Obesity and the Growth Hormone Axis

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12.1 Introduction to the growth hormone/insulin-like growth factor (GH/IGF-1) Axis

The GH/IGF-1 axis refers to the collective and coordinated actions of GH and IGF-1. Both hormones have a dramatic impact on adipose tissue (AT). GH promotes the release of stored energy by increasing lipolysis, decreasing lipogenesis, and influencing proliferation and differ-

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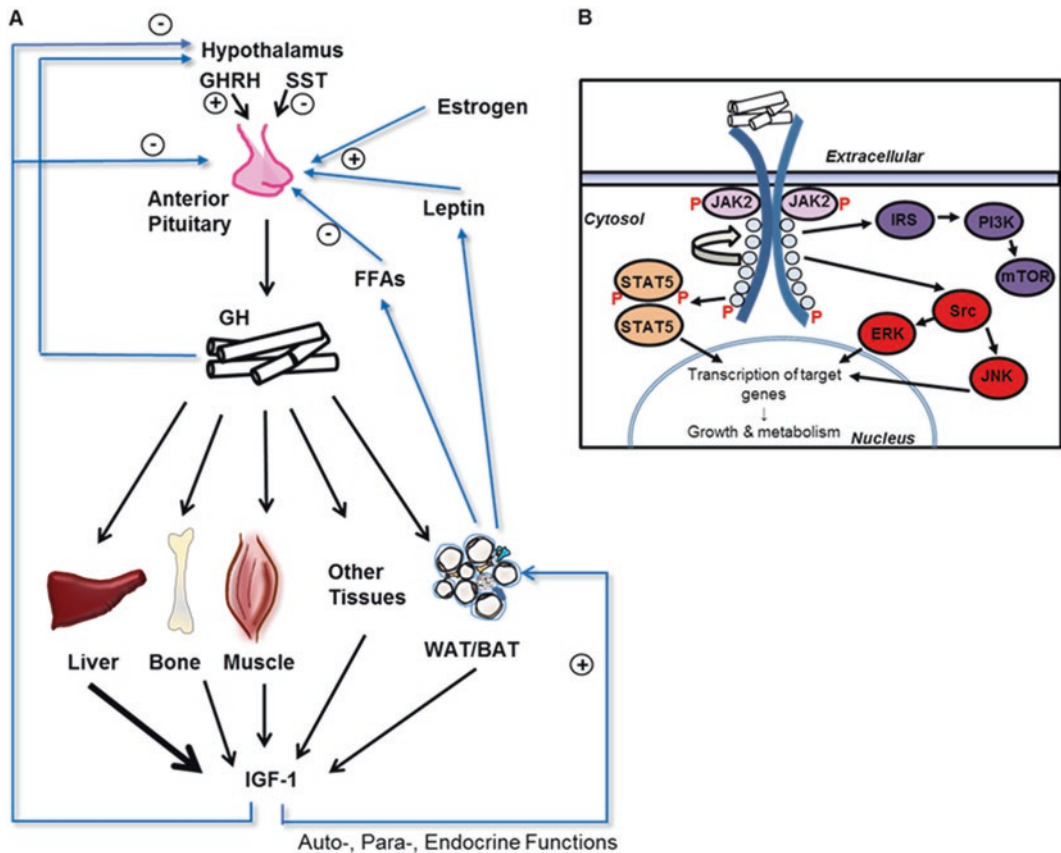e-mail: berrymad@ohio.edu

entiation of the preadipocytes (Moller and Jorgensen 2009). In contrast, IGF-1 appears to be critical for hyperplasia and lipogenesis in both white and brown AT (Boucher et al. 2016). Thus, lipid metabolism and AT mass are drastically altered via this axis.

Human GH (hGH) is a 191 amino acid peptide hormone made up of four alpha helices and two disulfide bonds. The primary form of GH is 22 kDa; however, additional isoforms have been described with different molecular weights, including 20 kDa (which is the second most prominent form), 24 kDa, and 17.5 kDa forms. The vast majority of GH is produced, stored, and secreted by specialized cells in the anterior pituitary called somatotrophs. In humans, four additional closely related genes have been described in the GH gene cluster, including *CSL*, *CSA*, *GHV*, and *CSB*; however, production of these alternate forms of GH are limited to the placenta during pregnancy in females and are thought to be important for fetal growth and development (Chellakooty et al. 2004).

Secretion of GH occurs in a pulsatile fashion. GH synthesis and release are stimulated by GH-releasing hormone (GHRH) and inhibited by somatostatin (SST), which are both produced in the hypothalamus (Fig. 12.1a). Multiple feedback loops contribute to the regulation of GH release. For example, high serum GH levels act directly on the hypothalamus to inhibit GH release by inducing SST release and inhibiting GHRH secretion (Muller 1990; Muller et al.

Fig. 12.1 (**a**) Regulation of pituitary GH. Growth hormone-releasing hormone (GHRH) and somatostatin (SST) are released from the hypothalamus and stimulate or inhibit GH secretion, respectively. The GH-GHR interaction results in production of IGF-1 by various target tissues. IGF-1 and GH act in a negative feedback manner to reduce GH secretion. GH secretion is altered by other factors such as leptin, free fatty acids (FFAs), and estrogen. (**b**) The intracellular signaling cascade of GHR in response to GH bind-ing. GH binding to the GHR induces a canonical pathway that includes GHR-JAK2-STAT5. STAT5 is phosphorylated and activated in response to GH binding and regulates gene transcription. Other signaling pathways include insulin receptor substrate (IRS) 1 and subsequent activation of mechanistic target of rapamycin (mTOR) and activation of extracellular signal-regulated kinase (ERK) and c-Jun N-terminal kinase (JNK) via Src. (Adapted with permission Berryman et al. (2015) and Kopchick and Andry (2000))

1999). Additionally, high serum IGF-1 levels act on the hypothalamus and the pituitary to decrease GH secretion (Muller 1990; Muller et al. 1999).

Once secreted, circulating GH binds to the GHR on various tissues (Fig. 12.1b). The GHR is a class 1 cytokine receptor that exists as a pre-formed homodimer (Brooks and Waters 2010). The receptor is expressed ubiquitously in tissues throughout the body, including but not limited to muscle, white and brown AT, liver, kidneys, heart, intestines, and lungs (Brown et al. 2005; Zou et al. 1997; Vikman et al. 1991). The extracellular GH-binding domain of the GHR can be cleaved by metalloproteases and/or alternatively spliced to produce a soluble GH-binding protein that is also found in circulation with ~50% of circulat-ing GH being bound to this GH-binding protein (Herrington et al. 2000). Upon GH binding to the predimerized receptor, a conformational change in the intracellular domain of GHR results in transphosphorylation and activation of associated tyrosine kinases (JAK2) (Brooks et al. 2014). As a result, tyrosines in the cytoplasmic domain of GHR are phosphorylated, which provide a docking site for signal transducer and activator of transcription 5 (STAT5) and result in the recruit-ment of additional intracellular signaling mole-cules (Brooks et al. 2014). Phosphorylation and

activation of STAT5 allows for dissociation from the GHR, dimerization and translocation to the nucleus, where it regulates gene expression (Wells 1996). While the JAK-STAT pathway appears to predominate in most cells, additional pathways, such as mechanistic target of rapamycin (mTOR), extracellular signal-regulated kinase (ERK), and c-Jun N-terminal kinase (JNK) (Brooks and Waters 2010), are also activated in response to GH binding to GHR.

As stated previously, production of IGF-1 resulting from GH-GHR signaling is an important mediator of GH action as hinted in IGF-1's previously accepted name somatomedin or "to mediate the actions of GH." While IGF-1 is produced in many tissues and functions in a paracrine and autocrine manner, the vast majority (70–90%) of IGF-1 found in the bloodstream – referred to as "endocrine" IGF-1 – comes from the liver. While the majority of this chapter will focus on GH's action, it is important to note that the tight association between GH signaling and IGF-1 production often makes it difficult to discern the effects of GH versus that of IGF-1.

12.2   Role of GH in Nutrient Metabolism

GH plays a role in a variety of pathways related to energy metabolism and storage, counterbalancing the effect of insulin. In the postprandial state, GH secretion is suppressed, and insulin levels are increased, promoting glucose uptake and adipogenesis (Moller and Jorgensen 2009; Rabinowitz et al. 1965). In contrast, under fasting conditions, GH levels increase, and insulin levels are suppressed, increasing lipolysis and hepatic glucose output. Figure 12.2 further depicts the role of GH in major metabolic tissues.

As AT is the largest energy reservoir in the body, it is not surprising that GH has a significant influence on AT. For example, administration of human GH (hGH) stimulates lipolysis when injected into healthy humans or GH deficient (GHD) patients (Beck et al. 1957; Raben and Hollenberg 1959; Ikkos et al. 1959). The striking lipolytic effect of GH is thought to be mediated, in part, through the stimulation of hormone-sensitive lipase (HSL), a critical enzyme for
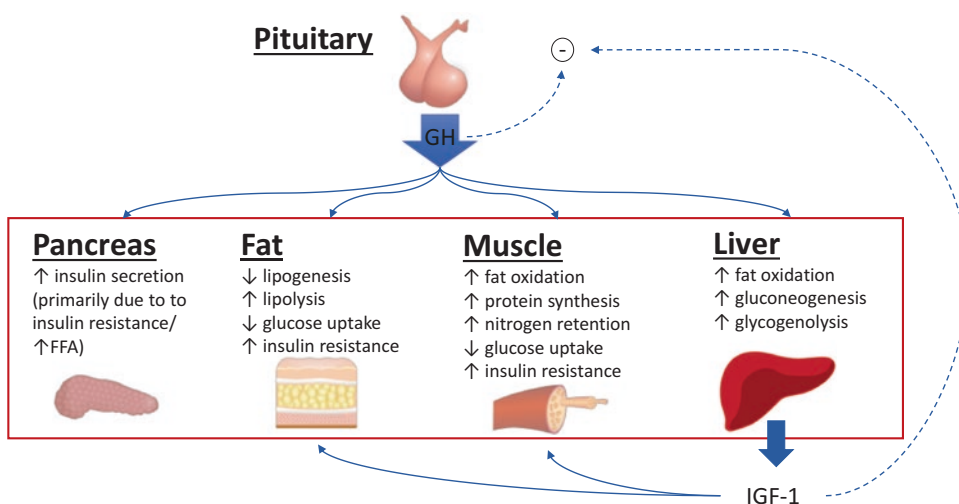

Pituitary

GH

Pancreas
↑ insulin secretion (primarily due to insulin resistance/ ↑FFA)

Fat
↓ lipogenesis
↑ lipolysis
↓ glucose uptake
↑ insulin resistance

Muscle
↑ fat oxidation
↑ protein synthesis
↑ nitrogen retention
↓ glucose uptake
↑ insulin resistance

Liver
↑ fat oxidation
↑ gluconeogenesis
↑ glycogenolysis

IGF-1

Fig. 12.2 Summary of metabolic effects of GH. GH promotes insulin secretion from the pancreas, which is primarily due to the increase in insulin resistance in other tissues as well as the increase in circulating free fatty acids. In fat, GH increases lipolysis and decreases lipogenesis, leading to increased free fatty acids in circulation and decreased adiposity. In the muscle, GH increases fat oxidation, protein synthesis, and nitrogen retention while decreasing glucose uptake. In the liver, GH increases fatty acid oxidation and glucose production while decreasing hepatic fat content. Endocrine IGF-1 is mainly produced by the liver and acts in a negative feedback loop to decrease GH secretion from the pituitary indicated by the dashed arrow. Chronic excess GH and increased IGF-1 induce insulin resistance and hyperglycemia contributing to the diabetogenic effect of GH

lipolysis (Florini et al. 1996; Franco et al. 2005; Yang et al. 2004; Yip and Goodman 1999; Richelsen et al. 2000). However, more recent evidence has implicated other molecules in GH's lipolytic action, including adipose triglyceride lipase, perilipin, and cell death-inducing DFFA-like effector A (Karastergiou et al. 2016). Because of GH's potent lipolytic effect, the total amount of AT is dramatically reduced under conditions of GH excess (Abrahamsen et al. 2004; Chihara et al. 2010). In addition to an increase in lipolysis, GH impairs lipogenesis, with many studies pointing to a decrease in lipoprotein lipase (LPL) protein activity (Richelsen et al. 2000; Murase et al. 1980; Asayama et al. 1984). Interestingly, both spontaneous and stimulated GH secretion are blunted with obesity (Rasmussen 2010), which could further exacerbate the excess in AT accumulation as will be discussed in more detail later in this chapter.

GH also impacts nutrient metabolism in the liver. GH stimulates hepatic glucose production through gluconeogenesis and glycogenolysis, but whether GH preferentially stimulates one pathway remains unclear as there is evidence to support both possibilities (Lindberg-Larsen et al. 2007; Sakharova et al. 2008; Ghanaat and Tayek 2005; Hoybye et al. 2008). In addition, GH has been shown to play a key role in hepatic lipid processing (Fan et al. 2009b; Cui et al. 2007). That is, a reduction in circulating levels of GH or defects in hepatic GH signaling results in hepatic steatosis that can be somewhat alleviated with GH treatment (Kredel and Siegmund 2014; Diniz et al. 2014; Nishizawa et al. 2012). More recently, GH has been shown to inhibit hepatic de novo lipogenesis (Cordoba-Chacon et al. 2015; Christ et al. 1999) and potentially promote ectopic fat deposition in extrahepatic tissues (Wang et al. 2007).

The skeletal muscle is another major target of GH. GH is well known to promote nitrogen retention and protein synthesis in this tissue (Jorgensen et al. 1990; Moller et al. 2009). In the fasting state, GH preserves positive nitrogen balance, maintains lean body mass, and increases resting energy expenditure (Mulligan et al. 1998). Unlike the role of GH in AT, GH upregulates LPL mRNA expression and induces FFA uptake (Khalfallah et al. 2001; Oscarsson et al. 1999) and fat oxidation in skeletal muscle (Bastie et al. 2005; Kim et al. 2009; Ehrenborg and Krook 2009). Typically, GH secretion is inhibited by an excess of macronutrients; however, some evidence suggests that certain amino acids promote GH secretion (van Vught et al. 2008). Collectively, this suggests that there is a link between GH and amino acid metabolism and that the metabolic effects of GH are largely dependent on nutritional state.

As a chapter focused on GH and obesity, it is important to emphasize that GH is well known to be a diabetogenic hormone, inducing insulin resistance, hyperinsulinemia, and hyperglycemia (Fathallah et al. 2015). For example, classic studies show that fasting and postprandial perfusion of GH through the brachial artery inhibits muscle glucose uptake in an acute manner (Rabinowitz et al. 1965; Rabinowitz and Zierler 1963; Fineberg and Merimee 1974). There appears to be multiple ways in which GH contributes to insulin resistance. There is evidence that GH may directly block insulin-signaling intermediates, such as p85α, and suppress insulin receptor substrate 1 (IRS-1)-associated phosphatidylinositol 3-kinase (PI3K) activity, both key modulators of insulin signaling (del Rincon et al. 2007). However, this evidence is mainly limited to rodent models. The increase in glucose output by the liver as well as the increased lipolysis, which causes substrate competition between lipids and glucose, also contributes to GH's diabetogenic effect. Moreover, some evidence shows that GH may affect insulin secretion by influencing β-cell function (Zhang et al. 2004; Shin-Hye and Mi-Jung 2017). In fact, prolonged exposure to elevated levels of GH may lead to pancreatic β-cell failure, resulting in type 2 diabetes (Shadid and Jensen 2003). However, a study using β-cell growth hormone receptor knockout (βGHRKO) mice on a high-fat diet shows that GH is necessary for β-cell proliferation and glucose-stimulated insulin secretion (Wu et al. 2011). Thus, it is imporant to recognize that the affect of GH on β-cell function is complex.

12.3 Clinical Conditions and Mouse Lines with Alterations in the GH Axis

Extremes in the GH/IGF-1 axis in both humans and mice have allowed researchers to uncover many of GH's actions. Examples of these extremes include (1) elevated GH action found in humans with acromegaly/gigantism and bovine GH (bGH) transgenic mice, (2) decreased GH action found in GHD in humans and GHR antagonist (GHA) mice among other mouse lines, and (3) complete GH resistance found in humans with Laron syndrome (LS) and GHR gene-disrupted (GHR-/-) mice. While a more detailed summary will be provided below, Table 12.1 summarizes the general effects associated with these clinical conditions along with a comparable mouse line of excess, reduced, and absence of GH signaling. Note that these mouse lines share many features with the clinical conditions, making them a valuable resource to do more invasive experimental measures.

12.3.1 Acromegaly and Gigantism

Acromegaly is a rare disorder characterized by chronically elevated circulating GH levels and subsequently increased production of IGF-1. In adults and children, acromegaly can arise from various etiologies. The most common cause of acromegaly is a somatotropic pituitary adenoma; yet, other causes include ectopic tumors outside the pituitary gland that produce GH or GHRH (Melmed 2009, 2011; Katznelson et al. 2014). Adults with acromegaly can experience headaches and visual impairment associated with the tumor mass and symptoms related to elevated GH action, including frontal bossing, coarse facial features, and soft tissue swelling; as such, a common diagnostic sign for acromegaly is a change in ring, shoe, or hat size (Katznelson et al. 2011; Abreu et al. 2016). In children, prior to the closure of the epiphyseal growth plate, gigantism results (Kopchick et al. 2014). Since excess GH action disrupts glucose homeostasis, individuals with acromegaly are reported to have increased fasting glucose levels, insulin resistance, and

Table 12.1 Phenotypic summary of GH clinical conditions and comparable mouse line

	Excess GH action		Reduced GH action		Absent GH action	
Variable	Acromegaly/ gigantism	bGH	GHD[a]	GHA[b]	Laron	GHR-/-
GH defect	Hypersecretion of GH	Transgenic for bovine GH	Many variations	Transgenic for GHR antagonist gene	Mutation of GHR	Disruption of *Ghr* gene
GH action	↑↑	↑↑	↓	↓	Absent	Absent
GH	↑↑	↑↑	↓	↑	↑	↑
IGF-1	↑↑	↑↑	↓	↓	↓↓	↓↓
Growth/body weight	↑↑[a]	↑↑	↓ ↔[a]	↓	↓↓	↓↓
Insulin sensitivity	↓	↓	↑	↓ ↔	↑↓ [c]	↑
Lifespan	↓	↓	↔	↔	↔	↑

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↑ increase, ↔ no change, ↓ decrease

[a]Depends on age of onset

[b]Comparable to congenital GHD

[c]Depends on Israeli or Ecuadorian cohort. Israeli cohort tends to have higher insulin levels (Laron et al. 2006)

type 2 diabetes (Abreu et al. 2016). Acromegaly results in a twofold increase in overall mortality with the most common causes of death being heart disease, such as cardiac hypertrophy and congestive heart failure (Abreu et al. 2016; Colao et al. 2004; Katznelson et al. 2011), and cancer, such as colon, breast, and thyroid cancer (Rokkas et al. 2008; Rogozinski et al. 2012; dos Santos et al. 2013; Jenkins 2006). Overall, if individuals with acromegaly do not receive treatment, their lifespan is projected to be decreased by an average of 10 years (Melmed 2009). Treatment resolves the elevated levels of GH and IGF-1, arrests tumor growth, manages the complications and pituitary function, and restores mortality rates to normal (Melmed et al. 2014). Typically to accomplish the above goals, an individual with acromegaly may undergo transsphenoidal surgical resection, radiation of the pituitary adenoma, or biochemical management through SST analogs or pegvisomant (Katznelson et al. 2014). After reduction of the tumor and suppression of GH action through surgery or medication, patients have reduced incidence of comorbidities and increased adiposity.

12.3.2 Growth Hormone Deficiency (GHD)

GHD is a disease in children and adults defined by low levels of GH and IGF-1, resulting from various abnormalities in the GH-IGF-1 axis (Mullis 2007). The pathogenesis of GHD differs between congenital and acquired deficiencies. Congenital GHD can broadly manifest from either the absence of the pituitary gland or genetic mutations in GH, GHRH, or pituitary transcription factors crucial to pituitary development (Mullis 2007). Meanwhile, acquired GHD arises from different and widely varying causes, including nonfunctioning pituitary adenoma, central nervous system (CNS) trauma, idiopathic hypopituitarism, and treatment of pituitary adenomas and CNS tumors that lead to hypopituitarism (Alatzoglou et al. 2014). The clinical presentation of GHD depends upon the age of onset. Children with congenital or acquired GHD exhibit stunted growth and increased fat mass;

they also have a higher risk of developing hyperlipidemia and dramatic hypoglycemic episodes (Smuel et al. 2015). The lack of growth tends to be more exaggerated for children with congenital GHD than children diagnosed with acquired GHD. Adults with GHD present with more generalized and nonspecific symptoms, including decreased muscle mass and energy, lower bone density, anxiety, depression, and increased adiposity along with an overall decline in quality of life (Molitch et al. 2011; Reed et al. 2013). Treatment goals for GHD also depend on the age of onset. Administration of recombinant hGH increases linear growth, reduces the risk of increased adiposity, and improves self-reported quality of life (Alatzoglou et al. 2014; Grimberg et al. 2016). However, long-term GH therapy in children has been correlated with a higher incidence of type 2 diabetes and is controversial on whether it promotes the development of malignancies or shortens lifespan (Alatzoglou et al. 2014). In adults, GH therapy reduces generalized symptoms yet increases the risk of developing type 2 diabetes. Due to these potential harmful effects of GH therapy, children and adults need to be carefully assessed and managed to ensure the best treatment outcome.

12.3.3 Laron Syndrome (LS)

GH insensitivity, more commonly known as LS, is a disorder characterized by high GH and low IGF-1 levels. Most commonly caused by an autosomal recessive mutation in the *GHR* gene, individuals with LS present similar to patients with congenital GHD with extremely stunted growth. This mutation confers the GHR protein nonfunctional; thus, the downstream effects of GH, including the production of IGF-1, are severely attenuated (Laron et al. 1968). Due to the loss of negative feedback from IGF-1, these individuals have elevated circulating GH levels (Laron et al. 1968). LS is characterized by severe growth retardation, obesity, and reduced lean body mass (Laron and Kauli 2016). The risk of developing insulin resistance and type 2 diabetes varies among the different LS cohorts in Israel, Turkey, and Ecuador. For instance, the cohorts in Israel

and Turkey have higher levels of insulin and can develop type 2 diabetes later in life (Agladioglu et al. 2013; Laron and Kauli 2016). On the other hand, a cohort of LS patients from Ecuador appear to maintain insulin sensitivity and be protected from type 2 diabetes (Guevara-Aguirre et al. 2015). To date, the reason behind these differences in cohorts is not well understood and is being currently explored. Interestingly, all cohorts of LS appear to be protected from developing cancer (Shevah and Laron 2007; Steuerman et al. 2011; Laron and Kauli 2016; Guevara-Aguirre et al. 2011). Through treatment with recombinant IGF-1 (rIGF-1), LS individuals observe a resolve in the growth discrepancy and an increase in bone mineral density; however, severe adverse reactions, including increased adiposity and insulin resistance, can accompany these benefits (Laron 2015).

12.3.4 Mouse Lines

Many different animal models exist to explore the physiological and metabolic impact of GH action. This section will concentrate on mice with alterations in GH action for the following reasons: (1) mice are anatomically, physiologically, and genetically similar to humans with fairly short gestation periods and lifespans; and (2) mouse genomes are easy to manipulate, allowing for alterations in GH action at the whole-body and tissue-specific level. While many mouse lines are available with alterations in the GH/IGF-1 axis, this chapter will describe the most well-studied lines as well as those lines most in common to the aforementioned clinical conditions.

12.3.5 Increased GH Action

Bovine GH transgenic mice Bovine GH transgenic (bGH) mice have been genetically engineered to constitutively overexpress GH (Fig. 12.3). Similar to acromegaly, bGH mice have elevated plasma levels of GH and IGF-1 (Kopchick and Laron 1999). Overall, this mouse line experiences increased lean mass and

decreased fat mass, as will be discussed more in the next section. bGH mice also have similar comorbidities as acromegaly. For instance, bGH mice have disrupted glucose homeostasis, insulin resistance, and hyperinsulinemia (Kopchick and Laron 1999; Berryman et al. 2004; Palmer et al. 2009). bGH mice also develop cardiomegaly and hepatomegaly and have marked cardiac, vascular, and kidney damage (Berryman et al. 2006; Kopchick et al. 2014; Miquet et al. 2013). Additionally, bGH mice have a greater incidence of tumors and dramatically shorter lifespans, reduced by approximately 50% compared to their littermate controls (Bartke 2003; Kopchick et al. 2014). Due to these similarities, bGH mice provide an opportunity to more invasively study the condition of acromegaly.

12.3.6 Decreased GH Action

There are multiple mouse lines with decreased GH action that mimic the clinical states associated with reduced GH action. Examples include the GHA mouse line, which has decreased GH action and similar to congenital GHD, and the GHR-/- mouse line, which do not have a GHR and are similar to LS (Fig. 12.3). In addition, there are hypopituitarism mouse lines (Ames dwarf and Snell dwarf) that lack GH as well as other pituitary-derived hormones. More recently, two separate adult-inducible lines with reduced GH action have been described that mimic acquired GHD. In addition, several tissue-specific GHR knockouts have been generated to explore the influence of GH on individual cells, tissues, and organs (List et al. 2014; Romero et al. 2010; Lu et al. 2013; Wu et al. 2011; List et al. 2013; Fan et al. 2009a, 2014; List et al. 2015; Mavalli et al. 2010). These tissue-specific lines, while helpful in elucidating the effect of GH on a particular tissue, do not replicate a clinical condition and so will not be discussed in detail in this chapter.

Mice with hypopituitarism Ames and Snell dwarf mice were among the first mice described with a genetic mutation that resulted in GHD and overall hypopituitarism. Both mouse lines exhibit dwarfism, increased adiposity, improved glucose tolerance,

Fig. 12.3 Mice with altered GH action. From left to right: a wild-type mouse, a bGH mouse with increased GH action, a GHA mouse with decreased GH action, and a GHR-/- mouse with no GH action. (Figure adapted and reused with permission Berryman et al. (2011))
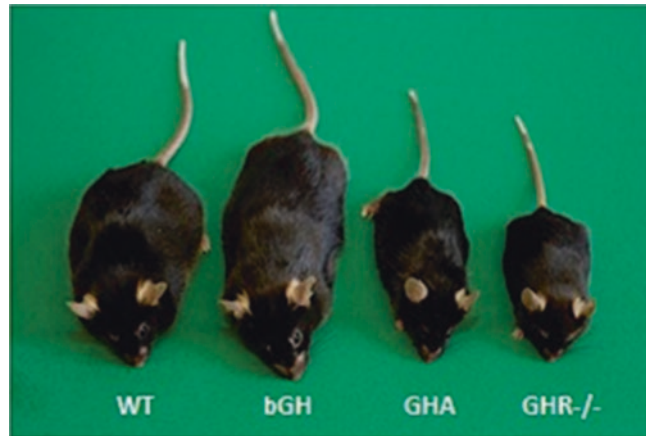
increased insulin sensitivity, and extended lifespans (Bartke & Westbrook, 2012; Hill et al. 2016). Similar to congenital GHD individuals, these mice have mutations in homeobox protein prophet of PIT1 (PROP1) for Ames mice and pituitary transcription factor (PIT1) for Snell mice that results in improper development of the pituitary gland (Bartke and Westbrook 2012; Flurkey et al. 2001; Andersen et al. 1995; Sornson et al. 1996; Junnila et al. 2013). Importantly, these dwarf lines experience deficiencies in three anterior pituitary hormones (prolactin, GH, and thyroid-stimulating hormone), making it difficult to determine the specific contribution of GH to their phenotypes (Bartke & Westbrook, 2012). Still, many of their features are shared with GHR-/- mice, suggesting that GH is critical to the observed phenotype (Bartke & Westbrook, 2012).

GHR antagonist transgenic mice GHA mice have a number of similarities with congenital GHD. GHA mice express a mutated bGH gene, in which the codon for glycine at position 119 is substituted for a larger amino acid (Chen et al. 1991). This single substitution results in the production of a protein that competes with endogenous GH for GHR binding and results in a marked reduction, but not elimination, of GH-induced intracellular signaling. GHA mice are intermediate in size between the global GHR knockout (GHR-/-) and wild-type (WT) mice (Fig. 12.3) (Kopchick et al. 2014). GHA mice have overall reduced levels of IGF-1 and lean mass but increased adiposity (Berryman et al.

2004). Yet, these mice maintain insulin sensitivity and are protected from developing type 2 diabetes and comorbidities associated with obesity, even when placed on a high-fat diet (HFD) (Yang et al. 2015), although there is evidence that their insulin sensitivity deteriorates with advancing age (Berryman et al. 2014). Strikingly, the GHA mice are the only mice that have decreased GH action and do not exhibit a significant increase in lifespan (Coschigano et al. 2003; Berryman et al. 2013).

GHR-/- mice The GHR-/- mice are analogous to LS patients (Kopchick and Laron 2011). Both are dwarf and resistant to GH action with very low IGF-1 and elevated GH levels (Zhou et al. 1997) (Fig. 12.3). GHR-/- mice have decreased lean mass, smaller organs, and increased total adiposity (Berryman et al. 2004; Berryman et al. 2010). Yet despite excess AT throughout life, these mice are also extremely insulin sensitive (Berryman et al. 2004; Lubbers et al. 2013). Interestingly, these mice are resistant to many age-associated complications compared to their littermate controls. In contrast to what is observed in bGH mice, GHR-/- mice are protected from neoplastic diseases (Ikeno et al. 2009). Furthermore, GHR-/- mice are extremely long-lived, living about a year longer than a typical mouse. This increased lifespan has been reproduced in different laboratories and under different experimental conditions, including alterations in sex, genetic background, and diet composition (Coschigano et al. 2003; Bonkowski et al. 2006; Brown-Borg et al. 2009).

Reduction of GH action in adulthood All the mouse lines reported thus far have the alteration in GH action throughout life. More recently, two mouse lines have been genetically engineered to have a decrease in GH action in adulthood; therefore, these lines more closely resemble adult-onset GHD. One of these mouse lines, the adult-onset-isolated GHD line (AOiGHD), employs the inducible Cre-Lox system and diptheria toxin to ablate somatotrophs (Luque et al. 2011). Circulating levels of GH and IGF-1 are decreased but still detectable in these mice after induction. Interestingly, even partial GH disruption, as shown in these mice, has a dramatic impact on metabolic function, resulting in improved insulin sensitivity. A second line, called aGHRKO for adult-onset GHR deletion, was developed in which the *Ghr* is temporally deleted using an ubiquitously expressed tamoxifen-inducible Cre-Lox system (Junnila et al. 2016). These mice have improved insulin sensitivity, increased adiposity, and, at least in the female mice, improved longevity (Junnila et al. 2016). However, it is important to note that there are limitations to this line as the *Ghr* gene is not disrupted in a similar fashion in all tissues, which could influence interpretation of the data generated with these mice.

12.4   Adipose Tissue and GH

Circulating GH levels have an inverse relationship with AT mass in both humans and mice. As expected and in accordance with significant changes in fat mass, GH influences adipokine secretion as well as other properties of AT. The action of GH on AT provides a unique perspective on the relationship between AT and health. That is, we typically associate excess fat mass with a decrease in insulin sensitivity and other obesity-related chronic conditions, whereas a reduced AT mass is usually considered favorable for metabolism and health. Mice with excess GH action, such as bGH mice, are lean but exhibit deleterious metabolic and lifespan consequences; conversely, mice with a reduction in GH action are obese yet lack the metabolic dysfunction

associated with obese states. These contradictory and counterintuitive phenotypes – unhealthy leanness and healthy obesity – allow us to examine not only the biological effects of GH on AT but also the properties of excess AT that contribute to overall metabolic dysfunction.

12.4.1 Body Composition

Excess GH reduces overall adiposity. For example, in individuals with acromegaly, AT mass is drastically reduced (Bengtsson et al. 1989; Moller and Jorgensen 2009; Berryman et al. 2004) while normalizing GH levels when treating acromegaly increases adiposity (Bengtsson et al. 1989; Gibney et al. 2007). Likewise, adult bGH mice are leaner than littermate controls, having notably less fat mass for most of their adult lives (Fig. 12.4) (Berryman et al. 2004). However, the longitudinal body composition data for bGH mice reveals several important observations regarding fat mass, more than can be feasibly observed with clinical populations. First, while they show resistance to midlife gains in AT, bGH mice have greater fat mass at younger ages (less than 3 months of age for males and 4 months of age in females), suggesting a role of the GH/IGF-I axis in establishing the number of adipocyte-competent cells within the tissue (Palmer et al. 2009). Second, male and female mice respond differently to excess GH, with females showing some delay and less exaggerated changes in body composition. This longitudinal study reveals the importance of both age and sex when studying the effects of GH on AT. Finally, bGH mice are also resistant to diet-induced obesity and exhibit distinct patterns of nutrient partitioning with high-fat feeding, in particular having preferential accumulation of lean tissue instead of AT (Olsson et al. 2005; Berryman et al. 2006).

Conversely, decreased GH action consistently increases adiposity. Children and adults with GHD have increased fat mass with greater truncal fat deposition (Boot et al. 1997; De Boer et al. 1992), which begins to reverse with the administration of hGH (Rodriguez-Arnao et al. 1999).

Similar to the decreased GH action in GHD adults and children, LS patients experience increased central and total adiposity (Laron & Kauli, 2016). Likewise, mice with decreased GH action have increased fat mass, although there is evidence that the trend may be age- and/or sex-dependent. For example, Ames and Snell mice have been reported to have increased adiposity (Bartke and Westbrook 2012; Hill et al. 2016). However, a cross-sectional study with Ames mice reports that while both female and male Ames mice have a higher percentage of body fat compared to WT controls at younger ages, the percentage of body fat is decreased relative to the WT controls at older ages (Heiman et al. 2003). Longitudinal body composition data are also available for GHR-/-, GHA, and aGHRKO mice; all three lines have increased fat mass throughout life, albeit the increase in AT is less dramatic for females (GHA and GHR-/- mice shown in Fig. 12.4) (Berryman et al. 2014; Berryman et al. 2010; Junnila et al. 2016). Further, when GHA and GHR-/- mice are fed a HFD, both lines are more susceptible to gaining additional fat mass when compared to WT mice and yet remain resil-ient to the detrimental effects of high-fat feeding on glucose homeostasis and insulin sensitivity (Robertson et al. 2006; Berryman et al. 2006; Yang et al. 2015).

12.4.2 Adipokines

As would be expected with such dramatic changes in adiposity, adipokine levels are altered in clinical states and mouse lines with altered GH-induced signaling. Overall, GH action is negatively correlated with leptin and adiponectin levels. For example, individuals with acromegaly have decreased levels of leptin and adiponectin, while treatment increases leptin levels (Lam et al. 2004; Silha et al. 2003; Sucunza et al. 2009; Reyes-Vidal et al. 2014). Other adipokines, such as vaspin, visfatin, and omentin, have also been shown to be increased in acromegaly and decreased upon or after treatment (Ciresi et al. 2015; Olarescu et al. 2015b). Notably, two visceral AT adipokines, vaspin and visfatin, have been proposed as biomarkers of visceral AT dysfunction with acromegaly (Ciresi et al. 2015).
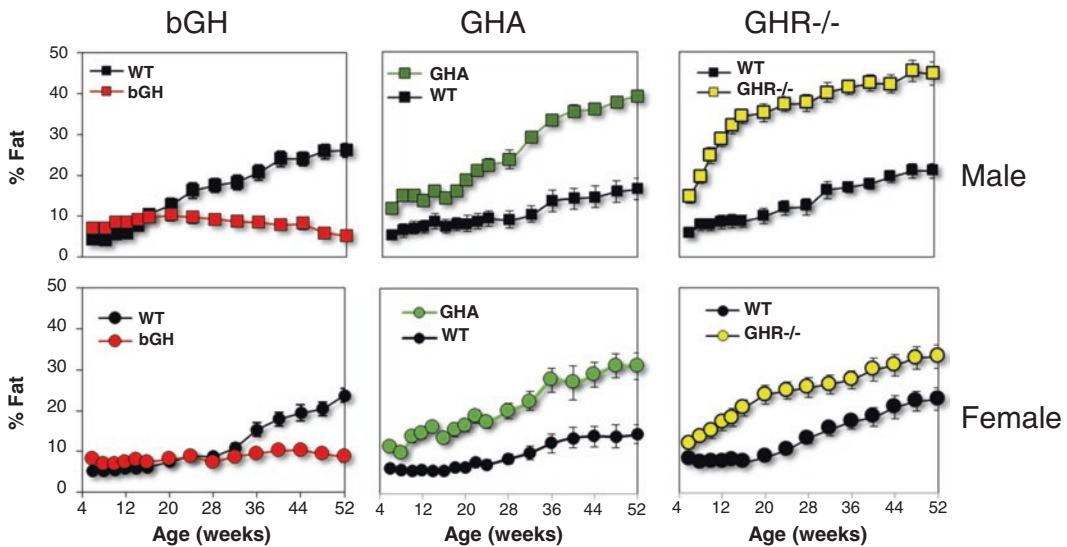

Fig. 12.4 Comparison of body fat percentage in mice with altered GH action. Male and female bGH mice have greater body fat percent than WT mice earlier in life, a trend that starts to reverse at 4 and 6 months of age, respectively (left). Fat percentage is greater in male and female GHA mice compared to controls throughout life. Male GHR-/- mice have markedly increased body fat percent compared to controls and appear to rapidly accumulate fat during the first 4 months of life. Increased percentage of fat is also observed in female GHR-/- mice compared to controls, albeit not as drastic. (Republished with permission Troike et al. (2017))

bGH mice, like the clinical correlate, also have decreased levels of leptin, adiponectin, and resistin (Lubbers et al. 2012).

While data from GHD patients varies based on age and likely etiology, adipokine levels in LS and mouse lines with reduced GH action are fairly consistent and show an overall opposite trend seen in acromegaly and bGH mice. For GHD, children before puberty have been shown to have no alterations in leptin, visfatin, resistin, and omentin levels (Ciresi et al. 2016). However, another study reports children with GHD treated with GH have increased leptin levels and reduced resistin and tumor necrosis factor-alpha (TNF-α) levels (Meazza et al. 2014). GH treatment tends to increase visfatin and decrease leptin and omentin (Ciresi et al. 2016). Children and adults with LS experience increased leptin levels; similarly,

total adiponectin and high molecular weight (HMW) adiponectin are elevated (Laron 2015). As for mouse lines with reduced GH action, Ames, Snell, GHA, GHR-/-, AOiGHD, and aGHRKO mice have either unchanged or elevated leptin levels, which is partly dependent on age, and have markedly elevated total and HMW adiponectin levels (Lubbers et al. 2012; Bartke and Westbrook 2012; Masternak et al. 2006. The exception to this observation is the AOiGHD mice, in which adiponectin levels are unchanged (Lubbers et al. 2012). Of note, when placed on a HFD, Ames mice appear to be protected from pro-inflammatory adipokines with no difference in adiponectin or leptin levels compared to Ames mice on a standard chow diet (Hill et al. 2016).

As summarized in Table 12.2, leptin and adiponectin show an interesting relationship with fat

Table 12.2 Summary of AT in mice with altered GH

Mouse line	GH signaling	% fat mass	Leptin	Adiponectin	Citations
bGH	↑	↑ early life (before 3 months) ↓ later life (after 4 to 6 months in males and females, respectively)	↓	↓	Palmer et al. (2009), Berryman et al. (2004), Wang et al. (2007)
AOiGHD	↓ in adulthood (starting at 10–12 weeks of age)	↑ (after induction)	↑	↔	Luque et al. (2011), Lubbers et al. (2013)
aGHRKO	↓ in adulthood (starting at 6 weeks of age)	↑ (after induction)	↔	↑	Junnila et al. (2016)
GHA	↓	↑ (increases dramatically with advancing age)	↑ (increases dramatically with advancing age)	↑	Berryman et al. (2004), Yakar et al. (2004), Lubbers et al. (2013), Berryman et al. (2014)
GHR-/-	Absent	↑	↔, ↑	↔,↑	Berryman et al. (2004), Berryman et al. (2006), Berryman et al. (2010), Li et al. (2003), Egecioglu et al. (2006), Lubbers et al. (2013)
Snell	↓	↑	↑	↑	Heiman et al. (2003), Wang et al. (2006), Wang et al. (2007)
Ames	↓	↑	↔, ↑	↑	(Bartke (2008), Flurkey et al. (2001), Alderman et al. (2009), Combs et al. (2003), Lubbers et al. (2013)

↑ increase, ↔ no change, ↓ decrease

mass and GH signaling. That is, adiponectin and leptin are both increased with a reduction in GH signaling and decreased with excess GH signaling. Although leptin levels are consistent with what would be expected based on fat mass, low levels of leptin rather than high levels of leptin are more commonly associated with improved insulin sensitivity, an improved metabolic profile, and increased longevity (Stenholm et al. 2011; Arai et al. 2011). Unlike leptin, adiponectin is considered a beneficial adipokine and is usually negatively associated with obesity and positively associated with insulin sensitivity and longevity (Stenholm et al. 2011; Arai et al. 2011). In these mice as well as the comparable clinical conditions, adiponectin is positively associated with fat mass. This unusual relationship has given significant attention to these adipokines and their role in promoting the GH-induced phenotype.

12.4.3 GH Alters AT in a Depot-Specific Manner

Data from both clinical studies and mice reveal that GH's effects are not uniform across all AT depots. In fact, even without considering clinical conditions of extreme GH action, visceral adiposity is a stronger indicator of 24-h endogenous GH secretion than total fat mass (Vikman et al. 1991), suggesting a close association between GH action and visceral depots in humans. Accordingly, while subcutaneous and visceral depots are decreased with acromegaly, the greatest reduction of white AT mass occurs in the visceral depot (Freda et al. 2008). In humans with GHD, GH treatment (0.013–0.026 mg/kg/day) reduces total body fat by 9.4%, with again the visceral AT being more impacted than subcutaneous AT (30% versus 13% reduction, respectively) (Bengtsson et al. 1993). In another study, after GHD adults were treated with GH, total body fat decreased with the largest decrease observed in the visceral depots as compared to subcutaneous (Johannsson et al. 1997). However, there is also clinical evidence for targeting subcutaneous depots. That is, male and female patients with LS have marked increases in subcutaneous and intra-

abdominal AT and, in particular, have a larger percentage of fat distributed in the arms (subcutaneous) when compared to control patients (Laron et al. 2006). Clearly, data from humans has demonstrated a depot-specific role of GH's impact on fat mass; yet, the ability to directly compare depots from the same clinical sample is challenging.

A more detailed understanding of the depot differences is made possible by using mouse lines, where more invasive procedures and multiple depot sampling can be made with a single animal. Overall, a reduction in GH action causes a striking and specific enlargement of the subcutaneous depot (Fig. 12.5). This significant increase in the subcutaneous depot is illustrated for GHR-/- mice in Fig. 12.5c. The trend is not as clear with an excess of GH action since depot mass appears to be similarly reduced in all AT depots; however, molecular characterization of the AT depots reveals a more significant impact in subcutaneous depots as compared to others (Benencia et al. 2014). The targeted impact of GH on subcutaneous AT is readily apparent when comparing AT histology among depots. As shown in Fig. 12.5a and b, hematoxylin- and eosin-stained tissue sections from mouse lines with extremes in GH action show dramatic alterations in morphology and adipocyte size in subcutaneous AT; yet, the epididymal tissue is fairly uniform. Many other examples in the literature support depot-specific differences at the cellular or molecular level. Although not an exhaustive list, some recent examples of depot-specific differences are provided in Table 12.3.

12.4.4 GH as a Treatment Modality for Obesity? Pros vs Cons

With the escalating rates of obesity nationally and globally, methods for obesity management are desperately needed. For almost three decades, numerous studies have attempted to evaluate the efficacy of using GH for obesity management, many of which are summarized in Table 12.4. In part, the attention given to GH is related to its ability to reduce fat mass while preserving lean
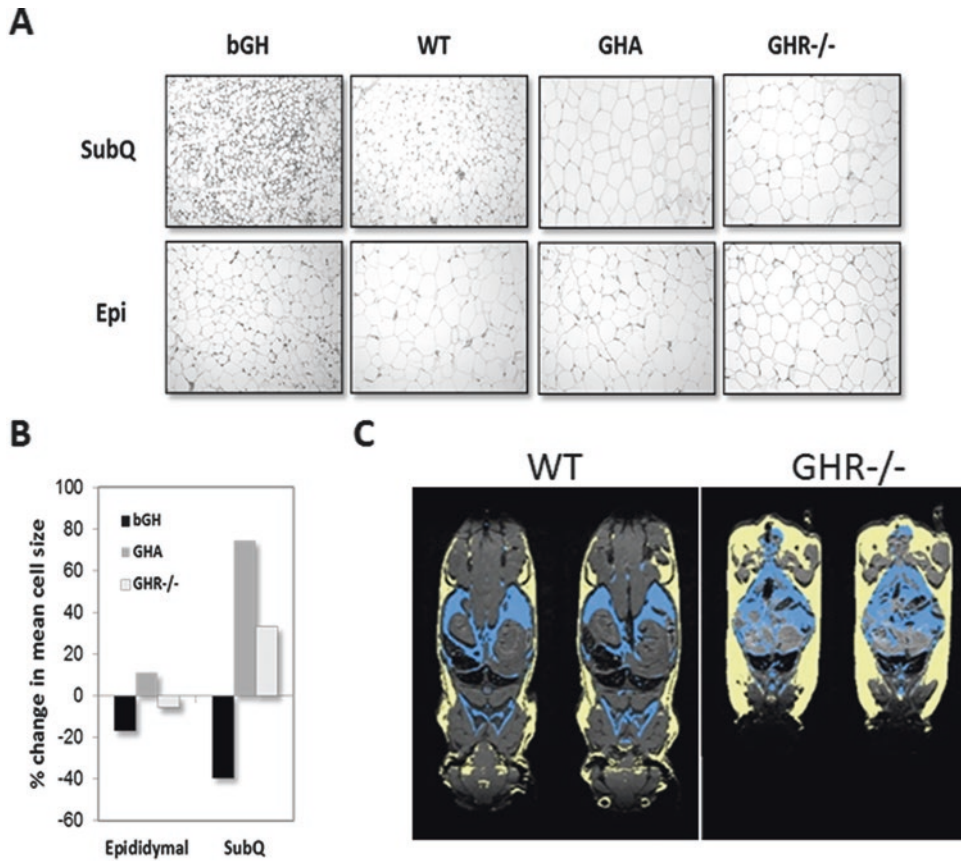
Fig. 12.5 Depot-specific differences due to extremes in GH. (**a**) Hematoxylin and eosin staining of subcutaneous (SubQ) and epididymal (Epi) AT. Tissue samples were obtained from 6-month-old GHR-/-, GHA, bGH, and control mice. (**b**) Quantification of adipocyte size from these mice. (**c**) Adiposity in GHR-/- mice. Regional body fat distribution of male WT mice (left) and male GHR-/- mice (right) using magnetic resonance imaging (MRI). The mouse is positioned with the anterior part at the bottom of the image. Subcutaneous AT is highlighted yellow and intra-abdominal blue. (Adapted with permission Berryman et al. (2011))

mass. In addition, human obesity, especially in the visceral depots, is associated with markedly suppressed spontaneous and stimulated GH secretion (Rasmussen 2010). Of note, circulating IGF-1 levels remain unaffected or only slightly lowered with obesity. Likewise, substantial weight loss has been shown to restore GH secretion patterns (Rasmussen et al. 1995). Thus, restoring GH levels appears to be a viable means to combat obesity. Overall, GH at therapeutic levels has shown a fairly consistent reduction in total and visceral AT in clinical trials (Table 12.4). Further, many of the studies that used calorie restriction showed the added benefit of attenuating the loss of lean body mass with GH treatment (Clemmons et al. 1987; Snyder et al. 1988; Snyder et al. 1990; Tagliaferri et al. 1998).

Despite the logic behind using GH therapeutically, its use is not without controversy. For example, a meta-analysis of 24 clinical studies on the use of GH therapy for obesity concludes that the effects on body composition and lipid profiles are very small and do not reduce weight sufficiently to be considered beneficial, even with very high doses (Mekala and Tritos 2008). It is important to note that there are many confounding factors in these studies that likely contribute to the different responses, including GH dose, inclusion/exclusion criteria, sample size, length of follow-up, and timing of glucose and

Table 12.3 Evidence for depot-specific differences in mice due to extremes in GH action

Reference	Model System	Research Focus	Findings
Benencia et al. (2014)	bGH mice	Immune cell infiltration in AT	↑ immune cell infiltration (macrophage, T cells) mainly in subcutaneous and mesenteric depots with little change in epididiymal AT ↑ in gene expression related to T-cell infiltration/activation in subcutaneous but not epididymal AT
Stout et al. (2014)	bGH, Snell, Ames, GHR-/-, and GH-injected mice	Cellular senescence in AT	bGH females: ↑ cellular senescence in all depots except periovarian GH-injected WT females: ↑ cellular senescence in subscapular and mesenteric depots GHR-/- and Snell females: ↓ cellular senescence in subcutaneous AT Ames: ↓ cellular senescence in paraovarian, mesenteric, and subcutaneous GHR-/-: ↓ cellular senescence all depots except mesenteric
Flint et al. (2006)	GHR-/- mice	Proliferation and differentiation of preadipocytes	Subcutaneous adipocytes proliferate, differentiate, and respond to hormones in a similar manner to controls, but perigonadal adipocytes do not
Kelder et al. (2007)	GHR-/- mice	CideA expression	↓ cell death-inducing DFF45-like effector-A (CideA) levels in subcutaneous AT but not retroperitoneal or epididymal
Lubbers et al. (2013)	bGH, GHA, GHR-/-, AoiGHD, and Ames mice	Adiponectin expression	Circulating adiponectin levels correlated strongly with subcutaneous fat mass Higher adiponectin levels in subcutaneous AT of GHR-/- mice
Stout et al. (2015)	GHR-/- mice	Depot whole-genome microarrays	Differences in gene expression related to metabolic function and inflammation among epididymal, subcutaneous, retroperitoneal AT were detected
Sackmann-Sala et al. (2013)	GHR-/- mice	Proteomic analysis of depot differences	Lower levels of Glut4 protein in subcutaneous AT of GHR-/- mice, no difference in epididymal AT Retroperitoneal depot particularly affected by GHR deletion and age
Hjortebjerg (2017)	bGH, GHR-/- mice	Expression of insulin, GH and IGF-1 receptors, and IGF-1	↑ IGF-1 RNA levels in subcutaneous, epididymal, and retroperitoneal depots in bGH mice, but ↓ in all depots in GHR-/- mice ↓ insulin receptor expression in retroperitoneal and mesenteric depots in bGH mice, but ↑ in subcutaneous, retroperitoneal, and mesenteric depots in GHR-/- mice
Olarescu et al. (2015a)	GHR-/-, bGH mice	AT-derived mesenchymal stem cell	Increased differentiation in cells isolated from subcutaneous AT vs epididymal Increased differentiation in cells isolated from subcutaneous GHR-/- than from bGH mice

insulin measurements relative to GH dose (Berryman et al. 2013). There are also adverse side effects that have been reported with GH therapy. For example, 20–40% of obese individuals that have received GH develop similar effects seen in acromegaly, including fluid reten- tion and carpal tunnel syndrome (Shadid and Jensen 2003). Of greater concern, obesity leads to an insulin-resistant state, which might be fur- ther exacerbated by the diabetogenic properties of GH. Although some studies show deteriora- tion in glucose metabolism with GH treatment

Table 12.4 Select clinical studies in which GH was used to treat obesity

Citation	Duration	Study design	GH dose	Starting BMI kg/m^2	Δ total body fat	ΔVisceral AT
Clemmons et al. (1987)	3 weeks	Open crossover + CR	0.1 mg/kg IBW	42.5% > IBW	↔	ND
Snyder et al. (1988)	10 weeks	Open + CR	0.1 mg/kg IBW	30–67% > IBW	↔	ND
Snyder et al. (1990)	5 weeks	Open crossover + CR	0.2 mg/kg IBW	30–65% > IBW	↔	ND
Skaggs and Crist (1991)	4 weeks	RPCT	0.08 mg/kg IBW	30–50	↓	ND
Richelsen et al. (1994)	5 weeks	RPCT crossover	0.03 mg/kg IBW	34.5	↓	↓
Johannsson et al. (1997)	9 months	RPCT	9.5 µg/kg	≈30	↓	↓
Tagliaferri et al. (1998)	4 weeks	RPCT + CR	0.3 mg/kg IBW	35.9	↔	ND
Kim et al. (1999)	12 weeks	RPCT + CR	8.6 µg/kg	≈29	↓	↓
Franco et al. (2005)	12 months	DB, RPCT	8 µg/kg	30	↓	↓
Bredella et al. (2012)	6 months	RPCT	Final dose 1.4 ± 0.1 mg	34.9	↓	↓

Symbols and abbreviations: ↑, increased; ↓, decreased; ↔, no difference; ND, not determined; DB, double blind; RPCT, randomized placebo-controlled trial; IBW, ideal body weight; CR, caloric restriction.

(Richelsen et al. 1994; Snyder et al. 1995, 1990; Bredella et al. 2012), many studies report improvement or no impact (Johannsson et al. 1997; Franco et al. 2005). For example, two studies that included obese individuals with diabetes show GH treatment not only reduced visceral AT mass and levels of LDL cholesterol but also improved insulin sensitivity (Nam et al. 2001; Ahn et al. 2006). Studies using diet-induced obese, diabetic mice would also suggest that high levels of GH are beneficial, improving body composition and glucose metabolism (List et al. 2009).

Another consideration is that changes in AT mass may not be the best clinical readout for GH's impact on obesity. As discussed previously in this chapter, GH causes a striking reduction in fat mass, but the quality of AT is suspect as increased cellular senescence, decreased adipogenesis, and altered immune cell infiltration occur in AT in mice exposed to excess GH. Overall, while GH has great potential for treating obesity, its cost, the concerns related to reported and suspected side effects, and the lack of larger and longer controlled trials make it unlikely that GH will be of therapeutic value for obesity in the near future.

Questions

1. What is the relationship between GH and IGF-1, and how do these hormones alter adipose tissue mass?
2. How does GH alter glucose metabolism? How would an increase or absence of GH signaling influence insulin sensitivity?
3. At least in mice, which depot appears to be most impacted by alterations in GH action?
4. How might excess GH in both mouse and man resemble a lipodystrophic state?
5. What are the pros and cons of using GH as a treatment modality for obesity?

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