INTRODUCTION

One of those lingering questions in ghrelin research concerns the apparent absence of an obvious phenotype consistent with deficient ghrelin signalling, namely the skinny dwarf, which is both horizontally and vertically challenged and likely has a host of metabolic and behavioural impairments (Figure 1). Subsequent to the discovery of ghrelin in 1999,1 its receptor in 1996 2 and the first synthetic ligands in the early 1980s 3-5 (and please take note of the somewhat unusual reverse timeline here), we have learned a very great deal about the important and diverse roles of the ghrelin signalling system in normal physiology, with its effects on food intake, growth hormone (GH) secretion and glucose homeostasis. Because these processes can be considered as essential to life, the question arises as to why mouse models of depleted ghrelin signalling are not all skinny dwarfs with a host of behavioural and metabolic problems. Here, we provide a systematic detailed review of the phenotype of mice with deficient ghrelin signalling to help better understand the relevance and importance of the brain ghrelin signalling system, with a particular emphasis on those questions that remain unanswered.

Abstract

Based on studies delivering ghrelin or ghrelin receptor agonists, we have learned a great deal about the importance of the brain ghrelin signalling system for a wide range of physiological processes that include feeding behaviours, growth hormone secretion and glucose homeostasis. Because these processes can be considered as essential to life, the question arises as to why mouse models of depleted ghrelin signalling are not all skinny dwarfs with a host of behavioural and metabolic problems. Here, we provide a systematic detailed review of the phenotype of mice with deficient ghrelin signalling to help better understand the relevance and importance of the brain ghrelin signalling system, with a particular emphasis on those questions that remain unanswered.

Keywords

appetite, arcuate nucleus, body growth, bone density, food intake, ghrelin, ghrelin knockout, GHSR, GHSR knockout, Ghsr-IRES-cre, GOAT knockout, growth hormone, hunger
deficient ghrelin signalling. The review is inspired by a somewhat serendipitous finding on our part: homozygous Ghsr-IRESCre mice have a skinny dwarf phenotype that appears to reflect the absence of a functional GHSR.9

2 | PREDICTED PHENOTYPE: DWARF

To set the stage, linking the ghrelin signalling system to GH and potentially also growth, it is relevant to mention that the ghrelin field dates back to the early 1980s, a time when pioneers such as Frank Momany and Cy Bowers were searching for the elusive endogenous GH-releasing hormone (GHRH), and had identified a group of short peptide GH secretagogues (GHS) derived from met-enkephalin as potential candidates.3,4 When GHRH was finally identified,10,11 it turned out to be entirely different in structure to these GHS, exerting its GH-releasing effects via a completely different receptor signalling system. Therapeutic interest in GHS grew increasingly, however, with the realisation that they greatly amplify the pulsatile pattern of GH release,12,13 acting by a direct pituitary4 and hypothalamic action.14,15 Pulsatility in the GH secretory profile is of paramount importance for stimulating growth, both in childhood and during puberty16-18 and GH has a dose-dependent effect on growth.19 Admittedly, it remains somewhat of an enigma why nature has invested so much effort into ensuring GH is released in a pulsatile manner to optimise growth, involving a dual neuroendocrine regulatory network provided by GHRH and inhibitory somatostatin, as well as a complex feedback regulation by GH and its effector, insulin-like growth factor 1, that has the capacity to be amplified when the ghrelin signalling system is activated. Nonetheless, GHS (including orally bioavailable non-peptide compounds) offered new possibilities not only to promote growth,20-22 but also to rejuvenate the GH-axis in the elderly, with benefits on lean and bone mass.5 Although GHS never made it to the clinic, they have provided much insight regarding the physiological roles of the ghrelin signalling system, namely with reference to the hypothalamic-GH-growth axis, even before ghrelin was discovered.

Ghrelin release is episodic, although it is not at all obvious that it operates as an amplifier of the pulsatile pattern of GH secretion. In humans, ghrelin is released from the empty stomach before meals and in association with hunger and, curiously, also reaches quite high levels in the middle of the night.23,24 Likewise, in laboratory rodents, ghrelin release is greatest in situations of energy deficit such as fasting.25 In line with this, there are data indicating that an important physiological role of ghrelin is to help prevent hypoglycaemia, with effects exerted, at least in part, by enhancing GH release during fasting or periods of food restriction.26 Thus, the pattern of ghrelin secretion links better to the diabetogenic effects of GH (when food is scarce) rather than for its growth-promoting effects (which are suppressed in times of famine).

However, it remains unclear whether the ghrelin signalling system has a role in linear growth. There have been three genetic studies in humans in which GHSR mutations have been associated with short stature,27-29 with five mutations linked to loss of constitutive activity of GHSR.27,29 Another population-based study (in 3 UK cohorts) found no association between common variations in GHSR and body height in adults or children.30 In animal models of deficient ghrelin signalling (and there are a very great number to choose from) (Table 1), extracting growth data is somewhat of a challenge because (i) body length is not usually measured directly, with body weight as a surrogate (and note that rodents continue to grow throughout their life); (ii) the studies are more focused on potential anti-obesity effects rather than body growth; and (iii) any growth-linked differences are often lacking/subtle and/or sexually dimorphic. Some loss-of-function models did not detect a relevant phenotype,31,32 whereas others found a modest effect (Table 1), for which it is unclear if they are lean or growth retarded, or some combination of the two (ie, skinny dwarfs). Mice deficient in preproghrelin (ghrl−−), although having a reduced GH pulse amplitude, have only a mild suppression of growth.33 In another study, female (but not male) GHSR-null (ghsr−−) mice on a chow diet started to differ in body weight at 12 weeks of age, weighing 11.7% less (and with 35.6% reduced body fat) than wild-types by week 19. However, any effect on body length in these mice was barely detectable.34 Another study reported that ghsr−− mice (GHSR-KO here) have a lower body weight from 4 months of age.35 It is only recently, however, that the full growth and growth hormone

**FIGURE 1** Hunting for the skinny dwarfs in ghrelin research
release pattern phenotype has been characterised in both males and females. It was found that there was a reduction in linear growth in ghsr−/− mice correlated with a reduced pituitary GH content. Curiously, pulsatile GH secretion was decreased in adult but not adolescent ghsr−/− female mice. In male ghsr−/− mice, pulsatile GH release was only diminished during adolescence and did not correlate with linear growth. In a previous study, we noted that homozygous Ghsr-ires-Cre male mice (that lack GHSR expression and are unresponsive to ghrelin) are lighter (by approximately 10%) in body weight than heterozygous or wild-type mice already at postnatal day (PND) 12, persisting into adulthood. Not only were the homozygotes shorter in length (determined at PND65), dual-energy X-ray absorptiometry scans revealed that they had a decreased bone area and a lower bone mineral content. Although we did not have the possibility to follow their GH secretory pattern, GH levels during fasting were reduced in the homozygous (and also heterozygous) Ghsr-ires-Cre mice, despite having higher circulating ghrelin levels.

3 PREDICTED PHENOTYPE: SKINNY

Growth hormone is lipolytic. In the late 1990s, our laboratory obtained funding for a project based on the idea that GHS treatment, by engaging the GH axis, should reduce body fat and hence body weight. Sometimes it is good to be wrong (or perhaps naïve). We found that chronically daily GHS-injected mice increased their body weight and body fat content, clearly via a GH-independent mechanism. Although it may be beneficial to mobilise stored fat upon fasting or when food is unavailable, it is also important to replenish these stores. Indeed, one of the first things we learn about ghrelin is that it stimulates food intake, acting as an orexigenic hunger hormone. There are thousands of articles backing these claims, although it is important to point out that the actual role for this hunger hormone may be to initiate meals or to organise food intake into meals, rather than to cause over-eating per se.

There is no doubt whatsoever that acute peripheral ghrelin injection is orexigenic, as first described by Wren and colleagues in 2000. In this particular study, the orexigenic effect of ghrelin was only detected at 1 hour after peripheral injection but not at later time points, raising the question of whether its orexigenic effects are rather short-lived. This is unlikely, however, because later studies reported that cumulative food intake was elevated after a single i.p. ghrelin injection at the 2-, 3- and 4-hour time points (at a dose of 1 or 10 nmol) and at various time points between 30 min and 5 hours (at a dose of approximately 1 nmol). We have also observed a heighten feeding response at >2 hours after a single i.p. ghrelin (approximately 100 μg) injection to rats returned to their home cage after a behavioural task during which access to their regular chow was denied. Collectively, these data suggest that, in situations where food is available, ghrelin administered by the i.p. route rapidly increases food intake to a level at which satiation can be reached but that the overall time window for the orexigenic action of ghrelin could be much longer if food is scarce or not immediately available. This profile of action, taken together with data showing that the circulating levels of ghrelin are highest preprandially in humans, strongly supports a physiological role for ghrelin in hunger and meal initiation.

Perhaps, because ghrelin is orexigenic, it is assumed to be “obesity-promoting”. The evidence suggests, however, that obese individuals are not hyperghrelinemic, with the notable exception being Prader-Willi patients, for whom elevated ghrelin may contribute to their obesity. Paradoxically, dietary obesity appears to be associated with impaired ghrelin signalling. Daily peripheral injections of ghrelin or GHS to mice can cause an increase in body fat and weight gain, although the mechanism may relate more to a decrease in fat utilisation rather than an increased in food intake. Indeed, the actual amount of food eaten by rats at 1 hour after a single ghrelin injection may appear to be a large increase (ie 3.5-4.5 fold) but this is actually a small increase in the amount of food eaten (from 0.35 g to around 1.2-1.6 g) and insufficient to impact on 24-hour food intake (which is around 18-20 g). Ghrelin injection studies such as these are normally performed during the light phase when rodents are inactive and have a low level of spontaneous eating and when endogenous circulating ghrelin levels are assumed to be lowest. One reason why the feeding response to peripheral ghrelin is minimal during the light phase could be that this corresponds to a time when the action of ghrelin is opposed by the high circulating levels of liver-enriched antimicrobial peptide 2 (LEAP2), a recently discovered endogenous GHSR antagonist, for which circulating levels are determined by metabolic status.

The central ghrelin signalling system is powerfully orexigenic. Ghrelin is able to drive a feeding response when delivered to most brain areas where GHSR is located (for localisation of GHSR in rats and mice, see Zigman et al). This includes not only areas essential for energy homeostasis in the hypothalamus and brainstem, but also areas involved in cognition, memory and emotional reactivity (hippocampus, amygdala), as well as areas involved in reward (nucleus accumbens and tegmental areas). Indeed, by engaging these pathways, the effects of ghrelin on feeding extend beyond food intake to include food choice, binge-like eating, food anticipation, food reward, food motivation and food intake during stress exposure, and may even convey the negative valence signal of hunger.

With all of these reported effects of ghrelin, it can be asked why mice with deficient ghrelin signalling are not skinny and anorectic. Even if some studies in models of deficient GHSR signalling have found body weight to be unaffected, many others have reported the opposite. This skinny phenotype was especially noticed at older ages or when challenged with a high-fat diet (HFD) early in life or an activity-based anorexia (ABA) protocol. However, daily food intake in these models was generally unaffected with the exception of HFD and ABA studies and a GHSR-mutant model that lacks GHSR constitutive activity, as well as a ghrelin-induced feeding response and GH release.
### TABLE 1  Studies using rodent models with genetic alterations in the ghrelin signalling system, grouped by model (from large scale to specific alterations) and in chronological order

| Model                  | GH release | Growth | IGF-1 | Glucose                                                                 | Food intake                                                                 |
|------------------------|------------|--------|-------|-------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| Ghrelin-KO mice        | –          | Normal | Normal | Normal glucose (data not shown)                                        | Normal at 8-24 weeks (♂ and ♀)                                             |
|                        |            |        |       | Normal serum insulin in fed and fasted                                 | Normal change after 24-h fast (♂ and ♀)                                     |
|                        |            |        |       | Normal change after 24-h fast (♂ and ♀)                               | Intact i.p. ghrelin-induced response (♂ and ♀)                               |
|                        |            |        |       | Normal change when fed high-fat and high-protein diets for 10 weeks   |                                                                             |
|                        |            |        |       | Normal fat % in 8-week old                                             |                                                                             |
|                        |            |        |       | Normal fat % after 10 weeks on high-fat and high-protein diets         |                                                                             |
|                        |            |        |       | Normal BMD in 8-week old                                               |                                                                             |
|                        |            |        |       | Normal serum leptin in fed and fasted                                   |                                                                             |
|                        |            |        |       | Fertile, normal litter size and composition                             |                                                                             |
|                        |            |        |       | Extensive evaluation of organs revealed no difference                  |                                                                             |
| Ghrelin-KO mice        | ↑ Pituitary GH mRNA on HFD ↑ liver GHR mRNA on HFD | Normal length at 8 weeks (♂) | Normal serum level Trend ↑ liver mRNA | ↓ Serum glucose and insulin | Normal 24-h and circadian pattern on chow diet (♂) Slightly ↑ after 24-h fast (♂) |
|                        |            |        |       | Normal at 0-20 weeks (♂ and ♀)                                          |                                                                             |
|                        |            |        |       | Normal gain on HFD (♂ and ♀)                                            |                                                                             |
|                        |            |        |       | Normal lean and fat mass on chow diet (♂)                               |                                                                             |
|                        |            |        |       | Trend ↑ lean mass and ↓ fat mass on HFD (♂ and ♀)                        |                                                                             |
|                        |            |        |       | Normal BMR, RQ, serum TG, cholesterol and non-esterified FA on chow diet | Normal expression of hypothalamic neuropeptides (♂)                         |
|                        |            |        |       | Normal litter composition                                               |                                                                             |
| Ghrelin-KO mice        | –          |       | –     | ↑ Glucose-induced insulin release                                      |                                                                             |
|                        |            |        |       | ↓ glucose, ↑ insulin in GTT, normal blood glucose in ITT                |                                                                             |
|                        |            |        |       | ↓ HFD-induced blood glucose, ↑ HFD-induced blood insulin (also in GTT)  |                                                                             |
| Ghrelin-KO mice        | –          |       | –     | –                                                                       |                                                                             |
|                        |            |        |       | Normal fed and fasted blood glucose and plasma insulin and C-peptide, ↓ GTT-induced blood glucose, ↑ GTT-induced plasma insulin, ↑ peripheral insulin sensitivity | Normal                                                                           |
| Ghrelin-KO mice        | –          |       | –     | –                                                                       | Normal F1 and feeding patterns                                               |
|                        |            |        |       | Normal on chow and HFD                                                   |                                                                             |
|                        |            |        |       | ↓ Blood glucose on 50% CR                                                 |                                                                             |
| Ghrelin-KO mice        | –          |       | –     | –                                                                       |                                                                             |
|                        |            |        |       | –                                                                       |                                                                             |
TABLE 1

Studies using rodent models with genetic alterations in the ghrelin signalling system, grouped by model (from large scale to specific alterations) and in chronological order

| Model     | GH release | Growth I | G I F - 1 | Glucose | Food intake | Body weight | Adiposity | Other                                                                 | Notes                                                                 | Reference          |
|-----------|------------|----------|-----------|---------|------------|-------------|-----------|-----------------------------------------------------------------------|----------------------------------------------------------------------|--------------------|
| Ghrelin- KO mice | Normal | Normal | Normal | Normal blood glucose (data not shown) | Normal serum insulin in fed and fasted | Normal at 8-24 weeks (♂ and ♀) | Normal fat % in 8-wk old (♂ and ♀) | Normal BMD in 8-week old (♂ and ♀) | Normal serum leptin in fed and fasted (♀) | Fertile, normal litter size and composition Extensive evaluation of organs revealed no difference | Sun et al 200331    |
|           |           |          |          |         |            |             | Normal at 0-20 weeks (♂ and ♀) | Normal lean and fat mass on chow diet (♂) | Normal BMR, RQ, serum TG, cholesterol and non-esterified FA on chow diet, ↓ RQ on HFD (♂) | Normal litter composition | Wortley et al 200432 |
|           | ↓ On HFD (♂, not in ♀) | ↓ Fat mass and serum leptin on HFD | Normal at 0-20 weeks (♂ and ♀) | ↑ Pituitary GH mRNA on HFD ↑ liver GHR mRNA on HFD | ↑ PTT in feeding after repeated fast | ↑ Glucose-	induced insulin release ↓ glucose, ↑ insulin in GTT, normal blood glucose in ITT | ◄ HFD-induced blood glucose, ↑ HFD-induced blood insulin (also in GTT) | Normal RQ, ↑ EE and LA on HFD↓ serum TG, cholesterol and ALT/ AST | ↓ Only (shown) | Wortley et al 200582 |
|           |           |          |          |         |            |             | ↓ Number of hippocampal dendritic spines, rescued by ghrelin injection Impaired memory in spatial-dependent novel object recognition | Normal ghrelin-induced ↑ in DA turnover in NAcc | d only? | Abizaid et al 200683 |
|           |           |          |          |         |            |             | ↓ RQ in dark period only, only in young mice ↑ HP in young but not old mice Mostly normal GE | Normal ghrelin-induced ↑ in DA turnover in NAcc | d only | De Smet et al 200684 |
|           |           |          |          |         |            |             | d only | Normal core T°, EE and ↓ RQ only on chow | Normal core T°, EE and ↓ RQ only on chow | d only | Sun et al 200684 |
|           |           |          |          |         |            |             | Normal at 4-12 weeks | Normal adaptation to scheduled-feeding Normal feeding memory in a food search test | Normal at 4-12 weeks | d only | Sato et al 200887 |
|           |           |          |          |         |            |             | Normal on chow and HFD | Normal core T°, EE and ↓ RQ only on chow | Normal core T°, EE and ↓ RQ only on chow | d only | Sun et al 200870 |
|           |           |          |          |         |            |             |          | ↑ Toxin-induced loss of SN TH cells and reduction of striatal dopamine | Study of ghrelin protective effects on SN TH cells | d only? | Andrews et al 200988 |

(Continues)
| Model          | GH release | Growth | IGF-1 | Glucose | Food intake                      |
|---------------|------------|--------|-------|---------|----------------------------------|
| Ghrelin-KO mice | –          | –      | –     | –       | Normal on ad libitum feeding     |
| Ghrelin-KO mice | –          | –      | –     | –       | Normal in younger and older mice |
| Ghrelin-KO mice | –          | –      | –     | –       | Normal in younger and older mice |
| Ghrelin-KO mice | ↓ Response on day 9 of CR | –      | –     | ↓ Blood glucose on day 4 of CR |
| Ghrelin-KO mice | –          | –      | –     | –       |                                   |
| Ghrelin-KO mice | –          | –      | –     | –       |                                   |
| Ghrelin-KO mice | –          | –      | –     | –       |                                   |
| Ghrelin-KO mice | Blunted ↓ pituitary content with age ↓ pulsatility and MPB, but normal basal secretion and peak numbers and normal GHRH-induced release in young mice | Trend ↓ length Blunted ↓ with age | – | – | – |
| Body weight                        | Adiposity         | Other                                                                 | Notes         | Reference                      |
|-----------------------------------|-------------------|----------------------------------------------------------------------|---------------|--------------------------------|
|                                   | –                 | Normal basal body T° Cold and fasting-induced thermoregulatory and sleep deficit | $\varnothing$ only | Szentirmai et al. 2009$^{39}$ |
|                                   | –                 | Normal exploratory behaviour Blunted acute and attenuated repeated cocaine-induced ↑ LA ↑ ghrelin-induced ↑ striatal dopamine content | $\varnothing$ only | Abizaid et al. 2011$^{30}$ |
| Normal on ad libitum feeding      | –                 | Slightly delayed FAA 40% CR scheduled feeding $\varnothing$ only? |               | Gunapala et al. 2011$^{91}$ |
| Normal in younger and older mice  | Normal fat lean mass in younger and older mice | LA normal in younger and older mice | $\varnothing$ only | Ma et al. 2011$^{72}$ |
|                                   | –                 | ↓ LH orexin cells $\varnothing$ only |               | Lamont et al. 2012$^{22}$ |
|                                   | –                 | No plasma AG and DAG detected | Same CR protocol as in$^{26}$ $\varnothing$ only | Li et al. 2012$^{26}$ |
|                                   | –                 | ↑ basal time in open arms but abolished ARS-induced ↑ open arm entries in EPM, ↑ basal but ↓ ARS-induced time in centre of OF, ↓ basal but normal ARS-induced grooming in novel environment, normal basal but ↓ ARS-induced time in light arena in light-dark box, ↑ ARS-induced Fos response in PVN and ↑ basal and ARS-induced PVN CRH cells, impaired ACTH and CORT response to ARS, ↑ basal EW Fos/urocortin1 cells but blunted ARS-induced ↑ EW fos/urocortin1 cells | $\varnothing$ only | Spencer et al. 2012$^{93}$ |
|                                   | –                 | ↓ CPP for ethanol, ↓ ethanol-induced LA, ↓ ethanol intake and preference but normal saccharin and quinine intake and preference in two bottle choice test | $\varnothing$ only? | Bahi et al. 2013$^{36}$ |
|                                   | –                 | ↓ Neuronal proliferation in dentate gyrus of hippocampus (no effect on glial cell proliferation) ↓ alternation rates in Y-maze and ↓ memory of familiar objects | $\varnothing$ only | Li et al. 2013$^{35}$ |
| Normal                            | –                 | ↑ Hypothalamic GHRH, SRIH and AgRP, but not NPY and POMC expression in young mice Change in hypothalamic NPY, AgRP and POMC expression in old mice Normal GHSR expression Normal GHRH and SRIH hypothalamic content | $\varnothing$ only | Hassouna et al. 2014$^{33}$ |

(Continues)
| Model                  | GH release | Growth | IGF-1              | Glucose                                      | Food intake                                      |
|------------------------|------------|--------|--------------------|----------------------------------------------|-------------------------------------------------|
| Ghrelin-KO mice        | –          | –      | ↓ Blood IGF-1      | –                                            | ↓ in young mice Normal ghrelin-induced ↑         |
| Ghrelin-KO mice        | –          | –      | –                 | Normal blood glucose during ITT and GTT on HFCS and 10% sucrose diets ↑ plasma insulin during GTT on HFCS diet, normal on 10% sucrose diet | Normal on HFCS, 10% sucrose and chow diets       |
| Ghrelin-KO mice        | –          | Normal | –                 | –                                            | Normal fast-induced response                     |
| Ghrelin-KO mice        | –          | –      | –                 | –                                            | ↓ in young mice only                             |
| Ghrelin-KO mice        | –          | –      | Normal            | Normal hyper- insulinemia on HFD              | Normal ↑ on HFD ↓ Stomach ghrelin expression, ↓ plasma AG and DAG and normal insulin Inducible ghrelin ablation | McFarlane et al 2014 |
| Ghrelin-KO in ob/ob mice | –          | –      | –                 | ↓ Fed and fastest blood glucose, ↑ fed plasma insulin, ↑ fastest plasma C-peptide, ↓ GTT-induced blood glucose, ↑ GTT-induced plasma insulin vs ob/ob | Same as ob/ob                                    |
| Ghrelin-KO Snord116del mice | –          | –      | Same as Snord116-del mice | Trend ↓ (♀, not in ♂) |                                                 |
| Ghrelin-DTR mice       | –          | –      | –                 | Normal hyper-insulinemia on HFD ↓ fasting blood glucose on 60% CR | Normal FI and normal ghrelin-induced response   |
| Body weight | Adiposity | Other | Notes | Reference |
|-------------|-----------|-------|-------|-----------|
| Normal in young mice, ↓ in old mice | Normal lean mass, partially preserved leanness in old mice | ↑ Endurance in young mice, partially prevented ↓ grip strength and endurance in old mice | ♂ only | Guillory et al 2017<sup>76</sup> |
| Normal ghrelin-induced ↑ | Partially pre-vented ↑ fat mass in old mice | | | |
| ↑ on HFCS diet but normal on 10% sucrose or chow diets | ↑ on HFCS diet only Normal lean mass | ↓ Activity in dark phase on HFCS diet, ↑ on 10% sucrose diet, ↓ EE on HFCS, no change on 10% sucrose diet, ↓ RER on 10% sucrose diet only | ♂ only | Ma et al 2017<sup>77</sup> |
| Normal | – | Impaired muscle regeneration and satellite cells self-renewal after cardiotoxin-induced injury | ♂ only | Angelino et al 2018<sup>78</sup> |
| Normal in young mice but ↓ in old mice | – | Trend ↓ liver mass in old mice, ↓ liver TG content and fat droplets in old mice | ♂ only | Guillory et al 2018<sup>79</sup> |
| ↓ % weight gain (♂, not in ♀) Normal (♂ and ♀) | – | ↑ Muscle performance in young and old mice, ↓ anxiety behaviour in old mice, ↓ muscular atrophy marker expression in young and old mice, protection against muscle mass loss during ageing, trend ↓ serum pro-inflammatory markers and trend ↑ serum anti-inflammatory markers | ♂ and ♀ | Rodriguez et al 2018<sup>80</sup> |
| Normal BMI | – | ↑ UCP2 expression in pancreas vs ob/ob | ♂ only | Agosti et al 2020<sup>81</sup> |
| – | – | Undetectable plasma AG, normal plasma epinephrine and norepinephrine and ↓ plasma CORT during clamp | ♂ only | Shankar et al 2020<sup>82</sup> |
| Same as ob/ob | Same as ob/ob | Same T° regulation problem, ↓ UCP2 expression in pancreas vs ob/ob | ♂ only | Sun et al 2006<sup>83</sup> |
| Same as Snord116del mice | Same as Snord116del mice | – | ♂ and ♀ | Rodriguez et al 2018<sup>84</sup> |
| Normal ↑ on HFD | Normal ↑ on HFD | ↓ Stomach ghrelin expression, ↓ plasma AG and DAG and normal insulin | Inducible ghrelin ablation | McFarlane et al 2014<sup>85</sup> |
TABLE 1 (Continued)

| Model                  | GH release | Growth | IGF-1               | Glucose                        | Food intake                                                                 |
|------------------------|------------|--------|---------------------|--------------------------------|-----------------------------------------------------------------------------|
| GHSR-KO mice           | Blunted ghrelin- and synthetic agonist-induced GH release, normal GHRH-induced GH release (♂) | –      | ↓ Serum IGF-1 (♀ and ♂) | Normal serum insulin in fed and fasted (♀) | Blunted response to i.p. ghrelin (♀) Normal at 10-24 weeks (♀ and ♂) Normal fasting-induced change (♀ and ♂) |
| GHSR-KO mice           | –          | –      | –                   | –                              | Normal feeding after one fast, but blunted ↑ in feeding after repeated fast |
| GHSR-KO mice           | –          | ↓ length on 60% HFD (♀) | –                              | ↓ Fasted blood glucose, plasma insulin, HOMA-IR and %Hb_{A1c} (♀ and ♂) | ↓ FI and feeding efficiency on 60% HFD (♀ and ♂) |
| GHSR-KO mice           | –          | –      | –                   | ↓ Fasted blood glucose and plasma insulin on chow only | ↓ blood glucose on 50% CR Normal response to fasting and refeeding |
| GHSR-KO mice           | –          | –      | –                   | Normal STZ-induced hyperglycaemia | ↓ STZ-induced hyperphagia |
| GHSR-KO mice           | –          | –      | –                   | –                              | Normal |
| GHSR-KO mice           | –          | –      | –                   | –                              | – |
| GHSR-KO mice           | –          | –      | –                   | –                              | – |
| GHSR-KO mice           | –          | –      | –                   | –                              | ↓ Intake of peanut butter on choice diet with chow and peanut butter (♀) |
| GHSR-KO mice           | –          | –      | –                   | –                              | Blunted stress-induced decrease in FI and CE |
| GHSR-KO mice           | –          | –      | –                   | –                              | – |
| GHSR-KO mice           | –          | –      | –                   | ↓ Glucose during ITT in old mice, ↓ insulin during GTT in young mice, ↓ glucose during GTT in old mice, ↑ insulin sensitivity in young and old mice | Normal in old mice |
| Body weight                     | Adiposity                        | Other                                                                 | Notes                  | Reference          |
|--------------------------------|----------------------------------|----------------------------------------------------------------------|------------------------|--------------------|
| Normal 0-21 postnatal days     | Normal fat % (♂ and ♀)           | Normal serum ghrelin and leptin in fed and fasted ♀                  | ♀ only♀               | Sun et al 2004<sup>73</sup> |
| Modest ↓ at 16-24 weeks         |                                  | Normal BMD and BMC (♂ and ♀)                                        |                       |                    |
| Normal fasting-induced change   |                                  | Normal muscle weight                                                |                       |                    |
|                                 |                                  | ▼ on 60% HFD (♂ and ♀)                                              | ▼ GH release (normal GHRH-GH release, agonist-induced and synthetic ♂) |                    |
|                                 | ▼ Whole body lipid (♂ and ♀)      | ▼ lipid content of feces                                            | ▼ liver weight, ▼ development of hepatic steatosis (♂), ▼ total cholesterol, ▼ glucagon on 60% HFD, ▼ metabolic flexibility on chow diet and HFD (♂ and ♀) | Longo et al 2008<sup>74</sup> |
|                                 | ↑ triglyceride secretion rate (♂) | ↑ RQ especially on HFD (♂ and ♀)                                   |                       |                    |
|                                 |                                  | Normal response to fasting and refeeding                            | ▼ FI and feeding       |                    |
|                                 |                                  | Normal core T°, EE and RQ on both diets                             | ▼ only♀               | Sun et al 2008<sup>70</sup> |
| Normal STZ-induced response     | Normal                           | Normal plasma total ghrelin and gastric emptying before and after STZ | STZ-induced diabetes model ▼ only♀ | Verhulst et al 2008<sup>103</sup> |
|                                 |                                  | Normal hypothalamic ghrelin mRNA expression after STZ               |                       |                    |
|                                 |                                  | ▼ STZ-induced hypothalamic AgRP and NPY mRNA expression             |                       |                    |
| Normal                          |                                  | Failed to adapt to feeding schedule                                 | ▼ only♀               | Blum et al 2009<sup>62</sup> |
|                                 |                                  | ▼ Fos expression in DMH, PVN and LH in response to schedule         |                       |                    |
|                                 |                                  | 4 hour Feeding schedule during light phase                          |                       |                    |
|                                 |                                  | ▼ on chow and HFD                                                   | Abolished alcohol-induced ↑ LA, ↑ NAcc dopamine release and CPP | Jerlhag et al 2009<sup>104</sup> |
|                                 |                                  | Normal basal body T°                                               | ▼ only♀               |                    |
|                                 |                                  | No cold and fasting-induced deficit                                |                       | Szentirmai et al 2009<sup>109</sup> |
| Normal on choice diet with      |                                  | Reduced peanut butter-induced ↑ in accumbal dopamine (♂)           | ▼                     | Egecioglu et al 2010<sup>55</sup> |
| chow and peanut butter (♀)      |                                  | ▼                              |                       |                    |
| Blunted stress-induced decrease | ▼ Relative to BW                 | Normal stress-induced ↑ plasma CORT and AG, ↑ Arc serotonin levels | Combined stressor paradigm ▼ only♀ | Patterson et al 2010<sup>105</sup> |
|                                 |                                 | ↑ stress-induced, ↑ PFC NA metabolite                              |                       |                    |
|                                 |                                 | Blunted stress-induced ↑ DA metabolite                              |                       |                    |
|                                 |                                 | Blunted CPP for palatable food on 50% CR                           | ▼ only♀               | Disse et al 2011<sup>106</sup> |
| ▼ at 4-22 months                |                                  | ▼ Fat mass and fasted serum leptin and ↑ lean mass at 18 months     |                       | Lin et al 2011<sup>113</sup> |
|                                 |                                 | ▼ adipocytes size in old mice, ▼ glucose and lipid uptake gene expression, ▼ lipogenesis |                       |                    |
|                                 |                                 | ▼ Fasted TG, LDL and VLDL                                           |                       |                    |
|                                 |                                 | Normal HDL                                                          |                       |                    |
|                                 |                                 | ▼ 18-hour fasted plasma FFA                                         |                       |                    |
|                                 |                                 | Normal LA, ↑ O<sub>2</sub> consumption, EE, RMR, RQ in light and dark, metabolic flexibility in old mice |                       |                    |
|                                 |                                 |                       | ▼ only♀               |                    |

(Continues)
| Model                  | GH release | Growth | IGF-1 | Glucose | Food intake                                      |
|------------------------|------------|--------|-------|---------|-------------------------------------------------|
| GHSR-KO mice           | –          | –      | –     | –       | Normal in younger and older mice                |
| GHSR-KO mice           | –          | –      | –     | –       | ↓ Fasting blood glucose on LFD, ↓ fasting plasma insulin on HFD, normal glucose-induced plasma insulin first phase, but ↓ second phase and ↑ GIR during HGC on HFD, ↑ GIR and glucose disposal but ↓ liver glucose production during HIC on LFD and HFD, ↑ glucose uptake in WAT, BAT, muscle and cerebral cortex during HIC on HFD, ↓ plasma glucose during PTT on HFD |
| GHSR-KO mice           | –          | –      | –     | –       | ↓ on ABA model                                   |
| GHSR-KO mice           | –          | –      | –     | –       | Normal rapamycin-induced plasma insulin         |
| GHSR-KO mice           | –          | –      | –     | –       | Blunted rapamycin-induced stimulation of FI on chow |
| GHSR-KO mice           | –          | –      | –     | –       | Blunted CSDS-induced ↑ blood glucose and plasma insulin |
| GHSR-KO mice           | –          | –      | –     | –       | Normal                                          |
| GHSR-KO mice           | –          | –      | –     | –       |                                                |
| Body weight | Adiposity | Other | Notes | Reference |
|-------------|-----------|-------|-------|-----------|
| Normal in younger mice but ↓ in older mice | ↓ Fat mass and ↑ lean mass in older mice only ↑ UCP1 expression in BAT | LA normal in younger and older mice ↑ EE and RMR in older mice only ↓ cholesterol and TG in older mice | ♀ only | Ma et al 2011<sup>72</sup> |
| ↓ Fasting BW on LFD but not on HFD | - | ↓ Liver UCP2 mRNA expression on HFD, normal BAT UCP1 mRNA expression | ♀ only? | Qi et al 2011<sup>78</sup> |
| ↓ on ABA model | - | Reduced FAA | ABA model ♀ only | Verhagen et al 2011<sup>54</sup> |
| - | - | ↓ VTA, NAcc shell and LH Fos and ↓ LH Fos/orexin double labelling in anticipation of scheduled meal | ♀ only | Lamont et al 2012<sup>92</sup> |
| - | - | Blunted rapamycin-induced alteration in glucose metabolism on chow and ↓ rapamycin-induced derangement of glucose metabolism and insulin sensitivity on HFD Normal rapamycin-induced ↑ plasma AG on chow | Rapamycin: inhibitor of mTOR path-way important for ghrelin production and secretion | Xu et al 2012<sup>107</sup> |
| - | - | ↓ WAT proinflammatory cytokines expression on HFCS diet, ↓ ATM on chow, ↓ proinflam-matory ATM on both chow and HFCS diet, ↓ liver lipid accumulation and steatosis on HFCS diet | ♀ only | Ma et al 2013<sup>108</sup> |
| Blunted CSDS-induced weight gain | ↓ BAT and subcuta-neous WAT after CSDS, ablished CSDS-induced ↑ WAT, BAT, adipocyte size, plasma leptin in aged mice | Normal CSDS-induced ↑ plasma CORT but abolished CSDS-induced ↑ plasma AG and RER, abolished CSDS-induced ↑ plasma CORT, IL-6 and mediobasal hypothalamus NPY and AgRP expression in aged mice | ♀ only | Patterson et al 2013<sup>60</sup> |
| Normal | - | ↑ Daily activity and delay to adapt in constant light but normal in constant dark conditions, normal circadian period but ↑ daily activity on light-dark schedule, earlier activity peak on feeding schedule and constant light and ↓ activity and delay in FAA on feeding schedule and constant dark | ♀ only? | Lamont et al 2014<sup>109</sup> |
| ↓ BW on HFD | ↓ Hepatic lipid and TG and ↓ plasma TG on HFD, blunted ghrelin-induced ↑ lipid accumulation in cultured hepatocytes | - | ♀ only | Li et al 2014<sup>110</sup> |
| Model                      | GH release | Growth | IGF-1 | Glucose                                                                 | Food intake                                                                 |
|----------------------------|------------|--------|-------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| GHSR-KO mice               | –          | –      | –     | ↑ BAT insulin-R and insulin-R substrate 1 expression in middle-aged and old mice | Normal at any age                                                           |
| GHSR-KO mice               | –          | –      | –     | –                                                                         | –                                                                          |
| GHSR-KO mice               | –          | –      | –     | –                                                                         | –                                                                          |
| GHSR-KO mice               | –          | –      | –     | ↓ HFD intake on intermittent access to HFD but normal on daily access. ↓ % calories eaten from HFD and ↑ % from chow on both intermittent and daily access | –                                                                          |
| GHSR-KO mice               | –          | –      | –     | Improved GTT-induced glucose response on HFD                              | –                                                                          |
| GHSR-KO mice               | –          | –      | –     | Normal CORT-induced fasting blood glucose but better glucose clearance in GTT | Normal CORT-induced ↑ FI but ↑ feeding efficiency                           |
| GHSR-KO mice               | –          | –      | –     | –                                                                         | –                                                                          |
| GHSR-KO mice               | –          | –      | –     | –                                                                         | –                                                                          |
| GHSR-KO in ob/ob mice      | –          | –      | –     | Worsened hyperglycaemia, ↓ plasma insulin, trend ↓ plasma glucagon, ↑ glucose and ↓ in response to GTT, normal ITT-induced glucose vs ob/ob mice | Same as ob/ob mice                                                         |
| GHSR-KO rats               | –          | –      | –     | –                                                                         | –                                                                          |

TABLE 1 (Continued)
| Model | GH release | Growth IGF - 1 | Glucose | Food intake | Body weight | Adiposity | Other | Notes | Reference |
|-------|-------------|----------------|---------|-------------|-------------|-----------|-------|-------|-----------|
| GHSR-KO mice | – | – | | | ↑ BAT/BW in young mice but normal at later ages and ↑ BAT UCP1 expression in middle-aged and old mice | ↑ EE in middle-aged and old mice, normal PA at any age, ↑ BAT thermogenic signalling in old mice | ↓ | only | Lin et al 2014\(^{111}\) |
| | – | – | | Abolished preference for ♀, ↑ latency for sexual interaction with a ♀, ↓ mounting behaviour | | | | only | Egecioglu et al 2016\(^{112}\) |
| ↓ at the end of the experiment | – | Blunted HFD-induced ↑ Nacc shell Fos expression | Binge-like feeding (2 hour HFD access in addition to ad lib chow) | | | | | only | King et al 2016\(^{113}\) |
| Blunted HFD-induced ↑ Epididymal fat on HFD | ↓ Epididymal fat on HFD | ↓ Inflammatory adipokines and ↑ anti-inflammatory adipokine in epididymal fat on HFD, ↓ macrophage infiltration and adipose inflammation and ↑ macrophage anti-inflammatory polarisation on HFD | | | | | | only | Yuan et al 2018\(^{114}\) |
| ↑ CORT-induced ↑ BW | Trend ↓ Fat mass but normal CORT adipogenic effect, ↑ CORT-induced ↑ plasma leptin, normal CORT-induced ↑ liver adiposity, steatosis and inflammation | ↓ CORT-induced PFC UCP2 expression | | | | | | only | Hay et al 2019\(^{115}\) |
| Normal | – | Normal fear acquisition, fear extinction, LA, time spent in centre of OF and time spent in the open arms of EPM, ↓ saccharin preference | | | | | | only | Pierre et al 2019\(^{116}\) |
| ↓ in adulthood (♂ and ♀) | Normal fat mass and plasma leptin | ↓ Arc GHRH and NPY expression (♂, not in ♀), ↓ triceps surae weight, ↑ AG (♂ and ♀), ↓ Arc NPY and GHRH expression (♂, not in ♀) | | | | | | only | Labarthe et al 2021\(^{116}\) |
| – | – | ↑ Latency to approach and ↓ investigation of novel ♀ and ↑ social vigilance behaviours Normal motivation for palatable food, normal behaviour in OF | | | | | | only | Park et al 2021\(^{117}\) |
| Same as ob/ob mice | Same body composition and lipid profile as ob/ob mice | Same plasma TG, cholesterol, HDL, LDL and FAA and same LA and EE as ob/ob mice, lower RER vs ob/ob mice ↑ Whole pancreas UCP2 expression | | | | | | only | Ma et al 2012\(^{118}\) |
| – | – | Normal plasma AG ↓ hippocampus dentate gyrus neurogenesis and number and density of sPnnes in young mice, normal performance in water maze test and radial arm maze | | | | | | only | Cahill et al 2014\(^{119}\) |

(Continues)
| Model                  | GH release         | Growth          | IGF-1         | Glucose                      | Food intake                                      |
|------------------------|--------------------|-----------------|---------------|------------------------------|--------------------------------------------------|
| GHSR-KO rats           | –                  | –               | –             | –                            | –                                                |
| GHSR-KO rats           | Abolished ghrelin-induced GH release | –               | –             | Normal blood glucose         | ↓ FI Abolished ghrelin-induced response |
| GHSR-null mice         | –                  | No or modest ↓  | Normal serum level | ↓ blood glucose on chow diet (g) | Blunted response to i.c.v ghrelin (♀) ↓ FI, feed efficiency, BECG and GEE on HFD |
| GHSR-null mice         | –                  | –               | –             | –                            | No ghrelin-induced response
No CSDS-induced ↑ in feeding |
| GHSR-null mice         | –                  | –               | –             | –                            | –                                                |
| GHSR-null mice         | –                  | –               | –             | –                            | ↓ Fasting blood glucose ↓ HFD intake, but normal chow intake during conditioning sessions Blunted response to s.c. ghrelin |
| GHSR-null mice         | –                  | –               | –             | Blunted ghrelin-induced ↑ plasma glucagon and glucose, ↓ fasting plasma glucagon and glucose | –                                                |
| GHSR-null mice         | –                  | –               | –             | –                            | Normal consumption of HFD "dessert"               |
| GHSR-null mice         | –                  | –               | –             | –                            | Normal leptin-induced ↓ on chow Normal leptin-resistance on HFD Normal leptin-induced ↓ after overnight fast |
| GHSR-null mice         | –                  | –               | –             | –                            | Respond equally to CS+ and CS−                    |
| GHSR-null mice         | –                  | –               | –             | –                            | –                                                |
| GHSR-null mice         | –                  | –               | –             | –                            | ↓ Fast-induced refeeding                           |
| GHSR-null mice         | –                  | –               | Normal        | Normal                       | –                                                |
| GHSR-null mice         | –                  | –               | –             | Normal                       | Normal                                           |
| Body weight | Adiposity | Other | Notes | Reference |
|-------------|-----------|-------|-------|-----------|
| ↓ | ↑ % BAT, normal gonadal fat mass | Operant responding for alcohol self-administration, normal microbial diversity | ♂ only? | Zallar et al 2019¹²⁰ |
| ↓ on HFD | ↓ on HFD but normal serum leptin, normal serum leptin on chow diet | Ghrerlin-induced Arc Fos expression ↓ RQ and LA | ♂ and ♀ | Zigman et al 2005⁵⁴ |
| No change | - | - | ♂ only | Lutter et al 2008⁶³ |
| - | - | ↑ Toxin-induced loss of SN TH cells | Study of ghrelin protective effects on SN TH cells ♂ only? | Andrews et al 2009⁸⁸ |
| ↓ BW gain during study | - | CSDS-induced social isolation Normal plasma AG and DAG, ↓ CORT after CSDS ↓ CPP for HFD after CSDS | CPP for HFD after CSDS exposure ♂ only | Chuang et al 2011¹²² |
| - | - | Normal fasting plasma AG and DAG | ♂ only | Chuang et al 2011¹²³ |
| - | - | Normal fasting ↑ AG Normal fast-induced breakpoint responding Blunted AG-induced breakpoint increase | Operant responding for HFD ♂ only | Davis et al 2012¹²⁴ |
| Normal leptin-induced ↓ on chow | - | Normal fasting-induced ↑ plasma AG | ♂ only | Perello et al 2012¹²⁵ |
| Normal | - | Normal Fos response to CS+ and CS− in amygdala | Cue-potentiated feeding ♂ only? | Walker et al 2012⁶⁵ |
| - | - | ↑ Anxiety (♀) | rAAV vector-mediated overexpression | Jensen et al 2016¹²⁶ |
| Normal fast-induced response | - | ↓ Fast-induced NPY and Fos expression in the Arc | ♂ only | Fernandez et al 2018⁹⁹ |
| Slight ↓ (♂, not in ♀) Slight ↓ % weight gain (♂ and ♀) | - | - | ♂ and ♀ | Rodríguez et al 2018⁶⁹ |
| Normal | Normal | Normal survival and plasma AG | ♂ only | Mani et al 2020¹²⁷ |

(Continues)
| Model | GH release | Growth | IGF-1 | Glucose | Food intake |
|-------|------------|--------|-------|---------|-------------|
| GHSR-null mice | – | – | – | Normal baseline and chronic CORT-induced ↑ glucose clearance during GTT, normal plasma insulin | Normal baseline and normal chronic CORT-induced ↑ |
| GHSR-null Snord116del mice | – | – | – | Same as Snord116del mice | – |
| GHSR- and CB1R- double null mice | – | – | – | Normal | Normal |
| Ghsr- IRES-Cre mice | – | ↓ Length in old mice | Normal | Normal glucose homeostasis and insulin sensitivity | Normal FI and meal pattern |
| GHSR-A203E mutant mice | Blunted ghrelin-induced ↑ plasma GH (♀) | Normal body and femur length in younger mice, ↓ body and femur length in older mice (♂) | ↓ plasma IGF-1 | ↓ blood glucose on 60% CR (♀) | ↑ FI on chow (♂ and ♀) ↑ FI/BW (♀, not in ♀) ↓ feed efficiency (♂, not in ♀) Blunted ghrelin-induced response (♀) |
| Ghsr-IRESCre mice | ↓ Serum GH in Het and trend ↓ in Hom | ↓ body length in Hom | ↓ serum IGF-1 in Hom | ↓ Fasting blood glucose and serum insulin in Hom and Het | Normal in adulthood Blunted ghrelin-induced response in Hom |
| GHSR-Q343X mutant rats | – | – | – | – | ↓ Feeding response to fasting and ghrelin injection |
| GHSR-Q343X mutant rats | – | – | – | – | Blunted ghrelin-induced response |
| GHSR-Q343X mutant rats | Ghrelin-induced response from a lower ghrelin dose and lower threshold of desensitisation (♂), normal CR-induced plasma GH (♀) | Normal nose-to-anus length (♀ and ♂) | – | ↑ HOMA-IR (♀) ↑ oral glucose-induced glycaemia but normal insulin (♀) Normal CR-induced glycaemia (♂) Normal GHSR agonist-induced response, dose-response curve shifted leftward - enhanced GHSR sensitivity (♀) Normal when adjusting for BW (♂ and ♀) |
| GHSR-Q343X mutant rats | Blunted ghrelin-induced response | – | – | Normal blood glucose during GTT and normal fasting serum insulin on HFD | Normal acute fast-induced rebound feeding, but ↓ response over 24 hours ↓ intake/BW on HFD ↓ palatable food intake |
| GHSR-Q343X mutant rats | – | – | – | – | – |
| Body weight | Adiposity | Other | Notes | Reference |
|-------------|-----------|-------|-------|-----------|
| ↑ baseline and normal chronic CORT-induced BW gain | Normal chronic CORT-induced ↑ fat/BW and ↑ WAT and BAT, normal plasma leptin | Normal baseline oestrous cycle length and normal chronic CORT-induced ↑ Normal plasma AG and LEAP-2 Blunted CORT-induced ↓ centre time in OF | ♂ only | Silver et al 2021^{128} |
| Slight ↓ % weight gain (♀, not in ♂) | ↓ (♀, not in ♂) | – | ♂ and ♀ | Rodríguez et al 2018^{69} |
| Same as CB1R-null mice | Same as CB1R-null mice | Trend ↓ survival Normal plasma AG | ♂ only | Mani et al 2020^{127} |
| ↓ | ↓ Fat mass, normal lean mass | ↑ EE and body T° ↓ blood cholesterol | On chow diet ♂ only? | Pfluger et al 2008^{68} |
| Normal BW and ↓ % weight gain in younger mice ↓ BW in older mice (♀) | Normal fat and lean mass on 60% CR (♀) | Blunted ghrelin-induced ↑ RER (♀) A203E corresponds to human GHSR-A204E mutation ♂ and ♀ | Torz et al 2020^{73} |
| ↓ in Hom from PND 12 Blunted ghrelin-induced ↑ in Hom ↓ fasting BW in Hom | ↓ Fat mass in Hom | ↓ Arc Ghsr expression in Het, none in Arc, VTA and IPBN of Hom Blunted ghrelin-induced Fos response in Arc of Hom ↑ serum AG in Hom ↓ bone area and BMC in Hom Wt, Het and Hom, ♂ only | Peris-Sampedro et al 2021^{9} |
| – | – | Blunted ghrelin-induced ↑ interdigestive motility in stomach or duodenum Normal plasma AG Premature stop codon at C-terminus ♂ only | Bülbül et al 2011^{129} |
| – | – | Blunted cocaine locomotor sensitisation ♂ only | Clifford et al 2012^{130} |
| Normal at 4 weeks, but ↑ at 3 months (♀ and ♂) ↓ CR-induced BW loss (♀) | ↑ Fat mass and plasma leptin (♀ only) but normal lean mass (♂ and ♀) | Normal AG (♂) Attenuated CR-induced ↑ plasma AG and DAG (♂) ♂ and ♀ | Chebani et al 2016^{131} |
| Normal gain on HFD | Normal WAT and BAT weight and Trend ↓ fasting serum leptin on HFD | Normal fasting serum PYY_{3-36} and AG, ↑ Arc NPY, trend ↑ Arc AgRP, normal Arc ObRb and POMC on HFD, ↓ LA, ↓ FAA ♂ only | MacKay et al 2016^{132} |
| – | – | ↑ Latency to approach ♀ for the first time, ↓ anticipatory behaviour to ♀ presentation Similar consummatory sex behaviours ♂ only | Hyland et al 2018^{123} |

(Continues)
| Model | GH release | Growth | IGF-1 | Glucose | Food intake |
|-------|------------|--------|-------|---------|-------------|
| GHSR-Q343X mutant rats | – | – | – | Better glycaemia maintenance on CR | Normal FI and meal pattern on chow, normal FI on CR Normal sucrose preference and consumption in two bottle test |
| GHSR re-expression in the hindbrain of GHSR-null mice | – | – | – | Rescued fasting hypoglycaemia | Blunted ghrelin-induced response |
| GHSR re-expression in the VTA of GHSR-null mice | – | – | – | – | ↑ in response to new environment Normal after habituation |
| GHSR re-expression in the VTA of GHSR-null mice | – | – | – | – | – |
| GHSR expressed solely in TH neurones (mice) | – | – | – | ↓ Fasting blood glucose | Partially restored response to s.c. ghrelin |
| GHSR re-expression in the Arc AgRP cells of GHSR-null mice | – | – | – | Normal basal blood glucose Normalised fasting plasma glucose and glucagon Normal fasting plasma insulin Rescued blood glucose during 60% CR (♂) | Normal Normal fasting-induced refeeding Partially restored ghrelin-induced response |
| aP2 expressing tissue-specific GHSR-KO mice (WAT, BAT, neurones, macrophages, bone marrow) | Abolished ghrelin-induced GH release | ↑ Insulin sensitivity during ITT in young but not old ♂ ↑ glucose clearance during GTT in young and old ♂, normal plasma insulin during GTT in young but ↓ in old ♂ ↑ Insulin-induced WAT glucose uptake in old ♂ | ↑ in response to novel agonist-induced ↑ LA and HP, normal RMR, ↑ LA and FAA Normal RMR |
| Adipose tissue-specific GHSR-KO mice | – | – | – | Normal GTT and ITT profiles on chow, Improved glucose tolerance in GTT and insulin sensitivity in ITT on HFD | Normal on chow and HFD |
| Neuronal GHSR-KO mice | – | Normal | Normal | ↓ fasting insulin on chow and HFD ↓ fasting blood glucose only on HFD ↓ ITT-induced blood glucose ↓ GTT-induced glucose and insulin | Blunted response to ghrelin, Normal fast-induced refeeding on chow, ↑ on HFD Normal daily FI on HFD, slight ↓ on chow |
| Body weight | Adiposity | Other | Notes | Reference |
|-------------|-----------|-------|-------|-----------|
| ↑ BW at 12 weeks and normal fasting-insulined BW loss and regain after refeeding | Normal relative to BW at 12 weeks | Normal response to novel environment, to amphetamine and anorexigenic response to DA receptor D2 agonist, ↑ GHSR agonist-induced ↑ LA | ↓ and ♀ | Marion et al 2020134 |
| Better BW maintenance on CR |  | Faster performance in operant conditioning for sucrose (♀), normal LA and FAA Normal RMR and EE but ↑ RER only in light phase, normal blood AG and DAG on ad lib but ↓ fasting-induced ↑ AG and DAG |  |  |
|  |  | Abolished ghrelin-induced Arc Fos response in Arc, PVN and AP |  | Scott et al 2012135 |
| Normal | Normal fat and lean mass | ↑ RER and oxygen consumption ↑ cocaine-induced hyperactivity |  | Skov et al 2017136 |
|  |  | ↓ Latency to approach but normal investigation of a novel ♂, normal motivation for palatable food and normal behaviour in OF |  | Park et al 2021137 |
|  |  | Restored ghrelin- and CSDS-induced CPP for HFD Normal social interaction after CSDS | CPP for HFD after CSDS exposure | Chuang et al 2011138 |
| Normal | Normal | Restored ghrelin-induced Arc Fos response ↑ fasting gluconeogenesis gene expression in liver (♀) |  | Wang et al 2014139 |
| Normal in young ♂ but ↓ in young ♀ ↓ BW in old ♂ | Normal fat and lean mass in young ♂ but ↓ fat mass in young ♀ ↓ fat mass in old ♂ | Normal PA in young and old ♂, normal EE and RMR in young but ↑ in old ♂, ↑ RER in young and old ♂ ↑ thermogenesis and UCP1 expression in BAT during cold exposure in old ♂, normal macrophage phenotype |  | Lin et al 2018140 |
| Normal on chow ↓ on HF | Normal fat and lean mass on chow, ↓ fat mass, but normal lipogenic genes and leptin expression in epididymal WAT on HFD with ↓ size of epididymal WAT and BAT | ↓ GHSR expression in epididymal WAT and BAT, but not in inguinal WAT ↓ PA, but ↑ EE and RMR and normal RER on chow, ↑ PA and EE and trend ↑ core body T°, but ↓ RMR and normal RER on HFD ↑ angiogenic gene expression and microvasculature and ↓ adipocytes size and macrophage marker in epididymal WAT on HFD |  | Lee et al 2021141 |
| ↓ on chow and HFD | ↓ on HFD ↑ cold resistance and ↑ expression of thermogenic regulatory genes in s.c. fat and BAT on chow and HFD | ↑ RER on chow but ↓ RER on HFD ↑ LA and HP, normal RMR, ↑ plasma AG, ↑ Wheel running on HFD | Synapsin-Cre not activated identically in all brain areas | Lee et al 2016142 |

(Continues)
| Model                                      | GH release               | Growth       | IGF-1        | Glucose                                      | Food intake                                      |
|--------------------------------------------|--------------------------|--------------|--------------|----------------------------------------------|-------------------------------------------------|
| PVN GHSR knockdown in rats (Continued)     | -                        | -            | -            | -                                            | Normal                                                          |
| Antisense GHSR mRNA under TH promoter (rats) | Normal secretory pattern (♀), ↓ pulse frequency over 8-hr (♀), GHRP-2-induced GH response ↓ (♀ and ♀) | ↓            | ↓ Plasma IGF-1 only in ♀ | -                                            | ↓ at 3-8 weeks (♀), ↓ at 3-6, 8 and 9 weeks (♀) Blunted feeding response to i.c.v. GHRP-2 injection (♀?) |
| AgRP neuromodulatory GHSR-KO mice          | Abolished ghrelin-induced GH release | Normal       | Normal       | ↓ fasting blood glucose, but normal blood glucose during GTT and ITT, ↓ plasma insulin during GTT, normal blood glucose and plasma insulin during GTT on HFD, ↓ blood glucose during ITT | Normal on chow and HFD, Abolished ghrelin-induced response, Normal chronic-ghrelin induced response |
| Somatotroph-specific GHSR-KO mice          | Abolished AG-induced GH release and abolished chronic AG-induced ↑ pituitary GH mRNA, abolished fasting- and 60% CR-induced GH release | -            | Normal       | Normal blood glucose response to acute and chronic AG Normal blood glucose after fasting and on ad lib Normal 60% CR-induced blood glucose and glucagon | Blunted response to acute and chronic AG Normal acute refeeding after fast, but ↓ 24-hour refeeding |
| β-cell-specific GHSR-KO mice               | -                        | -            | -            | ↓ Fasting blood glucose, plasma insulin and serum glucagon, normal glucose but ↓ plasma insulin during GTT, improved insulin sensitivity during ITT, ↓ insulin in first phase secretion | Normal FI |
| Silenced IPBN GHSR cells in mice           | -                        | -            | -            | -                                            | ↓ Total energy intake, especially ↓ sucrose -lard intake on HFHS diet |
| GOAT-KO mice                               | -                        | -            | -            | -                                            | -                                                              |
| GOAT-KO mice                               | -                        | -            | -            | Normal GTT on MCTD | ↑ on MCTD |

TABLE 1 (Continued)
| Body weight | Adiposity | Other | Notes | Reference |
|------------|-----------|-------|-------|-----------|
| ↓ BW gain in days after surgery | Trend ↑ UCP2 expression in WAT, Normal UCP1 and UCP3 expression in BAT and SK, respectively | ↓ Blood ghrelin | Short hairpin-GHSR injected into the PVN | Shrestha et al 2009¹⁴⁰ |
| ↓ + leaner | ↓ epidydimal + mesenteric (♂), ↓ mesenteric + retroperitoneal (♀) | Normal plasma ghrelin and prolactin | ♂ and ♀ | Shuto et al 2002¹⁴¹ |
| Normal on chow, ↓ gain on HFD | Normal fat content on chow, ↓ fat gain on HFD, ↓ chronic ghrelin-induced fat gain | Normal LA, EE and RMR on chow, normal LA and RMR but ↑ EE, cold resistance and BAT and inguinal fat UCP1 expression on HFD ↑ Arc Agrp, normal Npy, trend ↓ Pomc and ↓ Mc4r expression on HFD | ♂ only | Wu et al 2017¹⁴² |
| Trend ↓ on CR | ↓ Fat on CR, but normal lean mass | Normal PA, RER, RMR on ad libitum, ↑ PA, RER and trend ↑ FAA, but normal EE, trend ↓ RMR, ↓ core body T° and ↓ BAT Ucp1 and Ucp3 expression on CR, ↑ hypo-thalamic Agrp, normal Npy, trend ↓ Pomc and ↓ Mc4r expression on CR | 40% CR ♂ only | Wu et al 2019¹⁴³ |
| Blunted AG-induced ↑ BW Normal 60% CR-induced BW loss | ↓ AG-induced ↑ fat mass Normal lean mass, normal 60% CR-induced ↓ fat mass and ↑ lean mass | ↑ 60% CR-induced ↑ plasma AG ↑ 60% CR-induced ↑ plasma CORT | ♂ only (except for FI) | Gupta et al 2021¹⁴⁴ |
| Normal BW | Normal fat and lean mass | Normal PA, EE and RER | ♂ only | Pradhan et al 2021¹⁴⁵ |
| ↓ on HFHS diet, not on chow Normal CE on HFHS diet and chow | ↓ on HFHS diet | HFHS diet: chow, lard, 9% sucrose solution and water offered together | ♂ only | Le May et al 2021¹⁴⁶ |
| - | - | Lack AG | ♂ only? | Gutierrez et al 2008¹⁴⁷ |
| Normal on chow, on HFD, ↓ on MCTD | Normal on chow and HFD, ↓ on MCTD | ↑ EE in light phase, normal RQ on MCTD | ♂ only? | Kirchner et al 2009¹⁴⁸ |

(Continues)
| Model                  | GH release                              | Growth        | IGF-1                                    | Glucose                                                                 | Food intake                                                                 |
|------------------------|-----------------------------------------|---------------|------------------------------------------|-------------------------------------------------------------------------|----------------------------------------------------------------------------|
| GOAT-KO mice           | Normal on ad lib feeding, but ↓ on CR, rescued by ghrelin infusion | Normal on ad lib feeding and CR | ↓ GTT-induced glucose and ↑ insulin on chow and HFD ↓ Fasting blood glucose, reversed by ghrelin and GH infusion, normal insulin and glucagon on 60% CR | Normal                                                                 |                                                                 |
| GOAT-KO mice           | –                                       | –             | –                                        | –                                                                        | –                                                                          |
| GOAT-KO mice           | –                                       | –             | –                                        | Normal insulin sensitivity                                             | Normal on chow                                                             |
| GOAT-KO mice           | ↓ Response to CR                         | –             | –                                        | ↓ Blood glucose, reversed by lactate, pyruvate, alanine or octanoate injection, normal plasma glucagon and insulin, ↓ plasma lactate and pyruvate, ↓ liver and muscle glycogen, ↓ glucose production rate, rescued by octanoate injection | –                                                                          |
| GOAT-KO mice           | –                                       | –             | –                                        | –                                                                        | Normal cold T°-induced ↑                                                  |
| GOAT-KO mice           | Trend ↓ during pregnancy                 | –             | –                                        | –                                                                        | –                                                                          |
| GOAT-KO mice           | ↓ Total, basal and pulsatile secretion and MPB in young mice only ↑ pulse number, secretory events and irregularity Normal pituitary content | Normal length and linear growth | ↑                                                                       | –                                                                        | –                                                                          |
| GOAT-KO mice           | ↓ Fasting levels on CR                   | –             | –                                        | ↓ Fasting blood glucose on CR, restored by chronic, but not by acute GH infusion | –                                                                          |
| Body weight | Adiposity | Other | Notes | Reference |
|-------------|-----------|-------|-------|-----------|
| Normal on chow, HFD and 60% CR | Normal on chow, HFD and CR | Normal adaptation to 60% CR scheduled feeding, lethargic and nearly moribund at day 7 of CR Plasma AG not detectable on ad lib feeding or CR, ↑ DAG on ad lib feeding, not CR | ♂ only | Zhao et al 2010^26 |
| Trend ↓ on HFD | Normal body composition, normal serum lipids on HFD | Normal ghrelin mRNA expression, absence of serum AG but ↑ serum total ghrelin, normal RQ ↑ Circulating secondary bile acids from ↑ intestinal reabsorption | ♂ only | Kang et al 2012^149 |
| Normal | – | – | Same CR protocol as in^26 | Li et al 2012^80 |
| Normal | – | – | Normal basal body T° Normal response to 8 hours at 4°C ± fast Normal cold T°-induced ↑ EE | ♂ only? | Heppner et al 2013^150 |
| Normal | – | – | Absent plasma AG, normal plasma DAG, blunted pregnancy-induced ↑ pituitary preproghrelin expression and ↓ hypothalamic and trend ↓ pituitary preproghrelin expression with and without pregnancy | ♂ only - pregnant and non-pregnant | Trivedi et al 2015^151 |
| Normal | Normal epigonadal fat | No blood AG detected, ↑ total ghrelin (DAG) Normal Arc/PeVN GHSR, GHRH, somatostatin and NPY expression Normal liver sex-specific gene expression Normal blood CORT | ♂ only | Xie et al 2015^152 |
| – | – | ↓ Fasting liver autophagy index and ↓ liver p-STAT5 on CR, both restored by chronic GH infusion ↓ fasting autolysosomes number on CR, restored by acute GH infusion ↓ liver ATP | Same 60% CR protocol as in^26 | Zhang et al 2015^153 |
TABLE 1 (Continued)

| Model                                | GH release | Growth | IGF-1 | Glucose | Food intake          |
|--------------------------------------|------------|--------|-------|---------|----------------------|
| GOAT-KO mice                         | –          | –      | –     | –       | Improved glucose tolerance but normal insulin resistance during ITT on HFD |
|                                      |            |        |       |         | –                    |
| GOAT-KO in ob/ob mice                | –          | –      | –     | –       | Same fasting insulin as ob/ob mice on chow (♂?), same GTT-induced glucose response as ob/ob mice on chow and MCTD (♂?) and same insulin resistance in ITT as ob/ob mice on MCTD (♂?) |
|                                      |            |        |       |         | Same as ob/ob mice on MCTD (♂) |
| Central GOAT-knockdown in rats       | –          | –      | –     | –       | Normal FI starting BW on HFD |
| Ghrelin overexpressing mice          | –          | –      | –     | –       | Normal blood glucose after overnight fast and during GTT and ITT ↓ (RIP)/normal (RGP) glucose-induced plasma insulin |
|                                      |            |        |       |         | Normal ghrelin-induced response (♂ and ♀) Normal refeeding after fast |
| Ghrelin overexpressing mice          | Trend ↑ basal GH levels, Blunted ghrelin-induced ↑ release (♂) | – | – | – | Normal fasting plasma glucose, ↑ GTT-induced plasma glucose, ↓ insulin release and normal ITT-induced plasma glucose (♂) ↑ Daily FI at 6-16 weeks (♂ and ♀) Normal ghrelin-induced FI, ↓ leptin-induced anorexigenic effect (♂) |
|                                      |            | Normal length (♂?) | Normal at 16 weeks (♂?) |         |                 |
| Ghrelin overexpressing mice          | –          | –      | –     | –       | ↑ plasma glucagon and glucose |
|                                      |            |        |       |         | –                    |
| Trp3-ghrelin overexpressing mice     | Normal at 10 weeks and 1 year | Normal | Normal at 10 weeks and 1 year | Normal at 10 weeks ↑ GTT-induced glucose and ↓ insulin, blunted insulin-induced hypoglycaemia at 1 year | Normal |
|                                      |            |        |       |         |                       |
| Intra-islet ghrelin over-expressing  | –          | –      | –     | –       | Normal GTT response and glucose load-induced serum insulin (♂ and ♀) |
| mice                                 |            |        |       |         | –                    |
| Body weight | Adiposity | Other | Notes | Reference |
|-------------|-----------|-------|-------|-----------|
| Normal BW on HFD | Normal total, fat and lean mass on HFD | Normal BMD and BMC, ↓ % leukocytes in blood, ↑ spleen HFD-induced ↑ % macrophages, ↑ thymus % macrophages on chow and HFD | ↓ only | Stark et al 2016↑54 |
| Same as ob/ob mice on chow (♂ and ♀), trend ↓ on MCTD | Same as ob/ob mice on chow (♂ and ♀) | AG absent, same EE and RQ as ob/ob mice on MCTD (♂), trend ↑ LA on MCTD (♀) | ↑ only | Kirchner et al 2013↑56 |
| ↓ BW gain on HFD | - | ↓ Feed efficiency on HFD | ↓ only | Wellman et al 2015↑57 |
| Normal | Normal | Normal pituitary GHSR mRNA, normal islet morphology and β cell area, normal insulin mRNA and content in pancreas | RIP and RGP | Iwakura et al 2005↑58 |
| Normal (♂ and ♀) | Blunted ghrelin-induced ↑ in epididymal fat (♂) | - | Over-expression of the human ghrelin gene | Wei et al 2006↑59 |
| Normal (♂ and ♀) | Normal and normal plasma leptin (♂) | ↑ fasting plasma AG (♂ and ♀) ↓ blood CORT (♂?) ↑ UCP1 in BAT and O₂ consumption (♂?) ↑ EE (♀), but normal LA and RER (♀?) | Overexpression and production in stomach and brain | Bewick et al 2009↑60 |
| - | - | ↑ plasma AG and DAG | ↓ only | Chuang et al 2011↑23 |
| Normal at 10 weeks and 1 year | Normal | Normal ghrelin and GOAT expression in stomach, normal plasma AG, normal non-esterified FA, total cholesterol and TG at 1 year | ↑ Transgene expression in liver | Yamada et al 2010↑61 |
| - | - | ↑ Pancreatic and hypothalamic ghrelin and GOAT mRNA Normal plasma AG and DAG (♀) | RIP-mouse ghrelin cDNA-IRES-mouse GOAT cDNA fusion gene | Bando et al 2012↑62 |

(Continues)
| Model | GH release | Growth | IGF-1 | Glucose | Food intake |
|-------|------------|--------|-------|---------|-------------|
| DAG overexpressing mice | Trend ↓ blood GH,↓ pituitary GH mRNA, Dampered response to ghrelin | ↓ length | ↓ | Normal blood glucose and serum insulin | Normal feeding/BW |
| DAG overexpressing mice | Normal | Trend ↓ | – | Normal blood glucose and plasma insulin | ↓ |
| DAG overexpressing mice | – | Normal length | – | ↓ GTT-induced blood glucose Lower insulin-induced blood glucose ↑ plasma insulin | Normal during 22 weeks period |
| DAG overexpressing mice | – | Normal | Normal | Normal basal insulin, glucose uptake and insulin sensitivity | Normal |
| DAG overexpressing mice | – | – | – | Normal blood glucose, plasma insulin and non-esterified FA on chow, ↓ blood glucose and plasma insulin on HFD, ↑ insulin sensitivity in ITT, protection against obesity-induced hyperglycaemia and whole-body insulin resistance | Normal on chow and HFD |
| DAG overexpressing mice | – | – | – | Normal on chow, but abolished ↑ on HFD | – |
| DAG overexpressing mice | – | Normal | ↓ muscular IGF1 expression in old mice | – | – |
| DAG overexpressing dystrophin-null mdx mice | – | – | – | – | – |
| Ghrelinoma mouse model | Normal basal GH and ghrelin-induced response, but trend ↑ GHRH-induced response at 15 weeks | Normal length | ↑ at 12 and 15 weeks | ↑ Fasting blood glucose and GTT-induced blood glucose, ↓ glucose-induced insulin, normal ITT-induced blood glucose, normal basal insulin at 15 weeks | ↓ from 11 weeks Normal ghrelin-induced FI |
| Ghrelinoma mouse model | – | – | – | – | Normal |
TABLE 1

| Body weight | Adiposity | Other | Notes | Reference |
|-------------|-----------|-------|-------|-----------|
| ↓           | -         | ↑ Preproghrelin mRNA in all tissues examined, ↑ total ghrelin in plasma, stomach, cerebrum, heart and kidney, normal serum total protein and total cholesterol↑ pituitary GHSR mRNA | ♀ and ♂ | Ariyasu et al 2005[163] |
| ↓ at 44 weeks | ↓ Epididymal fat pad mass | ↑ Ghrelin mRNA in stomach, brain and liver, ↓ gastric emptying, ↓ plasma TG | ♀ only | Asakawa et al 2005[164] |
| Normal | ↓ Epididymal and perirenal fat | ↑ DAG in visceral fat only ↑ plasma DAG (not AG) | Driven from FABP4 promoter ♀ only | Zhang et al 2008[165] |
| Normal BMI | Normal fasting plasma glycerol and FFAs | Normal plasma AG, normal heart and gastrocnemius muscle weight, ↓ fasting-induced muscle wasting, ↓ denervation-induced muscle atrophy | ♀ only | Porporato et al 2013[166] |
| Normal BW | - | ↓ Proinflammatory tissue cytokine profile and prevention of obesity-associated ↑ muscle proinflammatory cytokines | ♀ only | Gortan et al 2016[167] |
| - | - | Improved muscle regeneration after cardiotoxin-induced injury, ↑ satellite cells number in non-injured muscle, ↑ satellite cells self-renewal and pool maintenance | ♀ only | Reano et al 2017[168] |
| Normal on chow and HFD | - | Improved vascular reactivity and prevented fat deposition in aortas on HFD | ♀ only | Zanetti et al 2019[169] |
| Normal BMI in young, adult, middle aged and old mice | - | Normal ↓ muscle performance with ageing, normal anxiety behaviour, protection against muscle mass loss during ageing, trend ↓ serum pro-inflammatory markers and trend ↑ serum anti-inflammatory markers | ♀ only | Agost et al 2020[170] |
| - | - | Amelioration of dystrophic phenotype and functional performance and ↓ satellite cell pool exhaustion | ♀ only | Reano et al 2017[168] |
| ↓ from 13 weeks | ↓ Fat mass and plasma leptin at 15 weeks | ↑ Plasma AG and DAG from 12 weeks, normal change in AG and DAG after fast and refeed, ↑ pituitary GHSR expression | ♀ only | Iwakura et al 2009[171] |
| Normal | - | ↑ plasma AG and DAG | ♀ only | Zhao et al 2010[172] |

(Continues)
TABLE 1 (Continued)

| Model | GH release | Growth | IGF-1 | Glucose | Food intake |
|-------|------------|--------|-------|---------|-------------|
| Ghrelin neuronal overexpressing mice | – | – | – | Normal GTT-induced blood glucose at 12 weeks, ↑ at 32 weeks, normal serum insulin | Small ↓, but disappeared when controlled for BW |
| Human ghrelin and GOAT liver expressing mice | – | – | – | – | Normal on MCTD |

| GHSR-1a overexpression in GHRH neurones (mice) | ↑ Pituitary content (♀, not in ♂) | Normal length at 5 months (♀ and ♂) | Normal tibial length | – | – | Normal calorie intake on chow or 30% fat diet (♀) |

Amygdala (BLd) GHSR overexpressing mice | – | – | – | – | – | – |

Note: All information included in this table refers to the comparison of the model with its wild-type littermates (if not stated otherwise). “?” means that clear information are not provided and, therefore, denotes a guess from the authors.

Abbreviations: ACTH, adrenocorticotrophic hormone; AG, acyl ghrelin; AgRP, agouti-related peptide; ALT/AST, alanine aminotransferase/aspartate aminotransferase; AP, area postrema; Arc, arcuate nucleus of the hypothalamus; ARS, acute restraint stress; ATM, adipose tissue macrophages; BAT, brown adipose tissue; BCAA, branched chain amino acids; BECG, body energy content gain; BLd, basolateral division of the amygdala; BMC, bone mineral content; BMD, bone mineral density; BMI, body mass index; BMR, basal metabolic rate; BW, body weight; CB1R, cannabinoid receptor type 1; CE, caloric efficiency; CORT, corticosterone; CPP, conditioned place preference; CR, calorie restriction; CRH, corticotrophin-releasing hormone; CSDS, chronic social defeat stress; CS₂, positive/negative conditioned stimulus; DA, dopamine; DAG, desacyl ghrelin; DMH, dorsomedial nucleus of the hypothalamus; DTR, dipeptidase toxin receptor; DXT, dipeptidase toxin; EE, energy expenditure; EPM, elevated plus maze; FFA, food anticipatory activity; (F)FA, (free) fatty acids; FI, food intake; FST, forced swim test; GE, gastric emptying; GEE, gross energetic efficiency; GH, growth hormone; GHRH, growth hormone-releasing hormone; GIR, glucose infusion rate; GLUT4, glucose transporter 4; GTT, glucose tolerance test; HDL, high density lipoproteins; HFCS, high fructose corn syrup; HDF, high-fat diet; HFHS, high-fat high-sugar; HGC, hyperglycaemic clamp; HIC, hyperinsulinaemic-euglycaemic clamp; HOMA-IR, homeostasis model assessment of insulin resistance; HP, heat production; IRES, internal ribosomal entry site; ITT, insulin tolerance test; KO, knockout; LA, locomotor activity; LDL, low density lipoproteins; LFD, low-fat diet; LH, lateral hypothalamus; IPBN, lateral parabrachial nucleus; MCTD, medium-chain triglyceride diet; MFO, mitochondrial fat oxidation; MPB, mass of GH secreted per burst; NA, noradrenaline; NAcc, nucleus accumbens; NPY, neuropeptide Y; ObRb, leptin long receptor isoform; OF, open field; PA, physical activity; PeVN, periventricular nucleus; PFC, prefrontal cortex; PND, postnatal day; POMC, pro-opiomelanocortin; PTT, pyruvate tolerance test; PVN, paraventricular nucleus of the hypothalamus; RER, respiratory exchange rate; RGP, rat glucagon promoter; RIP, rat insulin II promoter; RMR, resting metabolic rate; RQ, respiratory quotient; SK, skeletal muscle; SN, substantia nigra; SRIH, somatotrophin-releasing inhibitory hormone; STZ, streptozotocin; TG, triglycerides; TH, tyrosine hydroxylase; T°, temperature; UCP1/2/3, uncoupling protein 1/2/3; VLDL, very low density lipoproteins; VTA, ventral tegmental area; WAT, white adipose tissue.

4 | PREDICTED PHENOTYPE: GLUCOSE HOMEOSTASIS

Concurrent with the discovery of the orexigenic potential of ghrelin, Broglio et al75 provided evidence recognising that it also influences blood glucose in humans. In line with this, peripheral ghrelin administration to rodents has been shown to increase blood glucose, reduce insulin levels and attenuate insulin responses in vivo,76,77 whereas genetic deletion (and/or pharmacological blockade) of ghrelin or GHSR has been demonstrated to affect glucose homeostasis in the opposite manner.9,34,78 A key question here is whether ghrelin is a good guy or a bad guy for glucose homeostasis and the answer likely lies in the physiological context. Indeed, although the ghrelin system contributes to hyperglycaemia in various pathological states linked to diabetes, the glucoregulatory actions of the hormone appears more likely to have developed to protect against life-threatening hypoglycaemia.79 Of note, although any dysfunction in the ghrelin system only causes a slight drop in blood glucose (or does not affect the latter) under non-fasting conditions, this effect becomes increasingly severe as the calorific restriction aggravates: a drop of blood glucose into the lower range of normal occurs if animals are fasted overnight, as was the case in
**TABLE 1**

| Body weight | Adiposity | Other | Notes | Reference |
|-------------|-----------|-------|-------|-----------|
| ↓ from 20 weeks | Normal body composition | ↑ Serum total and AG overall activity, but normal total EE | ↓ only Ghrelin overexpression also in liver | Reed et al 2008<sup>172</sup> |
| ↑ on MCTD, normalised when returned on chow | ↑ on MCTD | Lack AG on chow, high AG and ↑ total ghrelin, ↓ EEs and trend ↑ RQ, ↓ MFO in SK on MCTD, EE and RQ normalised when returned on chow | ↓ only? | Kirchner et al 2009<sup>148</sup> |
| Normal at weaning, slight ↑ post-weaning, normal in adulthood (♀ and ♂), ↓ gain after 2 months of chow diet, trend ↓ gain after 2 months of 30% fat diet, normal chronic GHRP-6-induced gain (♀) | Smaller ovarian, inguinal, renal and mesenteric fat pads after 2 months of chow diet, trend ↓ fat pads size after 2 months of 30% fat diet (♂) | ↑ GHRH mRNA in hypothalamic extracts, normal prolactin pituitary content (♀ and ♂), blunted Fos response to GHRP-6 in Arc only (♀) | Fertile and normal litter size | Lall et al 2004<sup>173</sup> |
| - | - | ↑ BLd Fos (♀), mostly normal behaviours in OF and EPM before and after acute stress (♂), ↓ anxious behaviour in EPM when ↑ lateral amygdala Ghshr expression (♀), normal stress-induced blood CORT, ↓ BLd SHT1aR expression | rAAV vector-mediated overexpression | Jensen et al 2016<sup>126</sup> |

Our study<sup>9</sup>, whereas life-threatening hypoglycaemia develops with more chronic caloric restriction.<sup>26,70,73,80,81</sup> This finding is consistent across models and hence points towards a critical role of the ghrelin system in the prevention of life-threatening hypoglycaemia.

### 5 | CONCLUDING COMMENTS

*Skinny dwarfs*, the "ghremlins" in ghrelin research, may exist but have remained somewhat hidden from view because diverse models of deficient ghrelin signalling did not cause a consistent and/or dramatic phenotype in line with that predicted from ghrelin injection studies. Homozygous *Ghsr*-iRES-Cre mice emerge, however, as a novel model for exploring deficient ghrelin signalling, in which GH secretion, body growth and glucose homeostasis are impaired.<sup>7</sup>

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The authors declare that they have no conflicts of interest.

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