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Endocrine FGFs and their signaling in the brain: Relevance for energy homeostasis

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ABSTRACT

Since their discovery in 2000, there has been a continuous expansion of studies investigating the physiology, biochemistry, and pharmacology of endocrine fibroblast growth factors (FGFs). FGF19, FGF21, and FGF23 comprise a subfamily with attributes that distinguish them from typical FGFs, as they can act as hormones and are, therefore, referred to as endocrine FGFs. As they participate in a broad cross-organ endocrine signaling axis, endocrine FGFs are crucial lipidic, glycemic, and energetic metabolism regulators during energy availability fluctuations. They function as powerful metabolic signals in physiological responses induced by metabolic diseases, like type 2 diabetes and obesity. Pharmacologically, FGF19 and FGF21 cause body weight loss and ameliorate glucose homeostasis and energy expenditure in rodents and humans. In contrast, FGF23 expression in mice and humans has been linked with insulin resistance and obesity. Here, we discuss emerging concepts in endocrine FGF signaling in the brain and critically assess their putative role as therapeutic targets for treating metabolic disorders.

1. Introduction

The increased number of patients with metabolic disorders, such as obesity, type 2 diabetes (T2D), and hypertension, has imposed a severe threat to global health in recent decades. These abnormalities have been associated with alteration in energy homeostasis, triggered by a disparity between energy consumption and expenditure and a sedentary lifestyle, which predisposes individuals to metabolic diseases (Abdalla, 2017). The costs attributed to the rising number of metabolic disorders are devastating, with estimated hundreds of billions of dollars spent each year on medical treatment alone (van den Broek-Altenburg et al., 2022).

Tightly synchronized interactions between the central nervous system (CNS) and peripheral metabolic tissues are essential for maintaining energy homeostasis (Roh et al., 2016). Through the combination of a wide range of signals from the periphery, such as nutrients, gut-derived molecules, and adiposity-related hormones, the brain receives information on the status of various peripheral organs which are crucial to the absorption of nutrients, energy storage, or energy consumption (Kim et al., 2018; Roh et al., 2016).

The hypothalamus, therefore, has received significant attention, given its capacity to orchestrate peripheric signals and elicit a response through the secretion of neuroendocrine molecules that control energy and glucose metabolism (Waterson and Horvath, 2015), which regulates food behavior, energy expenditure, insulin secretion, gluconeogenesis, and fatty acid/glucose metabolism in adipose tissues and skeletal muscles (Roh et al., 2016). Notably, many of these effects are intermediated by the autonomic nervous system, which innervates peripheral tissues and can enhance or reduce their activities (Seoane-Collazo et al., 2015).

In this review, we explore the current state of research on the central role of endocrine fibroblast growth factors (FGFs) in regulating energy homeostasis. We also detail the contribution of FGFs to numerous brain signaling processes that affect energy consumption and expenditure and limitations in our understanding of the biology and pharmacology of endocrine FGFs. In addition, we discuss how the signaling of endocrine FGFs in the brain is relevant to disease and human health and their therapeutic applications in metabolic diseases.

2. The fibroblast growth factors (FGFs) superfamily

The FGF superfamily comprises 22 structurally and evolutionarily correlated proteins, which are associated with a wide range of functions,

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such as cell proliferation, migration, differentiation, and repair (Cuevas-Ramos and Aguilar-Salinas, 2016).

FGFs are categorized as intracrine, paracrine, or endocrine, based on their biochemical function, sequence analogies, and evolutionary relationships (Itoh et al., 2015; Ornitz and Itoh, 2015) (Fig. 1). Most FGFs exert paracrine actions once they are retained in the surrounding extracellular matrix due to their high affinity for heparan sulfate glycosaminoglycan (Ornitz and Itoh, 2015). Paracrine FGFs are subdivided into 5 subfamilies: the FGF1 subfamily, comprising FGF1 and FGF2; the FGF4 subfamily, comprising FGF4, FGF5, and FGF6; the FGF7 subfamily, which consists of FGF3, FGF7, FGF10, and FGF22; the FGF8 subfamily, comprising FGF8, FGF17, and FGF18; and the FGF9 subfamily, formed by FGF9, FGF16, and FGF20 (Ornitz and Itoh, 2015).

The intercellular FGF family, including FGF11, FGF12, FGF13, and FGF14, are not secreted and interact with the inner carboxy-terminal domain of voltage-gated sodium channels. This interaction promotes the correct distribution of these channels at the axon during development and regulates its functions in neurons and cardiomyocytes (Goetz et al., 2009; Goldfarb et al., 2007; Liu et al., 2003; Ornitz and Itoh, 2015).

Finally, FGF15, FGF19, FGF21, and FGF23 represent the endocrine family of FGFs. FGF15 and FGF19 are orthologs in vertebrates, called FGF15 in rodents and FGF19 in other vertebrates, including primates and humans (Jones, 2012). In this review, we refer to these as FGF15/19. The endocrine FGFs display particular features that give them low affinity to heparan sulfate and, therefore, can escape the extracellular matrix of the tissue of origin and act as an endocrine molecule (Goetz et al., 2007; Ornitz and Itoh, 2015). The structural uniqueness of endocrine FGFs that allows their systemic circulation also reduces their affinity for fibroblast growth factors receptors (FGFRs) (Goetz et al., 2007; Harmer et al., 2004), which is compensated by a single-pass transmembrane glycoprotein, named klotho (α- or β-klotho), that act as co-receptor to bind, dimerize, and activate their cognate FGFRs (Degirolamo et al., 2016). This co-receptor stabilizes the interaction between the FGFs and their receptors, achieving proper signal transduction at their target tissues (Goetz et al., 2007; Kurosu and Kuro-O, 2009). Endocrine FGFs are critical for the maintenance of homeostasis, as their signaling is associated with the regulation of carbohydrates, lipids, phosphate, and bile acid metabolism, in addition to the canonical FGF functions (Ding et al., 2012; Phan et al., 2021).

3. Fibroblast growth factors receptors (FGFRs)

Paracrine and endocrine FGFs achieve their functions by binding and activating the cell-surface FGFR family of tyrosine kinase receptors (Beenken and Mohammadi, 2009). Like FGFs, FGFRs have already been found in invertebrates, indicating that FGF/FGFR signaling was conserved during the evolution (Burdine et al., 1997; Muha and Müller, 2013).

There are four FGFR genes (FGFR1–FGFR4) that encode FGF receptors, which are composed of three extracellular immunoglobulin-like domains (IgI–IgIII), a single-pass transmembrane helix, and two intracellular domains with tyrosine kinase activity (Mohammadi et al., 2005). The IgI domain is responsible for receptor autoinhibition in the absence of appropriate ligands and regulates the receptor affinity with the FGFs (Kalinina et al., 2012). Located between the IgI and IgII domains is a flexible, negatively charged connector, known as acid box, which participates in FGFR interaction with partner proteins and receptors' autoinhibition (Kalinina et al., 2012; Porębska et al., 2018). The IgII and IgIII domains are responsible for FGFs' binding site and specificity (Ornitz and Itoh, 2001). Additionally, the IgII domain comprises a positively charged heparan sulfate glycosaminoglycan binding region (Mohammadi et al., 2005).

An important feature of the FGFR family is the variety of FGFR isoforms, which include FGFRs with an extracellular ligand domain composed of two or three immunoglobulin-like looped domains, soluble secreted FGFR forms, and isoforms generated by alternative splicing, which profoundly modifies ligand-binding specificity (Miki et al., 1992). This alternative splicing occurs in the IgIII domain and is observed in FGFR1, 2, and 3, but not in FGFR4 (Eswarakumar et al., 2005), generating two alternative splicing variants, "b" and "c", for each of these FGFRs (Olsen et al., 2006; Yeh et al., 2003). This splicing event is essential to establishing directional FGF signaling between epithelial and mesenchymal cells (Eswarakumar et al., 2005). Therefore, there are seven FGFR variants: FGFR1-IIIb, FGFR1-IIIc, FGFR2-IIIb, FGFR2-IIIc, FGFR3-IIIb, FGFR3-IIIc, and FGFR4 (Phan et al., 2021). Although FGFRs

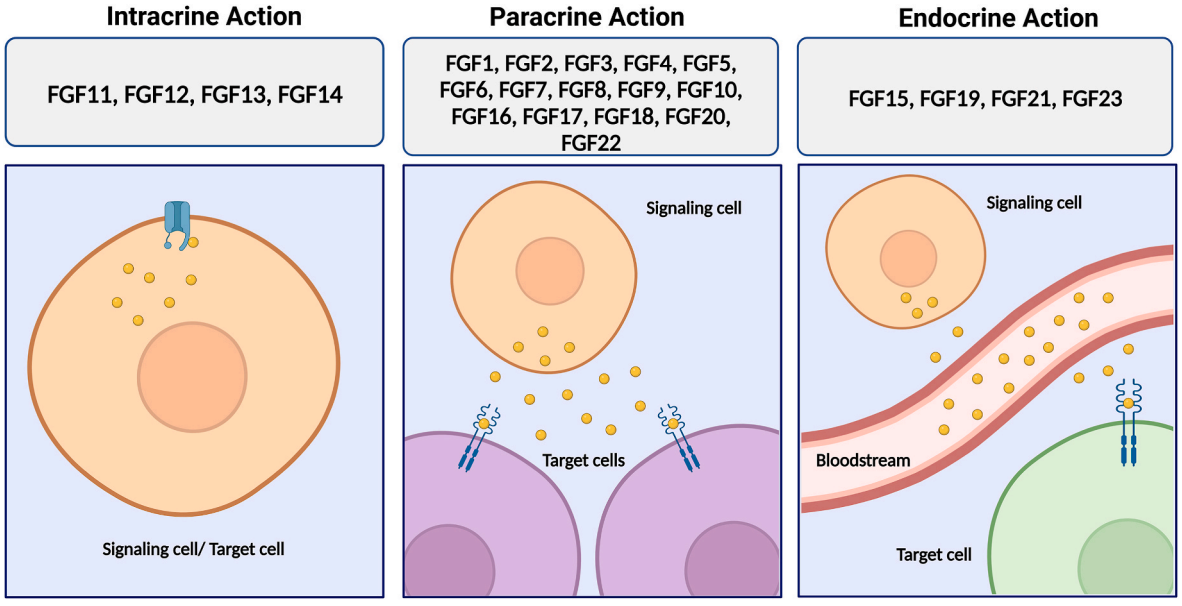

Fig. 1. Mechanisms of action of intracrine, paracrine, and endocrine FGFs. Intracrine FGFs are not secreted and are characterized by their ability to bind to and modulate voltage-gated sodium channels. Paracrine FGFs are locally secreted and act on nearby target cells by diffusion, with functions involved in multiple developmental and physiological processes. Endocrine FGFs are secreted and act on distant target cells through the systemic circulation, with roles in multiple metabolic processes. The figure was created with BioRender software (https://www.biorender.com).

are encoded by different genes, their sequence exhibits high homology, differing from 56% to 71% (Itoh et al., 2015; Itoh and Ornitz, 2004).

After the ligand binding, FGFRs dimerize, allowing the cytoplasmic kinase domains to be transphosphorylated and become activated (Yayon et al., 1991), inducing the pleiotropic responses that result in the diversity of cellular effects induced by this large family of growth factors (Eswarakumar et al., 2005). Different ligands induce subtle differences in receptor dimerization, which can translate into receptor activation changes, resulting in distinct biological responses (Goetz and Mohammadi, 2013).

The activated FGFRs phosphorylate adaptor proteins for four main intracellular signaling pathways: *i*, Ras/mitogen-activated protein kinase (MAPK); *ii*, phosphoinositide 3-kinase (PI3K)/AKT; *iii*, signal transducer and activator of transcription (STAT); and *iv*, phospholipase C gamma (PLCγ) (Beenken and Mohammadi, 2009; Eswarakumar et al., 2005; Ge et al., 2011; Goetz and Mohammadi, 2013; Turner and Grose, 2010), which will regulate the expression of different target genes, as summarized in Fig. 2.

A key intracellular signaling pathway activated by the binding of endocrine FGFs to FGFRs is the extracellular-signal-regulated kinase (ERK) cascade (Adams et al., 2012; Ding et al., 2012; Ge et al., 2011; Kharitonenkov et al., 2005; Yang et al., 2012), a major signaling cassette of the MAPK signal transduction that mediates the signals from the activation of cell surface receptors to regulate gene expression (Raju et al., 2014). Previous studies demonstrate that MAPK/ERK signaling is quickly induced in the hypothalamus of mice by FGF21 (Douris et al., 2015; Liang et al., 2014; Yang et al., 2012) and FGF19 (Marcelin et al., 2014). Notably, Douris and colleagues showed that FGF21 promotes ERK1/2 phosphorylation in cultured hypothalamic slices (Douris et al., 2015), confirming that FGF21 effects in the brain are direct and not due to a secondary signal from the periphery. While the cell-autonomous effect of FGF19 in promoting ERK1/2 phosphorylation has not yet been evaluated in hypothalamic cell lines, it was previously observed that FGF19 induces ERK1/2 phosphorylation in adipocytes and hepatocytes in a dose-dependent manner (Kurosu et al., 2007), as well as in myoblasts (Kurosu et al., 2007) and colorectal adenocarcinoma cell line (Ghosh et al., 2014), providing evidence that ERK activation may also be a direct downstream target for FGF19.

FGFR1, FGFR2, and FGFR3 are broadly expressed in the CNS (Bookout et al., 2013; Fon Tacer et al., 2010; Hultman et al., 2019; Ryan et al., 2013; Yazaki et al., 1994) and the "IIIc" isoforms of these receptors are predominant in the brain (Fon Tacer et al., 2010), including the hypothalamus (Kaminskas et al., 2019; Sun et al., 2007). However, FGFR4 mRNA expression is slight or undetected in the mouse brain (Fon Tacer et al., 2010; Hultman et al., 2019). Interestingly, Ryan and colleagues (Ryan et al., 2013) showed that FGFR4 expression is present in the hypothalamus of rats, suggesting species-specific divergence in FGFR4 expression across mammal species. Moreover, FRFR1 and FGFR4 mRNA levels were downregulated by high-fat diet (HFD) in rat hypothalamus (Ryan et al., 2013), implying that FGF/FGFR signaling may be impaired in obesity.

Notably, FGFRs were found to be expressed with region and cell-specificity in the brain. FGFR1 mRNA is expressed preferentially in neurons, while FGFR2 and FGFR3 mRNAs are expressed preferentially in glial cells (Yazaki et al., 1994). The uniqueness of FGFRs being expressed in specific cells in the brain indicates that these receptors may play different roles.

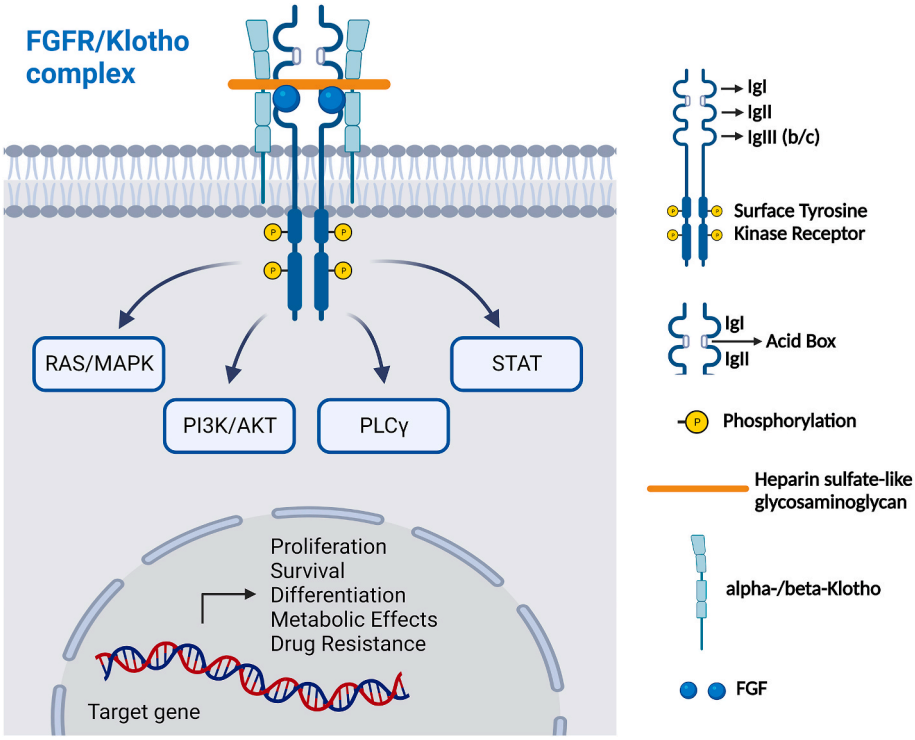

Fig. 2. Schematic representation of the canonical FGF/FGFR signaling pathway. Fibroblast growth factor receptors (FGFRs) are a family of tyrosine kinase receptors expressed on the cell membrane, comprised of an extracellular domain encompassing three immunoglobulins (Ig)-like domains (IgI, IgII, and IgIII), a single-pass transmembrane domain, and an intracellular tyrosine kinase domain. Located between the IgI and IgII is the acid box, which is the stretch of acidic amino acids responsible for FGFR interaction with partners other than fibroblast growth factors (FGFs). Within IgII is the heparan sulfate glycosaminoglycan binding domain, which helps to stabilize FGF–FGFR interaction. Splice variants in the IgIII domain of FGFR1, FGFR2, and FGFR3 lead to two variants for these receptors, labeled either IIIb or IIIc isoforms. The binding of appropriate FGFs to FGFRs triggers conformational changes in the receptors, resulting in dimerization and activation of FGFRs. The activated FGFRs phosphorylate adaptor proteins for four major intracellular signaling pathways: RAS/mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3K)/AKT, phospholipase C gamma (PLCγ), and signal transducer and activator of transcription (STAT), which will regulate the expression of different target genes. The figure was created with BioRender software (https://www.biorender.com).

4. Klotho proteins

The klotho (KL) protein was originally identified as an aging-suppressor gene that extends life span (Kim et al., 2015). KL overexpression in mice promotes resistance to oxidative stress, increases synaptic plasticity, and enhances cognition (Dubal et al., 2015; Kurosu et al., 2005, 2007), while its disruption by mutation or knockout accelerates the development of aging-like phenotypes (Kuro-o et al., 1997; Kurosu et al., 2006). The KL gene comprises five exons and encodes a single-pass transmembrane protein with a short cytoplasmic domain (Kim et al., 2015; Wu et al., 2007). The extracellular domain of KL protein can also be cleaved by proteases, such as ADAM metallopeptidase domain 10 (ADAM10), and released in the blood and cerebrospinal fluid (CSF) to act as a hormone (Kim et al., 2015; Kuro-o et al., 1997; Kurosu et al., 2005).

There are two subtypes of KL transmembrane proteins: alpha-klotho (KLA) and beta-klotho (KLB) (Guthrie et al., 2022). Both of them have an extracellular domain containing two tandem glycosidase-like domains, also referred to as pseudo-glycoside hydrolases, designated KL1 and KL2 (Guthrie et al., 2022; Shiraki-Iida et al., 1998). KLA displays 42% amino acid sequence homology with KLB (Kim et al., 2015), having the primary structures of KL1 more conserved than KL2 (Ito et al., 2000).

The KL proteins act as co-receptors that coordinate the interaction between the endocrine FGFs and the FGFRs (Bono et al., 2022; Goetz et al., 2007; Kurosu et al., 2006; Tohyama et al., 2004). As FGF19 subfamily members have a poor heparin-binding affinity that enables them to act as endocrine factors, their binding with their respective receptors is impaired (Kurosu et al., 2007). Thus, KL proteins act by increasing the affinity between FGFs and FGFRs, interacting simultaneously with the ligand FGFs and the receptor, forming a ternary complex (Bono et al., 2022; Kurosu et al., 2007; Yang et al., 2012). KLA and KLB can physically interact with FGFR1-IIIc, 3-IIIc, and 4 (Fon Tacer et al., 2010; Mohammadi et al., 2005), demonstrating a difference in binding specificity, with KLA binding to FGF23 (Goetz et al., 2007; Kurosu et al., 2006), whereas KLB interacts with FGF15/19 and FGF21 (Hultman et al., 2019; Kurosu et al., 2007; Lan et al., 2017).

The obligatory presence of KL to stabilize the interaction between members of endocrine FGFs with their receptors restricts the target tissues of this subfamily, as its effects will only be observed in cells that express the receptor and co-receptor (Adams et al., 2012; Goetz et al., 2007; Guthrie et al., 2022; Hultman et al., 2019; Kurosu et al., 2007). Although FGFRs are widely expressed in several tissues and cell types (Fon Tacer et al., 2010), the expression of co-receptors of the KL family is more limited. In the periphery, KLA is highly expressed in the kidney and parathyroid gland (Ben-Dov et al., 2007; Kim et al., 2015), while in the brain, it has already been detected in the choroid plexus (Kim et al., 2015; Kuro-o et al., 1997; Li et al., 2004; Vo et al., 2018), cerebellum (German et al., 2012; Lim et al., 2015), hippocampus, hypothalamus, and amygdala (Clinton et al., 2013; Olauson et al., 2017; Zhao et al., 2020). Meanwhile, KLB is expressed predominantly in adipose tissue, the liver, and the kidneys, but it also can be expressed in skeletal muscle and some brain regions like the hypothalamus and hippocampus (Fon Tacer et al., 2010; Guthrie et al., 2022; Xu and Sun, 2015; Yang et al., 2012). The expression of KLA and KLB in the brain is summarized in Table 1.

Several studies have shown that the knockout of α- or β-klotho in peripheral tissues impairs endocrine FGF signaling. KLA-deficient mice share many phenotypes with FGF23-deficient mice, including multiple aging-associated symptoms and diminished life expectancy, vascular calcification in the kidneys, hyperphosphatemia, muscle atrophy, and hypoglycemia (Kurosu et al., 2007; Nagai et al., 2003; Razzaque et al., 2006; Shimada et al., 2004a; Wu et al., 2007). On the other hand, Xunshan and colleagues have shown that HFD-fed mice lacking KLB are resistant to the effects of FGF21 administration, such as ameliorated insulin sensitivity, reduced body fat content, and improved lipids homeostasis (Ding et al., 2012). Furthermore, liver KLB knockout mice

Table 1

Klotho isoform	Experimental model	Brain area/cell type	References
Alpha-Klotho (KLA)	Human tissue rat	Cortex/neuronal cells	Lim et al., 2015 Clinton et al., 2013
		Cerebellum/Purkinje cells	Vo et al., 2018
	Human tissue		Lim et al., 2015
	129S1/SvImJ mouse		German et al., 2012
	C57BL/6J mouse		Olauson et al., 2017 Zhao et al., 2020
	Human tissue	Spinal cord/motor neurons	Vo et al., 2018 Lim et al., 2015
		Choroid plexus/ependymal cells	Kuro-o et al., 1997 Vo et al., 2018
	Human tissue		Li et al., 2004
	C57BL/6J and C3H/J mouse		Lim et al., 2015
	129S1/SvImJ mouse		German et al., 2012
	Sprague Dawley rat		Clinton et al., 2013 Olauson et al., 2017 Zhao et al., 2020 Ursem et al., 2021
		Hippocampus	Vo et al., 2018
	KLA mutant mice		Li et al., 2004
	Sprague Dawley rat		Clinton et al., 2013
	C57BL/6J mice		Zhao et al., 2020 Nagai et al., 2003
	Sprague Dawley Rat	Hypothalamus	Clinton et al., 2013 Olauson et al., 2017 Ursem et al., 2021
	Sprague Dawley Rat	Amygdala	Clinton et al., 2013 Olauson et al., 2017
Beta-Klotho (KLB)		Hypothalamus	Ding et al., 2012 Liang et al., 2014 Bookout et al., 2013
	C57BL/6J mouse		Hultman et al., 2019
	Klb-flox mouse		Bono et al., 2022 Owen et al., 2014 Talukdar et al., 2016a
	C57BL/6J mouse	Hindbrain	Bookout et al., 2013
	Human		Hultman et al., 2019 Owen et al., 2014
	C57BL/6J mouse	Nucleus Accumbens	Bookout et al., 2013
	Klb-flox mouse	Amygdala	Bono et al., 2022
	Klb-flox mouse	Subiculum	Bono et al., 2022
	Klb-flox mouse	Hippocampus	Bono et al., 2022

(*continued on next page*)

Table 1 (*continued*)

Klotho isoform	Experimental model	Brain area/cell type	References
	C57BL/6J mouse	Dorsal vagal complex	Ding et al., 2012 Bookout et al., 2013

share remarkable phenotypic similarities with FGFR4 and FGF15 knockout mice, as both present an increased production and excretion of bile acids (Goetz et al., 2007; Guthrie et al., 2022; Inagaki et al., 2005; Ito et al., 2005; Kurosu et al., 2007).

Even though KL family proteins are expressed in low levels and restricted to some areas of the CNS, they are still essential for the actions of endocrine FGFs in the brain. It was previously demonstrated that FGF21 can promote neuroplasticity, suppress neuroinflammation, and induce metabolic adaptations in mice (Bono et al., 2022; Bookout et al., 2013), and all these effects depend on the expression of KLB in different regions of the brain, including the hippocampus, hypothalamus, and hindbrain. By contrast, these effects were absent in mice lacking KLB in these brain areas (Bono et al., 2022; Bookout et al., 2013). Moreover, some studies have demonstrated that KLB knockout in the brain impairs the FGF15/19 and FGF21 actions on body weight loss in HFD-fed mice (Guthrie et al., 2022), demonstrating the dependence on the co-receptor to induce its effects on body weight regulation (Owen et al., 2014, 2015). Thus, the restricted expression of KLA and KLB in the brain is a crucial factor that ensures the specificity of the regions that will be responsive to FGF19 family members (Kurosu et al., 2007).

5. FGF15/19

In 1997, the mouse FGF15 was the first endocrine FGF to be identified and was originally recognized as a downstream target of the oncogenic transcriptional factor pre-B cell leukemia transcription factor 1 (E2A-PBX1) (McWhirter et al., 1997). Years later, through a homology-based DNA database search, FGF19 was identified in humans (Nishimura et al., 1999) and was subsequently found to be the orthologue of the mouse FGF15, based on conserved synteny around their loci (Itoh and Ornitz, 2008; Katoh, 2003). Rodent FGF15 and human FGF19 share 51% total amino acid identity (Nishimura et al., 1999) and the sequence and position of the farnesoid X receptor binding element that regulates the expression of these two genes is conserved (Inagaki et al., 2005).

The primary source of FGF15/19 is the enterocytes from the ileum, which secrete these FGFs in response to the postprandial signaling of bile acids (Fon Tacer et al., 2010; Inagaki et al., 2005; Jones, 2008). Once released into the lumen of the intestine, bile acids can enter enterocytes and activate the nuclear farnesoid X receptor (Kliewer and Mangelsdorf, 2015), which heterodimerizes with the retinoid X receptor and acts as a transcription factor, positively modulating FGF15/19 transcription (Inagaki et al., 2005). In mice, ileal concentrations of FGF15 mRNA are maximal 1 h postprandial (Potthoff et al., 2011), whereas in humans, serum concentrations of FGF19 increase 2–3 h after a meal (Lundåsen et al., 2006).

After reaching portal venous circulation, FGF15/19 signals on the liver to strongly repress the expression of CYP7A1, a rate-limiting enzyme involved in the bile acid biosynthesis pathway, which regulates postprandial bile acid homeostasis (Inagaki et al., 2005). FGF15/19 also promotes gallbladder filling (Choi et al., 2006). Notably, FGF15/19 shares several postprandial effects with insulin, the primary postprandial hormone, such as inhibition of gluconeogenesis and activation of glycogen and protein synthesis (Kir et al., 2011; Potthoff et al., 2012). However, an important difference with insulin is that FGF15/19 suppresses, rather than activates, hepatic fatty acid synthesis (Bhatnagar et al., 2009). Since serum insulin peaks occur 15 min after feeding, and the FGF15/19 peak occurs later (Lundåsen et al., 2006), these FGFs appear to exert a late-phase postprandial effect.

In rodents, FGF19 exerts potent antidiabetic and anti-obesogenic effects (Dolegowska et al., 2019). Venous injection of vector genome adeno-associated virus (AAV)-FGF19 in mice fed a high-fat, high-fructose, high-cholesterol diet improves insulin sensitivity, energy homeostasis, and lipid metabolism (Zhou et al., 2017a), while its transgenic overexpression in mice improves glucose tolerance and prevents the HFD-induced body weight gain and adiposity (Fu et al., 2004; Tomlinson et al., 2002). On the other hand, FGF15-deficient mice display higher adiposity and body weight when challenged by HFD (Alvarez-Sola et al., 2017) and impaired glucose tolerance, which is corrected by FGF19 administration (Kir et al., 2011).

One of the first signs that FGF19 could exert central actions was observed by Fu and colleagues (Fu et al., 2004), where it was shown that intracerebroventricular (ICV) injections of recombinant FGF19 in mice increase their metabolic rate to a degree comparable to its systemic administration. Although FGF15/19 is not expressed in the CNS of adult individuals (Fon Tacer et al., 2010), FGF15 and FGF19 are highly expressed in developing fetal brains (Gimeno et al., 2002; McWhirter et al., 1997; Nishimura et al., 1999). FGF15/19 can cross the blood-brain barrier (BBB), and even though its permeability is not as great as that of FGF21, it is found in the brain after 10 min of intravenous administration (Hsuchou et al., 2013), indicating that the CNS can respond to FGF19 administered in the periphery. The pharmacokinetics of FGF19 entry into the CNS is influenced by its circulating levels and display significant interactions with the liver and kidneys (Hsuchou et al., 2013).

It has previously been shown that FGF19 signaling in the brain induces hypophagia and body weight loss in rodents (Marcelin et al., 2014; Ryan et al., 2013). Acute ICV FGF19 reduces chow and HFD intake in rats, while in the presence of a pharmacological FGFR inhibitor, this effect is abolished (Ryan et al., 2013). In accordance, a single injection of FGF19 in HFD-fed mice also results in diminished food intake (Marcelin et al., 2014), suggesting a physiological role for hypothalamic FGF19/FGFR signaling controlling food behavior.

The hypothalamic melanocortin system plays a crucial role in regulating food behavior, body weight, and energy balance (Micioni Di Bonaventura et al., 2020). In this system, hormones released in the feeding state, such as leptin and insulin, secreted into the bloodstream by adipocytes and pancreatic β-cells, respectively, cross the BBB to bind and activate their receptors on pro-opiomelanocortin (POMC) neurons, promoting POMC processing for mature melanocyte-stimulating hormone (MSH), including alpha-, beta-, and gamma-MSH, which signals to decrease food consumption (Andermann and Lowell, 2017; Baldini and Phelan, 2019; Tung et al., 2006). Leptin also signals in the hypothalamus to inhibit the secretion of orexigenic agouti-related neuropeptide (AgRP) and neuropeptide Y (NPY) expressed by AgRP/NPY neurons (Baldini and Phelan, 2019). On the other hand, the circulating levels of leptin and insulin decrease under starvation, which increases the AgRP/NPY neuron activity (Baldini and Phelan, 2019). Furthermore, fasting stimulates the release of ghrelin, a stomach-derived orexigenic hormone that induces AgRP/NPY activity and, in turn, appetite (Yanagi et al., 2018).

Marcelin and colleagues investigated the hypothalamic neuronal population(s) that could be targeted by FGF19 in obese mice (Marcelin et al., 2014). This study demonstrated that FGF19 induces ERK1/2 phosphorylation only in the hypothalamic NPY neurons and not in POMC neurons, both located in the arcuate nucleus. Moreover, the number of NPY neurons co-expressing p-ERK1/2 was significantly increased after FGF19 administration (Marcelin et al., 2014). Interestingly, both HFD-fed and leptin-deficient ob/ob mice display a substantial reduction in the number of c-FOS positive NPY neurons in the arcuate nucleus after FGF19 administration, accompanied by a down-regulation of hypothalamic AgRP and NPY gene expression (Marcelin et al., 2014), implying that FGF19 repressed AGRP/NPY neuron

activation. The mechanism by which FGF19 reduces the expression of orexigenic neuropeptides in the hypothalamus is illustrated in Fig. 3.

Remarkably, AgRP/NPY neurons are known to send projections outside of the BBB, which allows these neurons to sense small changes in circulating hormone levels and relay this information to other downstream target neurons (Faouzi et al., 2007; Olofsson et al., 2013). Thus, when administered peripherally, FGF19 can modulate neuronal activity even without crossing the BBB.

Central administration of FGF19 is also known to improve glucose homeostasis in leptin-deficient ob/ob and HFD-fed mice (Marcelin et al., 2014; Morton et al., 2013), as well as in HFD-fed rats (Ryan et al., 2013), through insulin-independent mechanisms (Morton et al., 2013; Ryan et al., 2013). Moreover, the central melanocortin system also plays a crucial role in governing peripheral glucose homeostasis (Morton et al., 2013; Obici et al., 2001). It is known that ICV administration of FGF19 in melanocortin-4 receptor-deficient mice promotes improvement in glucose tolerance, suggesting that the melanocortin system may not be required for the glucose-lowering effects of central FGF19 action (Morton et al., 2013). However, a recent study has shown that the melanocortin-3 receptor in the ventromedial hypothalamus also exerts an important role in glucose disposal (Sutton et al., 2021). In this way, future work is warranted to test whether FGF19 can reduce blood glucose levels in models lacking the hypothalamic melanocortin-3 receptor.

It is still not fully understood whether the improvement in glucose tolerance observed after central FGF19 administration occurs before changes in body weight or whether it is a consequence of weight loss. Morton and colleagues demonstrated that low-dose ICV injection of FGF19 dramatically improves glucose tolerance in mice within 2 h (Morton et al., 2013). Moreover, central administration of FGF19 improved glucose metabolism and insulin signaling in HFD-fed mice independently of changes in body weight. While these findings suggest that glucose tolerance improvement occurs independent of body weight loss, the specific mechanism mediating these effects awaits further studies.

Although the hypothalamus is a crucial region for controlling energy homeostasis, extrahypothalamic regions, such as the hindbrain, have also been identified as FGF19 targets. Administration of FGF19 in the 4th ventricular of the brain reduces blood glucose levels in type 1 diabetic mice through a parasympathetic mechanism via the vagus nerve (Wean and Smith, 2021a). Additionally, central FGF19 increases glutamate release in the hindbrain dorsal vagal complex in hyperglycemic mice, an important homeostatic regulatory center, by increasing the activity of glutamatergic neurons located in the area postrema and nucleus tractus solitarius (Wean and Smith, 2021b). Since these neurons communicate with several other metabolic regulatory nuclei, FGF19 may alter neuroendocrine and behavioral aspects of metabolism in the brain, in addition to its modulations in parasympathetic output (Wean and Smith, 2021b).

Peripheral tissues also play an important role in regulating energy homeostasis and responding to the central administration of FGF19 (Marcelin et al., 2014). Lan and colleagues have shown that ICV administration of FGF19 in mice stimulates sympathetic outflow to brown adipose tissue (BAT) in a dose-dependent manner and causes corresponding increases in energy expenditure (Lan et al., 2017). Furthermore, ICV infusions of FGF19 improved peripheral insulin signaling in HFD-fed mice (Marcelin et al., 2014), contributing to increased glucose uptake. Evidence shows that FGF19 in the brain can also reduce blood glucose levels by suppressing the hypothalamic–pituitary–adrenal axis (Perry et al., 2015). Perry and colleagues demonstrated that FGF19 suppresses adrenocorticotropic hormone and corticosterone in type 1 diabetic mice, leading to reductions in whole-body lipolysis, hepatic acetyl-CoA concentrations, and pyruvate carboxylase activity, thereby suppressing hepatic gluconeogenesis (Perry et al., 2015).

Thus, these findings suggest that FGF15/19 exerts its metabolic effects via multiple pathways in the CNS and involves top-down mechanisms to regulate energy homeostasis. Future studies should be directed towards advancing the understanding of potential secondary effects of FGF15/19 in extrahypothalamic areas, such as the amygdala and nucleus tractus solitarius, as well as on peripheral tissues. Identifying the specific neuronal targets activated by FGF15/19 and evaluating its potential synergistic effect with other centrally-acting hormones, such as leptin and insulin, will clarify how the signaling triggered by these FGFs affects signaling pathways that regulate feeding behavior.

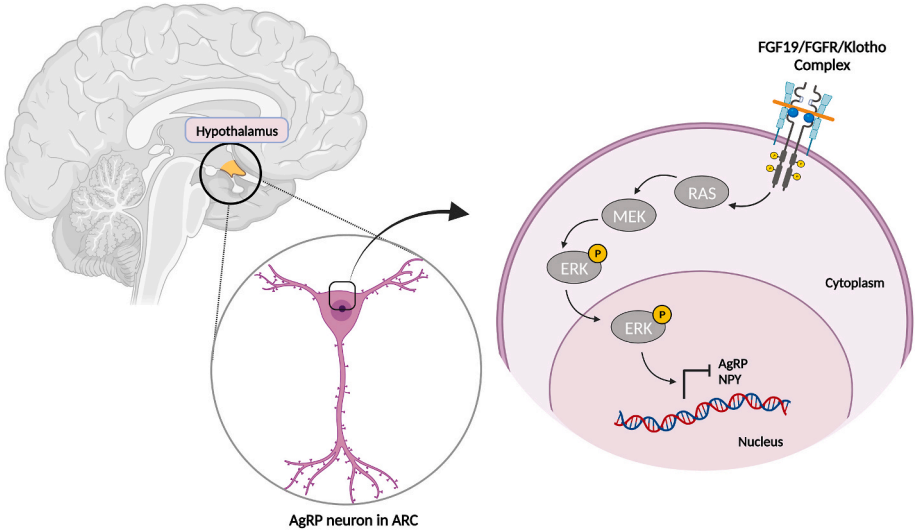

Fig. 3. FGF19 represses hypothalamic AgRP/NPY neuron activation. In the hypothalamus of fasted diet-induced and leptin-deficient ob/ob obese mice, FGF19 induces ERK1/2 activation, resulting in a substantial reduction in the number of c-FOS positive NPY neurons in the hypothalamic arcuate nucleus (ARC). This inhibition is accompanied by downregulation of AgRP and NPY gene expression in the medio-basal-hypothalamus of mice fasted for 24 h and centrally treated with FGF19, demonstrating a role for FGF19 in attenuating food intake through the repression of AgRP/NPY neuronal activation in obese mice models. AgRP: agouti-related protein; NPY: neuropeptide Y; MEK: mitogen-activated protein kinase; ERK: extracellular signal-regulated kinase. The figure was created with BioRender software (https://www.biorender.com).

6. FGF21

FGF21 was first identified in 2000, showing high expression in the liver of mice (Nishimura et al., 2000). Indeed, several other studies have confirmed the liver as the primary site of FGF21 production and secretion (Flippo and Potthoff, 2021); however, its expression is also found in white (Muise et al., 2008) and brown (Hondares et al., 2011) fat depots, skeletal muscle (Izumiya et al., 2008), pancreatic β-cells (Zhang et al., 2008), placenta (Dekker Nitert et al., 2014), and heart tissue (Planavila et al., 2013). Nonetheless, under physiological conditions, most systemic FGF21 appears to be derived from the liver (Markan et al., 2014).

The FGF21 gene expression regulation is complex as it involves different tissues and regulatory mechanisms, such as diet, nutrients, hormones, and dietary bioactive compounds (Erickson and Moreau, 2016; Tezze et al., 2019). In the liver of mice, crosstalk has been observed between FGF21 and peroxisome proliferator-activated receptor alpha (PPARα) signaling during fasting or under a ketogenic diet, in which PPARα is recruited in different targets of the FGF21 promoter (Badman et al., 2007; Inagaki et al., 2007). Moreover, glucagon stimulates hepatic FGF21 release through the protein kinase A (PKA) and cyclic adenosine monophosphate pathways and involves post-transcriptional mechanisms (Cyphert et al., 2014). Interestingly, FGF21 expression seems to follow the circadian rhythm (Erickson and Moreau, 2016) and is regulated by the first-order clock-controlled transcription factors, retinoic acid receptor-related orphan receptors, and nuclear receptors REV-ERBs, which coordinate the circadian expression of FGF21 directly (Estall et al., 2009; Wang et al., 2010), as well as indirectly through PPARα (Oishi et al., 2008).

Among FGF family members, human FGF21 is most similar (~35 % amino acid sequence homology) to human FGF19 (Dolegowska et al., 2019; Nishimura et al., 2000), and their functions overlap to a large extent, as both are associated with the maintenance of body weight and the regulation of glucose and lipid homeostasis (Dolegowska et al., 2019). FGF21 has been recognized as a powerful metabolic regulator which promotes ameliorated glucose uptake (Kharitonenkov et al., 2005; Markan et al., 2014), insulin sensitivity (Li et al., 2018; Markan et al., 2014; Wente et al., 2006), and fatty acid oxidation (Fisher et al., 2014; Potthoff et al., 2009) in peripheral tissues, as well as potentiates body weight loss and energy expenditure (Coskun et al., 2008; Emanuelli et al., 2014).

FGF21 is considered the crucial link between peripheral metabolic tissues and the brain. FGF21 is permeable to the BBB (Hsuchou et al., 2007) and is present in the CSF in humans (Tan et al., 2011) and in the hypothalamus of mice (Dolegowska et al., 2019), where it stimulates ERK1/2 phosphorylation (Dolegowska et al., 2019; Douris et al., 2015; Owen et al., 2015). Until recently, it was believed that FGF21 was not expressed in the CNS (Fon Tacer et al., 2010; Hsuchou et al., 2007); however, recent findings demonstrated that FGF21 can be expressed in distinct areas of the brain, including the retrosplenial cortex and thalamus (Zhou et al., 2022), and hypothalamic tanycytes (Geller et al., 2019). Interestingly, brain-derived FGF21 seems to regulate spatial memory formation by enhancing hippocampal neuron activation but not metabolism (Zhou et al., 2022).

A recent study demonstrates that FGF21 can be produced and secreted from hypothalamic tanycytes, a population of ependymal-glial cells that line the third ventricle, an optimal position to integrate multiple peripheral inputs (Geller et al., 2019). Geller and colleagues reported that the knockdown of tanycytic FGF21 from the hypothalamus of mice increases lipolysis in subcutaneous white adipose tissue (WAT) and energy expenditure through paracrine FGF21 signaling on other hypothalamic regions that stimulate sympathetic nervous system activity (SNS) (Geller et al., 2019).

There is strong scientific evidence suggesting that one of the mechanisms by which FGF21 signaling in the brain improves energy homeostasis in obese models depends on the stimulation of the sympathetic activity of WAT and BAT, which in turn increases energy expenditure (Douris et al., 2015; Geller et al., 2019; Owen et al., 2014). Owen and colleagues showed that ICV injection of FGF21 in mice increases sympathetic outflow to BAT in a time and dose-dependent manner (Owen et al., 2014), inducing UCP1 expression and lipolysis, effects which were blocked in the presence of pharmacological FGFRs inhibitor PD173074. Moreover, FGF21-mediated effects on energy metabolism depend on the neuropeptide corticotropin-releasing factor (CRF), as ICV injection of the CRF receptor antagonist (α-helical CRF) completely abrogated the effect of FGF21 in stimulating SNA innervation to BAT (Owen et al., 2014). However, the precise mechanism by which FGF21 interacts with CRF to stimulate SNS activity remains to be determined.

Along these lines, Douris and colleagues demonstrate that FGF21 infused via the lateral ventricle of the brain increases norepinephrine turnover in the inguinal WAT and BAT of mice (Douris et al., 2015), effects which were abrogated in the presence of the nonselective β-blocker propranolol. The action of FGF21 in increasing sympathetic activity is likely mediated through its signaling in the hypothalamic paraventricular nucleus, which enhances cholinergic activity and triggers downstream adrenergic outflow from sympathetic ganglia to promote norepinephrine release in adipose tissues (Nguyen et al., 2014). Furthermore, mice lacking β-adrenoceptors are unable to initiate browning following central or peripheral administration of FGF21, demonstrating that a functional adrenergic system is required for FGF21 actions (Douris et al., 2015). The central actions of FGF21 in increasing sympathetic outflow to adipose tissues are summarized in Fig. 4.

While these works suggest that the body weight loss in mice was not caused by modulation in food intake but instead was attributable to increased energy expenditure associated with BAT-thermogenesis, several other studies also highlight the hypophagic action of FGF21 or its analogs in protecting against obesity in other species, such as in obese pigs (Christoffersen et al., 2019), Siberian hamsters (Murphy et al., 2013), and obese monkeys (Adams et al., 2013; Kliewer and Mangelsdorf, 2019; Talukdar et al., 2016b; Thompson et al., 2016), and therefore FGF21 may be considered as an anorexigenic hormone. In addition, these studies point to potential differences in the mechanisms of actions of FGF21 across mammal species.

FGF21 is also a crucial regulator of macronutrient intake. It is known that the consumption of fructose (Dushay et al., 2015), alcohol (Choi et al., 2023; Søberg et al., 2018), and diets with high protein restriction or high in carbohydrates (Maida et al., 2016) increases FGF21 plasmatic concentration. Interestingly, using gain-of-function studies, von Holstein-Rathlou and colleagues demonstrated that liver-derived FGF21 enters circulation to signal in the brain to repress simple sugar consumption and sweet-taste preference in mice (von Holstein-Rathlou et al., 2016). Similar effects were also observed by Talukdar and colleagues in mice and monkeys (Talukdar et al., 2016a), as well as by Alves and colleagues in humans (Alves et al., 2022). The mechanism underlying these effects is not fully understood; however, there is evidence that FGF21 signaling in the paraventricular nucleus and glutamatergic neurons in the ventromedial hypothalamus are required to regulate sugar intake (Jensen-Cody et al., 2020; von Holstein-Rathlou et al., 2016). These findings are consistent with FGF21 functioning as a satiety hormone that signals centrally to suppress sugar intake by acting in glutamatergic neurons in hypothalamic areas. Since circulating levels of FGF21 are increased in response to carbohydrate consumption in rats and humans (Dushay et al., 2015; Sánchez et al., 2009), the actions of FGF21 in promoting reduced sugar intake may represent a negative feedback loop to limit its consumption.

Central FGF21 signaling also regulates adaptive and homeostatic changes in food behavior and metabolism during protein restriction by increasing the preference for protein intake without affecting total energy intake (Hill et al., 2019). Protein restriction induces a macronutrient-specific appetite for protein (Chaumontet et al., 2018), and in the absence of FGF21 signaling in the brain, mice are unable to generate a metabolic response to protein restriction by increasing

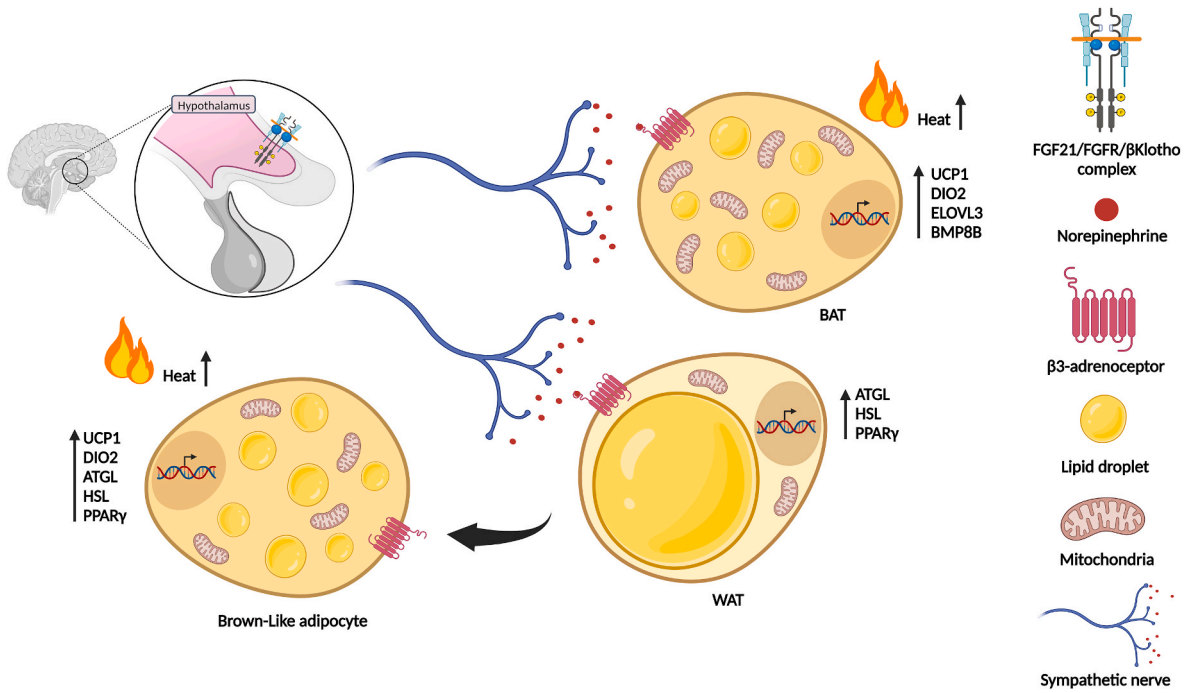

Fig. 4. FGF21 acts centrally to stimulate sympathetic nerve activity in brown and white adipose tissue. FGF21 acts on the hypothalamus to activate the cholinergic signal, increasing norepinephrine release from the sympathetic ganglia and adrenergic activity in brown adipose tissue (BAT) and white adipose tissue (WAT). Norepinephrine binding in β3-adrenoceptors on brown and brown-like adipocytes activates downstream intracellular signaling that stimulates the expression of uncoupling protein-1 (UCP1), which uncouples aerobic respiration from mitochondrial ATP generation to dissipate heat. Moreover, FGF21 also potentiates the gene expression of thermogenic marker deiodinase 2 (DIO2) in brown and brown-like adipocytes, as well as increases elongation of very long chain fatty acids like 3 (ELOVL3) and bone morphogenic protein 8b (BMP8B) transcription in brown fat. In WAT, adrenergic signaling induced by FGF21 enhances the lipolyses markers adipocyte triacylglycerol lipase (ATGL) and hormone-sensitive lipase (HSL), which promote the hydrolysis of triglycerides. In white and brown-like adipocytes, central FGF21 signaling also promotes increased expression of peroxisome proliferator-activated receptor γ (PPARγ), which is known to induce a brown fat gene transcription program in white adipocytes. The figure was created with BioRender software (https://www.biorender.com).

protein consumption (Hill et al., 2019). This same study showed that FGF21 signaling in the CNS increases protein intake in chow-fed mice, suggesting that FGF21 signaling in the brain changes macronutrient preference toward proteins, even without protein restriction (Hill et al., 2019). The neuronal subpopulations, as well as the downstream mechanism involved in these effects, remain unclear.

Recently, Claflin and colleagues showed that FGF21 signaling only to glutamatergic but not GABAergic neurons is required for FGF21 to promote body weight loss (Claflin et al., 2022). This finding is consistent with other studies that demonstrated that FGF21 signals in glutamatergic neurons suppress sugar intake (Jensen-Cody et al., 2020) and promote weight loss following the consumption of a low-protein diet (Flippo et al., 2020). Interestingly, it was proposed that FGF21 action in neural cells coexpressing the leptin receptor and glutamate regulates body weight, suggesting that leptin signaling in the brain may be required for FGF21's effects to promote weight loss (Claflin et al., 2022). Additionally, central administration of FGF21 and leptin in combination displays a potent effect on reducing body weight by regulating both energy intake and expenditure, indicating that FGF21 may require, at least partially, leptin signaling to promote its effects in body weight loss (Claflin et al., 2022).

The central FGF21 administration is also associated with glucose homeostasis improvement. Infusion of FGF21 into the lateral cerebral ventricle ameliorates hepatic insulin sensitivity in rats (Sarruf et al., 2010). This effect must be mediated by enhanced inhibition of hepatic glucose production and gluconeogenic gene expression. However, starvation is one of the first stimuli associated with hepatic FGF21 expression in mice (Inagaki et al., 2007; Oishi et al., 2008). It is known that FGF21 acts on the hypothalamus to promote CRF expression (Patel et al., 2015), which might activate the hypothalamus-pituitary-adrenal axis to increase systemic corticosterone and glucocorticoid levels, a prominent feature of starvation (Bookout et al., 2013; Potthoff et al., 2009). The increased glucocorticoids induced by FGF21 stimulate hepatic gluconeogenesis and suggest the liver's nonautonomous effect of FGF21 in stimulating hepatic glucose production (Bookout et al., 2013; Liang et al., 2014). These data recognized an interorgan crosstalk between the liver and the brain as an important way for FGF21 to control glucose homeostasis.

Like FGF15/19, FGF21 exerts its beneficial metabolic effects via multiple CNS pathways and requires top-down mechanisms to regulate energy homeostasis. Future studies are needed to address further the relative contribution of peripheral versus central action in mediating the FGF21 metabolic effects and should explore whether and how its signaling sensitizes different hormones to regulate food consumption and energy storage and use. Furthermore, the particularities in FGF21 actions that may vary depending on species and sex will also be fundamental for its consolidation in preclinical models.

7. FGF23

Fibroblast growth factor 23 (FGF23) was the latest endocrine FGF to be identified and was originally discovered by a homology-based DNA database search in mice (Vervloet, 2019; Yamashita et al., 2000). Human FGF23 was simultaneously identified as the mutated gene in autosomal dominant hypophosphatemic rickets (ADHR) patients and as a causative factor of tumor-induced osteomalacia, both caused by renal phosphate wasting (Consortium, 2000; Shimada et al., 2001; White et al., 2001b).

The FGF23 is secreted into the systemic circulation primarily by osteocytes and osteoblasts in bone (Fon Tacer et al., 2010; Yoshiko et al., 2007) and exerts paracrine and endocrine effects. Recent studies showed that locally secreted FGF23 may act as a regulator of bone

mineralization in an autocrine/paracrine manner (Murali et al., 2016a, b). Lower amounts of FGF23 are also identified in several other tissues, such as endocrine organs (parathyroid glands, ovaries, and testes), the heart, and some brain areas (Fon Tacer et al., 2010; Yamashita et al., 2000). However, it is unknown whether the FGF23 content found in these tissues comes from local synthesis or systemic circulation.

Like the other endocrine FGFs, FGF23 can signal through FGFRs associated with KL proteins. FGF23 can signal through FGFR3-IIIc and FGFR4 receptors (Kurosu et al., 2006) in a KLA-dependent manner; however, FGFR1-IIIc appears to be the primary receptor for this FGF (Chen et al., 2018; Goetz et al., 2012; Kurosu et al., 2006; Urakawa et al., 2006). Unlike the other FGFs cited here, some studies highlight the ability of FGF23 to activate FGFR3-IIIc and FGFR4 signaling in a KLA-independent manner (Grabner et al., 2015; Murali et al., 2016b). Thus, the FGF23 signaling through the FGFR1-IIIc/KLA complex is commonly referred to as "canonical", while signaling independent of KLA interaction with FGFR3-IIIc and FGFR4 is referred to as "non-canonical" (Ho and Bergwitz, 2021).

Full-length FGF23 is the active form of this hormone, required for efficient signaling through FGFR (Shimada et al., 2002; Wolf and White, 2014), though FGF23 can also be proteolytically cleaved between Arg179 and Ser180, releasing inactive N- and C-terminal fragments (Wolf and White, 2014). This cleavage is an important mechanism for regulating FGF23 activity once the mutation that prevents FGF23 cleavage increases its active form, one of the related causes of the development of ADHR (Bai et al., 2003; Shimada et al., 2002; White et al., 2001a). The lack of FGF23 cleavage may also cause of other disorders, such as cardiovascular diseases and stroke, and all of these conditions are related to increased circulating FGF23 (Itoh et al., 2015; Wright et al., 2014). Other studies demonstrate that C-terminal fragments can compete with full-length FGF23 for binding the FGFR-KLA complex, decreasing the effects of FGF23 (Goetz et al., 2010) and, therefore, being a regulatory mechanism for this hormone signaling.

Several studies have provided evidence that FGF23 is present in some brain areas, such as the hippocampus, hypothalamus, caudate putamen, amygdala, ventrolateral thalamic nucleus, and in the CSF (Kunert et al., 2017; Li et al., 2018; Ursem et al., 2021; Yamashita et al., 2000). Despite being found in the CNS, gene, and protein expression of FGF23 in the brain is inconsistent across studies (Fon Tacer et al., 2010; Kaminskas et al., 2019; Laszczyk et al., 2019; Ursem et al., 2021). Thus, most of the FGF23 content found in the brain may come from peripheral organs that secrete the hormone into circulation (Ursem et al., 2021). The transport of FGF23 into the brain can be through the BBB or across the blood-CSF barrier (Ursem et al., 2021).

FGF23 is described as a major endocrine regulator of phosphate homeostasis, which affects whole-body metabolism (Goetz et al., 2010; White et al., 2001b). Phosphate is an essential element that has important roles in cell maintenance, as it is a component of the cell membrane and the nucleic acids, and also participates in cell metabolism, ATP formation, and regulation of intracellular signaling pathways, mainly through the phosphorylation of enzymes and proteins (Peacock, 2021). Therefore, maintaining a normal phosphorus concentration is essential for optimal cellular function (Goetz et al., 2010). FGF23 acts in the kidney, inhibiting phosphate reabsorption in the proximal renal tubule by reducing the expression of the type II sodium-dependent phosphate transporters and suppressing parathyroid hormone synthesis in the parathyroid gland, which decreases the circulating phosphate levels (Ben-Dov et al., 2007; Shimada et al., 2004b; Vidal et al., 2020).

Under normal conditions, FGF23 signaling is one of the mechanisms that allow phosphate concentrations to remain at constant physiological levels. It is known that FGF23 deficiency causes hyperphosphatemia, while its excess causes hypophosphatemia (García Martín et al., 2020). This imbalance in phosphate concentrations can result in several complications. The drop in phosphate levels can lead to a rise in plasma calcium concentration, contributing to hypercalciuria, metabolic encephalopathy, delirium, seizures, and impaired cardiorespiratory function (García Martín et al., 2020). In addition, studies have indicated that hypophosphatemia may be related to a reduction in glucose tolerance and an increase in insulin resistance (Haap et al., 2006). On the other hand, hyperphosphatemia can be related to the development of chronic kidney disease (García Martín et al., 2020). Furthermore, there is evidence that high concentrations of FGF23 in serum or CSF induce memory deficits and dementia (Drew et al., 2014; Liu et al., 2011). In humans, high FGF23 levels in CNS are correlated with impulsive behavior and poor cognitive performance in hemodialysis patients (Drew et al., 2014; Li et al., 2018).

It has been shown that ICV injection of FGF23 increases the hypothalamic expression of NPY and AgRP in rats, which can stimulate food intake (Ursem et al., 2022). Another report shows that FGF23 is present in the hypothalamus and the third ventricle of rats, including areas with tanycytes (Ursem et al., 2021), a subpopulation of cells known to play a role in food intake (Langlet, 2019). With these data, the presence of FGF23 in these brain regions may indicate a possible involvement of FGF23 in controlling appetite and energy balance.

Several studies have shown a relationship between the regulation of FGF23 expression and energy and glucose metabolism (Fernández-Real et al., 2013; Ursem et al., 2018; Wojcik et al., 2012b; Yeung et al., 2020). Insulin and insulin-like growth factor 1 (IGF1) can control the expression of FGF23, down-regulating its synthesis by inhibiting the transcription factor forkhead box protein O1 (FOXO1) (Bär et al., 2018). Another mechanism by which expression of FGF23 is regulated is through the AMP-activated protein kinase (AMPK) signaling pathway (Vidal et al., 2020). AMPK can be activated in osteoblast cell cultures by low levels of cellular energy, where it suppresses the expression of FGF23, while the inhibition of AMPK increases the levels of this FGF (Glosse et al., 2018a). Therefore, energy levels appear to be an important control of FGF23 production. In addition, obese humans (Marsell et al., 2009), HFD-fed mice (Glosse et al., 2018b), and insulin-deficient mice (Bär et al., 2018) display increased circulating concentrations of FGF23, while mice fed a low-calorie diet had reduced FGF23 levels (Vidal et al., 2020). Once patients and mice with metabolic disorders begin suffering from inflammation, the higher FGF23 levels may be due to the increase in proinflammatory markers (Ito et al., 2015). In addition, leptin levels were also found to increase circulating FGF23 (Tsuji et al., 2010). As the leptin circulating levels are proportional to fat mass (Woods et al., 1998), its higher concentration in obese individuals may contribute to excessive FGF23 levels.

Thus, to better understand the role of FGF23 in energy homeostasis, further studies are still needed to investigate the effects of circulating FGF23 in peripheral tissues and the central nervous system to elucidate and differentiate its peripheral and central effects. Moreover, its possible effect in stimulating food intake should be further explored, mainly in models and individuals where FGF23 is elevated, such as in obesity and diabetes. Since insulin exerts an essential role in the hypothalamic regulation of food intake, as well as in the inhibition of FGF23 expression, and obese individuals have peripheral and central resistance to this hormone, strategies aimed at improving insulin sensitivity, such as physical exercise, may be promising to attenuate exacerbated FGF23 levels and regulate eating behavior.

8. Limitations of endocrine FGFs therapeutical properties

The safety and efficacy of targeting endogenous FGFs and/or their exogenous administration have limitations. There is evidence that pharmacological levels of FGF19 are implicated in developing hepatocellular carcinoma by stimulating STAT3 transcription, which induces the expression of carcinogenic and pro-inflammatory genes in the liver (Zhou et al., 2017b). Much of the research investigating in vivo FGF19-mediated effects on metabolism has been done with acute or a few days of treatment, and under these conditions, FGF19 appears to be physiologically advantageous for key mechanisms to regulate metabolism. Therefore, it is unlikely that targeting endogenous FGF19 will

result in carcinogenesis (Sawey et al., 2011); however, whether chronically elevated levels of FGF19 might play a role in tumorigenesis remains to be clarified.

A question of particular concern is how the research performed in mice administered FGF19 translates to the human response to FGF19, given that the species might display a difference in FGFRs and KLB expression. This limitation could be overcome using more translational preclinical models, such as pigs and monkeys, that naturally express FGF19 and have receptors that more closely match human FGFRs and KLB. Moreover, it is important to consider that FGF15/19 reduces bile acid biosynthesis in the liver by inhibiting the rate-limiting enzyme involved in bile acid production (Kliewer and Mangelsdorf, 2015). Nevertheless, the effects of pharmacological concentrations of FGF15/19 on bile acid metabolism need to be better elucidated.

The capacity of FGF19 and FGF21 to promote SNS activation by increasing NE release also needs to be further explored, as it remains unclear whether the SNS activation is local for adipose tissues or systemic. Considering the cardiovascular side effects that systemic NE could exert, these clarifications are crucial for further therapeutic approaches to be developed.

Another potential but controversial deleterious effect of FGF21 is in bone homeostasis. FGF21 has been reported to cause bone loss in mice (Li et al., 2017; Wei et al., 2012); however, these reports have not been independently validated in rodents (Li et al., 2017) or obese non-human primates (Andersen et al., 2018).

It is worth mentioning that most of the studies discussed here were performed in male animals and that the observed effects could be different in females, as female sex hormones and the estrous cycle are known to alter the body's physiology and metabolism (Kautzky-Willer et al., 2016; Lee, 2018). For example, FGF21 is significantly lower in women compared with men after adjustment for age and body mass index (Kralisch et al., 2013). Moreover, endocrine FGFs have been experimentally used in animal and cell models, much of them with genetic modifications, and therefore, the results could not be entirely translated to humans.

9. Endocrine FGFs in humans and clinical trials

It has been previously demonstrated that FGF19, FGF21, and FGF23 circulating levels are modulated in humans with metabolic deregulations. There is a negative correlation between serum FGF19 levels and obesity (Gallego-Escuredo et al., 2015; Gómez-Ambrosi et al., 2017; Morón-Ros et al., 2021; Mráz et al., 2011) and T2D (Roesch et al., 2015) in humans. On the other hand, FGF21 circulating levels are higher in obese individuals (Dushay et al., 2010; Gallego-Escuredo et al., 2015; Gómez-Ambrosi et al., 2017; Mraz et al., 2009; Zhang et al., 2008), type 2 diabetic patients (Kralisch et al., 2013; Mraz et al., 2009; Roesch et al., 2015), and subjects with increased amounts of intrahepatic fat (Dushay et al., 2010; Li et al., 2010). The increased circulating levels of FGF21 may occur due to a compensatory response to metabolic stress, such as elevated free-fatty acids and insulin in the blood, and may be a consequence of the higher expression of FGF21 in the liver, as was recently observed in hepatic biopsies from obese and type 2 diabetic patients (Gallego-Escuredo et al., 2015; Giralt et al., 2015; Roesch et al., 2015).

Regarding FGF23, its levels are elevated in obese people (Marsell et al., 2009), individuals with increased energy intake (di Giuseppe et al., 2015), and patients with diabetes mellitus (Garland et al., 2014; Hanks et al., 2015; Vervloet et al., 2012), suggesting that energy levels may regulate FGF23. Furthermore, some studies have shown a positive correlation between FGF23 concentrations and body weight in elderly individuals (Fayed et al., 2018; Fernández-Real et al., 2013; Marsell et al., 2009; Mirza et al., 2011). However, in obese adolescents, a significant inverse correlation between FGF23 and fasting insulinemia and insulin resistance is observed (Wojcik et al., 2012a,b). Accordingly, in adolescents with obesity and insulin resistance, FGF23 levels are reduced compared with obese adolescents with normal insulin responsiveness (Wojcik et al., 2012b), suggesting that FGF23 may contribute to insulin sensitivity in obese adolescents.

As central administration is still an unusual route for drug administration in humans, most therapeutic approaches have aimed to potentiate the endogenous expression of endocrine FGFs or provide the individual with their pharmacological forms. In recent decades, several clinical trials employing endocrine FGFs have been conducted in humans with obesity, T2D, and nonalcoholic steatohepatitis (NASH), most of them using chemical analogs. Endocrine FGF analogs are pharmacological compounds that mimic their actions and differ from endogenous FGFs as they have a longer half-life (Giralt et al., 2015; Kharitonenkov et al., 2007). Studies published to date have found that endocrine FGF analogs retain the beneficial effects of endogenous FGFs on metabolism and weight loss when used as pharmacological tools to treat obesity in rodents and humans (Phan et al., 2021). Ongoing registered clinical trials using the endocrine FGFs as therapeutic agents in metabolic disorders are summarized in Table 2.

The FGF19 analog NGM282, also referred to as Aldafermin, has stood out in clinical research due to its safety and efficacy in treating NASH. NGM282 reduces liver fat content and fibrosis, improves serum parameters, and attenuates the nonalcoholic fatty liver disease markers in NASH patients (Harrison et al., 2018, 2020, 2021). Furthermore, NGM282 exerts a homeostatic control of cholesterol efflux to prevent atherosclerosis (Zhou et al., 2019).

The FGF21 analog LY2405319 has shown comparable bioactivity to endogenous FGF21 with ameliorated biopharmaceutical properties (Kharitonenkov et al., 2013). LY2405319 administration in diabetic obese patients reduces dyslipidemia, fasting insulin, and body weight (Gaich et al., 2013). Similar effects were also observed in monkeys administered LY2405319, such as lower blood glucose, insulin, triglyceride, and cholesterol levels, as well as reduced body weight (Adams et al., 2013). Another FGF21-based therapy is the long-acting FGF21 analog PF-05231023 (Dong et al., 2015). PF-05231023 was effective in reducing triglyceride levels in obese hypertriglyceridemic adult individuals with or without T2D, as well as in non-human primates (Kim et al., 2017). PF-05231023 administration also resulted in body weight loss and improvement in lipid profile in type 2 diabetic subjects and non-human primates (Talukdar et al., 2016b).

Recently, a polyethylene glycol-modified (PEGylated) recombinant human FGF21 analog, known as Pegbelfermin (BMS-986036), was reported to be promising in reducing hepatic fat accumulation in NASH patients (Sanyal et al., 2019; Verzijl et al., 2020) and in improving insulin sensitivity and dyslipidemia in subjects with obesity and T2D (Charles et al., 2019). Another PEGylated FGF21 analog, called Pegozafermin (BIO89-100), was effective and well tolerated for NASH patients, reducing liver fat accumulation and circulating lipids (Loomba et al., 2023).

Regarding FGF23-based therapies, most have been employed in patients with X-linked hypophosphatemia (XLH), an inherited disease characterized by excessive FGF23 levels, which indirectly reduces gut and renal absorption of phosphate by decreasing the synthesis of 1,25-dihydroxyvitamin D3 (Beck-Nielsen et al., 2019). The use of KRN23, known as Burosumab, which is a human anti-FGF23 monoclonal antibody that binds to FGF23 and inhibits its biological activity, has shown to be safe and effective in XLH patients (Carpenter et al., 2014). However, considering that it still needs to be better understood whether and how the signaling triggered by FGF23 affects glycemic and energy homeostasis in preclinical models, there are no records thus far of clinical trials using FGF23 for this purpose.

Therefore, endocrine FGF research is currently focused on applying the knowledge from preclinical studies to clinical applications. Results to date have highlighted therapies based on endocrine FGFs as effective, safe, and tolerable for humans, providing new avenues for treating metabolic diseases. However, considering the lack of long-term studies on these compounds' safety and effectiveness, we cannot address the implications of the chronic use of these therapies. Furthermore, ongoing

Table 2

Condition	Study Title	Clinical Trials Identifier:	Recruitment Status	Study Design and Interventions	Location
Type 2 Diabetes	Phase 2 Study of NGM282 in patients with Type 2 Diabetes	NCT01943045	Completed	Drug: NGM282 (FGF19 analog) Enrollments: 81 participants Allocation: Randomized Double-blind and placebo-controlled Phase: 2 Doses and Mode of administration: Not available Duration: 28 days	Australia and New Zealand
Type 2 Diabetes	Phase 1 Single ascending dose and multiple ascending dose and study of NGM282 in healthy adult participants	NCT01776528	Completed	Drug: NGM282 (FGF19 analog) Enrollments: 119 participants Allocation: Randomized Double-blind and placebo-controlled Phase: 1 Doses and Mode of administration: Not available Duration: 7 or 14 days	Australia
Nonalcoholic Steatohepatitis	Study of NGM282 in patients with Nonalcoholic Steatohepatitis	NCT02443116	Completed	Drug: NGM282 (FGF19 analog) Enrollments: 254 participants Allocation: Randomized Triple-blind and placebo-controlled Phase: 2 Doses: 0.3, 1, 3 or 6 mg Mode of administration: Not available Duration: 24 weeks	United States, Australia, and Puerto Rico
Type 2 Diabetes	A study of LY2405319 in participants with Type 2 Diabetes	NCT01869959	Completed	Drug: LY2405319 (FGF21 analogue) Enrollments: 47 participants Allocation: Randomized Double-blind and placebo-controlled Phase: 1 Doses: 3, 10, or 20 mg once daily Mode of administration: subcutaneous Duration: 28 days	United States
Type 2 Diabetes	Safety, tolerability, and effect of LY2405319 after multiple injections in subjects with Type 2 Diabetes	NCT00481117	Completed	Drug: LY2405319 (FGF21 analog) Enrollments: 37 participants Allocation: Randomized Double-blind and placebo-controlled Phase: 1 Doses: 1, 3, 10, or 20 mg once daily Mode of administration: subcutaneous Duration: 7 or 28 days	India, Mexico, New Zealand, and South Africa
Type 2 Diabetes	Safety and tolerability of ascending intravenous doses of PF-05231023 in adult subjects with Type 2 Diabetes	NCT01396187	Completed	Drug: PF-05231023 (FGF21 analog) Enrollments: 50 participants Allocation: Randomized Triple-blind and placebo-controlled Phase: 1 Doses: 5, 25, 100, or 200 mg twice a week Mode of administration: intravenous Duration: 4 weeks	United States
Type 2 Diabetes	Safety and tolerability of escalating intravenous doses of PF-05231023 in adult subjects With Type 2 Diabetes	NCT01285518	Completed	Drug: PF-05231023 (FGF21 analog) Enrollments: 84 participants Allocation: Randomized Triple-blind and placebo-controlled Phase: 1 Doses: 0.5, 1.5, 5, 15, 50, 100, or 200 mg once daily Mode of administration: intravenous Duration: 1–22 days	United States
Obesity	Multiple dose study of PF-05231023 in obese adult subjects	NCT01923389	Terminated	Drug: PF-05231023 (FGF21 analog) Enrollments: 4 participants Allocation: Randomized Quadruple-blind and placebo-controlled Phase: 1 Doses: 100 mg twice a week Mode of administration: intravenous Duration: 4 weeks Placebo-Controlled	United States

(*continued on next page*)

Table 2 (*continued*)

Condition	Study Title	Clinical Trials Identifier:	Recruitment Status	Study Design and Interventions	Location
Type 2 Diabetes	Multiple dose study of PF-05231023 in adult subjects who have poor lipid control with and without Type 2 Diabetes Mellitus	NCT01673178	Completed	Drug: PF-05231023 (FGF21 analog) Enrollments: 107 participants Allocation: Randomized Quadruple-blind and placebo-controlled Phase: 1 Doses: 25, 50, 100, or 150 mg once a week Mode of administration: intravenous Duration: 4 weeks	United States
Type 2 Diabetes	Single ascending dose trial in patients with Type 2 Diabetes	NCT01492465	Terminated	Drug: AMG 876 (FGF21 analog) Enrollments: 47 participants Allocation: Randomized Quadruple-blind and placebo-controlled Phase: 1 Mode of administration: subcutaneous or intravenous Doses and duration: Not available	United States
Type 2 Diabetes	Multiple ascending dose study in subjects with Type 2 Diabetes	NCT01856881	Terminated	Drug: AMG 876 (FGF21 analog) Enrollments: 86 participants Allocation: Randomized Quadruple-blind and placebo-controlled Phase: 1 Mode of administration: subcutaneous Doses and duration: Not available	United States
Nonalcoholic Steatohepatitis	A study of BMS-986036 in subjects with Non-Alcoholic Steatohepatitis	NCT02413372	Completed	Drug: BMS-986036 (a PEGylated FGF21) analog) Enrollments: 184 participants Allocation: Randomized Double-blind and placebo-controlled Phase: 2 Doses: 10 mg once a day or 20 mg once a week Mode of administration: subcutaneous Duration: 16 weeks	United States
Type 2 Diabetes	A study to evaluate BMS-986036 in obese adults with Type-2 Diabetes	NCT02097277	Completed	Drug: BMS-986036 (a PEGylated FGF21) analog) Enrollments: 219 participants Allocation: Randomized Double-blind and placebo-controlled Phase: 2 Doses: 1, 5, and 20 mg once daily or 20 mg once a week Mode of administration: subcutaneous Duration: 12 weeks	United States and Canada
Liver Fibrosis **Nonalcoholic Fatty Liver Disease** **Nonalcoholic Steatohepatitis**	A study of experimental medication BMS-986036 in adults with Nonalcoholic Steatohepatitis and Stage 3 Liver Fibrosis	NCT03486899	Completed	Drug: BMS-986036 (a PEGylated FGF21) analog) Enrollments: 197 participants Allocation: Randomized Quadruple-blind and placebo-controlled Phase: 2 Doses, mode of administration, and duration: Not available	United States and Japan
Hepatic Cirrhosis **Liver Fibrosis** **Nonalcoholic Fatty Liver Disease** **Nonalcoholic Steatohepatitis**	A study of experimental medication BMS-986036 in adults with Nonalcoholic Steatohepatitis and Liver Cirrhosis	NCT03486912	Completed	Drug: BMS-986036 (a PEGylated FGF21) analog) Enrollments: 155 participants Allocation: Randomized Quadruple-blind and placebo-controlled Phase: 2 Doses, mode of administration, and duration: Not available	United States and Japan

(*continued on next page*)

Table 2 (*continued*)

Condition	Study Title	Clinical Trials Identifier:	Recruitment Status	Study Design and Interventions	Location
Severe hypertriglyceridemia	Study to explore the efficacy and safety of BIO89-100 in subjects with Severe Hypertriglyceridemia	NCT04541186	Completed	Drug: BIO89-100 (a PEGylated FGF21) analog) Enrollments: 85 participants Allocation: Randomized Double-blind and placebo-controlled Phase: 2 Mode of administration: subcutaneous Doses and duration: Not available	United States, Czechia, Hungary, and Poland
Morbid Obesity	Glucose homeostasis pre and post bariatric surgery	NCT00981500	Completed	Intervention: Bariatric surgery (Roux-en-Y gastric bypass, sleeve gastrectomy, or gastric banding) Enrollments: 60 participants	United States

NGM282 (also called Aldafermin) is an engineered analog of endogenous FGF19. LY2405319, PF05231023 (also known as CVX343), and AMG876 (also known as AKR-001) are engineered long-acting analogs of endogenous FGF21. BMS-986036 (also called Pegbelfermin) and BIO89-100 (referred as Pegozafermin) are polyethylene glycol-conjugated (PEGylated) recombinant analogs of human FGF21.

and future studies should provide information on how endocrine FGF signaling differs across individual characteristics, including age, gender, and ethnicity.

10. Conclusion and perspectives

Several preclinical and clinical studies have indicated that endocrine FGFs, especially FGF19 and FGF21, are promising therapeutic target molecules for treating metabolic diseases, as judged by their ability to improve glucose control and promote body weight loss. As discussed here, many of the beneficial effects of endocrine FGFs depend on their signaling in the CNS (Fig. 5). The presence of endocrine FGF receptors and co-receptors in brain areas closely involved in the control of glucose and energy metabolism, such as the hypothalamus, highlights the action of these molecules as important endocrine signals. As a result of this signaling, the brain itself, or the peripheral tissues (through autonomic nervous system innervation), respond in a way that promotes a healthy phenotype.

Future research should explore the central effects of endocrine FGFs on various peripheral tissues and how their signaling through the different FGFRs may confer differential effects. Lastly, it remains to be determined precisely how endocrine FGFs cross the BBB at physiologic and supra-physiologic concentrations to regulate metabolism. Considering the increased number of studies in recent years, we may be able to gain a greater understanding of the biology of endocrine FGFs and use this knowledge to develop more approaches for the prevention and treatment of metabolic disorders.

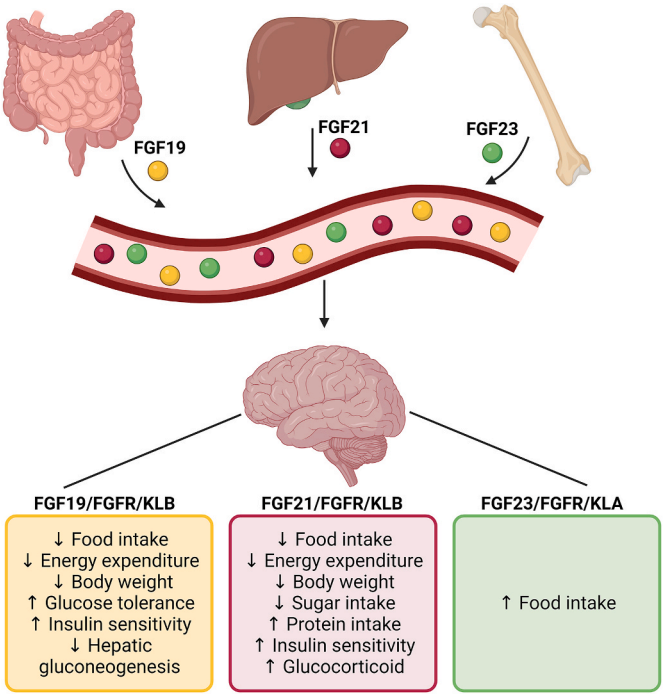

Fig. 5. Effects of central signaling of endocrine FGFs on glucose and energy metabolism. FGF19 is produced by the intestine and, its signaling in the brain improves energy homeostasis, stimulating pathways that decrease food intake and stimulate energy expenditure. In addition, its central action also improves glucose uptake and peripheral insulin sensitivity and reduces glucose production by the liver. FGF21 is abundantly produced in the liver, and like FGF19, its central effects have been associated with reduced body weight through stimulation of energy expenditure and reduced food intake. FGF21 is also an important regulator of macronutrient intake, increasing protein intake preference and decreasing sugar intake. Moreover, central FGF21 signaling increases fasting glucocorticoid levels, increasing hepatic glucose production under starvation. FGF23 is produced by bone and plays a crucial role in phosphate metabolism, which is essential in regulating intracellular signaling pathways. Contrary to what was observed for FGF19 and FGF21, central FGF23 signaling has been associated with increased food intake. FGFR: fibroblast growth factor receptor; KLA: alpha-klotho; KLB: beta-klotho. The figure was created with BioRender software (https://www.biorender.com).

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CRediT authorship contribution statement

Lucas Zangerolamo: contributed to the data collection, writing, and graphical designs. **Marina Carvalho:** contributed to the data collection, writing, and graphical designs. **Licio A. Velloso:** contributed to the discussion, writing and editing, All authors reviewed and approved the final version of the manuscript. **Helena C.L. Barbosa:** contributed to the discussion, writing, and editing, All authors reviewed and approved the final version of the manuscript. All authors contributed to the study's conception and design.

Declaration of competing interest

The authors have declared that there are no conflicts of interest.

Data availability

No data was used for the research described in the article.

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