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Metabolic actions of the growth hormone-insulin growth factor-1 axis and its interaction with the central nervous system

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Abstract

The growth hormone/insulin growth factor-1 axis is a key endocrine system that exerts profound effects on metabolism by its actions on different peripheral tissues but also in the brain. Growth hormone together with insulin growth factor-1 perform metabolic adjustments, including regulation of food intake, energy expenditure, and glycemia. The dysregulation of this hepatic axis leads to different metabolic disorders including obesity, type 2 diabetes or liver disease. In this review, we discuss how the growth hormone/insulin growth factor-1 axis regulates metabolism and its interactions with the central nervous system. Finally, we state our vision for possible therapeutic uses of compounds based in the components of this hepatic axis.

Keywords GH · IGF-1 · Energy balance · Brain · Liver

Abbreviations

ARC	Hypothalamic arcuate nucleus
AgRP	Agouti-related peptide
BAT	Brown adipose tissue
bGH	Bovine growth hormone
CNS	Central nervous system
GH	Growth hormone
GHR	Growth hormone receptor
GHRLD	Liver-specific deletion of growth hormone receptor
hGH	Human growth hormone
IGF-1	Insulin growth factor-1
IGFBPs	Insulin growth factor binding proteins
IGF-1R	Insulin growth factor-1 receptor
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NEFA	Non esterified fatty acid
NPY	Neuropeptide Y
mGH	Mouse growth hormone
ob/ob mice	Leptin deficient mice
POMC	Proopiomelanocortin
rhIGF-1	Recombinant human IGF-1
SS	Somatostatin
T2DM	Type 2 diabetes mellitus
Tg	Transgenic
WAT	White adipose tissue

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1 Introduction

Obesity is reaching pandemic proportions in the world and becoming a major social, economic and health problem [1, 2]. The increased incidence of this condition has precipitated comorbidities such cardiometabolic disease, type 2 diabetes mellitus (T2DM) and liver diseases, including non-alcoholic fatty liver disease and non-alcoholic steatohepatitis (NAFLD/NASH), that negatively impacts public health globally [3, 4].

One critical factor in the development of obesity is dysregulated feeding behaviour, a complex process regulated mainly by the central nervous system (CNS) according to homeostatic and hedonic drives [5, 6]. In the hypothalamus the arcuate nucleus (ARC) is the main neuronal core involved in homeostatic response, integrating information about the levels of nutrients and hormones in the periphery, and modulating the energy balance accordingly [7, 8]. The ARC is composed of two antagonistic neuronal populations, the neuropeptide Y/Agouti-related peptide (NPY/AgRP) neurons that induce a positive energy balance [9], and proopiomelanocortin (POMC) neurons that in turn induce a negative energy balance [10]. Both neuronal types are involved in the regulation of food intake, energy expenditure and nutrient partitioning. However, not all of the neuronal signals that control feeding behaviour originate in the brain; some are produced in the gastrointestinal tract or in the liver and these signals are transmitted to the brain.

In line with this, the experiments performed in the early 1960s by the group of Russek laid the grounds for the hepatostatic theory, which proposed that signals produced by the liver may contribute to changes in feeding behaviour [11]. The hepatostatic theory originated from the observation of a more pronounced decrease in food intake in dogs after direct administration of glucose into the liver of compared to systemic administration of glucose [12, 13]. However, recent experimental data has contributed to increasing knowledge and led to a more refined theories [14, 15].

The liver is a master metabolic organ that integrates peripheral nutrient status to control proper energetic homeostasis. Endocrine factors such as insulin, growth hormone (GH), and glucagon transmit information on the peripheral energetic status to the liver, but this organ also integrates signals directly from the nutrients themselves. Another relevant signal is the insulin growth factor-1 (IGF-1), a crucial factor in the control of metabolism, that is regulated by the action GH in the liver. In this review, we describe how the GH-IGF-1 axis controls energy balance and how metabolic actions may be induced by the activity of these factors in the CNS.

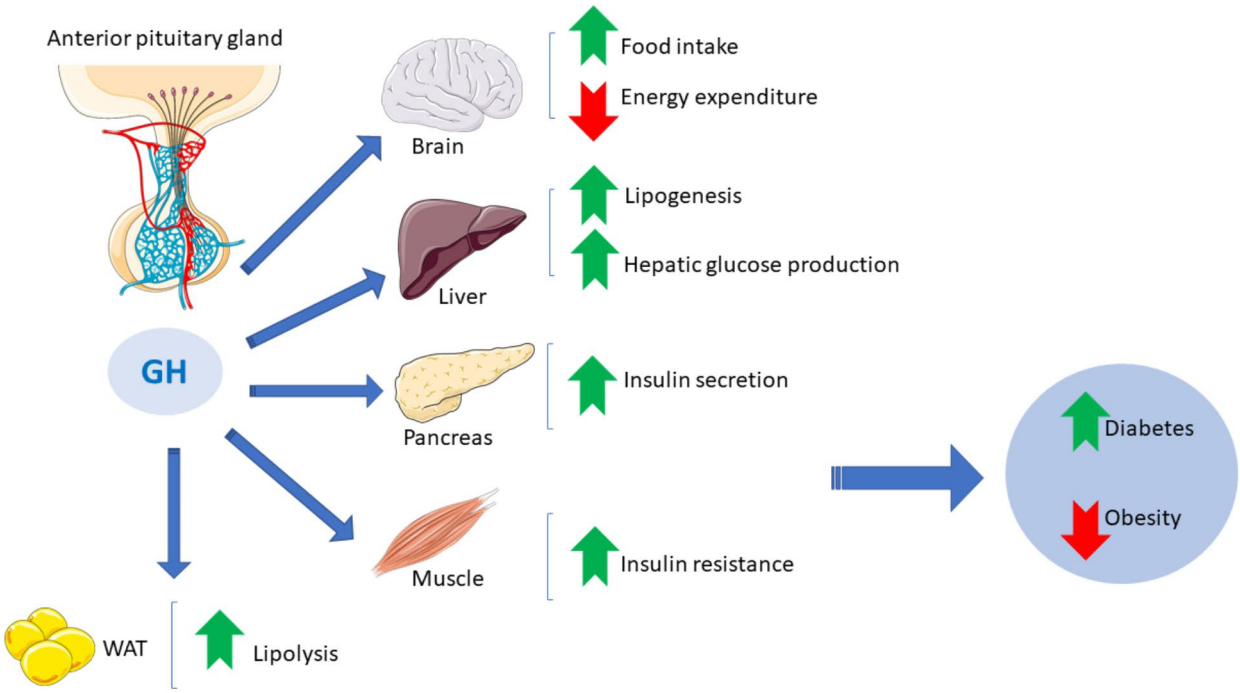

Fig. 1 Description of the metabolic actions elicited by GH. GH is released from the pituitary as a potent lipolytic agent however decreases insulin sensitivity and triggers hepatic glucose production, in turn leading to a diabetogenic state. Abbrevations used: GH: growth hormone; WAT: white adipose tissue

2 Growth hormone

Growth hormone (GH), also known as somatotropin, is an amino acid peptide of 191 aa and a molecular weight of 22.650D that is released from the anterior pituitary somatotrophs [16–18]. GH secretion is regulated mainly by two hypothalamic hormones, the growth hormone-releasing hormone and somatostatin (SS), also refereed as growth hormone-inhibiting hormone [17, 19, 20]. In addition to these canonical regulators, the gastric hormone ghrelin (GH-releasing peptide) is also an endogenous and strong GH secretagogue [21–24]. Ghrelin binds and activates its receptor, the growth hormone secretagogue receptor 1a, in the hypothalamus to induce GH secretion [25, 26].

GH binds to the GH receptor (GHR), a member of the class I cytokine receptor family, and an amino acid dimeric receptor with an extracellular domain, a single-pass transmembrane domain, and a cytoplasmic intracellular domain [27]. The GHR is located mainly in epiphyseal plates in long bones and spine, liver, muscles, and adipose tissue [18, 20, 28]. GH binding to its receptor leads to activation of several intracellular signal cascades, including mitogenic signaling through Janus kinase signal transducers and activators of transcription, mitogen-activated protein kinase, phosphoinositide-3-kinase/Protein kinase B/mammalian target of rapamycin pathways and phospholipase C/Protein kinase C [29, 30].

GH presents a pulsatile secretion pattern, with phases of sudden release (dark phase), separated from each other by periods when there is no discharge.

2.1 Metabolic actions of GH:

GH is a pleiotropic hormone that, in addition to regulate linear growth has important biological functions such as the regulation of metabolism (Fig. 1). In the following sections we describe the relationship of GH with some metabolic diseases.

2.1.1 GH and obesity:

GH is an anabolic hormone with an important impact on body weight and insulin homeostasis. Despite its name, there is an inverse relationship between body weight and GH levels in rodents [31, 32]. Moreover, humans with defective expression of GH receptor (GHR, Laron's syndrome) and GHR knockout (GHR-/-) mice are obese, with reduced IGF-1 levels and increased insulin sensitivity [33–36]. Conversely, transgenic (Tg) mice expressing the bovine GH gene (bGH) are characterized by increased IGF-1 levels, accelerated growth, increased lean body mass and decreased white adipose tissue (WAT) mass [37, 38]. Moreover, genetic models of obesity, such as leptin deficient (ob/ob) mice, and obese humans have lower levels of circulating GH [31, 39–41]. Notably, GH increase lipolysis in adipocytes and enhance triglyceride secretion from the liver. Since GH directly influences fat mass by promoting lipolysis and preventing lipogenesis, obese patients have compromised GH-directed lipolytic and anti-lipogenic actions[34]. Thus, GH has a clear impact on body weight because of its action on lipid metabolism.

2.1.2 GH and NAFLD/NASH:

In line with these outcomes, other reports link the lipolytic effects of GH with the liver (Extensive reviewed in [42]). In this regard, diet-induced fatty liver is associated with reduced circulating GH [43]. Consistently, the liver-specific deletion of GHR (GHRLD) in mice results in a marked decrease in serum IGF-1 levels, significant increases in fat mass and serum lipids, and severe hepatic steatosis associated with systemic insulin resistance [44, 45]. Moreover, the rescue of GHR signalling in the liver of GHRLD mice completely restored hepatic triglycerides and glucose tolerance. In contrast, infusion of recombinant human IGF-1 (rhIGF-1) failed to correct hepatic steatosis, although circulating GH was restored to normal, indicating an IGF-1-independent effect of GH in hepatic steatosis[44]. These outcomes are also observed in humans, with patients with Laron´s syndrome or hypopituitary adults with growth hormone deficiency exhibiting NAFLD [45–48]. In agreement patients with acromegaly have lower levels of hepatic steatosis [49, 50].

Interestingly, the identification of differences between humans and mice is important to translational research. In line with this, the development of sophisticated mice models such the chimeric mice with humanized livers [51] may be of particular interest for assessing the role of GH on liver diseases. For example, mouse GH (mGH) cannot bind to human GHR (hGHR) in the liver of the humanized mouse due to species differences. However, treating these mice with human growth hormone (hGH) ameliorated fatty liver development [52]. Therefore, this mouse model will be useful tool for investigating the mechanism of the action of hGH on human hepatocytes in vivo as well as the role of GH in the onset of NAFLD/NASH.

2.1.3 GH and diabetes mellitus:

GH has also been described as a diabetogenic agent with the ability to increase hepatic glucose production [53]. GH influences glucose homeostasis by negatively affecting insulin sensitivity, leading to a compensatory increase in insulin secretion that predisposes patients to diabetes. It has

recently been reported that GH might also stimulate insulin secretion by directly affecting the function of pancreatic β cells in both animals and humans [54, 55].

2.2 GH targets the brain to mediate energy balance

Several studies have linked the action of GH in the brain to energy balance (For review see [56]). For example, GHR is widely expressed in the ARC [57] and GH-deficient or GHR-knockout (-/-) mice exhibit reduced formation of AgRP and POMC projections to postsynaptic targets [58]. Brain-specific GHR-deficient mice exhibited increased body weight, mostly due to excessive lean mass [59] possibly due impaired GH negative feedback. Consistently, GH overexpression in the CNS results in hyperphagia-induced obesity associated with insulin resistance and dyslipidaemia [60].

More specific studies with conditional mutant mouse models in specific neuronal populations reinforce these arguments. For example, GHR deletion in POMC cells blunts the glucoprivic hyperphagia following 2-deoxy glucose administration [61]. Also, genetic GHR inhibition in AgRP or POMC neurons decreases the density of the neuronal projections to other hypothalamic neurons[62]. In addition, pharmacological or genetic central activation of GH signalling triggers the expression of AgRP neurons in mice [59] and fish [63] and concomitantly increases food intake while reducing energy expenditure. Consistently, GH administration in humans increases the levels of plasmatic AgRP protein levels, and this effect is reversible after pharmacological GH inhibition [64]. While mice with specific deletion of GHR in AgRP neurons are comparable to wild type animals in ad libitum conditions, the mutant mice showed reduced activation of AgRP neurons after acute or chronic food deprivation [59]. Additionally, the impairments induced by the lack of GH signalling in the AgRP neurons are extensive to brown adipose tissue (BAT) thermogenesis and energy expenditure under chronic starvation conditions in those mice[59]. Interestingly, the increase in food intake associated with low glucose levels is blunted in GHR-AgRP (-/-) mice compared to the intake by the control mice. In addition, the treatment with an antagonist of GH as pegvisomant, prevented the decrease in glucose levels and the decline in energy expenditure associated with chronic food restriction. Altogether, these findings point to a key role of GH signalling in AgRP neurons in the induction of metabolic responses to preserve the proper energy balance during times of famine.

2.3 Therapeutic action of GH:

Since GH is a potent lipolytic hormone and an inverse relationship has been reported between GH and body weight in mice and humans, therapies aimed to activate GH activities has been suggested as a possible therapeutic target against obesity.

In this sense, a vaccine against SS, the main negative regulator of GH has been developed with interesting results in preclinical models. Specifically, SS vaccination reduces around 10% of body weight in mice fed high fat diet [65]. In line with this, a clinical study shown modest reduction of fat mass and a mild increase in lean mass in obese individuals after a long-term treatment with GH [66]. Accordingly, therapies aimed to activate GH levels are proposed to alleviate NAFLD in a context of obesity. For example, GH administration lead to a significant reduction in liver fat content in obese patients with NAFLD [67, 68]. Interestingly, currently there are two clinical trials which results are not published yet, studying the action of the GH stimulation on subjects with NAFLD (NCT02217345; NCT03375788).

Conversely, immunological or pharmacological approaches that are capable of inhibit GH signalling represent a promising approach to facilitate weight loss and improve the efficacy of obesity treatments, by possibly preventing compensatory decreases in energy expenditure during food restriction [69–71]. For example, a vaccine targeting ghrelin, a potent GH secretagogue with orexigenic activity [72], has been developed but however with mixed results. Whereas an anti-ghrelin antibodies has been shown to be effective in the induction of energy expenditure in mice and pigs [73–75], in humans no weight loss has been shown in clinical trials despite a strong anti-ghrelin immunological response [69, 76, 77].

Another line of research proposed the use of SS and its analogues for the treatment of specific obesity states associated with hyperinsulinemia. As we commented before, SS is a potent GH inhibitor but suppresses the secretion of other hormones such as insulin or glucagon [78]. Several studies have shown that SS and its analogues (octreotide and lanreotide) may limit insulin release and consequently decrease adipogenesis and weigh gain [70, 71]. Some clinical trials, both in children and adults, have recently examined the possible usefulness of the administration of SS analogues in hyperinsulinemic states [71, 79, 80]. Octreotide has been found to be effective in reducing hyperinsulinemia and body weigh in children's associated with hypothalamic obesity such as craniopharyngiomas [71, 81]. Similar results were obtained in adult obese people but in this case the effect over body weight is less effective than in children's [79, 82, 83].

Thus, seems that SS and its analogues has potentially therapeutic use against obesity by reducing insulin secretion

in children with hypothalamic obesity and in adults with hyperinsulinemic obesity.

There is currently no clear explanation for the controversial findings regarding the strategy of inhibit or activate GH signaling, but it is believed that the processes that involves metabolic regulation are highly complex and that this may sometimes lead to counterintuitive findings.

Since GH is also the primary inducer of IGF-1 expression in the liver, and since together with insulin these anabolic hormones exert potent metabolic effects, we focus on the metabolic actions of IGF-1 in the following section.

3 Insulin growth factor 1

IGF-1 is produced mainly in the liver by the action of GH [84, 85] and circulates bound to insulin growth factor binding proteins (IGFBPs), which act as transport proteins, modulate IGF-1 bioavailability, prolong its half-life, and regulate its activity in target tissues and clearance [86]. The human IGF-1 gene is located on chromosome 12q23.2, consist of 6 exons of > 84 kilobases, which, through alternative splicing from two promoters, generates multiple pre-propeptide transcripts [87]. IGF-I mediates its actions by binding to and activating the IGF1 receptor (IGF-1R), a ubiquitously expressed cell-surface tyrosine kinase receptor [88]. The IGF-1R gene consists of 21 exons of 315 kilobases and is located in chromosome 15q26.3. The IGF-1R is synthesized as a single polypeptide precursor structurally similar to the insulin receptor [89]. IGF-1 activates the IGF-1R and induces receptor autophosphorylation activating multiple signal cascades such the phosphatidylinositol 3-kinase/protein kinase B, RAS/RAF/MEK and Mitogen-Activated Protein Kinases/extracellular regulated kinase pathways [90].

3.1 Insulin growth factor-1 and its metabolic actions

IGF-1 has several metabolic effects on lipid metabolism, glucose homeostasis, and insulin sensitivity (Fig. 2). Therefore, in this section we state how the dysregulation of IGF-1 levels affects these processes and thus its implication on the most common metabolic diseases.

3.1.1 IGF-1, obesity and liver disease:

In line with the prominent role of IGF-I in lipid metabolism, this hormone has been linked to markers of metabolic syndrome, diabetes, insulin resistance, and obesity [91, 92].

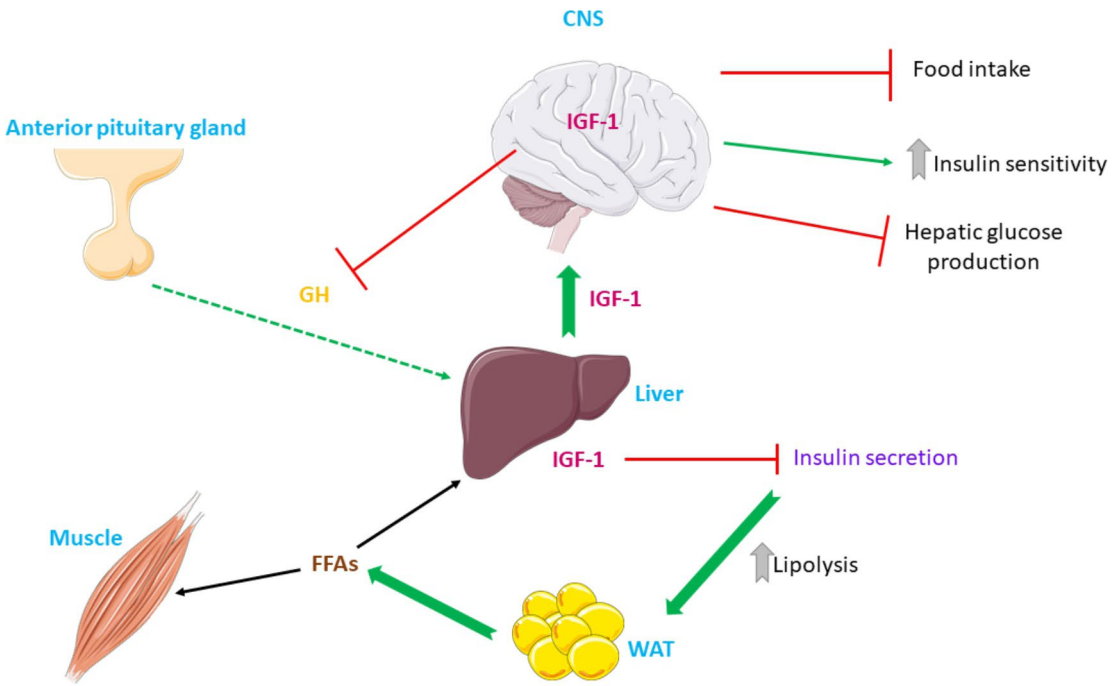

Fig. 2 Description of the metabolic actions elicited by IGF-1. IGF-1 is released mainly from the liver and improves insulin sensitivity by suppression of insulin secretion, in turn leading to augmented lipolysis in adipose tissue and promotion of NEFA use in muscle and liver. Abbrevations used: CNS: central nervous system; GH: growth hormone; IGF-1: insulin growth factor-1; FFAs: free fatty acids; WAT: white adipose tissue

Also, it is inversely correlated with body mass index [93]. Further, abnormal circulating IGF-1 levels are present in obese humans, as well as in animal models of obesity [91]; and circulating IGF-1 inversely correlates to visceral fat mass [94, 95]. In addition, another study have reported that circulating IGF-1 correlates to increased adiponectin levels and reduced prevalence of metabolic syndrome [96], while the severity of liver steatosis seems to be inversely correlated with circulating IGF-1 levels [97]. This can in part be explained by the interference on IGF-1 and insulin signalling of circulating non esterified fatty acids (NEFAs) once taken up by the liver and by their accumulation leading to hepatic steatosis.

3.1.2 IGF-1 and insulin sensitivity and glucose homeostasis

Studies in humans showed that IGF-1 administration increased lipid oxidation, energy expenditure and improves insulin resistance [98–100], and these effects are believed to be due to IGF-1 suppression of insulin secretion, in turn leading to augmented lipolysis in adipose tissue and promotion of NEFA use in muscle and liver. IGF-1 promotes fatty acid transport in muscle [99, 101, 102] and its specific inhibition in this tissue causes severe consequences, such as insulin resistance and eventual development of diabetes[101]. Consistently low circulating IGF-1 levels are also associated with reduced insulin sensitivity [103], glucose intolerance, and T2DM [103–105]. In line with this, several studies linked the action of IGF-1 and glucose homeostasis. For example, an epidemiological study revealed that patients with a polymorphism in the promoter region of the IGF-1 gene secreted 40% less IGF-1 than the control subjects [100, 106], were shorter and had increased prevalence of T2DM among the elderly [100, 107]. Moreover, another study supported the connection of IGF-1 and glucose homeostasis by showing that exogenous administration of IGF-1 enhanced insulin sensitivity in healthy adults [108, 109] and in T2DM patients [100, 110, 111]. Notably, the low levels of circulating IGF-1 are independently associated with hyperglycaemia and insulin resistance in adults [112, 113].

Consistent with human studies, mice heterozygous for genetically depleted IGF-1 develop glucose intolerance during fasting, whereas the homozygous hepatic IGF-1(-/-) mice show increased insulin resistance and glucose intolerance[114]. Further, liver-specific IGF-1 (-/-) mice developed muscle insulin resistance, showing an increase in insulin concentrations [115]. Interestingly, the glucose intolerance was ameliorated by administration of IGF-1 or the GHR antagonist pegvisomant [100, 116]. Importantly, the concomitant administration of IGF-1 and pegvisomant resulted in further enhancement of insulin sensitivity, suggesting that IGF-1, at supraphysiological doses, has important and independent effects on hepatic insulin sensitivity [100, 114]. In summary, IGF-1 enhances insulin sensitivity by suppressing insulin and GH secretion, and enhances insulin signalling indirectly by reducing NEFAs flux from the circulation to the liver and muscle. Hence, administration of IGF-1 at high doses typically results in hypoglycaemia, despite the improved downregulation of insulin concentrations in circulation [117, 118]. Since IGF-1 reduces serum GH levels by a feedback mechanism in the CNS, it may enhance insulin actions in the liver by suppressing the effects of GH on this organ [119]. Therefore, IGF-1 seems to indirectly modulate peripheral carbohydrate metabolism through suppression of GH and enhancement of insulin actions. To this, some experimental evidence suggests that some of these actions on carbohydrate metabolism are induced by the action of IGF-1 in the brain, as well.

3.2 IGF-1 action in the brain

IGF-1 and IGF-R1 are expressed together in common brain areas, suggesting paracrine or autocrine activity [120]. By crossing the blood brain barrier, IGF-related peptides may also act in the brain, and IGF-1 can be found in the cerebrospinal fluid, in the hypothalamus, and in the hippocampus. Some studies reported an association of low serum IGF-1 levels and cognitive dysfunction but also demonstrated a correlation between endocrine IGF-1 levels and other brain-related functions, including protection against cognitive and neurosensory deficits, depressive-like symptoms, and neurodegeneration [121, 122]. Furthermore, IGF-1 administration in the brain can improve insulin sensitivity in young animals and aged rats [123, 124]. Therefore, IGF-1 acts centrally to regulate insulin sensitivity and reduces hepatic glucose production in rodents. In line with these findings, additional experimental evidence supports the description of IGF-1 action in the brain. Central IGF-1 administration decreases food intake in chicks [125, 126] by increasing the levels of hypothalamic POMC and the phosphorylated form of protein kinase B [125]. Furthermore, central administration of IGF-1 decreased food intake in diabetic rats [127]. It is well known that the mechanism by which IGF-1 inhibits GH secretion in the pituitary involves the upregulation of hypothalamic SS [128]. Therefore, in the brain, IGF-1 seems to act not only to exert the negative feedback regulation of GH by its action on the pituitary but also regulates insulin resistance and food intake by its action in the hypothalamus.

3.3 Therapeutic use of IGF-1

Due to its importance in maintaining proper energy homeostasis, IGF-1 has been proposed as therapeutic agent for the treatment of different diseases. For example, IGF-1 analogues have been tested in clinical trials for the treatment of the short stature that is associated with GHR deficiency [129–131]. Furthermore, the use of rhIGF-1 (mecasermin) or an equimolar combination of IGF-1 and insulin growth factor binding protein-3 (mecasermin rinfabate) are marketed for the treatment of severe primary IGF-1 deficiency. Phase II clinical trials showed that mecasermin rinfabate enhanced insulin resistance and the glycaemic index in the type 1 diabetes mellitus and T2DM patients [131, 132]. Despite the clinical benefits, the safety of long-term administration of IGF-1 remains controversial due to several side effects, such as hypoglycaemia and loss of appetite [129, 133].

Interestingly, recent findings suggests that other members of the IGF family such as IGFBPs could be useful therapeutic targets over metabolic disorders. Both IGFBP-1 and IGFBP-2 have been positively correlated with insulin sensitivity in humans and data in animal's models implicate its direct involvement in the molecular regulation of insulin signaling and adiposity (For review see [134]).

4 Concluding remarks

In this review, we covered the metabolic actions the GH/IGF-1 axis, and its effect on energy balance. These endocrine signals that convey or are released from the liver appear not only as key metabolic factors directly implicated in obesity, T2DM and NAFLD/NASH by their action in glucose and lipid metabolism, but also as regulators of food intake and body weight through their action on the CNS. It is important to note that some authors propose the use of IGF-1 therapies only in states of IGF-1 deficits; however, other authors suggest that the problems with IGF-1 applications are based on dosing issue because most of the studies that investigate IGF-1 biology have been done with supraphysiological doses [85]. Notably growing experimental evidence describing the metabolic actions of IGFBPs could boost the research focus in therapeutic potential of IGF-1 system against insulin resistance or states associated with higher adiposity such as obesity.

On the other hand, the development of NASH models using chimeric mice may be of particular interest for assessing the efficacy and safety of new therapeutic agents involving GH-IGF-1 axis [52]. In this regard, if we taking into account that GH levels decrease with age, leading to a GH deficiency that in turn precipitates the development of NAFLD, these mice will be useful tools for investigating the role of hGH in age-dependent onset of NAFLD/NASH.

In conclusion, we highlight the activity of the hepatic GH-IGF-1 axis, as an interesting tool for the study and precise understanding of metabolic and liver diseases by its crosstalk with the brain.

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Declarations

Conflict of interest The authors declare that they have no conflicts of interest in the authorship or publication of this work.

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