG. 1).

Although peripheral injection of FGF1 could potentially signal centrally, it is less likely than centrally injected FGF1 to act systemically. This raises the challenging question as to the potential mechanism underlying glycaemic control by the central nervous system (CNS) and whether this can be exploited for therapeutic use. In this Review, we discuss the foundation for FGF1 and the CNS in glycemic control and how these two may interact to jointly improve glucose regulation. We then weigh the metabolic actions of FGF1 against other metabolically active FGFs. We conclude by noting factors that must be evaluated in the further development of FGF based therapeutics for clinical medicine.

Role of FGF1 in glucose control

Feeding suppression

Initial evidence for a central role of FGF1 in feeding suppression stemmed from reports of a postprandial increase in FGF1 and FGF2 levels in the cerebrospinal fluid (CSF) of rats[10–12]. In this context, glucose was identified as the crucial cue, as both intraperitoneal and intracerebroventricular (ICV) glucose injections were sufficient to induce FGF1 release into the CSF[10]. Moreover, ventricular microinfusion of FGF1 and FGF2 revealed a dose-dependent suppression of feeding in rats[10,12,13].

FGF1 acts in an autocrine and/or paracrine fashion, as binding to heparan sulphate proteoglycans prevents it from entering the circulation, thus necessitating its local production[14,15]. In the brain, ependymal cells lining the ventricular space constitute the main source of FGF1 production[10,16–18]. Upon glucose stimulation, FGF1 is secreted by ependymal cells and induces the expression of the early-response markers *Fos* (which encodes c-Fos) and *Hspb1* (which encodes heat shock protein β1) selectively in glucose-sensing tanycytes lining the ventral part of the third ventricle and in periventricular hypothalamic astrocytes[10,19–22]. The lack of FGF1-induced changes in *Fos* expression in hypothalamic neurons points to tanycytes and astrocytes as the primary cellular targets of secreted FGF1 in the brain[9,19,21]. *Fos* and *Hspb1* induction in astrocytes temporally correlates with the feeding inhibition elicited by ICV infusion of FGF1, which is strongest within the initial 2–6 hours but sustained for 24 hours[11,19,21]. FGF receptor 1 (FGFR1) is widely expressed throughout the hypothalamus[23,24]; internalization and retrograde transport of radioactively labeled ^{125}I-FGF1 and ^{125}I-FGF2 has been observed in distinct neuronal populations 18 hours, but not 5 hours, after ICV FGF1 administration[25]. FGF1 has therefore been postulated to suppress food intake in two phases, an early response mediated mainly by hypothalamic astrocytes followed by a neuron-dependent late response[19].

Based on the aforementioned findings, the initial negative impact of FGF1 on feeding behaviour is plausibly mediated by its activation of periventricular astrocytes, which in turn are known to modulate the activity of anorexigenic proopiomelanocortin (POMC) and orexigenic agouti-related peptide (AGRP) neurons in the arcuate nucleus[26–29]. Additionally, the lateral hypothalamic area (LHA) has been prominently implicated in the hypophagia-inducing actions of FGF1. Namely, orexin and melanin-concentrating hormone (MCH) expressing neurons within the LHA are considered important players in the regulation of food intake, arousal and motivated behaviour[30]. In rats, ^{125}I-FGF1 and ^{125}I-FGF2 are internalized by LHA neurons after ventricular infusion[25]. Moreover, bilateral LHA administration of antiserum raised against either FGF1, FGF2 or their receptor FGFR1, induced hyperphagia[10,31]. At the cellular level, FGF1 and FGF2 cause a PKC-dependent inhibition of a significant fraction of glucose-sensitive LHA neurons[10]. The LHA thus conceivably continues to suppress food intake, for a limited time window, after the initial activation of astrocytes by FGF1 has worn off.

Glucose lowering

In contrast to the feeding effect, the glucose-lowering effect of FGF1 in diabetic settings was discovered only in the past few years, and attempts to identify its cellular and molecular mechanisms are still in the early stages[8,9]. In addition, the food suppression component of both the central and peripheral FGF1 response is transitory, whereas the glucose-lowering effect is persistent[8,9].

In the periphery, the glucose-lowering effect of injected or endogenous FGF1 is in part mediated by the FGF1–FGFR1 signalling cascade. Adipose tissue has been identified as the primary target site of ‘endocrinized’ rFGF1, as AP2-Cre driven *Fgfr1* ablation negates its glucose lowering effects in 8-month old DIO mice[8]. Notably, endogenous FGF1 is induced during the fed state in adipose tissue by the nuclear receptor peroxisome proliferator-activated receptor γ (PPARγ), the same nuclear receptor targeted by insulin-sensitizing thiazolidinedione (TZD) drugs[32]. However, in contrast to TZDs, rFGF1 therapy does not result in adverse effects such as weight gain, bone loss or hepatic steatosis, which creates a very appealing safety profile relative to TZDs.

Endocrinized rFGF1 has been suggested to limit hypothalamic–pituitary–adrenal (HPA) axis activity and produce normoglycaemia in STZ-induced T1DM rats by decreasing hepatic glucose production, hepatic acetyl CoA levels and lipolysis[33]. However, the idea that suppression of the HPA axis is sufficient to counteract diabetic hyperglycaemia is still controversial[34,35]. Moreover, central injection of rFGF1 in the lateral or third ventricle of *ob/ob* mice profoundly lowers blood glucose levels, and does so without affecting plasma corticosterone levels[9]. A concordant explanation for both models would be that peripherally and centrally injected rFGF1 achieve similar effects through different paths[8,9]. Thus, peripheral action would be initiated by an FGFR1 signalling cascade in fat, whereas central FGF1 would act through an astrocyte–glial–neuronal circuit[36,37].

A second parallel between peripheral and central FGF1 action is that they each seem to rely on intact insulin signalling, as shown by a lack of efficacy in DIO mice treated with the insulin receptor antagonist S961 or in high-dose STZ-treated mice with β-cell ablation[9].

Additionally, both peripheral and central injections sustain glucose lowering without causing hypoglycaemia[8,9]. Nonetheless, and despite these parallels, central and peripheral mechanisms reflect significant differences. A single peripheral injection of FGF1 in diabetic rodents triggers acute glucose lowering (within hours) and multiple doses promote insulin sensitization in 3 weeks[8]. By contrast, a single ICV injection of FGF1 lowers glucose in about a week and sustains this effect beyond 16 weeks, without insulin sensitization[9].

Notably, while both FGF1 and FGF2 have been linked to the central regulation of food intake, only FGF1 displays glucose-lowering effects after peripheral injection in *ob/ob* mice[8]. This finding is however in contrast to a more recent (2016) metabolomics study, in which intravenous injection of FGF2 into STZ-induced diabetic rats lowered blood glucose levels[38]. Additionally, to our knowledge, no data describing the effects of central injection of FGF2 in diabetic animals is currently available. Notwithstanding this caveat, deviating functional repertoires of FGF1 and FGF2 despite overlapping receptor specificity could be explained by the possibility that distinct intracellular pathways are engaged following FGF1 and FGF2 receptor binding, evoked by characteristic structural changes in the intracellular receptor domains[39].

The sustained normalization of blood glucose levels in diabetic animals after a single ICV injection of FGF1, in the absence of hypoglycaemic episodes, clearly warrants further mechanistic investigations as an attractive alternative to current treatment methods. These results lead us to postulate the existence of an as yet unknown mechanism, by which a single central FGF1 injection might permanently increase peripheral uptake of glucose by the liver and skeletal muscle[9].

Central FGF1 effects — possible mechanisms

Glucose-sensing neurons

The significance of the brain in peripheral glucose homeostasis was first demonstrated by Claude Bernard in 1855, who showed that destruction of the hypothalamus in dogs induces hyperglycaemia[40]. Almost 100 years later, John Mayer proposed the existence of specialized hypothalamic cells that monitor changes in glucose concentrations and commence a corresponding chemical or electrical response[41]. Definite evidence for the existence of these glucose-sensing neurons (GSNs) was later provided by the identification of hypothalamic neurons that alter their firing activities in response to changes in extracellular glucose concentrations[42,43].

Since then, several specific GSN populations have been identified, mainly within the hypothalamus and different brain-stem structures[44,45]. Depending on whether their firing frequency is increased or decreased in response to rising extracellular glucose levels, they are termed glucose-excited (GE) or glucose-inhibited (GI) neurons, respectively[46,47]. Neurons can either utilize glucose directly or take it up in the form of lactate, which is produced by neighbouring astrocytes. During euglycaemia, brain glucose levels are believed to be in the range of 0.7–2.5 mM, reaching a maximum of 4.5 mM during severe plasma hyperglycaemia and dropping to 0.2–0.3 mM during plasma hypoglycaemia[48,49]. Glucose sensing in GE neurons occurs mechanistically similar to that in pancreatic β cells[50]. High extracellular glucose levels cause an increased intracellular ATP to ADP ratio, closure of ATP-sensitive potassium channels, subsequent depolarization of the plasma membrane and finally opening of voltage-sensitive calcium channels[46,51,52]. However, additional alternative glucose-sensing mechanisms have been proposed in GE neurons such as the transient response (TRP) channels[53] or the dimeric G-protein coupled sweet receptor T1R2–T1R3[54]. Cellular metabolism dependent and independent mechanisms have been reported for GI neurons. In GI neurons of the ventromedial nucleus of the hypothalamus (VMH), firing activity is negatively regulated by high glucose levels that inhibit the AMP-activated kinase (AMPK), which leads to Cl^- channel opening and hyperpolarization[55,56], whereas the existence of pharmacological glucose detectors has been proposed for orexin neurons[57].

Within the hypothalamus, GE and GI neurons have been identified in the arcuate nucleus, the ventromedial hypothalamus, the paraventricular hypothalamus (PVN) and the LHA[47]. Depending on their anatomical and neurochemical characteristics, the physiological response of GSNs is likely to vary, but altered reproduction, food intake and energy expenditure have so far been shown to be included in their functional repertoire[47]. In particular, ample evidence exists for the role of GI neurons, most notably in the VMH[58–61], in the sympathetic counter-regulatory response to hypoglycaemia, which triggers the secretion of glucagon and epinephrine from pancreatic α cells and the adrenal medulla, respectively, as well as hepatic glucose production[62,63].

Of all the GSN populations, only the LHA has so far been directly mechanistically implicated in FGF1 actions. As eluded to earlier, FGF1 application on LHA neurons decreased neuronal activity in 66% of GSNs and only 16% of non-GSNs[10]. At the same time, none of the tested VMH neurons responded to FGF1. Within the LHA, orexin neurons are inhibited, whereas MCH neurons are excited by physiological changes in glucose[64,65], which suggests that orexin neurons are the likely targets of FGF1 actions. Of note, reciprocal synaptic connections exist between orexin neurons and neurons in the ARC, and the orexin receptors OX1R and OX2R are widely expressed in neurons of the ARC, VMH, PVN and dorsomedial hypothalamus (DMH)[66,67]. In particular, orexin neurons have been shown to control, at least in part via the VMH, the sympathetic output to the liver and skeletal muscles, which modulates glucose production and uptake, respectively[68,69]. However, the persistent nature of the glucose-lowering effect, long after cellular signalling induced by exogenous FGF1 has abated, clearly suggests that additional mechanisms apart from the mere modulation of the activity of existing neuronal networks are at work.

Tanycytes — neurogenesis

Within the hypothalamus, tanycytes populate the floor and ventro-lateral aspect of the third ventricle, which places them in immediate proximity of the median eminence (ME), ARC, VMH and DMH[70,71]. They possess a long process that projects into the parenchyma, allowing them to come into close contact with neurons of the hypothalamic nuclei, thus potentially regulating neuroendocrine output and energy homeostasis[72]. Tanycytes are able to sense altering plasma glucose levels and respond to focally applied glucose by changes in intracellular Ca^{2+} signalling[73,74]. Importantly, tanycytes constitute a hypothalamic pool of neurologic progenitor cells in the adult nervous system[22,70,75,76], which holds particular relevance when considering the mechanistic ramifications of the long-lasting glucose-lowering effect of FGF1. Lineage-tracing experiments have revealed that the neuronal progeny of tanycytes populate mainly the ARC, but also the VMH, DMH and LHA[22,75]. Lineage-traced tanycytes have also been shown to give rise to astrocytes and proliferating progenitor cells in the hypothalamic parenchyma[22,75,77].

Metabolic stress associated with obesity and diabetes mellitus compromises the functional integrity of hypothalamic circuits that mediate inflammatory and neurodegenerative events, which ultimately contributes to the derailment of energy homeostasis[78]. In mice, hypothalamic inflammation is evident within the first few days of beginning a high-fat diet (HFD), and prolonged HFD exposure leads to a loss of POMC neurons and apoptosis in mature neurons, which underlines the exceptional vulnerability of the hypothalamus to over-nutrition[79–81]. The significance of neural regeneration originating from progenitor cells residing in the periventricular zone has been demonstrated most dramatically by the gradual ablation of AGRP neurons, which is compensated for by *de novo* formation of neurons within the hypothalamic parenchyma[82], whereas acute ablation of AGRP neurons in adult mice causes severe anorexia and death[83,84]. Similarly, weight loss induced by injection of ciliary neurotrophic factor in mice is counteracted by hypothalamic neurogenesis[76]. At the other end of the spectrum, leptin deficiency or DIO have been shown to disrupt neural stem cell proliferation in adult mice, thus preventing the adaptive remodelling of the arcuate nucleus[80,85]. Conversely, short-term HFD feeding is reported to promote neurogenesis in tanycytes of the median eminence at pre-adult ages[86], potentially indicating an initial compensatory attempt.

Analogous to other neural stem cell populations, tanycyte proliferation is stimulated by insulin-like growth factor 1 (IGF1) and FGF2[22,87]. A similar role for FGF1 in tanycyte self-renewal could promote neurogenesis to repair neural circuits that have deteriorated as a consequence of dietary insults (FIG. 2). Injection of a relatively small number of enhanced green fluorescent protein (eGFP)-labeled leptin receptor (LepR) positive neurons (isolated from embryonic day 13.5 embryos) into the hypothalamus of up to 1-week old LepR-deficient *db/db* mice was sufficient to cause a marked reduction in blood glucose levels that persisted for 9 and 13 weeks after transplantation[88]. Mirroring the effect of central FGF1 injection in *ob/ob* mice, rescue of peripheral glucose homeostasis in adult mice occurred without changes in plasma insulin levels[88]. Tracing the fate of the injected eGFP-labeled neurons established their synaptic and functional integration into hypothalamic neurocircuits, thereby proving the receptiveness of hypothalamic neuronal circuits to cell-mediated repair following metabolically inflicted damage[89].

Synaptic plasticity

Synaptic plasticity has been eluded to as a potential mechanism to explain the long-lasting glucose lowering effect of FGF1[9]. Such plasticity involves changes in synaptic activity and connectivity, thereby providing a mechanism by which neuronal circuits can adapt to and maintain responsiveness across a wide range of stimuli[90,91]. In contrast to the well-established role of synaptic plasticity in learning and memory formation, its function in the hypothalamic neuronal circuits in control of feeding behaviour has only recently been discovered[92,93]. The laboratory of Tamás Horváth was the first to show that neurons of the ARC alter their synaptic connections in response to physiological signals of nutrient availability such as ghrelin and leptin, which signal food deprivation and satiety, respectively[94]. Later, the same group reported that this phenomenon is not an exclusive feature of the ARC. Leptin was found to additionally regulate the synaptic organization of orexin neurons in the LHA[95], and ghrelin was shown to modulate synapse formation in the hippocampus[96] and ventral tegmental area (VTA)[97]. Furthermore, hypercaloric challenges in the form of a HFD was also found to induce synaptic remodelling in the ARC[98,99]. Interestingly, deviations in the synaptic inputs to satiety promoting POMC neurons might contribute to the difference in susceptibility of inbred mouse strains to DIO[98].

Depending on the energy state of the organism, synapses are formed or removed and the number of dendrites, as well as the amount of excitatory and inhibitory inputs, can be varied[92]. Synaptic adaptations are also accompanied by intracellular plasticity, encompassing, for example, mitochondrial fission or fusion in neurons of the ARC and the VMH[100–102], or uncoupling of mitochondrial respiration via mitochondrial uncoupling protein 2 in ARC neurons[103]. In AGRP neurons, synaptic plasticity in the response to ghrelin has been shown to involve a presynaptic AMPK-dependent positive feedback mechanism that allows the glutamatergic activation of AGRP neurons to persist for hours after ghrelin removal and its resetting by leptin administration[104]. Astrocytes, too, have been connected to the modulation of synaptic plasticity[105], by contacting and stripping dysfunctional synapses, releasing glial transmitters and taking up neurotransmitters from the synaptic cleft, thus representing the main defense against excitotoxicity and other neuronal insults[106,107]. The occurrence of reactive astrogliosis in response to both acute and chronic high-fat feeding[79,98] could therefore be potentially damaging to the synaptic plasticity of ARC neurons[108]. Additional support for the role of astrocytes in synaptic plasticity comes from the findings that hypothalamic astrocytes respond to leptin by changing levels of glutamate and glucose transporters[109].

Despite some initial evidence, if and how FGF1 affects synaptic plasticity to induce remission of diabetes mellitus has yet to be determined. Some connections between FGFs and synaptic plasticity, albeit not in the hypothalamus, have already been suggested by earlier studies. FGF2 was reported to promote axonal growth and sprouting after injury[110] and to influence hippocampal synaptic plasticity[111]. FGF1 has been found to modulate the synaptic plasticity of neurons in the cortico–striato–pallidal pathway involving the synergetic activation of FGFR1 and the G protein–coupled α2A adrenergic receptor[112]. Co-stimulation of both receptors caused a marked synergistic increase in neurite formation and spine density in striato–pallidal neurons, which involved a rapid and long-lasting MEK1/2 mediated ERK1/2 phosphorylation[112].

With regards to the enduring nature of the FGF1-driven normalization of blood glucose levels in diabetic animals, the hysteresis effect, which enables sustained activation of AGRP neurons even hours after the initial ghrelin stimulus, is particularly intriguing[104,108]. Whether central injection of FGF1 elicits a similar signal, causing long-lasting changes in the synaptic plasticity of as yet to be identified neuronal subpopulations and triggering the observed metabolic improvements, is an intriguing possibility. Given their activation by

FGF1[9,19,21] and their effect on neuronal health and functionality, astrocytes represent one avenue by which FGF1 could potentially affect neuronal plasticity in the hypothalamus (FIG. 2).

Central insulin signalling

Considering that FGF1-mediated glucose lowering depends on functional insulin signalling, it is important to note that all of the potentially involved central mechanisms outlined earlier are vulnerable to diminishing insulin signalling. Ablation of insulin receptor signalling in neurons of the ARC[113,114], the VTA[115] or the dorsal vagal complex in the brainstem[116], causes either impaired glucose homeostasis or obesity, whereas deletion of the insulin receptor in steroidogenic factor 1-expressing neurons of the VMH protects against DIO[117,118]. In 2016, deletion of the insulin receptor in astrocytes was shown to negatively affect their function and morphology, causing changes in glucose transport across the blood–brain barrier and ultimately impeding ARC neurons from monitoring and responding to systemic glucose changes[27]. Moreover, as discussed earlier, DIO and hyperinsulinaemia put a brake on neurogenesis in the hypothalamus[80,85], which could imply that insulin signalling must not come to a complete halt in order for a potential neurogenic effect of FGF1 to occur. Finally, the role of central insulin resistance in neuronal plasticity has become increasingly recognized as a potential cause of the development of cognitive impairment, which involves synapse deterioration and neurodegeneration[119,120].

Central FGF1-induced peripheral glucose uptake

Additional studies are required to address how ICV FGF1 induces increases in peripheral glucose clearance in the liver and skeletal muscle, without affecting circulating insulin levels, glucose-induced insulin secretion, insulin sensitivity or hepatic glucose output. Generally, GSNs are best known for their control of both sympathetic (SNS) and parasympathetic (PNS) branches of the autonomic nervous system[44]. In response to altering glucose levels, the range of actions mediated by the PNS includes the stimulation of pancreatic β-cell proliferation, insulin secretion and the secretion of glucagon during hypoglycaemia. SNS activity stimulates glucagon secretion and inhibits insulin secretion, promotes thermogenesis in brown adipose tissue, stimulates epinephrine secretion by the adrenal glands, enhances lipolysis in white adipose tissue and regulates hepatic glucose production[44,121]. There are however some indications that the brain has the capacity to lower blood glucose levels via both insulin-dependent and insulin-independent mechanisms[20]. In rats, electrical stimulation of VMH neurons or leptin injection into the VMH, but not the LHA, has been shown to increase peripheral glucose uptake, including that in skeletal muscle, independently of circulating insulin levels; these effects are abolished by blockade of the SNS[122,123]. Furthermore, leptin has been shown to rescue and restore normogylcaemia in insulin-deficient mice by reducing hepatic glucose production while increasing tissue glucose[124,125].

Metabolic improvements, originating from central FGF1 injections, are also possibly caused by changes in the gut–liver–brain axis[20,126]. In particular, the hepatic portal vein has a major role in hepatic and peripheral glucose disposal[127,128]. The portal vein is heavily innervated by vagal afferents expressing nutrient sensors and relaying the information to higher brain centres[128]. Glucose delivery directly into the portal vein increases net hepatic glucose uptake by a neural mechanism, as denervation of the liver or intraportal infusion of adrenergic blockers and acetylcholine reduces or increases, respectively, net hepatic glucose uptake in response to portal glucose delivery[127,129,130].

Nevertheless, FGF1 is likely to engage novel (neural) glucose-regulatory mechanisms or combinations thereof, as similar findings have so far not been reported. Likewise, the involvement of a humoral factor cannot be excluded at this stage.

Barrier to FGF1 success — mitogenicity

Though isolated as an *in vitro* growth factor, wild-type FGF1 presents the issue of potential *in vivo* mitogenicity. However, whole-body knockout of FGF1 causes no change in tissue growth and the only known defects are adipose inflammation and a severe form of diabetes mellitus in response to dietary stress[32]. In addition, several transgenic mouse lines constitutively over-expressing FGF1 have no described tumours or organ growth, which suggests *in vivo* safety over long periods of exposure[131–133]. Gene expression array studies have found FGF1 levels increased in breast, prostate and ovarian cancers, but a contribution beyond correlation has not been established[129]. Perhaps more importantly, targeted structure–function studies clearly suggest that the mitogenic and glucose-lowering potentials of FGF1 are separable. FGF1-induced growth *in vitro* is predominantly associated with FGFR3 and FGFR4, whereas glucose-lowering is mediated by FGFR1[8,134,135]. Indeed, FGFR3 and FGFR4 binding of FGF1 can be greatly diminished by mutations and/or deletions in FGF1 that leave its glucose lowering potential fully intact[8]. Thus, the potential for a therapeutically viable fully non-mitogenic human FGF1 variant seems highly plausible. Such a variant could be useful in the context of either a peripheral or central therapeutic injection strategy.

Alternatives to FGF1

As a class, FGF-targeted pharmaceuticals are not completely new prospects. Various members of the FGF family have been explored to treat conditions beyond metabolic disorders. Intravenous recombinant human FGF7 is an FDA-approved treatment for oral mucositis[136] whereas other members of the FGF family are being developed for the treatment of ischaemia, cerebrovascular disease and cardiovascular disease[135]. In addition, various FGFR modulators are in clinical trials for cancer treatment[137]. Although the high potential benefits of a non-mitogenic FGF1 therapy in the treatment of diabetes mellitus and its complications is tantalizing, the actions of FGF1 must still be validated in clinical trials[138,139].

Other FGFs, namely FGF 15/19 (FGF19 being the human form of the rodent FGF15) and FGF21, are known factors in energy homeostasis. To a certain extent, FGF19 and FGF21 have shown metabolic benefits upon central injection (Table 1). ICV injections of FGF19 in both *ob/ob* and DIO rodents yielded insulin-independent glucose lowering through a CNS mediated mechanism, with acute improvements occurring within a few hours of injection[140–143]. FGF21 injected ICV to DIO rodents garners metabolic benefits in the form of increased energy output and insulin sensitivity linked to weight loss[144,145]. In each case, the FGF effect either required multiple injections or did not have duration comparable to a one-time central injection of FGF1. Additionally, concern remains regarding the side effects of therapy with FGF19 and FGF21. FGF19 overexpression has been shown to promote hepatocellular carcinoma[146,147], and systemic FGF21 administration has not been fully divested from noticeable bone loss[148]. However, non-mitogenic FGF19 variants have been developed and acute benefits of FGF21 are currently being explored[135]. At this point, whether central adverse effects mirror these peripheral ones is unclear.

Clinical considerations for FGF1

Therapeutically, an intracranial injection might not be necessary in order to achieve a robust central effect. Achieving normoglycaemia resembling that of central FGF1 injection could possibly occur via an intranasal route. Derivatives of FGF1 given intranasally are able to locally induce angiogenesis and neuronal survival in rodents, with penetrance across the blood–brain barrier greatly enhanced when attached to defined transporter proteins[149,150]. Migration into the CNS is believed to occur through a combination of movement along the olfactory nerve, nasal mucosa capillaries and through cerebrospinal fluid via the cribriform plate[149,151]. Intranasal delivery of large biologic proteins is conceptually advantageous; however, this approach has yet to be adopted in an approved prescription drug. Also, whether a single nasal injection would be sufficient to confer the equivalent long-term benefits seen with central injection is unclear. In addition, even if sufficient levels of FGF1 could be transferred into the CNS this might or might not be optimal for key target sites. Developing a therapeutically effective FGF1 targeted to the CNS by means other than direct intracranial application would first require a better understanding of the specific brain regions mediating the peptide's metabolic actions. Nonetheless, the idea of a non-invasive route remains appealing in that it would greatly improve accessibility, as self-delivery of doses would be possible.

Controlling blood glucose by either peripheral or central delivery will go far to alleviate short-term complications of diabetes mellitus, such as hypoglycaemic episodes, hyperosmolar hyperglycaemic states, diabetic ketoacidosis and diabetic comas. Ultimately though, the success of any intervention to treat or possibly cure diabetes mellitus will rely on more than regulating glucose levels. The value of any solution must also be judged by its ability to limit chronic complications of diabetes mellitus, both microvascular (retinopathy, nephropathy and neuropathy) and macrovascular (namely cardiovascular disease). Traditionally, the standard of treatment has focused heavily on achieving glucose, and in turn HbA_{1c} targets. Current evidence indicates that microvascular complications can be greatly limited by reaching designated HbA_{1c} goals. The same clear, direct benefit of consistent glycaemic control in risk reduction as measured by HbA_{1c} cannot, however, be applied as confidently to macrovascular concerns[152–154]. It must be noted that in either case, increasing evidence points towards large intra-day fluctuations in glucose, specifically in postprandial glucose, as a driver of complications, independent of chronic hyperglycaemia. These acute changes are believed to create periods of exacerbated inflammation, oxidative stress and off-target glycation. The detriment of intra-day hyperglycaemia applies even in individuals with acceptable HbA_{1c} levels, who might be subject to multiple peaks and troughs throughout the day despite apparently sufficient metabolic control[155–157]. Current antidiabetic options, insulin in particular, frequently subject patients to these large variations in glucose levels. This phenomenon has not been observed in preclinical FGF1 studies thus far.

Along with large glycaemic swings, the contribution of T2DM to macrovascular complications can also be attributed to disruptions in PPARγ pathways that promote inflammation via vascular endothelial cells[158,159]. As already discussed, FGF1 works along the PPARγ axis. Hepatically, rFGF1 is able to reduce inflammation, thus by extension it could confer similar benefits on the cardiovascular system[160]. Furthermore, the ability of peripherally injected FGF1 to relieve insulin resistance[8] and normalize insulin levels in patients with T2DM would logically be expected to reduce the risk of stroke[161,162], diabetic retinopathy and hypertension[163].

Limitations of the current data

The failure of central FGF1 to work in DIO mice raises a major concern as to whether it would be effective in patients with T2DM and obesity. Alas, no data on peripheral or central actions of FGF1 in humans or non-human primates is presently available. It is therefore important to emphasize that most of the findings discussed in this Review were obtained from work performed in rodents; any extrapolation to humans must be done so critically. Despite the vast amount of knowledge obtained from animal models, only a finite number of antidiabetic drugs in preclinical development have successfully advanced to clinical use. To some extent, species-specific variations in glucose regulation can be blamed for the limited interspecies translatability. Notable examples include differences in the major site of peripheral glucose disposal, namely the liver in rodents and skeletal muscle in humans. Differences also exist in the hepatic glucose production rate, islet architecture, islet innervation and glucose sensing by pancreatic β cells[164,165].

Species differences on a genomic and proteomic level, as well as deviations in pathway engagement have been described with regards to glucose sensing in pancreatic β cells, which suggests a similar scenario for their central counterparts[164]. Furthermore, inbred diabetic mouse or rat models are often diabetic of monogenetic origin present from birth. These strains acquire rapid onset of obesity early in life mainly due to hyperphagia and decreased energy expenditure, with only moderate vascular and inflammatory complications. These models thus do not fully reflect the multifactorial disease aetiology in humans, in which environmental influences are superimposed on genetic risk factors and disease onset is more gradual and confounded by microvascular and macrovascular defects[166,167]. This limitation is particularly relevant in the development and treatment of T2DM. With the jury still out on the actions of FGF1 on the HPA axis, one must also consider that the adverse actions of toxic glucose analogues such as STZ (which are used for the induction of a diabetic pathophysiology in rodents) are not confined to the pancreas and include disruption to the HPA axis in their repertoire[168].

Conclusions

Clear mechanistic understandings of the endogenous and pharmacologic actions of FGF1 have yet to be described. However, the remarkable ability of peripherally delivered FGF1 to rapidly restore normal glycaemic levels in diabetic mouse models and function as an insulin sensitizer, combined with the longevity in glucose control achieved with central delivery, alludes to exciting opportunities for entirely new therapeutic approaches in the treatment of T2DM. This enthusiasm will gain credibility with preclinical results in higher-order mammals, and the development of truly non-mitogenic analogues.

Acknowledgments

E.G. is supported by the Swiss National Science Foundation (grant P2EZP3_172178). C.P.M. is a Howard Hughes Medical Institute Medical Research Fellow. R.M.E. is an Investigator of the Howard Hughes Medical Institute at the Salk Institute and March of Dimes Chair in Molecular and Developmental Biology, and is supported by NIH grants (DK057978, HL088093, HL105278, and ES010337), an NCI Cancer Center Support Grant (CA014195), the Glenn Foundation for Medical Research, and grants from Steven and Lisa Altman and the Leona M. and Harry B. Helmsley Charitable Trust (2012-PG-MED002).

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Review criteria

PubMed was searched for relevant topics, using the search terms “FGF1”, “FGF”, “type 2 diabetes”, “glucose-sensing neurons”, “glucose-lowering mechanisms”, “glucose homeostasis”, “glucose uptake”, “glycemic control”, “neuronal control”, “central control”, “food intake”, “appetite”, “neurogenesis”, ”synaptic plasticity”, “neuronal plasticity”, “tanycytes”,”hypothalamus”, “hypothalamic inflammation” and “intranasal”, and combinations thereof. No publication time constraints were applied. References cited in this article include both original research and reviews by experts in the field.

Key points

- Peripherally or centrally injected FGF1 confers potent metabolic benefits in type 2 diabetes mellitus
- FGF1 produced by ependymal cells of the central nervous system interacts with tanycytes, astrocytes and glucose-sensing neurons of the hypothalamus to influence feeding and glycaemic control
- Functional recovery of hypothalamic glucose-sensing neurons, as well as neural regeneration and synaptic plasticity, might be fundamental in achieving sustained remission of type 2 diabetes mellitus
- FGF1 has the potential to improve glycaemic control, in addition to microvascular and macrovascular complications, in patients with type 2 diabetes mellitus

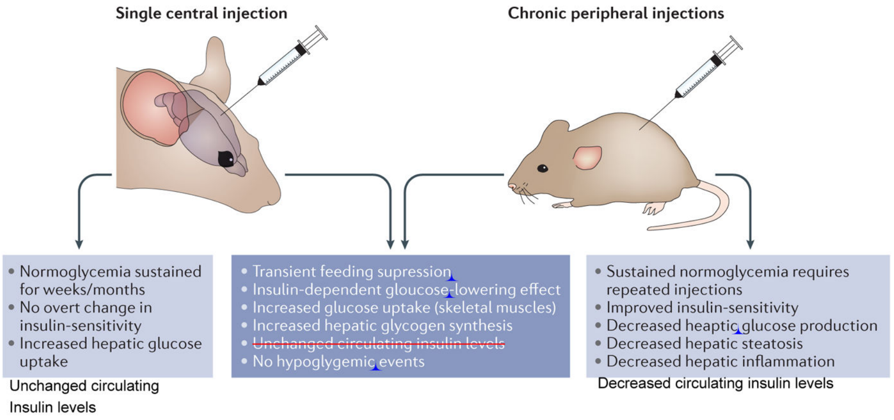

Figure 1. Unique and shared properties of central and peripheral FGF1 injections

Figure depicting metabolic properties of FGF1 when given either peripherally or centrally.

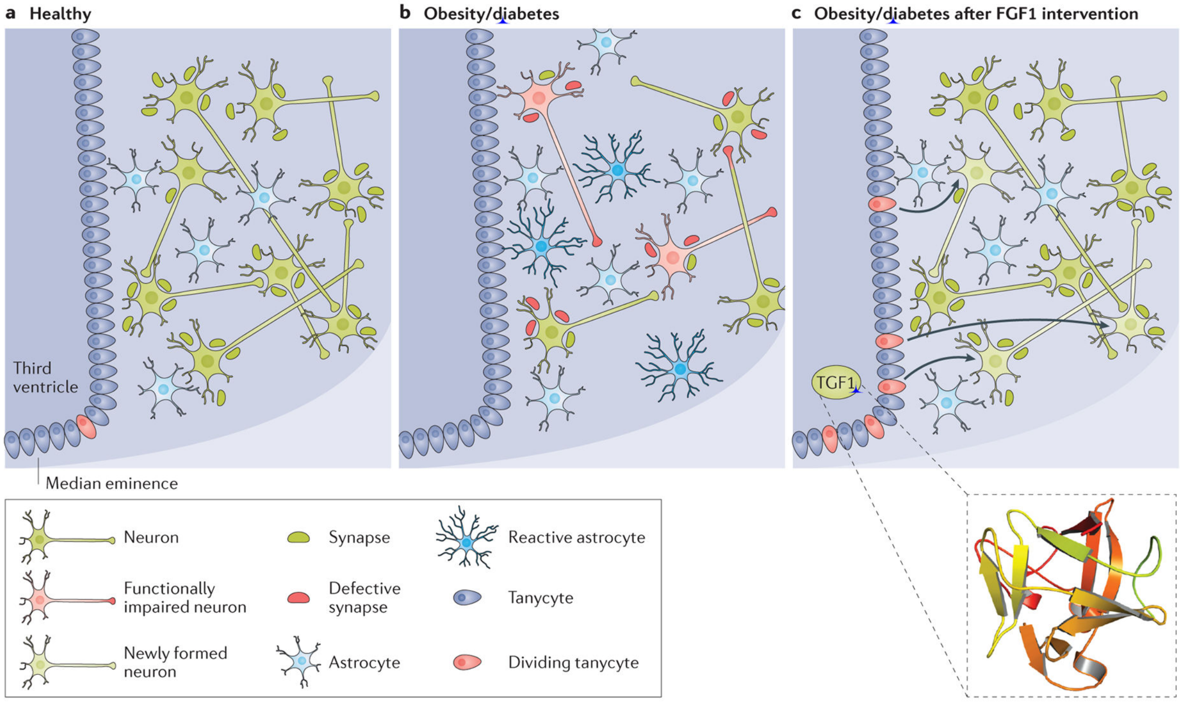

Figure 2. Mechanisms potentially engaged by FGF1 after central injection

Nutrient excess and lack of exercise are major risk factors for the development of the metabolic syndrome, obesity, diabetes mellitus, hypertension and dyslipidaemia. Pathological changes in peripheral organs are accompanied by hypothalamic inflammation and reduced remodelling of hypothalamic neurocircuits. Astrocytes undergo a process of hypertrophy and hyperplasia, commonly termed reactive astrocytosis or astrogliosis. Increasing neuronal insults, such as inflammatory or excitotoxicity signals contribute to a dysfunctional neuronal firing state and even neurodegeneration. Although rare in adult individuals, neurogenesis, originating from tanycytes in the third ventricular lining or periventricular astrocytes, is believed to amend some of the inflicted damage. However, aggravating metabolic conditions reduce the neurogenic potential of hypothalamic neuroprogenitor cells. Overall, this contributes to decreased central glucose sensing and peripheral glucose clearance. Owing to the limited data currently available, one can only speculate about the actions of fibroblast growth factor 1 (FGF1) within this network. Potentially, central FGF1 remedies the debilitated hypothalamic state in diabetes mellitus by restoring health (or number) of glucose-sensing neurons, (transiently) inducing neurogenesis, suppressing reactive astrocytes and restoring synaptic functionality, which ultimately leads to the observed restoration of normoglycaemia. Structure of human FGF1 (PDB ID 2HZ9).

Table 1

Comparison of FGF1 to FGF15/19 & FGF21 in diabetic animal models

General properties[1,2]	**FGF1**	**FGF15/19**	**FGF21**
Receptor specificity	All 7 isoforms; Glucose lowering via FGFR1	Primarily FGFR1 and FGFR4	Primarily FGFR1
Receptor binding requirements	Heparin dependent	β-klotho co-receptor dependent	β-klotho co-receptor dependent
Classification	Autocrine/Paracrine	Autocrine/Endocrine	Autocrine/Endocrine
Induction prompt & tissue	Fed state - Adipose	Fed state - Gut	Fasted state - Liver
Central actions[3,7]			
Feeding suppression	Transient	Transient	None*
Glucose lowering (duration)	Months	Hours	Hours
Hypoglycemic events	No	NA	NA
Insulin sensitizer**	No	No	No
Peripheral actions[2,8–12]			
Feeding suppression	Transient	None	None***
Glucose lowering (duration)	3–7 Days	Hours	Hours
Hypoglycemic events	None	NA	NA
Insulin sensitizer**	Yes	No	No

*Increased food intake

**Defined as increased insulin sensitivity not secondary to body weight loss (e.g. TZDs)

***Food consumption increased when normalized to dropping body weight

NA, no available data

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