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Review article

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Body weight regulation models in humans: insights for testing their validity

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Abstract

Maintaining a 'healthy' body weight is crucial for survival and involves a partially understood regulatory system that adjusts energy intake and energy output (expenditure and losses) for that purpose. Several models of body weight regulation exist, but experiments testing their validity are lacking. This Review elaborates on how to test the validity of body weight regulation models in humans. We begin by highlighting the interaction between the obesogenic environment and the individual's biological sensitivity to such environment, which triggers obesity in many, but not all, individuals. We discuss the identity of the regulated parameter(s), often considered to be body weight or body adiposity. We then focus on two models: set point and dual-intervention point. Under the set point model, obesity results from a malfunction of the system (leptin resistance) for preventing weight increases above the defended value. Under the dual-intervention point model, obesity occurs because the system tolerates a wide range of weights in some individuals. This key difference predicts different compensatory responses to energy balance perturbations in individuals according to their weight status, thus becoming instrumental in testing the validity of the models. Finally, we discuss the design of proof-of-concept experiments to advance the understanding of body weight regulation in humans.

Sections

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Key points

- The biological mechanisms that regulate body weight in humans are incompletely understood, yet their interaction with the environment determines body weight.
- The nature of the regulated parameter, often considered to be body weight, is indeed unknown. Adiposity, lean mass and glycogen stores, among other parameters, are also potential candidates.
- Different body weight regulation models have been proposed, which exert their regulation by triggering compensatory responses in energy intake and energy output (energy expenditure and energy losses).
- The set point model proposes that body weight is defended at a fixed level, whereas the dual-intervention point model proposes that body weight is maintained between two boundaries, that is, the lower and upper intervention points.
- We discuss key aspects for the design and interpretation of experiments aimed at testing the validity of body weight regulation models in humans, with a focus on comparing the set point and the dual-intervention point models.

Introduction

Obesity is a prevalent condition characterized by excessive body fat (adipose tissue) accumulation and is defined in adults by a BMI of 30 kg/m^2 or higher. Despite efforts to refine its diagnostic criteria, the definition of obesity remains primarily based on BMI[1,2]. Although rare monogenic forms of obesity have well-characterized causes[3], enabling genotype-specific treatment[3–7], the aetiology of common obesity remains unresolved[8,9]. The development of safe and effective strategies for preventing and treating obesity is urgent, given the rapid rise in its prevalence. In many countries, over one-third of the adult population is affected[10,11], and the global adult obesity prevalence rose from 4.6% in 1980 to 14.0% in 2019 (ref. 12). Analyses spanning the period from 1990 to 2022 confirm this trend, with obesity prevalence more than doubling in several countries[13]. By 2035, obesity prevalence is expected to reach one-quarter of the adult population worldwide[10].

This scenario has prompted interest in understanding the factors underlying the transition from a normal, healthy body weight to a high, potentially unhealthy body weight. In modern society, environmental factors (some not yet identified), including nutritional and non-nutritional drivers, favour a sustained positive energy balance in many individuals. This positive energy balance involves high energy intake relative to energy output (energy expenditure and losses in stool, teguments and urine). The primary cause of such an energy imbalance is seldom evident[9,14]. In most individuals, this positive energy balance is transient, because increases in body weight increase energy expenditure[15]. Therefore, energy expenditure eventually matches energy intake, reaching energy balance at a higher body weight. Notably, most adults maintain their body weight with fluctuations of <5%[16–18], a pattern that can be explained without invoking feedback mechanisms influencing energy intake or output[19,20].

In turn, the hyperphagia observed following forced underfeeding could be considered evidence for a system that actively regulates body weight[21–23]. If such a system exists, in the current obesogenic environment (Box 1), some individuals appear to regulate their weight at a low, 'healthy' level. By contrast, others gain excess weight to levels of obesity and maintain an energy balance at a high, 'unhealthy' body weight. This difference suggests that varying biological sensitivities to the obesogenic environment and the interactions of these biological sensitivities with the intensity of the obesogenic environment determine body weight (or BMI)[24]. Such individual gene-by-environment interactions can explain why the already wide BMI range of the Pima Indians living in the low-intensity obesogenic environment of a remote mountainous location in northwestern Mexico (from ~16 to ~36 kg/m^2) becomes even wider in the high-intensity obesogenic environment of the USA (from ~16 to ~70 kg/m^2)[25] (Fig. 1).

The parameter that this system regulates is currently unidentified, but is often considered to be body weight or body adiposity. For the sake of simplicity, we refer to body weight as the regulated parameter, while acknowledging that the actual regulated parameter could be another factor. A change in the regulated parameter beyond a certain level should lead to a compensatory response to oppose such a change and eventually re-establish the initial, defended level. Two opposing body weight regulation models originally describe such a system[26]: the set point[27] and the dynamic equilibrium models[28]. We consider these models as the 'primary models' of body weight regulation. On the one hand, the set point model proposes the existence of a set body weight that the organism actively maintains. When body weight is perturbed in either direction, various mechanisms defend the baseline weight and help the organism return to this weight[27]. On the other hand, the dynamic equilibrium model proposes that an organism's body weight results from the intensity of the obesogenic environment. If the intensity of the obesogenic environment increases or decreases, body weight will increase or decrease without active compensatory responses[28].

Four additional models derive from the set point and dynamic equilibrium models (extensively discussed elsewhere)[26]: settling point[29], Hall–Guo[30], operating point[31] and dual-intervention point[32,33]. We consider these models as 'secondary models' of body weight regulation. The settling point model[29] proposes that body weight stabilizes at a dynamic equilibrium influenced by energy intake, energy expenditure and environmental factors, rather than by a fixed set point. Upon energy balance perturbations, the settling point model proposes a weaker efficiency of the compensatory response compared with the set point model. Therefore, in the settling point model, body weight stabilizes (settles) at a new level instead of returning to the baseline body weight as in the set point model. This new, settled body weight would reflect the interaction between the intensity of the obesogenic environment and the body's biological sensitivity to the obesogenic environment. In the settling point model, a null compensatory response would result in a body weight as predicted by the dynamic equilibrium model; whereas a strong compensatory response would result in a body weight as predicted by the set point model. The Hall–Guo[30] and operating point[31] models propose that a set body weight exists but can be modified by the intensity of the obesogenic environment or the efficiency of the compensatory response. Finally, the dual-intervention point model[32,33] proposes that body weight changes according to the intensity of the obesogenic environment (as in the dynamic equilibrium model) but remains within a zone delimited by lower and upper boundaries. If body weight falls outside these boundaries, an active compensatory response (as in the set point model) is triggered to return body weight within the zone. Table 1 and Supplementary Table 1 summarize the features of these models, their differences and predictions in response to energy balance perturbations.

The models describing how body weight is maintained or restored following energy balance perturbations should be distinguished from causal models of obesity (such as the energy balance model or the carbohydrate-insulin model)[8]. Those models of obesity are concerned with mechanisms driving chronic weight gain rather than with those regulating body weight. Although such obesity-specific models offer valuable insight, they fall outside the scope of our current Review. Nevertheless, Table 1 and Supplementary Table 1 briefly describe how each body weight regulation model might contribute to the development of obesity under current obesogenic conditions.

This Review aims to elaborate on how to test the validity of body weight regulation models. We begin by discussing which physiological factors, beyond body weight, could potentially be the regulated parameter(s), and distinguishing between metabolic and compensatory responses to energy balance perturbations. We then focus on the set point and dual-intervention point models, whose predicted responses to energy balance perturbations differ according to the initial body weight. We chose the set point model because it is widely cited and is one of the models that assumes that compensatory responses occur regardless of an individual's body weight. We contrasted the set point model with the dual-intervention point model because the latter introduces a novel perspective on body weight regulation. This model is unique because compensatory responses to energy balance perturbations only proceed once a given body weight is reached[32]. Such a crucial difference between models is instrumental for testing their validity. Finally, we propose proof-of-concept experiments to test the predictions made by these models. Identifying which model, if either, accurately describes body weight regulation is crucial for elucidating the regulatory system involved. This knowledge would contribute to better strategies to maintain a 'healthy' body weight in humans.

Box 1 | The obesogenic environment

The obesogenic environment encompasses a constellation of external factors that promote excessive energy intake and low physical activity energy expenditure, thereby facilitating the development and persistence of obesity[191]. The obesogenic environment includes the built environment (urban design, transport infrastructure and land use patterns) that limits opportunities for physical activity[192] and the food environment, characterized by ubiquitous access to inexpensive, energy-dense foods and pervasive marketing that promotes their consumption[89]. Societal norms and structures, ranging from work schedules and school policies, to economic incentives and cultural attitudes, further shape behaviours towards a positive energy balance[193]. These factors operate at multiple levels. Microenvironments such as homes, schools and workplaces directly affect individual behaviour, while macroenvironments such as governance, education systems, market regulation and healthcare policy create broader conditions that enable or constrain health-promoting choices. The obesogenic environment is recognized as a central driver of the obesity epidemic by systematically favouring behaviours that increase energy intake and reduce energy expenditure. Notably, the obesogenic environment might also blunt weight loss efforts and promote weight regain following interventions[87,108,194].

Nevertheless, the obesity epidemic appears to have preceded the societal transformations commonly cited as the origin of the modern obesogenic environment[14]. This temporal mismatch suggests that environmental shifts occurring from the 1970s onwards might have amplified, rather than initiated, an underlying susceptibility to weight gain. Importantly, exposure to the obesogenic environment does not affect all individuals equally. Some individuals are markedly sensitive to environmental cues and rapidly gain weight, whereas others are more resistant and remain relatively lean. This heterogeneity implies biologically mediated differences in their susceptibility that are not captured by environmental measures alone. Obesogenic environment assessment typically involves objective and self-reported indicators, including neighbourhood walkability, access to healthy and unhealthy foods, physical activity patterns and screen time[195–197]. These multidimensional metrics offer a framework for quantifying environmental contributions to obesity risk and identifying populations most vulnerable to their effects.

The nature of the regulated parameter(s)

Although models of 'body weight' or 'body adiposity' regulation are often discussed, the actual nature of the regulated parameter is unknown. A simplified view defines body weight itself as the regulated parameter. The potential existence of a gravitostat that senses axial pressure on lower extremities supports this view[34–38]. Body weight could also be a surrogate of related entities such as the mass of body compartments (for example, adipose tissue mass), circulating concentrations of signalling molecules (such as leptin), or energy flux (such as metabolic rate). Under the concept of homeostasis, a sensor within the system should measure the regulated parameter. Then, within a control centre, the actual value of the parameter is compared against the range of values consistent with the viability of the organism (that is, the 'normal range' or 'set point'). The organism defends this range of values. Thus, the difference between the actual value and the set point (that is, the error signal) generates output signals towards effectors that adjust the value of the regulated parameter. Figure 2a shows the well-accepted homeostatic system regulating glycaemia under fed conditions. Figure 2b shows our limited knowledge of the potential regulatory system for body weight itself or another related parameter.

Adipose tissue mass

Adipose tissue mass has been proposed as the regulated parameter[39]. The discovery of leptin laid the foundation for the concept that adipose tissue mass might be under homeostatic regulation. Leptin is secreted by adipocytes in direct proportion to adipose tissue mass[40] and acts centrally to inhibit appetite[41]. This feedback supports a system in which deviations in adipose tissue mass trigger compensatory responses via changes in leptinaemia. The severe obesity seen in leptin-deficient mice[42] and humans[5,7] provides further evidence for the role of leptin in energy balance. Accordingly, leptin has been proposed as a key regulatory signal and as a candidate for the regulated variable in models of adipose tissue mass control. Of note, inducing whole-body lipid deposition or mobilization through dietary manipulations for 48 h did not alter the circulating concentrations of leptin in humans[43]. Thus, if adipose tissue mass is the regulated parameter, additional factors to leptin must also have a role in sensing adipose tissue levels.

Lean mass

Lean mass (or its constitutive organs) has also been proposed as a regulated parameter, offering an alternative to the commonly

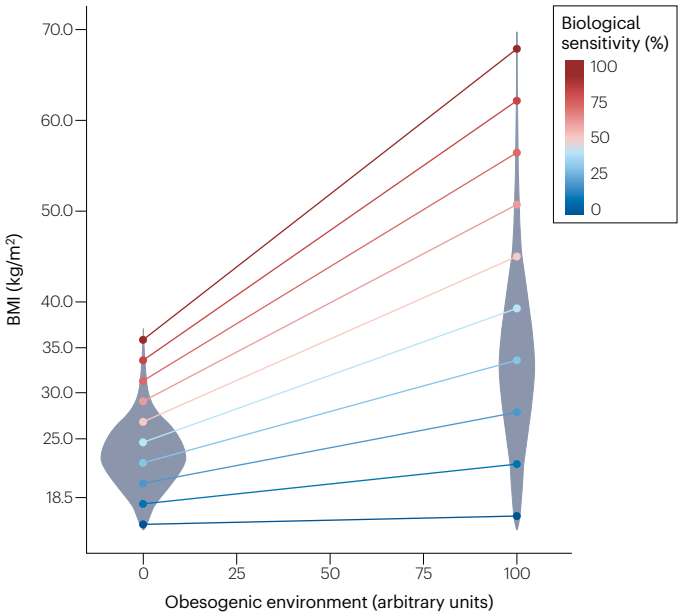

Fig. 1 | BMI is a function of the obesogenic environment intensity and biological sensitivity to the obesogenic environment. An individual's BMI will increase as a function of the intensity of the obesogenic environment, but the individual's biological sensitivity to the obesogenic environment will determine the lowest BMI they can maintain and their rate of BMI increase. Such interaction would explain the wider BMI variability observed in individuals living in a high-intensity obesogenic environment than in those living in a low-intensity obesogenic environment. The points represent ten individuals with different biological sensitivities to the obesogenic environment. The BMI range of those individuals corresponds to the BMI range observed in Pima Indians living in a remote mountainous location in northwestern Mexico or in the USA[25]. The violin plots represent simulated population distributions of BMI. In the lowest and highest obesogenic environments, the mean BMIs were set at 23 and 33 kg/m^2, respectively.

emphasized regulation of adipose tissue mass[44]. This idea is central to the 'collateral fattening' hypothesis that suggests that the body prioritizes preserving or restoring lean mass in response to nutritional deficits or developmental stress[44]. Adipose tissue is then accumulated secondarily (collaterally) to the biological drive to protect lean mass. Notably, the normal increases in lean mass and adipose tissue mass during growth, and the increases in adipose tissue mass in pregnancy, add further complexity to the regulatory system. The system regulating body weight (or its compartments) should allow (promote or tolerate) these physiological increases in lean and adipose tissue masses during growth and pregnancy. This phenomenon might explain the apparent bias of the system towards weight (or adipose tissue) gain, manifested as weaker compensatory responses to weight gain compared to weight loss[45].

Glycogen

Glycogen has also been proposed as a regulated parameter[46], thus suggesting the relevance of also regulating skeletal muscle and liver masses as the major compartments for glycogen storage. On the basis of observations in mice, Flatt observed that a lower carbohydrate balance for 1 day predicted higher ad libitum food intake on the next day[46]. The daily carbohydrate mass ingested is close to the amount of carbohydrate oxidized, thus maintaining a fairly constant carbohydrate store[47]. Therefore, Flatt[46] postulated that carbohydrate stores are defended through food intake and that such a process results in weight maintenance. Some studies in humans support this notion. In a 2007 study, 24-h carbohydrate balance (carbohydrate ingested minus carbohydrate oxidized) was inversely associated with the ad libitum energy intake over the following 3 days[48]. Likewise, in a 1995 study in which participants ate either low-carbohydrate, medium-carbohydrate or high-carbohydrate diets ad libitum, carbohydrate balance was negatively associated with the energy intake on the subsequent day[49]. These findings, however, have not been replicated in other studies[50–53]. The foods provided to assess ad libitum energy intake and the type of intervention to manipulate carbohydrate balance might explain the discrepancy between the findings in these studies. Notably, in another study from 2006, after a 15-day high-carbohydrate diet, participants with low carbohydrate balance gained more weight and fat mass in the next 4 years than participants with high carbohydrate balance[54]. Identifying a glycogen-sensitive signal influencing energy intake seems imperative to support the role of glycogen in weight regulation.

Glucocorticoids

Circulating concentrations of glucocorticoids were proposed as the regulated parameter by Hervey[55], and then by Cabanac and Richard[56]. Owing to the lipophilic nature of glucocorticoids, adipose tissue expansion will dilute (decrease) blood concentrations of glucocorticoids, triggering the hypothalamic release of corticotropin-releasing hormone (CRH). In male rats, CRH was shown to decrease energy intake and body weight[57], which should decrease adipose tissue mass and restore (increase) circulating concentrations of glucocorticoids. By contrast, adipose tissue loss will increase circulating concentrations of glucocorticoids and brain glucocorticoid content. In male rats, such changes increased energy intake[58,59]. Alternatively, the circulating concentrations of glucocorticoids might not be the regulated parameter but instead could signal the perturbation of the actual regulated parameter. For example, glucocorticoids (specifically corticosterone) mediate the effect of fasting-induced hypoleptinaemia in stimulating energy intake[58]. Individuals with obesity show lower[60] or similar[61–64] circulating concentrations of cortisol after an overnight fast compared with individuals with normal weight. The lower cortisol levels in individuals with obesity might represent an attempt to decrease energy intake and body adiposity. In turn, similar cortisol levels in groups with contrasting BMI do not provide a clear interpretation of the role of cortisol in body weight regulation. Furthermore, the fact that plasma concentrations of free cortisol increase similarly after interventions that increase body weight (overfeeding) as after interventions that decrease body weight (fasting)[65] does not support cortisol as a regulatory signal of energy balance. Together, the role of glucocorticoids as the regulated parameter sensitive to energy balance perturbations in humans is unclear.

Other proposed parameters

The regulated parameter might not be a unique signalling molecule or energy substrate, but rather an integrated process crucial for survival. This idea builds on Sorensen's 'adiposity force' theory[66], which posits that lipid accumulation in adipose tissue is actively promoted in anticipation of food scarcity. We extend this concept by proposing adipocyte turnover (that is, formation and death) and lipid turnover (that is, lipogenesis and lipolysis) as the regulated parameters. The extent of activation of these processes could determine energy balance and body weight. Indeed, mice with enhanced lipid storage capacity in adipose tissue gain more weight[67], whereas impaired lipid storage capacity

attenuates weight gain[68,69]. In humans, a lower in vitro lipolytic rate in subcutaneous adipocytes is associated with increased weight gain[16,70].

Cellular energy status (for example, ATP concentration) or dynamic measures of energy flux, such as ATP resynthesis rates or the ATP-to-AMP ratio, might represent the regulated variables. Blundell and colleagues[71,72] reported a strong coupling between energy intake and resting energy expenditure, suggesting that energy flux might be sensed to drive energy intake. Casanova and colleagues[73] proposed a central role for hepatic energy expenditure in this process. These findings appear consistent with evidence that metformin alters cellular energetics[74] and, by increasing circulating levels of GDF15 (refs. 75,76) (a protein released from stressed cells[77]), suppresses appetite and increases energy expenditure in mice[75]. Together, these observations point to a potential role for cellular energetics in shaping compensatory responses to energy imbalance.

Other peripheral organs beyond adipose tissue, skeletal muscle and liver might harbour regulated parameters and release molecules relevant to energy homeostasis, as reviewed elsewhere[78,79]. The gastrointestinal tract releases the hormones ghrelin and GLP1 upon nutrient ingestion, potentially reflecting alterations in a gut-regulated parameter. Even bone, kidney and immune tissues might sense energy status, releasing signals influencing central pathways controlling energy intake and output[78]. Thus, regulated parameters could reside across multiple organs, with their outputs converging on the brain.

Perturbations in energy balance challenge body energetics and affect the regulated parameter, whatever its nature. In this scenario, the organism activates metabolic and compensatory responses to ensure the appropriate function of tissues and organs and defend the 'normal' values of the regulated parameter. The following sections discuss the metabolic and compensatory responses and introduce the main characteristics of the set point and dual-intervention point models.

The metabolic and compensatory responses to perturbations in energy balance

Upon perturbations in energy balance, the organism switches between energy sources (endogenous versus exogenous) and energy fuels (lipids, carbohydrates, proteins) to sustain ATP production[80]. This represents the metabolic response. An additional response occurs to specifically re-establish energy balance, which is the compensatory response[81–84] (Fig. 3). The compensatory response includes a passive component resulting from body mass changes. Weight gain or loss increases or decreases energy expenditure, respectively[15]. Such changes in energy expenditure progressively offset the initial energy imbalance, eventually reaching a neutral energy balance. This passive component is the sole compensatory response according to the dynamic equilibrium model. According to the other models, the compensatory response includes an active component (Table 1). The active component would exert its effect via signals that alter food-seeking behaviour, energy intake and energy output. For example, via modulation of circulating levels of leptin, as described in the following two sections. Thus, the active compensatory response would minimize the change in body weight owing to perturbations in energy balance and eventually re-establish the original body weight.

Table 1 | Summary of the main features of the body weight regulation models in humans

Model features	Primary models		Secondary models			
	Set point[27]	Dynamic equilibrium[28]	Settling point[29]	Hall–Guo[30]	Operating point[31]	Dual-intervention point[32,33]
Existence of a predetermined body weight in adulthood	Yes	No	Yes	Yes	Yes	Yes (delimited by upper and lower intervention points)
Active compensatory responses to body weight changes	Yes	No	Yes	Yes	Yes	Yes, after falling outside the lower or upper intervention points
Effectiveness[a] of the compensatory response to overfeeding in healthy individuals	High	NA	Variable and lower than the set point	Low	High	Non-existing between the intervention points; high once above the upper intervention point
Intensity of the compensatory response in very lean individuals versus those with obesity exposed to starvation	Similar	NA	Similar	Similar	Similar	Stronger in very lean individuals as their weight should be below the lower intervention point
Intensity of the compensatory response in very lean individuals versus those with obesity, both living in a high-intensity obesogenic environment and exposed to controlled overfeeding	Uncertain	NA	Similar	Uncertain	Uncertain	Similar as the weight of individuals in both groups should be above their upper intervention point
Role in obesity aetiology under the current obesogenic environment	Due to resistance to the active compensatory response	Due to non-existing active compensatory response	Due to weak active compensatory response	Due to a drift up in the set point	Due to a drift up in the set point, resistance to active compensatory response, or both	Due to drift up in the upper intervention point

NA, not applicable. [a]Measured in a properly working system.

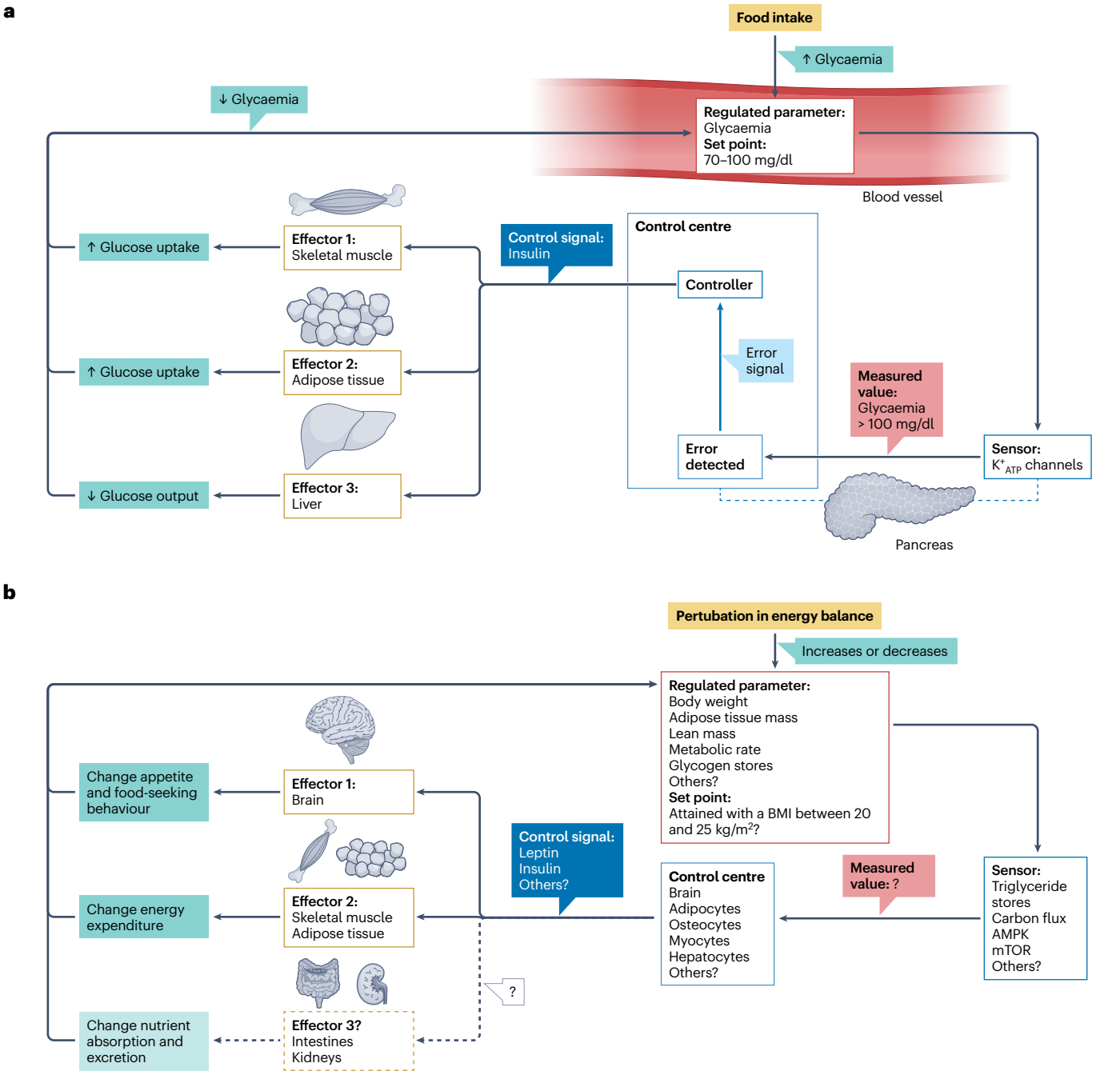

Fig. 2 | Models of homeostatic regulation. a, The system of homeostatic regulation of blood levels of glucose (glycaemia) in the fed state. **b**, A proposed system of homeostatic regulation of body weight (or another related parameter) in a positive or negative energy balance. The BMI range of 20–25 kg/m^2 was selected on the basis of evidence indicating the lowest risk of all-cause mortality[140,141].

Evidence for this active compensatory response includes hyperphagic behaviour following periods of forced underfeeding, with energy intake exceeding pre-restriction levels[21,23]. Another example is the reductions in energy expenditure in response to weight loss and the increases in energy expenditure in response to weight gain that occur beyond what can be predicted owing to changes in body mass and composition (so-called adaptive thermogenesis)[83]. Such an active compensatory response could underlie the observation, in a 1995 study, that individuals who underwent 6 weeks of overfeeding spontaneously lost an average of 55% of the gained weight during the subsequent 6 weeks of ad libitum intake[85]. Similar trajectories were noted in another study in which participants experienced 8 weeks of controlled overfeeding

followed by 6 months of free-living conditions[86]. Conversely, weight regain is typical after a hypocaloric diet, even when implementing dietary recommendations for sustained weight loss[87]. In turn, exercise interventions often produce a weight loss lower than predicted based on the exercise-induced energy expenditure[88]. Although these phenomena suggest the existence of active compensatory responses, behavioural and environmental influences, such as resumption of previous dietary and activity patterns, among others[89], probably also contribute. Notably, studies using sodium–glucose co-transporter (SGLT2) inhibitors provide compelling support for active compensatory responses[90]. Although these agents induce a covert energy loss via glucosuria, individuals unconsciously lose less weight than predicted. Thus, as stated by Stunkard[91], "most obese persons will not stay in treatment. Of those who stay in treatment, most will not lose weight, and of those who do lose weight, most will regain it". The compensatory response explains this phenomenon.

The active compensatory response occurs at the level of energy intake through changes in eating behaviour (appetite, food-seeking behaviour, satiation (the process leading to meal termination) and satiety (the process after a meal inhibiting further eating))[88,92,93]. Energy expenditure during the resting, postprandial, and/or non-resting conditions also has a role in the compensatory response[83,94]. Other potential mechanisms might proceed at the level of intestinal energy absorption and urinary and body surface energy losses[92,95,96]. The metabolic and compensatory responses might operate coordinately[21,81]. Thus, metabolites and hormones triggered by the metabolic response might trigger the compensatory response.

Importantly, the models of body weight regulation predict different strengths of compensatory responses depending on the initial body weight. The dual-intervention point model argues that the strength of these responses varies with the individual's weight[32]. By contrast, the set point model and all the other models of body weight regulation assume body weight-independent compensatory responses[26]. This distinction is critical as it enables testable predictions that differentiate the dual-intervention point model from the set point and related models (Table 1).

The set point model

The classic model explaining body weight regulation is the set point model, which would operate according to a fixed body weight set point, similar to the fixed set point for body temperature or glycaemia[27,39]. Body weight deviations from the set point would activate compensatory responses in energy intake and output to maintain body weight[97]. Evidence shows that the weight loss induced by energy restriction plateaus after a few months, with subsequent weight regain once the intervention stops[87,98–100]. This pattern is consistent with a mathematically modelled response based on the set point model[30]. Similarly, body weight increases during overfeeding and returns to baseline values when the intervention stops[85,86,101]. These data support the set point model that prevents permanent decreases or increases in body weight.

The set point is believed to reside within the central nervous system[102]. Afferent signals from peripheral organs would inform the brain about body weight deviations from the set point. Then, an efferent signal would adjust energy intake, energy output or both to maintain body weight close to the set value. Leptin, an anorexigenic hormone secreted in direct proportion to body adipose tissue mass[40], would provide a control signal to the set point model[102–104] (Fig. 2b). Reducing adipose tissue mass decreases leptinaemia[105], which appears to facilitate a drop in energy expenditure beyond what can be explained by decreases in body mass (that is, metabolic adaptation)[106–108]. The decrease in circulating levels of leptin also reduces its anorexigenic effect, thus stimulating food intake to re-establish adipose tissue mass[109]. By contrast, gains in body weight and adipose tissue mass increase the release of leptin and other hypothetical humoral factors (from adipose tissue, liver and skeletal muscle, among other organs) with anorexigenic and thermogenic actions[38,78,79,93,104]. However, the

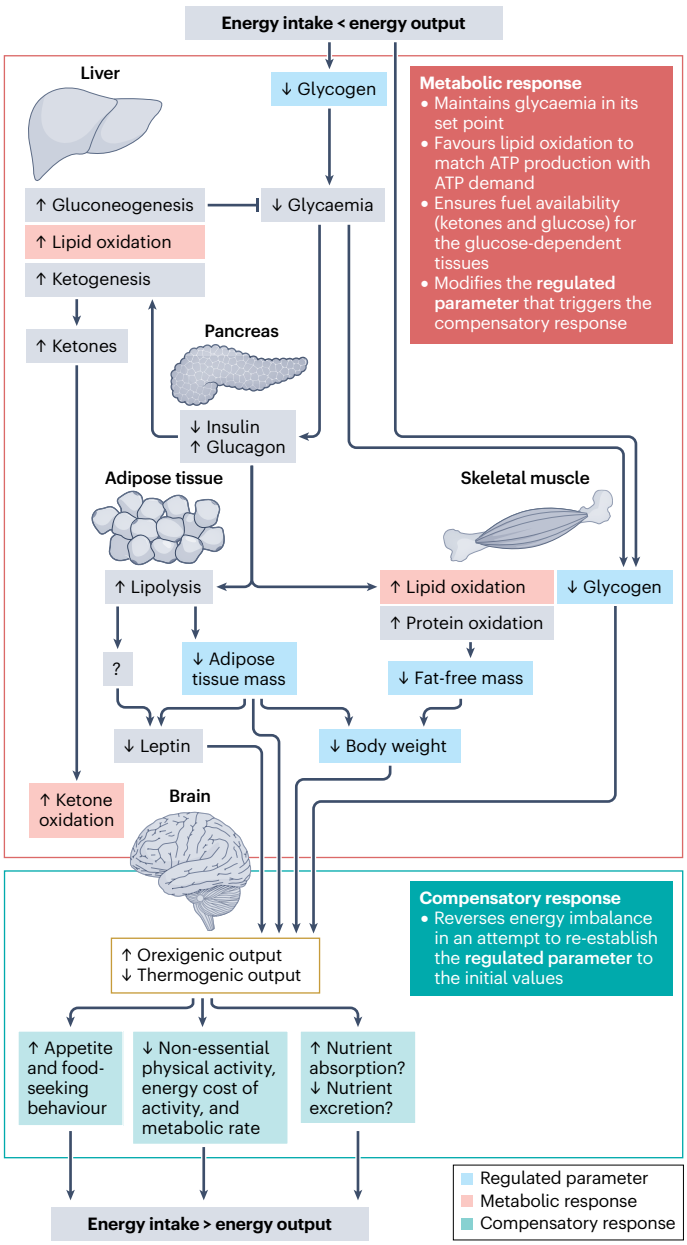

Fig. 3 | Metabolic and compensatory responses to energy deficit. The metabolic response will preserve the fuel energy supply to tissues while maintaining glycaemia. The compensatory response includes a passive component dependent on body weight changes. As a result, energy expenditure changes, preventing further energy imbalance. The compensatory response also includes an active component to re-establish the preceding energy balance by altering energy intake and energy output.

effect of leptin (and other factors) driving the compensatory responses to energy deficit or excess has been proposed to be asymmetrical[45,110]. Reducing adipose tissue mass and leptin such that body weight is below the set point sharply increases the compensatory response. Yet, increasing adipose tissue mass and leptin such that body weight is above the set point elicits a weak compensatory response. Consequently, upward deviations of body weight from the set point will result in obesity. Such deviations suggest that the effects of hyperleptinaemia (and other potential signals) in re-establishing the original body weight are altered in obesity. Indeed, administration of recombinant leptin did not lead to weight loss[111] or only caused moderate and highly variable weight loss in humans, even after increasing leptinaemia 19 times compared with a placebo condition[103]. Under the set point model, obesity is thus hypothesized to reflect a state of resistance to signals triggered by weight gain (such as leptin resistance[112]), while sensitivity to signals triggered by weight loss is preserved. This resistance might explain why the excessive body weight in individuals with obesity becomes difficult to reverse, but the experimental increase in body weight induced by forced overfeeding often returns to its initial values once the intervention ends[85,86]. This view that obesity arises because 'something is wrong' has driven sustained efforts to identify and correct the underlying defect.

The dual-intervention point model

Levitsky[33], further elaborated by Speakman and colleages[32,97,113,114], proposed an alternative model, the dual-intervention point model. Speakman and colleagues pointed out that the set point model does not explain why, when exposed to an obesogenic environment, some individuals develop obesity, whereas others do not[32,113]. They posit that leptin resistance is a contrived condition to explain obesity under the set point model[26]. Neither does the set point model explain the small but persistent body weight gain over the adult life course[115–117]. The dual-intervention point model states that body weight falls between two boundaries, so-called lower and upper intervention points[32,97,114]. A decrease in body weight below the lower intervention point would activate compensatory responses in energy intake and output to regain weight. As in the set point model, circulating levels of leptin are conceived as a major driver of that compensatory response[38,104]. In turn, an increase in weight above the upper intervention point would activate compensatory responses in energy intake and output to decrease body weight. This compensatory response to reduce weight appears to be independent of leptin, with other, still unidentified, signals playing a part[38,79,93,104,118]. The zone between boundaries represents a zone of indifference with weak or absent regulation of body weight[32,97]. Within this zone, body weight is primarily influenced by behavioural and environmental factors, as proposed in the dynamic equilibrium model[29,32].

The intervention points would have evolved in response to natural and independent selective pressures. The lower point ensures minimal energy storage to survive periods of food scarcity and preserve reproductive function[119], whereas the upper point reduces predation risk, a frequent event for early human ancestors[120]. Mathematical modelling considering the mortality risk due to wasting (associated with low body weight or low adiposity) and predation (associated with high body weight or high adiposity) shows a reduced mortality risk over a range of weight or adiposity, thus supporting a two-point model[97]. As humans evolved intellectually, socially and economically, they became top predators with their predation risk diminishing[113,121]. The selective pressure on the upper intervention point was relieved, leading to spontaneous, random mutations of its determining genes[113]. The upper intervention point has progressively shifted upwards, with the extent of this drift varying according to the number and functional relevance of mutated genes in weight regulation. Consequently, some individuals now show a broader zone of indifference, which will interact with the intensity of the obesogenic environment to determine body weight (Fig. 4). At one extreme, most individuals exposed to a low-intensity obesogenic environment should manifest a normal body weight independently of how broad their zone of indifference is (Fig. 4a). At the other extreme, all individuals exposed to a high-intensity obesogenic environment should show an increase in their body weight until it approaches their upper intervention point. Consequently, individuals

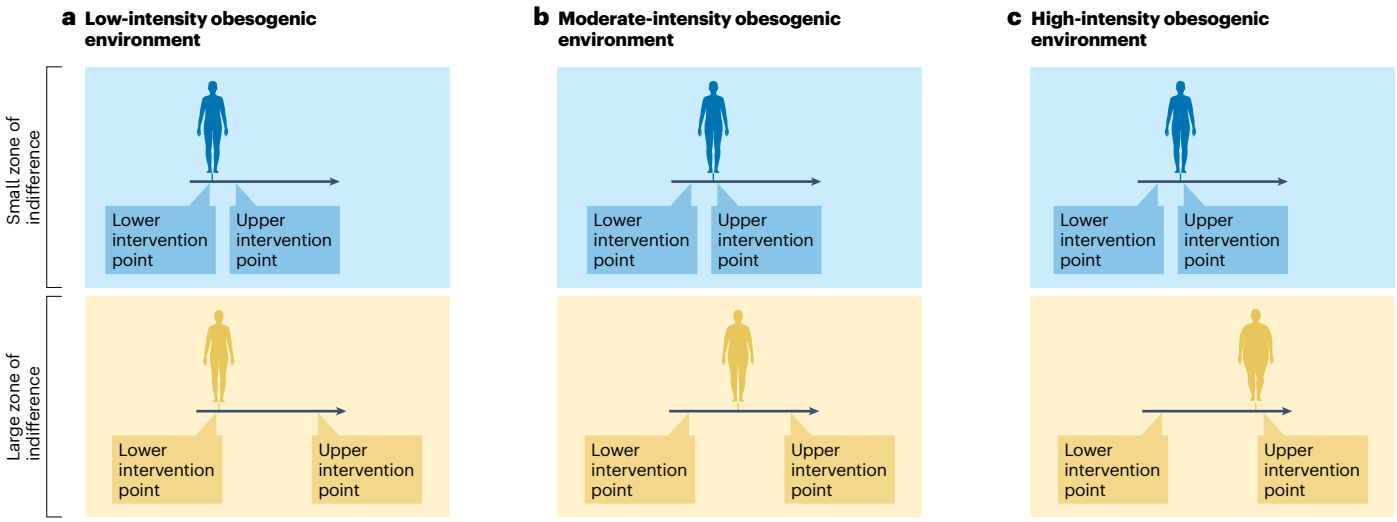

Fig. 4 | Predicted body weight according to the broadness of the zone of indifference in the dual-intervention point model and the intensity of the obesogenic environment. In each panel, the arrow indicates increasing body weight. The upper panels represent individuals with no drift or a small drift in the upper intervention point, whereas the lower panels represent individuals with a large drift in the upper intervention point. The vertical lines over the arrows are the predicted body weight in a low-intensity (panel **a**), moderate-intensity (panel **b**) and high-intensity (panel **c**) obesogenic environment.

with a drifted upper intervention point will develop obesity, whereas those harbouring fewer mutated genes will remain lean (Fig. 4c).

The body weight of individuals exposed to an obesogenic environment of oscillating intensity will fluctuate between the lower and upper intervention points without triggering active compensatory responses. Thus, only the metabolic response to underfeeding or overfeeding will be triggered, but not the active compensatory response intended to re-establish body weight. This pattern is consistent with the fluctuations in body weight between non-holiday and holiday seasons[115]. This model could also explain why, after some years, individuals could gain, for example, approximately 30 kg when their BMI increases from 20 to 30 kg/m^2 (for someone 1.75 m tall)[117]. As elevated body weight does not result from a dysregulated system (such as leptin resistance) under this model, there will be no physiological attempt to restore body weight provided the body weight is below the upper intervention point. The model could explain why weight loss cannot 'correct' the attenuated cerebral neuronal activity induced by intragastric infusion of nutrients[122] or the tendency to engage in less energetically demanding behaviours (such as sitting)[123] observed in individuals with obesity. Furthermore, the model could explain the asymmetric pattern observed in BMI distribution over time, whereby individuals with higher BMI appear more prone to further weight gain[14,124,125]. Such individuals would have a high upper intervention point.

A major criticism of this model is that individuals with excess body weight often struggle to lose even 5% of body weight (that is, approximately 5 kg for someone with a BMI of 30 kg/m^2 and a stature of 1.75 m). This difficulty in losing weight occurs even though the body weight of these individuals is expected to be far away from the lower intervention point, and thus, the compensatory responses should not be triggered. Increased hunger has been found in some[100,126] but not all[127–129] trials of individuals undergoing diet-induced weight loss. Furthermore, compensatory changes are also observed in energy expenditure[83,130]. These observations challenge the existence of the lower intervention point, thereby also questioning the upper intervention point. Nevertheless, some compensatory responses, especially increased hunger, might result from the conscious perception of being food-restricted. Indeed, individuals on an ad libitum diet low in ultra-processed foods for 2 weeks lost approximately 2% of their body weight without an apparent change in appetite[131], thus suggesting that weight loss is not necessarily accompanied by increased hunger.

Testing the validity of body weight regulation models in humans

Determining which models apply to humans could inform more effective strategies for obesity prevention and treatment. Elucidating the existence of a set point or intervention points is a challenge requiring insightful experiments. Those experiments should be conducted in humans, considering that the dual-intervention point model proposes that the intervention points have separated over time in the *Homo* genus, and so findings from animal models might not be directly applicable to humans.

Accomplishing this challenge is constrained by the unknown identity of the regulated parameter (be it adipose tissue mass, lean mass or another factor), as the nature of this parameter fundamentally shapes the interpretation of experimental findings. The identity of the regulated parameter will also influence the magnitude and duration of the energy balance perturbation to elicit a meaningful change in the defended value and its compensatory response[26]. Another constraint is accurately measuring the active compensatory response in energy intake and output. Energy intake and the drive to eat are complex behaviours influenced by physiological, cultural and environmental factors[132]. For instance, a robust biological factor stimulating appetite can coexist with a cultural factor constraining food intake[133]. Measuring the compensatory responses in energy output also has some limitations. Regarding energy expenditure (the sum of resting-related, physical activity-related and food-related energy expenditure[15]), identifying compensatory responses in resting energy expenditure and the thermic effect of food is feasible using indirect calorimetry. However, determining a compensatory response in physical activity energy expenditure[15] is methodologically challenging. Although it can be measured in the controlled conditions of whole-body room indirect calorimeters, the level and type of physical activities under these circumstances differ from free-living conditions[15,134,135]. Doubly labelled water combined with indirect calorimetry is commonly used to estimate physical activity energy expenditure under free-living conditions. This method of calculating (not measuring) physical activity energy expenditure has limitations, including the assumptions of a constant resting metabolic rate throughout the day and a fixed thermic effect of food of 10% of total daily energy expenditure. Unfortunately, accurate measures of physical activity energy expenditure in free-living conditions are still unavailable[136–138]. In addition, energy losses via stool and urine are rarely measured due to practical challenges (multi-day collection requirements) and analytical complexities[139]. Consequently, researchers often assume uniform losses across individuals, which disregards interindividual variability[95,96].

Clarifying the nature of the regulated parameter is critical for designing experiments to test competing models of body weight regulation. If adipose tissue mass is the regulated variable, interventions would require sustained energy imbalances over long periods (weeks) to elicit measurable compensatory responses. By contrast, shorter term perturbations (days) might suffice if the regulated parameter were a more labile substrate (such as glycogen). Identifying the regulated variable would also enable targeted manipulations while holding other components constant, providing cleaner tests of model predictions. Establishing this foundation is essential to advancing experimental designs capable of distinguishing between competing theoretical frameworks.

Regardless of the constraints, both models predict testable compensatory responses after perturbing energy balance. The set point model predicts that individuals should maintain a relatively constant and low (normal) body weight at a set value determined by biology. Decreases or increases in body weight should activate compensatory responses. The dual-intervention point model predicts that compensatory responses will only be triggered when an individual's body weight falls below or increases above their intervention points. The lower intervention point should be less variable among individuals, reflecting an evolved minimum weight or adiposity preventing mortality due to starvation[114]. This minimum value should be near the lowest BMI associated with the lowest mortality risk (approximately 20 kg/m^2)[140,141]. The upper intervention point varies among individuals and depends on the extent of the drift due to genetic mutations. The compensatory responses to energy balance perturbations should differ depending on how close body weight is to an intervention point. By contrast, the set point model predicts that the compensatory response to energy deficit should be similar regardless of body weight.

In response to energy excess, the prediction of the set point model is unclear, because individuals with obesity might display attenuated responses to excess energy consumption owing to leptin resistance.

A relevant consideration is the intensity of compensatory responses to energy deficit versus excess. These responses were proposed to be asymmetrical, with stronger reactions to energy deficits[110], although experimental testing is lacking. Indeed, in a 1995 study, adaptive thermogenesis seemed to be higher following 10% weight gain than 10% weight loss, but no formal comparison was reported[83]. Although weight gain and loss do not correspond to equivalent energy balance perturbations (owing to differences in the energy involved to gain or lose a unit of body weight[142,143]), the study suggested an asymmetrical response with stronger reactions to energy excess.

Compensatory responses to weight gain or loss can also take different amounts of time to manifest, so the duration of the experiment could determine the responses detected. Just 24–48 h of fasting or covert energy restriction (that is, decreases in the energy content of the diet that individuals are not aware of) are enough to increase hunger and thus promote a subsequent compensatory energy intake[144,145]. Similarly, a reduced energy intake can rapidly reduce energy expenditure, partly due to a reduction of nutrient-induced thermogenesis, although interindividual variability suggests additional, still unidentified mechanisms[146]. Other compensatory responses could emerge over weeks or months, such as changes in levels of appetite-regulating hormones or energy expenditure that have been observed months after weight loss[100,130]. Finally, work from 2025 has emphasized the importance of time in the energy allocation trade-offs, particularly those involving physical activity, suggesting that these trade-offs evolve over months or years, well beyond the time frame of most studies[147]. The following section offers a framework for evaluating the compensatory responses to underfeeding and overfeeding in individuals with contrasting BMIs.

Box 2 | Body weight regulation models in men versus women

In the dual-intervention point model, the lower intervention point in women is speculated to also be determined by the level of adiposity required to support reproductive function, as indicated by amenorrhoea in women with low adiposity[119]. Therefore, the minimum adiposity to prevent wasting-dependent mortality while maintaining reproductive function might determine the lower intervention point in women, which might be higher than in men, as indicated by the higher body fat percentage in women than in men at similar BMIs[198]. Leptin appears to be a major signal activating compensatory responses to adipose tissue loss and regulating reproductive function in women. Indeed, in women with amenorrhoea, leptin administration improves reproductive function even in the presence of a reduction in body weight and/or adiposity[119]. Leptin also regulates circulating levels of thyroid hormone[5] and sympathetic[199] activities. Circulating levels of leptin are strongly associated with body adipose tissue and are thus considered to inform the brain of the size of the body's adipose tissue mass[102]. Notably, sex is another major determinant of circulating levels of leptin, with women showing higher concentrations than men for a similar adipose tissue mass[40,200]. Whether these sex differences in the selective pressures for body weight and/or adiposity, circulating leptin concentration or both determine sex-dependent compensatory responses to prolonged fasting is unknown.

Compensatory response to underfeeding

The response to energy deficit in individuals with contrasting BMIs can help compare the validity of the models. If the set point model is valid, energy deficit should activate similar compensatory responses regardless of the individual's initial body weight (Table 1). However, if the dual-intervention point model is valid, the compensatory responses in individuals with low body weight (near the lower intervention point) should be triggered earlier, be stronger, or both, compared with responses in individuals with higher body weight (far from the lower intervention point) (Table 1). These predictions should be influenced by the proximity of the body weight to the lower intervention point. The body weight of individuals with healthy underweight (also called 'constitutional thinness'[148]) should be close to the lower intervention point and thus these individuals are a suitable population for assessment. Thus, the models can be examined by comparing the compensatory responses to fasting and subsequent refeeding between individuals with healthy underweight and individuals with obesity. A faster or greater recovery of energy balance over the fasting–refeeding period would indicate a stronger compensatory response. Intriguingly, although relevant features of the regulation models differ between men and women, neither the set point model nor the dual-intervention point model predicts sex-specific responses (Box 2).

Another relevant aspect for interpreting the validity of the models is the nature of the regulated parameter. For example, the fat-free mass-to-fat mass ratio of weight loss is higher in leaner individuals than in those with more adiposity[149]. Consequently, an energy deficit producing the same degree of weight loss in individuals with a different BMI will translate into different changes in body composition. If, for example, the regulated parameter is adipose tissue mass, then the magnitude of perturbation in the regulated parameter would not be the same between individuals, and neither would be the expected compensatory response. The ideal experimental design is to compare the compensatory response for a comparable perturbation in the regulated parameter. This discussion about the composition of weight loss highlights the relevance of identifying the regulated parameter, which has not yet been accomplished. Therefore, this knowledge gap should be considered when interpreting experimental findings.

Additional factors influencing the predictions are the strategy to induce an energy deficit and the extent of the deficit. Strategies can include decreasing the amount of food eaten[150] or the energy density of the food through non-caloric sugars and fat substitutes[151–153]. Energy deficit can also be induced by increasing energy expenditure through physical activity[88,154], decreasing mitochondrial efficiency[155–157] or increasing energy losses via faeces and/or urine[90,158]. Notably, energy deficits due to dietary restriction induce a greater appetite and subsequent energy intake compared with energy deficits from increased physical activity[159,160]. These findings support the notion that appetite regulation is sensitive to energy flux[161]. The best strategy, if any, is unclear. Strategies involving food restriction and substantial physical activity might be relevant as they emulate the energy challenges that human ancestors faced. Regarding the extent of energy deficit, a plausible approach is to fully restrict energy intake for a similar period among individuals (for example, 24–48 h of fasting)[162]. Because energy requirements differ among individuals due to differences in body weight[15], comparing the compensatory response after a similar period between individuals with contrasting body weight will be confounded by differences in the absolute energy deficit[163]. By contrast, matching the absolute negative

energy balance (in kilocalories) will require different fasting periods, which could influence the compensatory responses detected.

The type of food to assess the compensatory response is also relevant. The models of body weight regulation do not seem capable of maintaining body weight in the obesogenic environment, as suggested by the overfeeding in individuals with free access to various palatable foods[164]. Similarly, a 2024 study exposed participants to 24 h of energy balance or fasting, and then ad libitum energy intake during a 24-h period was measured[144]. During the ad libitum intake, participants ate whatever and whenever they wanted from 40 food items available in vending machines. Unexpectedly, ad libitum energy intake was as high after 24 h of energy balance as it was after 24 h of fasting. The expected compensatory response in energy intake thus appeared to be masked due to the hedonic characteristics of the food. Indeed, food intake is commonly called homeostatic or hedonic[165], depending on the drive to eat. Therefore, bland foods should be provided when assessing the compensatory response in energy intake, to promote homeostatic rather than hedonic intake.

The leptin response to underfeeding might provide information on the validity of the models, and it seems to align with the prediction of the dual-intervention point. Compared with individuals with obesity, lean individuals show a greater relative (percentage) decrease in leptinaemia and adipose tissue leptin production after a 22-h fast[166]. Such a hypoleptinaemic state could represent an early signal for activating appetite-related compensatory responses in lean individuals[167,168]. However, leptin action might change according to the concentration of free leptin (its biologically active form), which depends on the balance between leptin and the soluble form of the leptin receptor (sObR)[169]. In individuals with normal weight, 72 h of fasting decreased their leptinaemia by 80% and doubled their circulating concentration of sObR[169]. Thus, reducing leptin secretion and increasing the circulating levels of sObR could represent an attempt to suppress leptin action to re-establish energy balance during fasting. The effect of prolonged fasting on the circulating sObR concentration in individuals with obesity is unclear.

The metabolic response during underfeeding might influence the compensatory response, as depicted in Fig. 3. If so, metabolic responses to prolonged fasting (>14–120 h) do not seem to support any model. For instance, during fasting, individuals with normal weight show greater increases in circulating levels of non-esterified free fatty acids (NEFA) and β-hydroxybutyrate (βOHB) than individuals with obesity[162,170,171]. NEFA inhibit food intake, as observed upon central administration of oleic acid in rats[172]. Some authors have proposed that low postprandial circulating concentrations of NEFA reflect a status of energy deprivation that triggers appetite and food intake[173,174]. Therefore, fasting-induced increases in circulating concentrations of NEFA would inhibit appetite, with a greater effect in individuals with normal weight than in those with obesity. In turn, elevations in circulating concentrations of βOHB suppress appetite in humans[175], energy intake in contexts of high carbohydrate availability in humans[176], food intake in rats[177], and sympathetic nervous activity in mice[178]. βOHB antagonizes the sympathetic G protein-coupled receptor 41 (GPR41)[178], a receptor expressed in sympathetic ganglia neurons[178]. *Grp41*-deficient mice exhibited attenuated reductions in heart rate and oxygen consumption during fasting compared with wild-type mice[178]. Taken together, although increases in the circulating levels of NEFA and βOHB have a role in the metabolic response, they do not seem to be involved in the compensatory response to underfeeding because their effects on energy intake and expenditure do not promote a restoration of the energy balance.

Compensatory response to controlled overfeeding

In response to controlled overfeeding, the stronger the compensatory response, the lower the weight gain. During the experimental conditions of a controlled overfeeding, the compensatory response should not include energy intake despite appetite being suppressed, because energy intake is fixed among individuals. Considering the inter-individual variability in overfeeding-induced appetite suppression[179], however, energy intake should have a role once ad libitum food intake is resumed. Therefore, under controlled overfeeding, the compensatory response should depend on energy output (that is, energy expenditure and energy losses).

The influence of the initial body weight on the intensity of the compensatory response predicted by the set point model is uncertain (Table 1). Lean individuals could be more sensitive to leptin (versus those with obesity) and therefore manifest a stronger compensatory response to overfeeding. However, in individuals with obesity, controlled overfeeding could overcome leptin resistance and determine similar compensatory responses as in individuals with normal weight. As the dual-intervention point model only predicts a compensatory response after an individual's body weight is above the upper intervention point (Table 1), the proximity to this point will determine the probability of triggering the response. Such proximity will depend on the intensity of the obesogenic environment where individuals live. In a low-intensity obesogenic environment, the body weight of individuals should be far from the upper intervention point, and no compensatory response should be triggered by controlled overfeeding (Fig. 4a). In a moderate-intensity obesogenic environment, body weight will only be close to the upper intervention point in individuals with the upper intervention point at a lower level (Fig. 4b). Only in these individuals would a compensatory response be triggered. Constitutionally thin individuals could help test this prediction, as they are thought to have an upper intervention point at a lower level than most people in the general population[78]. In a high-intensity obesogenic environment, the compensatory response should be strong regardless of BMI because body weight will be close to the upper intervention point in all individuals (Fig. 4c). This last scenario is the most likely case in modern societies.

Several overfeeding studies have shown similar weight gains or energy costs of weight gain (energy required to gain 1 kg of body weight) in individuals with high BMI versus individuals with low BMI[85,180,181]. A similar energy cost of weight gain in individuals with different BMI could be consistent with the prediction based on the set point model. Such a pattern is also consistent with the dual-intervention point model in high-intensity obesogenic environments, where the body weight of all individuals is close to their upper intervention point. In a moderate-intensity obesogenic environment, however, the energy cost of weight gain is expected to be higher in individuals with low BMI, because their body weight would be closer to their upper intervention point. Presumably, a high-intensity obesogenic environment prevailed in studies conducted in the USA or UK in the 1980s and 1990s[85,180,181]. By contrast, in a study published in 1963 (ref. 182), for a similar energy excess, lean individuals gained less weight than those with obesity. This pattern appears only consistent with the dual-intervention point model in a moderate-intensity obesogenic environment, where lean individuals are expected to have a body weight closer to their upper intervention point than individuals with obesity. This study was conducted in Edinburgh (Scotland) in the 1950s, potentially representing a moderate-intensity obesogenic environment. Although speculative, such an interpretation highlights the complex interaction between environment and genetics driving body weight. Upcoming experiments

contrasting the observed and predicted responses of the models should consider those interactions.

Conclusions

World societies have strived to improve access to food energy[183]. Such an effort has been paralleled by increased body weight in many individuals[12]. Thus, an increasing proportion of the population, sensitive to that high-intensity obesogenic environment, manifests or will manifest obesity[10,12]. The mechanistic basis for explaining enhanced sensitivity to the obesogenic environment is under debate. The fact that individuals with normal weight or obesity appear similarly competent in maintaining their low and high body weight[16–18], respectively, adds further complexity.

We compared two models in their predictions of the compensatory responses to energy balance perturbations. The leptin response to energy deficit (prolonged fasting) seems to fit the prediction of the dual-intervention point model, whereas other responses do not support either model. Future studies should comprehensively assess energy intake and output during and after energy deficit in individuals with a body weight close to their lower intervention point (for example, healthy underweight) or far from their lower intervention point (BMI >25 kg/m^2). Assessing energy intake from foods free of hedonic cues also becomes relevant. Such an approach will avoid potential bias due to consuming highly palatable foods and provide a proof-of-concept for the validity of the dual-intervention point model.

Overfeeding studies could test the validity of the dual-intervention point model if individuals with a body weight close to and far from their upper intervention point can be identified. Proximity to that upper intervention point will depend on the intensity of the obesogenic environment. Developing better ways to estimate the intensity of the obesogenic environment is crucial, especially at the micro level (such as at home). Then, a comprehensive analysis of the energy balance during and after controlled overfeeding should allow the identification of compensatory responses. If energy output has a role in the compensatory response, this fact should become clear during controlled overfeeding. The change in energy expenditure upon energy balance perturbations shows high interindividual variability, distinguishing 'thrifty' and 'spendthrift' phenotypes[146,184]. Nevertheless, specific individual traits explaining such phenotypes have not been identified. Such interindividual variability might lie in how close the individuals' body weights are to their upper intervention point. Of note is the potential compensation through intestinal energy absorption during controlled overfeeding, which has seldom been considered[185,186]. Further assessment of the emergence of the intestinal microbiota as a relevant factor influencing energy absorption in humans[95] is warranted. In controlled overfeeding, changes in eating behaviour should occur, which could influence energy intake after resuming ad libitum eating.

Future studies should preserve a balanced inclusion of men and women. First, women have a higher prevalence of obesity than men[12,13,134]. Second, there is a sex difference in the mass and distribution of adipose tissue, circulating concentrations of leptin and other adipose tissue and metabolic features with potential relevance for body weight regulation[187,188]. The pattern noted in men might therefore not apply to women. Indeed, weight loss induced by anti-obesity drugs shows a greater effect in women than in men[189,190].

In conclusion, the need for further investigation into the models that regulate body weight is underscored. The dual-intervention point model partially explains the responses observed in humans undergoing underfeeding or overfeeding. There is a need for proof-of-concept physiological experiments and a comprehensive assessment of the active compensatory responses to energy balance perturbations.

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