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EDITED BY
Cinthia Garcia-Luna,
National Institute of Psychiatry Ramon de la Fuente Muñiz (INPRFM), Mexico

REVIEWED BY
Francisco Díaz-Castro,
August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Spain

*CORRESPONDENCE
Maria Paula Cornejo
✉ pcornejo@imbice.gov.ar

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Brain-acting hepatokines: its impact on energy balance and metabolism

Lucía Giovanini[1], Nahuel Wanionok[1], Mario Perello[1,2] and Maria Paula Cornejo[1]*

[1]Laboratory of Neurophysiology of the Multidisciplinary Institute of Cell Biology [IMBICE, Argentine Research Council (CONICET) and Scientific Research Commission, Province of Buenos Aires (CIC-PBA), National University of La Plata], La Plata, Buenos Aires, Argentina, [2]Department of Surgical Sciences, Functional Pharmacology and Neuroscience, University of Uppsala, Uppsala, Sweden

The liver is recognized for its central role in energy metabolism, yet emerging evidence highlights its function as an endocrine organ, secreting a variety of proteins—hepatokines—that influence distant tissues. Hepatokines not only regulate metabolic processes by acting on peripheral tissues but also exert direct effects on brain function. In this mini-review, we discuss the existing literature on the role of "brain-acting" hepatokines including IGF-1, FGF21, LEAP2, GDF15, and ANGPTLs, and their impact on energy balance and metabolism. We review the existing evidence regarding their roles in metabolism through their action in the brain, and their potential implications in metabolic disturbances. By integrating insights from recent studies, we aim to provide a comprehensive understanding of how liver-derived signals can modulate energy balance and metabolism.

KEYWORDS

hepatokines, brain, metabolism, energy balance, liver

Introduction

Energy metabolism encompasses the complex biochemical pathways by which organisms extract, convert, and store energy from nutrients such as lipids, carbohydrates, and proteins. The energy obtained from nutrients is expended in numerous physiological processes (i.e., resting, activity-induced and diet-induced energy expenditure), and the difference between the energy obtained and the energy expended makes up energy balance. When the amount of energy obtained continuously surpasses the amount expended, there is an excessive storage of energy that ends with an increase in body weight, leading to overweight and obesity. In recent decades, the world has witnessed an alarming rise in the prevalence of overweight and obesity. These conditions are hallmarked by persistent energy imbalance and profound metabolic dysregulation, and they now represent major public health challenges. Obesity, in particular, is a well-established risk factor for a spectrum of metabolic diseases, most notably type 2 diabetes mellitus (T2DM; Schnurr et al., 2020) and metabolic-associated steatotic liver disease (MASLD; Younossi et al., 2016). While lifestyle and environmental factors play critical roles, growing evidence highlights the contribution of endogenous signals in the development and maintenance of these metabolic disorders. Among these, liver-derived peptides—collectively known as hepatokines—have recently emerged as key regulators of systemic metabolism (Zhang et al., 2023). Not only do hepatokines influence peripheral tissues, but a subset also communicates directly with the brain to modulate metabolism, appetite, and energy expenditure. Here, we aim to synthesize current knowledge on brain-acting hepatokines (Figure 1), emphasizing their emerging roles as metabolic integrators and potential therapeutic targets in the context of obesity and related disorders.

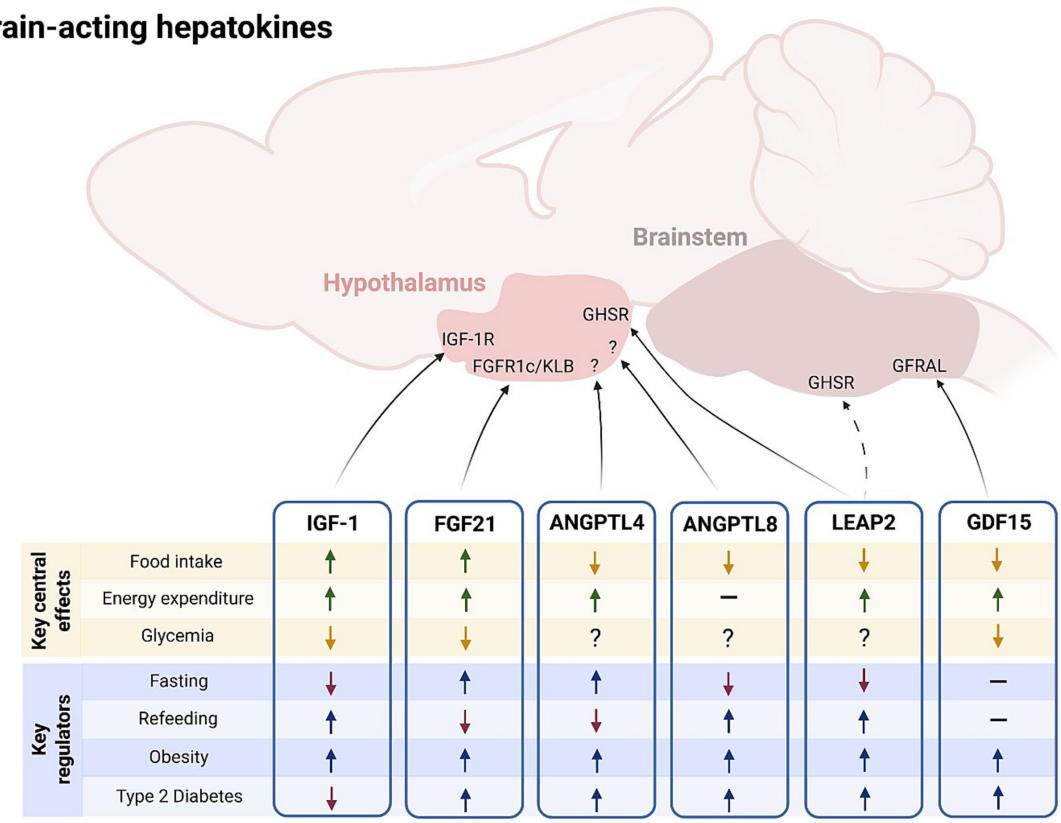

FIGURE 1
Brain-acting hepatokines: key central effects and key regulators. Liver-derived hepatokines FGF21, IGF-1, LEAP2, GFD15, ANGPTL4 and ANGPTL8 act on the central nervous system to modulate energy balance and metabolism (key central effects). Circulating levels of these brain-acting hepatokines vary according to the energetic status and in certain metabolic disorders (key regulators). ANGPTL, angiopoietin-like protein; FGF21, fibroblast growth factor 21; GDF15, growth differentiation factor 15; IGF-1, insulin-like growth factor 1; LEAP2, liver-expressed antimicrobial peptide 2. Figure created under the license of BioRENDER (https://BioRender.com/zelorai, license number: SH285C03YT).

Liver-to-brain communication

The liver plays a central role in regulating multiple aspects of energy metabolism, acting as a metabolic hub that coordinates nutrient processing, glycogen storage, lipid synthesis, glucose and lipid homeostasis, and hormonal signaling in response to feeding and fasting. The liver also has a predominant endocrine function since up to 40% of liver transcripts encode secreted peptides with multiple regulatory functions (Uhlén et al., 2015). Hepatocytes, the main cellular type of the liver, produce and secrete a variety of peptides called hepatokines, which serve as key mediators through which the liver communicates metabolic information to distant tissues, including the brain. In Table 1, we listed the main recognized hepatokines, indicated their receptors or target systems and organs, and also cited evidence implicating each hepatokine in the modulation of metabolism and energy balance.

Hepatokines are one of the ways by which the liver and the brain communicate. The liver also receives sympathetic and parasympathetic innervations that allow the brain to regulate liver function, and also the liver to convey metabolic information to the brain. Of note, multisynaptic brain projections to the liver comprise hypothalamic and medullary brain regions (Stanley et al., 2010), and sensory information from the hepatic portal vein reaches medullary brain centers through vagal afferents (Zsombok et al., 2024; Garcia-Luna et al., 2021). Interestingly, pharmacogenetic and optogenetic manipulation of specific hypothalamic neuronal populations modulates the expression of hepatic enzymes involved in glucose homeostasis (Kwon et al., 2020; Coutinho et al., 2017).

Hepatokines are constitutively secreted into circulation and reach distant tissues, including the brain, to modulate multiple aspects of metabolism (Schulze et al., 2019). Like other circulating factors, hepatokines can access the brain through distinct mechanisms: by crossing the blood–brain barrier, by diffusing through fenestrated capillaries in specialized brain regions, or by crossing the blood-cerebrospinal fluid (CSF) barrier constituted by hypothalamic tanycytes and choroid plexus cells (Rawal et al., 2022). In the brain, two essential hubs in the control of metabolism are the hypothalamus and the medulla. In the hypothalamus, the arcuate nucleus (ARH) plays a pivotal role in sensing circulating factors and transmitting peripheral information to other hypothalamic and extra-hypothalamic nuclei. The ARH comprises different neuronal subtypes (Campbell et al., 2017), including those co-expressing neuropeptide Y (NPY) and agouti-related peptide (AgRP), and neurons co-expressing pro-opiomelanocortin (POMC) and cocaine-and amphetamine-regulated transcript. Together with the ARH, the hypothalamic paraventricular (PVH), dorsomedial and ventromedial nuclei, and also the lateral hypothalamic area are all interconnected and form a neural network with key regulatory roles in metabolism (Jais and Brüning, 2022). In the medulla, the dorsal vagal complex (DVC)–comprising the dorsal motor nucleus of the vagus, the

TABLE 1 Metabolic implications of hepatokines.

Hepatokine	Receptor/Target system	Target organs	Metabolic implications	
			In rodent models	In humans
Activin E (inhibin subunit beta E)	Heterotetrameric complex of activin receptor IIA and receptor-like kinase 7 (ALK7)	Liver and adipose tissue	Suppresses lipolysis (Griffin et al., 2023) Stimulates energy expenditure and increases insulin sensitivity (Hashimoto et al., 2018) Positive correlation between expression of activin E gene and insulin resistance (Sekiyama et al., 2019)	Loss-of-function mutations in the activin E gene contribute to healthier fat distribution (Deaton et al., 2022) Correlation between increased expression of activin E gene expression and insulin resistance (Sugiyama et al., 2018)
Adropin	G protein-coupled receptor 19 (GPR19) Notch1 ligand NB3/Contactin6 (CNTN6)	Brain, liver, adipose tissue, muscle, cardiovascular system	Adropin-overexpressing mice or systemic adropin treatment attenuates hepatic steatosis and insulin resistance in DIO (Kumar et al., 2008) Adropin-deficient mice exhibited dyslipidemia and insulin resistance (Gao et al., 2014) Adropin administrations improve glucose homeostasis and protect against DIO (Gao et al., 2019)	Lower adropin levels in T2DM patients (Zang et al., 2018) and in patients with MASLD (Kutlu et al., 2019)
ANGPTL3	Lipoprotein lipase (LPL) activity modulation through ANGPTL3-4-8 complex Different receptors according to cell type	Liver, adipose tissue, skeletal muscle, and cardiac tissue	ANGPTL3-overexpressing mice show increased plasma triglycerides, cholesterol and non-esterified fatty acids (Koishi et al., 2002)	Positive correlation between circulating ANGPTL3 and plasma glucose, insulin, and HOMA-IR levels in patients with insulin resistance (Jensen-Cody and Potthoff, 2020) Loss-of-function mutations in the ANGPTL3 gene produce lower plasma LDL cholesterol and triglycerides (Kersten, 2021)
ANGPTL4 (fasting-induced adipose factor (FIAF))	Lipoprotein lipase (LPL) activity modulation through ANGPTL3-4-8 complex Integrin α5/β1 and α5β3 (keratinocytes)	Brain, liver, adipose tissue, skeletal muscle	ANGPTL4-deficient mice have lower plasma triglycerides, whereas ANGPTL4-overexpressing mice show increased plasma triglycerides (Sylvers-Davie and Davies, 2021)	ANGPTL4 deficiency is associated with higher circulating HDL cholesterol levels (Sylvers-Davie and Davies, 2021) Loss-of-function mutation in ANGPTL4 gene results in lower plasma triglycerides and higher HDL cholesterol (Olshan and Rader, 2018)
ANGPTL6 (angiopoietin-related growth factor (AGF))	Not described	Liver, adipose tissue, skeletal muscle	ANGPTL6-overexpressing mice show enhanced insulin sensitivity (Oike et al., 2005) ANGPTL6-deficient mice show impaired insulin sensitivity and decreased energy expenditure (Ebert et al., 2014)	Higher ANGPTL6 plasma levels in T2DM patients (Ebert et al., 2014) and in obese individuals (Qaddoumi et al., 2020) Increased serum ANGPTL6 levels precedes the development of metabolic syndrome (Namkung et al., 2011)
ANGPTL8 (lipasin or betatrophin)	Lipoprotein lipase (LPL) activity modulation through ANGPTL3-4-8 complex Leukocyte immunoglobulin-like receptor B (LILRB3, cardiomyocytes)	Brain, liver, adipose tissue, skeletal muscle, cardiac tissue	ANGPTL8-deficient mice show disrupted triglycerides metabolism (Wang et al., 2018) ANGPTL8-overexpressing mice show increased plasma triglycerides (Zhang, 2012)	Positive correlation between serum ANGPTL8 levels and the severity of MASLD (Lee et al., 2016) Controversial results on plasma ANGPTL8 levels and obesity (Luo and Peng, 2018)

(Continued)

TABLE 1 (Continued)

Hepatokine	Receptor/Target system	Target organs	Metabolic implications	
			In rodent models	In humans
Fetuin A (Alpha-2-HS-glycoprotein)	Insulin receptor	Liver, adipose tissue, skeletal muscle	Fetuin A-deficient mice show improved insulin sensitivity and resistance to DIO (Mathews et al., 2002)	SNPs in fetuin A gene are associated with T2DM (Mathews et al., 2002; Andersen et al., 2008) Increased circulating fetuin A levels in humans with a high liver fat content
FGF21	Heterocomplex of FGF receptor 1c (FGFR1c) and the co-receptor Klotho-β (KLB)	Brain and adipose tissue	Decreases blood glucose levels and improves insulin sensitivity in diabetic rodents (Kharitonenkov et al., 2005) FGF21-deficient mice show lower blood glucose levels (Liang et al., 2014) FGF21-overexpressing mice show reduced body weight and plasma insulin levels (Owen et al., 2014)	Increased FGF21 plasma levels in individuals with obesity, insulin resistance, MASLD and T2DM (Zhang et al., 2008; Ďurovcová et al., 2010; Dushay et al., 2010; Cheng et al., 2011) Treatment with FGF21 analog improves dyslipidemia, decreases body weight and improves fasting insulin levels in patients with T2DM and obesity (Gaich et al., 2013)
Follistatin	Binds and neutralizes activins	Liver, adipose tissue, pancreas, skeletal muscle, brain, placenta	Follistatin-overexpressing mice show a decrease in abdominal fat content, increased glucose clearance, and improved plasma lipid profiles (Singh et al., 2017) Follistatin treatment promotes white adipose tissue browning (Li et al., 2019)	Increased plasma follistatin levels in T2DM patients (Hansen et al., 2013; Sylow et al., 2020) Higher hepatic follistatin expression in MASLD patients (Tong et al., 2022) Moderate increase in plasma follistatin levels in obese patients (Maïmoun et al., 2020)
GDF15 (macrophage inhibitory cytokine-1)	Glial-derived neurotrophic factor receptor alpha-like (GFRAL)	Brain, adipose tissue, skeletal muscle	GDF15 treatment decreases food intake and body weight (Hale and Véniant, 2021) GDF15-deficient mice show increased food intake and body weight, and impaired glucose tolerance (Wang et al., 2021) GDF15-overexpressing mice have diminished food intake and body weight, and also improved insulin sensitivity (Wang et al., 2021)	Higher plasma GDF15 in obese (Hale and Véniant, 2021) and in MASLD patients (Koo et al., 2018)
Hepassocin (fibrinogen-like protein 1 or hepatocyte-derived fibrinogen-related protein 1)	Epidermal growth factor receptor (EGFR)	Liver, adipose tissue, skeletal muscle	Hepatic overexpression of hepassocin induces hepatic steatosis, whereas hepassocin deletion improves high fat diet-induced hepatic steatosis (Wu et al., 2013) Hepassocin treatment improves liver functions in diabetic mice (Ou et al., 2017)	Increased hepassocin plasma levels in MASLD subjects (Wu et al., 2013) Higher plasma hepassocin levels in obese individuals (Huang et al., 2020) Increased plasma hepassocin in patients with T2DM (Abdelmoemen et al., 2019)
IGF-1	IGF1 receptor (IGF1R)	Skeletal muscle, brain	Animal models with reduced plasma IGF-1 show increased circulating GH, leading to hyperinsulinemia, lower insulin sensitivity, and impaired carbohydrate metabolism (Yakar et al., 2001; Yakar et al., 2004)	Higher circulating free IGF-1 in obese patients (Yakar et al., 2001; Frystyk et al., 1995) Altered plasma levels of IGF-BPs and free IGF-1 in T2DM patients (Clemmons, 2018)

(Continued)

TABLE 1 (Continued)

Hepatokine	Receptor/Target system	Target organs	Metabolic implications	
			In rodent models	In humans
LEAP2	Growth hormone secretagogue receptor (GHSR)	Brain, pituitary, pancreas	LEAP2 plasma levels are increased in DIO and in diabetic mice (Mani et al., 2019; Lugilde et al., 2022) LEAP2 treatment reduces food intake and feeding-induced increase of blood glucose (Ge et al., 2018; Hagemann et al., 2022)	LEAP2 treatment reduces food intake in an *ad libitum* meal and lowers postprandial plasma glucose and growth hormone concentrations (Hagemann et al., 2022) Increased plasma LEAP2 levels in obese subjects (Holm et al., 2022; Mani et al., 2019; Andreoli et al., 2024) and in T2DM patients (Li et al., 2022)
LECT2	Endothelial cell-specific orphan receptor (Tie1) CD209 antigen-like protein A (CD209a) Tyrosine kinase with immunoglobulin-like and EGF-like domains 1 (Tie1) Tyrosine protein kinase Met (MET) L1 cell adhesion molecule (L1CAM) Transferrin (Trf)	Skeletal muscle, liver, adipose tissue, endothelium	LECT2-deficient mice show increased insulin sensitivity (Lan et al., 2014) Circulating LECT2 levels correlate with hepatic triglycerides and responds to dietary changes preceding body weight changes (Chikamoto et al., 2016)	Circulating LECT2 correlates with the severity of obesity and insulin resistance (Lan et al., 2014) Increased plasma LECT2 levels in patients with MASLD and metabolic syndrome (Yoo et al., 2017) Increased circulating LECT2 in T2DM patients and negative correlation with HDL cholesterol in diabetic and obese subjects (Zhang et al., 2018)
Lipocalin 13	Binds to small hydrophobic molecules (fatty acids, phospholipids, steroids, among others)	Adipose tissue and liver	Contradictory results on the involvement of lipocalin 13 in glucose and lipid homeostasis (Cho et al., 2011; Sheng et al., 2011; Bühler et al., 2021)	Human LCN13 has not been identified yet
MANF	Neuroplastin receptor	Brain, liver, pancreas, adipose tissue, heart, kidney	MANF-deficient mice show increased blood glucose levels, decreased plasma insulin levels and lower body weight (Lindahl et al., 2014; Pakarinen et al., 2020; Danilova et al., 2019) MANF-overexpressing mice show higher energy expenditure and enhanced browning of inguinal adipose tissue (Wu et al., 2021) MANF administration retards body weight gain and improves glucose homeostasis in obese mice (Tang et al., 2022)	Elevated circulating MANF levels in prediabetic and T2DM patients (Wu et al., 2021; Fu et al., 2021) Plasma MANF levels reduced in MASLD patients (Sousa-Victor et al., 2019) Inconsistent results on circulating MANF levels in obesity (Tang et al., 2022)
Selenoprotein P	Apolipoprotein E receptor-2 (ApoER2) Megalin (lipoprotein receptor-related protein 2, LRP2) Lipoprotein receptor-related protein 1 (LRP1)	Liver, skeletal muscle, small intestine, colon, spleen, testis, kidney	Selenoprotein P treatment induces glucose intolerance and insulin resistance, whereas hepatic knockdown of selenoprotein P improved glucose intolerance and insulin resistance (Misu et al., 2010)	Increased plasma selenoprotein P levels in T2DM patients (Misu et al., 2010; Yang et al., 2011) Increased concentrations of selenoprotein P decrease the risk of metabolic syndrome (Gharipour et al., 2017)

(Continued)

TABLE 1 (Continued)

Hepatokine	Receptor/Target system	Target organs	Metabolic implications	
			In rodent models	In humans
SHBG	SHBG receptor	Liver, testis	SHBG-overexpressing mice gain less body weight under a high fat diet (Saez-Lopez et al., 2020)	SNPs in SHBG gene associated with increased risk of T2DM (Ding et al., 2009) Lower plasma SHBG levels in MASLD patients and associated with high-grade MASLD in patients with T2DM (Shin et al., 2011) Lower plasma SHBG levels in obese individuals (Cooper et al., 2015)
SMOC 1	Regulates cell-matrix interactions by binding to laminins, C-reactive protein, and tenascin-C	Liver, skeletal muscle	SMOC1 treatment improved glycemic control in lean mice without changes in insulin secretion (Montgomery et al., 2020)	Lower plasma SMOC1 levels in insulin-resistant individuals (Montgomery et al., 2020) No evidence that plasma SMOC1 levels are causally associated with T2DM, MASLD, and glycemic traits (Ghodsian et al., 2021)
Tsukushi	Modulates Wnt, transcription growth factor beta (TGF-β), cell communication network factor (CCN2/CTGF), and netrin signaling pathways	Liver, adipose tissue	Controversial results regarding tsukushi effects on energy balance (Mouchiroud et al., 2019a) and its involvement in MASLD rodent models (Xiong et al., 2019; Mouchiroud et al., 2019b)	Lower tsukushi plasma levels in obese individuals (Li et al., 2021) Higher circulating levels of tsukushi in subjects with metabolic syndrome (Li et al., 2023) Higher plasma Tsukushi levels in individuals with MASLD and positive correlation with the degree of liver steatosis and fibrosis (Lam et al., 2024)

ANGPTL, angiopoietin-like protein; DIO, diet-induced obesity; FGF21, fibroblast growth factor 21; GDF15, growth differentiation factor 15; HDL, high density lipoprotein; HOMA-IR, homeostatic model assessment for insulin resistance; GH, growth hormone; IGF1, insulin-like growth factor 1; LDL, low density lipoprotein; LEAP2, liver-expressed antimicrobial peptide 2; LECT2, Leukocyte cell-derived chemotaxin 2; MANF, mesencephalic astrocyte-derived neurotrophic factor; MASLD, metabolic-associated steatotic liver disease; SHBG, sex hormone-binding globulin; SMOC 1, SPARC related modular calcium binding 1; SNPs, single-nucleotide polymorphisms; T2DM, type 2 diabetes mellitus.

area postrema (AP), and the nucleus of the solitary tract (NTS)–contains multiple neuronal populations that are crucial for interpreting and relaying peripheral signals to the hypothalamus, and also to elicit autonomic responses via the vagus nerve (Abdalla, 2017). Emerging evidence suggests that hepatokines can act on these brain regions directly or indirectly, influencing central pathways that control metabolism, food intake, and energy expenditure.

Brain-acting hepatokines and metabolism

Insulin-like growth factor 1 (IGF-1)

IGF-1 is a peptide with structural homology to insulin produced in the liver, where its production is stimulated by growth hormone (GH), and is strongly implicated in the modulation of cell growth and differentiation. Plasma IGF-1 is bound to one of the six IGF-1 binding proteins (IGF-1BP), which modulate its effects. IGF-1 production is regulated by nutrient availability, with hepatic IGF-1 mRNA and plasma levels declining with fasting and increasing with refeeding (Straus and Takemoto, 1990; Clemmons, 2012). IGF-1 mainly signals through IGF-1 receptor (IGF-1R), which is ubiquitously expressed in peripheral organs and the brain. The net effect of IGF-1 is determined by the modulation of IGF-1 production, IGF-1BPs levels, and IGF-1R expression. We recommend consulting in-depth reviews for a comprehensive understanding of these regulatory mechanisms (Yuen et al., 2024; Clemmons, 2018). For instance, fasting decreases plasma IGF-1 levels in healthy subjects (Rahmani et al., 2019), whereas altered plasma IGF-1BPs levels are observed in obese patients, producing a subtle increase in free IGF-1 (Clemmons, 2012). Also, disturbed levels of circulating IGF-BPs and free IGF-1 are detected in T2DM patients, with changes depending on the progression of the pathology (Clemmons, 2018).

IGF-1 is produced in the brain during development, and some studies have shown that central IGF-1 modulates energy metabolism and energy balance in adulthood. Intra-cerebro-ventricular (ICV) IGF-1 injection lowers hepatic glucose production in hyperinsulinemic-clamped mice (Muzumdar et al., 2006) and improves insulin sensitivity of aged rats (Huffman et al., 2016). ICV IGF-1 treatment in mice increases food intake and enhances insulin sensitivity (Hong et al., 2017). Moreover, deletion of IGF-1R from kisspeptin-expressing neurons produces a decrease in food intake and an increase in energy expenditure exclusively in female mice (Wang et al., 2024). However, partial deletion of neuronal IGF-1R causes subtle metabolic phenotypes, including higher circulating triglycerides and free fatty acids and a moderate hyperglycemia (Kappeler et al.,

2008). Thus, the complexity of the IGF-1 system makes it difficult to dissect a specific modulatory role for central IGF-1 on energy balance and metabolism.

Fibroblast growth factor 21 (FGF21)

FGF21 belongs to the fibroblast growth factor family, a group of proteins involved in regulating multiple processes such as angiogenesis and embryonic development. FGF21 decreases blood glucose and improves insulin sensitivity in diabetic rodents (Kharitonenkov et al., 2005). FGF21 mRNA levels increase in the liver of high-sucrose diet consuming and diet-induced obese (DIO) mice (Fisher et al., 2010; Maekawa et al., 2017). Circulating FGF21 levels increase in fasted mice (Markan et al., 2014), in mice chronically fed high-sucrose diets (Maekawa et al., 2017), in DIO mice (Fisher et al., 2010), and in a mouse model of T2DM (Spolcová et al., 2014). In humans, circulating FGF21 increases during fasting (Fazeli et al., 2015). Also, circulating FGF21 is increased in overweight/obese individuals (Zhang et al., 2008; Ďurovcová et al., 2010), and in patients with MASLD (Dushay et al., 2010) and T2DM (Cheng et al., 2011), and in women with gestational diabetes (Tan et al., 2013). Moreover, plasma levels of FGF21 increase after gastric sleeve surgery (Al-Regaiey et al., 2024), whereas a decrease is detected in individuals with obesity/overweight and MASLD after weight loss (Erdem et al., 2024).

FGF21 is primarily produced in the liver and regulates energy balance and metabolism by acting on the brain, particularly in the hypothalamus (Hsuchou et al., 2007; Liang et al., 2014). In humans, FGF21 was detected in the CSF (Tan et al., 2013; Tan et al., 2011; Li et al., 2016). FGF21 acts via the FGF receptor 1c (FGFR1c), which is widely distributed in the mouse brain, whereas its co-receptor Klotho-β (KLB, (Ogawa et al., 2007)) is specifically present in the hypothalamic suprachiasmatic nucleus, the DVC, and also in the amygdala (Bookout et al., 2013; Bono et al., 2022; Claflin et al., 2022). KLB genetic deletion in hypothalamic neurons abolishes the reductions in body weight and plasma insulin observed in FGF21-overexpressing mice (Bookout et al., 2013). Moreover, hypothalamic KLB deletion blunts the increase in food consumption and energy expenditure and the decrease in plasma glucose and cholesterol observed in DIO FGF21-overexpressing mice (Owen et al., 2014). Interestingly, pharmacogenetic activation of KLB-expressing neurons increases energy expenditure and decreases body weight of DIO mice, and genetic deletion of KLB from glutamatergic neurons prevents FGF21 effects on energy expenditure and body weight (Claflin et al., 2022).

Studies performing central infusions of FGF21 also demonstrate its central effects. Chronic ICV injection of FGF21 improves insulin sensitivity of lean and DIO rats (Sarruf et al., 2010), whereas FGF21 ICV administrations lower body weight, percent body fat, and plasma glucose and cholesterol concentrations of DIO mice, effects dependent on hypothalamic KLB expression (Owen et al., 2014). Interestingly, ICV FGF21 treatment induces the expression of thermogenic genes and also increases sympathetic nerve activity in brown adipose tissue of DIO mice, both effects dependent on hypothalamic KLB expression (Owen et al., 2014). Moreover, ICV FGF21 administration to hypoglycemic FGF21-deficient mice normalizes their glycemia, which depends on the presence of FGFR1c in the PVH (Liang et al., 2014). Furthermore, ICV FGF21 administrations increase ERK1/2 expression in the mouse hypothalamus (Yang et al., 2012), whereas intra-PVH FGF21 injection increases ERK1/2 and CREB phosphorylation (Liang et al., 2014). Thus, the literature indicates that FGF21 impacts and depends on the activity of hypothalamic brain nuclei to modulate energy balance and metabolism, which supports the notion of FGF21 as a brain-acting hepatokine.

Liver-expressed antimicrobial peptide 2 (LEAP2)

LEAP2 was recently described as a ligand of the GH secretagogue receptor (GHSR) (Ge et al., 2018; M'Kadmi et al., 2019), which triggered a great interest on this hepatokine (Perelló, 2025). LEAP2 mRNA is predominantly found in liver hepatocytes and jejunal enterocytes of both mice and humans (Ge et al., 2018; Krause et al., 2003; Englund et al., 2024). LEAP2 is secreted via the constitutive secretory pathway, thereby its production is controlled at the gene expression level, with metabolic status as a key regulatory factor (Perelló, 2025). Liver LEAP2 mRNA levels decrease with fasting (Holm et al., 2022; Islam et al., 2020), and increase in DIO mice (Holm et al., 2022). Interestingly, liver LEAP2 mRNA decreases in mice fed with a ketogenic diet (Holm et al., 2022), whereas it increases in mice orally administered with glucose and corn oil (Islam et al., 2024). Circulating LEAP2 levels in mice decrease with fasting (Ge et al., 2018; Islam et al., 2020; Mani et al., 2019; Fernandez et al., 2022), whereas plasma LEAP2 is increased in DIO (Mani et al., 2019; Holá et al., 2023; Casado et al., 2024) and *ob/ob* mice (Lugilde et al., 2022), and in a mouse model of type 1 diabetes mellitus (T1DM) (Mani et al., 2019). Interestingly, LEAP2-overexpressing mice show enhanced body weight loss and impaired maintenance of glycemia under caloric restriction (Ge et al., 2018). Conversely, female LEAP2-deficient mice display increased food intake and enhanced body weight gain when fed a high fat diet (HFD) (Shankar et al., 2021). In humans, obese adults and children show increased plasma LEAP2 levels (Holm et al., 2022; Mani et al., 2019; Andreoli et al., 2024; Fittipaldi et al., 2020), which positively correlate with body mass index, percentage of body fat, and homeostatic model assessment of insulin resistance, among other parameters (Mani et al., 2019; Stark et al., 2023). Circulating LEAP2 levels are also increased and positively correlate with glycosylated hemoglobin in T2DM patients (Li et al., 2022). Interestingly, decreased plasma LEAP2 levels are detected in healthy men after exercise (Holm et al., 2022) and also in obese subjects after a short calorie restriction (Ragland and Malin, 2023).

Studies performing LEAP2 administrations demonstrate its ability to modulate energy balance. LEAP2 blunts fasting-induced food intake (Holá et al., 2022), and also diminishes food intake-induced increase in blood glucose in mice and humans (Hagemann et al., 2022). Interestingly, lipidized analogs of LEAP2 also display anorexigenic effects (Holá et al., 2022). The central effect of LEAP2 has also been addressed. ICV LEAP2 administration decreases HFD consumption of mice in a binge-like eating protocol (Cornejo et al., 2019), and also diminishes fasting-induced and spontaneous intake in rats and mice (Lugilde et al., 2022; Tufvesson-Alm et al., 2023). Chronic central administration of LEAP2 diminishes food intake and weight gain (Chu et al., 2022) and also reduces circulating triglycerides, while increasing energy expenditure and thermogenic biomarkers in brown adipose tissue of mice (Casado et al., 2024). To the best of our knowledge, only few studies have addressed the putative neuronal population mediating LEAP2 effects on food intake. LEAP2 was shown to hyperpolarize ARH

NPY-expressing neurons, preventing their activation by ghrelin (Mani et al., 2019). Accordingly, LEAP2-deficient mice show enhanced ghrelin-induced ARH activation, measured as c-Fos immunoreactivity (Shankar et al., 2021), whereas food-deprived mice ICV administered with LEAP2 show decreased fasting-induced c-Fos in the ARH (Fernandez et al., 2022). Moreover, chronic central LEAP2 administration increases c-Fos immunoreactivity in ARH POMC neurons and chemogenetic inhibition of POMC neurons blunts LEAP2's anorexigenic effect (Chu et al., 2022). Thus, experimental evidence demonstrates the ability of LEAP2 to modulate the activity of different hypothalamic neuronal populations, including ARH NPY and POMC neurons, which may mediate its effect on energy balance and metabolism.

Growth differentiation factor 15 (GDF15)

GDF15 is a divergent member of the transforming growth factor β superfamily. GDF15 mRNA is detected in multiple human and mouse tissues (Lockhart et al., 2020). Liver GDF15 mRNA levels are increased in *ob/ob* mice and Zucker diabetic fatty rats (Xiong et al., 2017), and also in DIO mice (Patel et al., 2019). Genetically modified rodent models have helped to understand the role of GDF15 on the regulation of energy balance. GDF15-deficient mice show increased food intake and body weight, and impaired glucose tolerance (Wang et al., 2021). Moreover, mice with genetic deletion of glial-derived neurotrophic factor receptor alpha-like (GFRAL), GDF15's receptor, show attenuated DIO and insulin resistance (Emmerson et al., 2017; Mullican et al., 2017; Hsu et al., 2017; Yang et al., 2017). Conversely, GDF15-overexpressing mice have diminished food intake and body weight, and improved insulin sensitivity (Wang et al., 2021). In humans, increased liver mRNA and plasma levels of GDF15 are found in individuals with MASLD (Koo et al., 2018), whereas circulating GDF15 is also increased in obese and T2DM patients (Wang et al., 2021).

GFRAL mRNA is selectively detected in the mouse and human hindbrain (Mullican et al., 2017; Hes et al., 2025). Central GDF15 administration diminishes food intake and induces c-Fos expression in the AP and NTS (Tsai et al., 2014; Worth et al., 2020), and, although the identity of GDF15-responding neurons remains elusive, GFRAL expression co-localizes with cholecystokinin-expressing neurons (Worth et al., 2020). Interestingly, systemic GDF15 treatment diminishes gastric emptying in rodents, an effect dependent on the vagal efferent pathway (Xiong et al., 2017), and also causes emesis in musk shrews (Borner et al., 2020). Furthermore, GDF15 induces taste aversion (Patel et al., 2019; Worth et al., 2020), an effect consistent with c-Fos induction in the amygdala of GDF15-administered mice (Hsu et al., 2017). Thus, the effects of GDF15 as a brain-acting hepatokine that regulates energy balance seem to be secondary to its effect on other processes such as gastric emptying or taste aversion, processes that rely on different central circuits.

Angiopoietin-like protein 4 (ANGPTL4)

ANGPTL4 belongs to the ANGPTL protein family, which are involved in angiogenesis. ANGPTL4 is produced in the liver and adipose tissue, and, to a lesser extent, in the pituitary and hypothalamus (Wiesner et al., 2004; Kim et al., 2010; Vienberg et al., 2015). In mice, liver and plasma ANGPTL4 peptide levels increase with fasting and decrease after refeeding (Kim et al., 2010). Interestingly, ANGPTL4 peptide levels—but not mRNA levels—increase in the hypothalamus of fasted mice (Wiesner et al., 2004; Kim et al., 2010), likely due to elevated circulating peptide. Hypothalamic ANGPTL4 mRNA is increased in mouse models of T1DM and T2DM (Vienberg et al., 2015). ANGPTL4-deficient mice show reduced plasma triglycerides when fasted (Köster et al., 2005), whereas they show enhanced body weight gain and visceral adipose tissue mass deposit, but improved glucose tolerance when fed a HFD (Janssen et al., 2018). Strikingly, deletion of ANGPTL4 from hepatocytes enhances plasma triacylglycerol clearance and insulin sensitivity, and also diminishes weight gain of DIO mice (Singh et al., 2021). Conversely, ANGPTL4-overexpressing mice show increased serum cholesterol and triglycerides (Köster et al., 2005). In humans, circulating ANGPTL4 is increased in T2DM patients (Babapoor-Farrokhran et al., 2015; McCulloch et al., 2020) and in obese individuals (Schinzari et al., 2021) and to decrease, together with body weight and fat mass, after bariatric surgery (Bini et al., 2022).

Only one study links the central effect of ANGPTL4 to energy balance (Kim et al., 2010). ICV ANGPTL4 suppresses fasting-induced hyperphagia and increases energy expenditure, effects absent with peripheral administration (Kim et al., 2010). Moreover, ICV ANGPTL4 decreases hypothalamic AMPK phosphorylation, and the pharmacologic inhibition of AMPK signaling blunts the effect of ANGPTL4 on food intake (Kim et al., 2010). Then, ANGPTL4's role as a brain-acting hepatokine needs further work to confirm its central effect on energy balance, although it seems evident that ANGPTL4's effect relies on hypothalamic circuits.

Angiopoietin-like protein 8 (ANGPTL8)

ANGPTL8 is another member of the ANGPTL protein family and is exclusively produced in the human liver, whereas its mRNA is detected in mouse liver and adipose tissue (Zhang, 2012). In mice, ANGPTL8 liver mRNA levels decrease with fasting and increase with refeeding (Quagliarini et al., 2012), HFD feeding (Zhang, 2012), and also in hyperinsulinemic (Zhang et al., 2020) and fatty liver mice (Lee et al., 2016). Circulating and CSF levels of ANGPTL8 are also higher in diabetic murine models (Meng et al., 2024). Liver ANGPTL8 overexpression increases serum triacylglycerol and very-low density lipoprotein concentrations (Cox et al., 2015), whereas ANGPTL8 deficiency produces a decrease in plasma triglycerides and improves glucose tolerance of DIO mice (Zhang et al., 2020). In humans, circulating ANGPTL8 levels decrease with fasting and increase with refeeding (Quagliarini et al., 2012). Plasma ANGPTL8 levels are also increased in individuals with T1DM (Espes et al., 2014), T2DM (Espes et al., 2014; Fu et al., 2014; Hu et al., 2014) and obesity (Fu et al., 2014), and positively correlate with hepatic steatosis in MASLD patients (von Loeffelholz et al., 2017). Interestingly, a recent study showed that ANGPTL8 CSF levels are increased in T2DM patients with cognitive dysfunction (Meng et al., 2024).

Only one study addressed ANGPTL8's central modulation of energy balance in mice. ICV ANGPTL8 administration decreases rebound feeding and body weight regain after fasting, whereas it affects fasting-induced c-Fos in hypothalamic nuclei (Wang et al., 2018). Also, chronic ICV ANGPTL8 administration decreases body weight and circulating free fatty acids (Wang et al., 2018). Thus, further studies supporting the

modulatory effect of ANGPTL8 on hypothalamic brain nuclei are needed to unequivocally establish its role as a brain-acting hepatokine.

Concluding remarks

Hepatokines have emerged as key players not only in peripheral metabolism but also in the complex regulation of brain function and whole-body energy balance. In this mini-review, we introduced the concept of "brain-acting hepatokines", those that impact on the activity of brain centers that control energy balance and metabolism. Although the current understanding of the specific roles of brain-acting hepatokines in the central nervous system remains uneven, accumulating evidence underscores their relevance in both health and disease. Their dual function—as metabolic messengers and potential therapeutic targets—highlights the urgency and promise of advancing research in this field. Furthermore, since plasma levels of brain-acting hepatokines are increased in pathological conditions implicating metabolic disturbances such as T2DM, MASLD, and obesity, their potential as biomarkers poses them as putative targets for early diagnosis, prevention, and monitoring of disease progression. Moreover, the possibility of a synergistic central effect of brain-acting hepatokines has been only incipiently studied. Continued exploration of hepatokine signaling pathways may unlock novel strategies to address metabolic disorders and neuroendocrine dysregulation.

Author contributions

LG: Conceptualization, Data curation, Writing – original draft, Writing – review & editing. NW: Conceptualization, Data curation, Writing – original draft, Writing – review & editing. MP: Conceptualization, Writing – original draft, Writing – review & editing. MPC: Conceptualization, Data curation, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The authors declare that no Gen AI was used in the creation of this manuscript.

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Glossary

AgRP - agouti-related peptide

AMPK - AMP-activated protein kinase

ANGPTL4 - angiopoietin-like protein 4

ANGPTL8 - angiopoietin-like protein 8

AP - area postrema

ARH - hypothalamic arcuate nucleus

CSF - cerebrospinal fluid

DIO - diet-induced obese

DVC - dorsal vagal complex

FGF-21 - fibroblast growth factor 21

FGFR1c - FGF receptor 1c

GDF15 - growth differentiation factor 15

GFRAL - glial-derived neurotrophic factor receptor alpha-like

GH - growth hormone

GHSR - GH secretagogue receptor

HFD - high fat diet

ICV - intra-cerebro-ventricular

IGF-1 - insulin-like growth factor 1

IGF-1BP - IGF-1 binding proteins

IGF-1R - IGF-1 receptor

KLB - Klotho-β

LEAP2 - liver-expressed antimicrobial peptide 2

MASLD - metabolic-associated steatotic liver disease

NPY - neuropeptide Y

NTS - nucleus of the solitary tract

POMC - pro-opiomelanocortin

PVH - paraventricular hypothalamic nucleus

T1DM - type 1 diabetes mellitus

T2DM - type 2 diabetes mellitus