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Review

Brain–body communication in metabolic control

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A thorough understanding of the mechanisms controlling energy homeostasis is needed to prevent and treat metabolic morbidities. While the contribution of organs such as the liver, muscle, adipose tissue, and pancreas to the regulation of energy has received wide attention, less is known about the interplay with the nervous system. Here, we highlight the role of the nervous systems in regulating metabolism beyond the classic hypothalamic endocrine signaling models and discuss the contribution of circadian rhythms, higher brain regions, and sociodemographic variables in the energy equation. We infer that interdisciplinary approaches are key to conceptually advancing the current research frontier and devising innovative therapies to prevent and treat metabolic disease.

Highlights

Energy homeostasis is achieved by the coordinated action of metabolic organs.

The peripheral nervous system innervates organs, connects them with the brain, and plays an important role in controlling energy homeostasis.

Brain–body communication is timed by molecular clocks controlling circadian rhythms.

Brain–body coordination of metabolism is influenced by cognition and demographic aspects.

The metabolic challenges of modern times

If the current obesity trend continues, nearly 2 billion adults will live with obesity in 2035 [1]. The obesity pandemic is a major driving force in the rise of physical and mental health problems such as type 2 diabetes, cardiovascular disease, some types of cancers, and depression [2–4]. These conditions significantly reduce the span and quality of life. Although lifestyle interventions, next-generation drugs, and bariatric surgery effectively reduce fat mass acutely and ameliorate metabolic disease, body weight is often regained in the long term, respawning metabolic comorbidities [5]. Preventing and treating obesity and/or the harmful impact of its comorbidities is one of the biggest challenges of our time.

The obesogenic environment is a main contributing factor to the rise in body weight [6]. The prompt availability of energy-rich foods leads to overeating, which results in a net energy surplus. Excessive energy intake results in ectopic lipid accumulation, perturbing normal tissue function and disrupting metabolic health [7]. The disease state alters endocrine- and neuronal-mediated feedback signals to the brain. Because these processes follow a circadian rhythm, the time of day is an important variable in metabolic homeostasis [8]. Gaining a thorough understanding of the pathophysiology of obesity and metabolic disease requires the adoption of a combination of interdisciplinary approaches from the fields of metabolism, neuroscience, chronobiology, and beyond.

In this review, we summarize the current understanding of the functional interplay between the major metabolic organs, the nervous system, and the circadian clock in the regulation of metabolic homeostasis. Further, we discuss the dynamics of this interplay in different environments and highlight the importance of considering the demographic context in which metabolic processes occur. We hope that this work will stimulate our readers to adopt multidisciplinary approaches when investigating the complex mechanisms regulating homeostasis and its disruption.

Peripheral organs in metabolic control

Metabolic homeostasis is the result of the coordinated actions of several organs (Figure 1) that, under physiological conditions, modulate systemic macronutrient levels via energy storage

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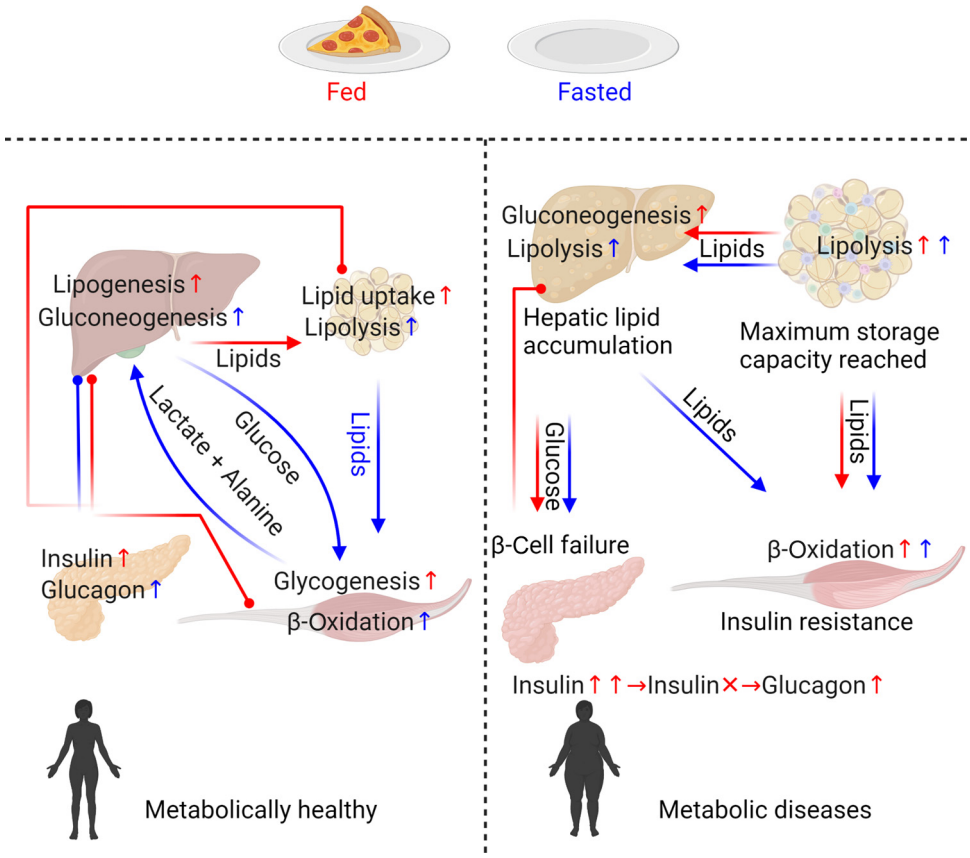

Figure 1. An overview of the interorgan coordination of metabolism in health (left) and disease (right) and in fed (red) versus fasted (blue) conditions. In the fed state, blood glucose levels rise, stimulating insulin secretion from the pancreas. Insulin binds to insulin receptors in other metabolic organs, regulating their function. In the liver, insulin stimulates lipogenesis, converting glucose to lipids that are subsequently mobilized to white adipose tissue for storage. This process is coordinated by insulin signaling as it stimulates lipid uptake in the white adipose tissue. Insulin stimulates glucose uptake in muscle that, if not metabolized via the glycolytic pathway to generate kinetic energy, is stored as glycogen via glycogenesis. In the fasted state, glucose scarcity causes the pancreas to secrete glucagon. Glucagon stimulates hepatic gluconeogenesis to sustain normoglycemia. The glucose produced in the liver is taken up by muscle and utilized to generate movement. The glycolytic byproducts lactate and alanine are secreted from the muscle and serve as substrates for hepatic gluconeogenesis. This forms metabolic cycles between these tissues referred to as the Cori and Cahill cycles. The glucose provided by the liver is not sufficient to meet the metabolic demand of the muscle. Therefore, lipids from the white adipose tissue are mobilized to generate muscle contractions, and muscle metabolism shifts from being mainly glycolytic in the fed state to mainly oxidative in the fasted state. Obesity-induced metabolic disease is believed to start when white adipose tissue is unable to store more lipids, which in turn results in chronic low-grade lipolytic activity. The resulting elevation of circulatory lipids will result in ectopic lipid accumulation and attenuating glycolytic rate in muscle. Subsequently, systemic insulin resistance will stimulate compensatory insulin secretion that eventually results in β-cell failure and chronic glucagon release. Figure created using BioRender (www.biorender.com).

[e.g., white adipose tissue (WAT) expansion], energy utilization (e.g., skeletal muscle contraction, adipose tissue thermogenesis) and by acting as control centers for energy utilization (e.g., pancreatic endocrine signaling, hepatic macronutrient conversion; Table 1). These mechanisms have been described in detail elsewhere [9–11]; therefore, only a brief overview with key points are presented in this section.

Table 1. Summary of metabolic organs and their main roles

Function	Organ
Storage	WAT
Consumption	Skeletal muscle and BAT
Control centers	Pancreas, liver, and nervous system

Energy storage

Food intake provides the body with chemical energy in the form of macronutrients. The energy is distributed to the organs based on their energy demand while the rest is stored in the liver, muscle, and WAT. WAT is the body's main energy reservoir. The lipid storage capacity of WAT is limited by its ability to generate new adipocytes, through a process termed adipogenesis, and to increase the size of existing ones [12]. When this limit is reached, the excess energy is stored ectopically in other organs, such as the liver and muscle, perturbing their metabolic activity [13] and contributing to the pathophysiology of metabolic disease. The theory that WAT storage capacity is associated with disease is supported by observations showing that the presence of a few relatively large fat cells (i.e., hypertrophic), rather than many smaller adipocytes, correlates with a higher incidence of type 2 diabetes [14,15]. When energy is needed, triglycerides are broken down through a process termed lipolysis. A main driver of lipolysis is the sympathetic nervous system, whose neurons innervate the adipocytes [16]. Free fatty acids and glycerol are released systemically and used as an energy substrate for other tissues. Lipolysis is perturbed in obesity, with chronic low-grade free fatty acid release further contributing to ectopic lipid accumulation [17].

Energy expenditure

When energy demand exceeds energy intake, the body mobilizes the stored energy from WAT. The chemical energy is converted to kinetic energy (physical movement) and thermal energy (heat). Physical activity, a major channel of energy expenditure, is beneficial for metabolic homeostasis. Exercise reduces blood glucose levels even under conditions of muscle insulin resistance, a hallmark of metabolic syndrome, by promoting glucose uptake independent of the insulin signaling pathway [11,18] and improves metabolic health independent of weight loss [19]. Another channel of energy expenditure is via thermogenesis. When the external temperature is low, the brain activates the autonomic nervous system. Sympathetic fibers, innervating the adipose tissue, release noradrenaline and uncouple energy expenditure in the form of heat [20]. The adipocytes capable of thermogenic activity are either brown [in brown adipose tissue (BAT)] or beige (in WAT). The discovery that humans have adipose tissue with thermogenic activity in adulthood [21] opened a new avenue to reduce body weight and propelled the search for interventions activating BAT and/or converting white adipocytes to beige. In rodents, administering β_3-adrenergic agonists increases energy expenditure and effectively reduces body weight [22]. Prolonged cold exposure and sustained physical activity can reprogram adipocytes in the WAT from white to beige. This phenomenon, termed 'browning' and mediated by sympathetic-induced UCP1 expression in WAT, turns the reservoir tissue of the body into a metabolically active, heat-releasing organ. The clinical relevance of adipose tissue browning remains under debate [20]. However, data from a recent study suggest that the decrease in energy expenditure over the past decades, which has contributed to the obesity pandemic, is due to lower basal metabolic rate (involving thermogenesis) rather than reduced locomotor activity [23]. Hence, increasing thermogenic capacity might be a complementary tool to sustain weight loss over longer periods.

Control centers

The pancreas and liver orchestrate macronutrient storage, release, and utilization. The pancreas senses systemic glucose levels and coordinates its uptake and release by the organs via the

antagonistic function of the pancreatic hormones insulin and glucagon, respectively [24]. Glucagon, secreted from α-cells of the pancreas, stimulates glucose production via gluconeogenesis and glycogenolysis (i.e., glycogen breakdown). Conversely, insulin, secreted from β-cells of the pancreas, shifts hepatic metabolism from gluconeogenesis and glycogen breakdown to glycolysis, *de novo* lipogenesis (DNL), and glycogen synthesis [11]. Insulin resistance prevents glucose uptake and results in compensatory efforts by the pancreas to produce more insulin. The overstimulated β-cells eventually perish, while α-cells continue to stimulate hepatic gluconeogenesis in the fed state, further contributing to hyperglycemia [25].

Taken together, the coordinated action of WAT, muscle, BAT, pancreas, and liver is crucial for the storage, supply, and utilization of energy and to maintain metabolic homeostasis. It is well known that disruption of this regulatory system is implicated in the onset and progression of metabolic disease [9,10]. Less appreciated is that peripheral neurons, by innervating virtually every organ and connecting them with the brain, represent an important component of such a control system. In the next section, we review both endocrine and neuronal routes enabling brain–body communication.

The brain integrates metabolic signals and regulates organ physiology

The importance of hormones in the regulation of homeostasis is textbook knowledge. In the brain, molecularly encoded hypothalamic neurons receive information on the body's energy state via circulating hormones and cytokines secreted by the organs [26] and coordinate the appropriate response to defend homeostasis [27,28]. While a critical role for extrahypothalamic areas in regulating energy homeostasis is emerging [29,30], the function of peripheral neurons in regulating brain–body communication has just started to be investigated. The axons of somatosensory neurons [in the dorsal root ganglia (DRG)] and vagal sensory neurons [in the jugular and nodose ganglia (NG)] innervate the organs and detect changes in their microenvironment. This information is relayed to the brain, forming the ascending pathway. The thalamus and the brainstem are major recipients of somatosensory and vagal inputs. The functional relevance of vagal connections has been pioneered in studies on the gut–brain axis (discussed extensively elsewhere [31]). Peripheral signals traveling along vagal afferents regulate various aspects of behavior and energy homeostasis [32] and participate in the etiology of mental disorders [31]. In line with this, stimulation of the vagus nerve emerged as a therapeutic tool for the treatment of several pathophysiological conditions, including obesity and diabetes [33,34]. Intriguingly, a subset of DRG neurons, traditionally known to relay pain, touch, and proprioceptive information [35], were shown to innervate metabolically active organs such as WAT and suggested to relay information to the brain [36]. Ablation of WAT-projecting somatosensory neurons alters WAT physiology resulting in changes in body weight and glucose homeostasis [37,38].

Endocrine and sensory feedback signals are integrated in the brain with salient external environmental stimuli (perceived via our senses; e.g., the smell and sight of food) to generate the appropriate behavioral (e.g., feeding), hormonal (e.g., via the hypothalamic-pituitary-adrenal axis), and autonomic-mediated physiological response to regulate homeostasis (Figure 2). Central activation of specialized sympathetic neurons [39], innervating the organs, coordinates metabolism by stimulating lipolysis (WAT) and gluconeogenesis (liver), inhibiting insulin production (pancreas), and inducing heat production (BAT) during a stressful event. When the stressor is removed, parasympathetic neurons are recruited to counteract sympathetic activity [40]. While sympathetic innervation of WAT, BAT, and liver has been confirmed, parasympathetic and sensory innervation of these tissues, and its function, is sometimes debated or remains to be confirmed [41,42]. Despite remarkable progress in our understanding of the neuroendocrine interactions regulating homeostasis, many questions remain to be answered. For instance, the unbiased molecular interrogation and functional characterization of parasympathetic neurons, and some of the largest

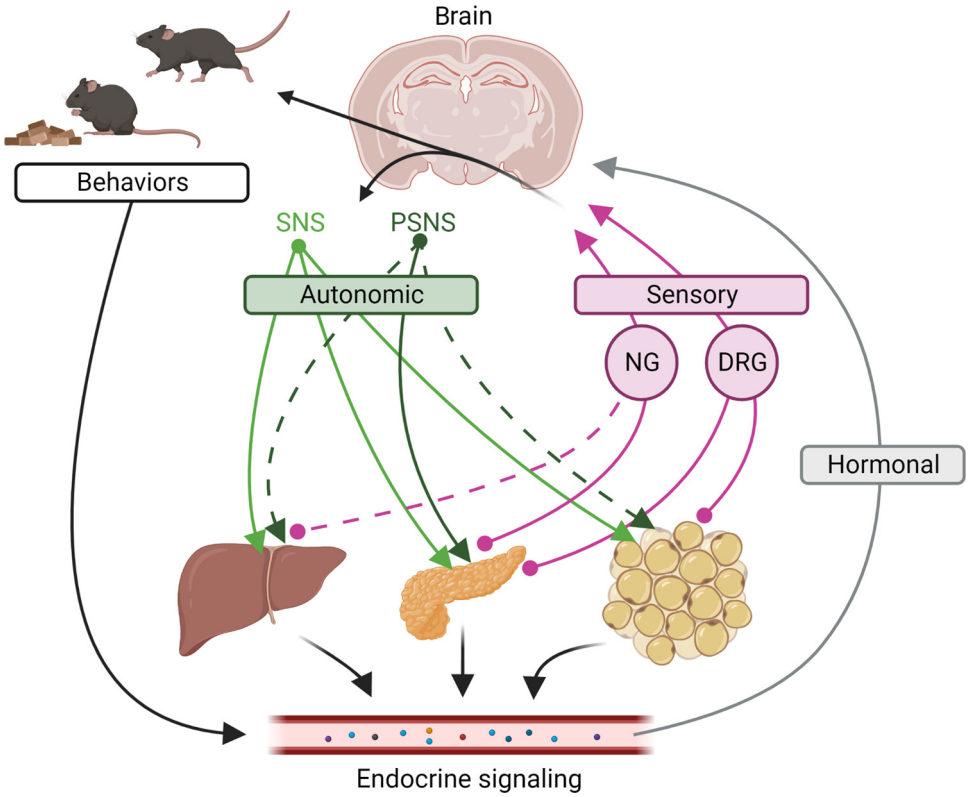

Figure 2. Representation of the peripheral nervous system as an integral component of the neuroendocrine system. Sensory neurons are located in the nodose ganglia (NG) or dorsal root ganglia (DRG) and connect the organs to the brain via the ascending sensory pathway (in pink). The descending autonomic nervous system is divided into the sympathetic (SNS; light green) and the parasympathetic (PSNS; dark green) branches. The brain integrates internal (sensory, hormonal) and external signals and generates behaviors and physiological responses by modulating the activity of autonomic neurons. These efferent neuronal signals control metabolism as well as hormone secretion in peripheral organs. Dashed lines represent undiscovered or debated innervation routes. Figure created using BioRender (www.biorender.com).

sympathetic ganglia (e.g., the celiac ganglion) is lacking. Tracing studies from WAT revealed the existence of specialized cells in the brain receiving sensory inputs from adipose tissue and delivering autonomic outputs to the adipocytes, therefore enabling a loop for signals to be exchanged. Whether endocrine, somatosensorial, and vagal inputs work in parallel or in synergy to coordinate the effector response and whether organs other than WAT possess similar loop-circuitry paths to the brain is, to the best of our knowledge, unknown. Interestingly, some areas implicated in the regulation of circadian rhythms, including the central circadian pacemaker located in the suprachiasmatic nucleus, were traced from WAT, liver, and pancreas, indicating a link between the brain clocks and metabolic organ regulation. Furthermore, many neuronal connections with peripheral organs were traced in extrahypothalamic regions [43–45], suggesting a role for higher brain functions in metabolic control. In the next sections, we discuss the role of the circadian system and cognition in metabolic control, in the context of modern societies.

The circadian system

Brain–body regulation of energy homeostasis has evolved in the context of day/night cycles and led to the evolution of genetically encoded molecular clocks whose function is to align metabolism

with the time of day [46]. These molecular clocks, which are present in every organ including the brain, communicate with each other via behavioral, endocrine, metabolic, and neuronal signals [8]. At its core, a molecular clock comprises a transcriptional–translational feedback loop with the activators BMAL1 and CLOCK forming a heterodimer, binding to E-box elements, and transcribing thousands of genes [47]. Among these are the *PER1-3* and *CRY1-2* genes forming a negative feedback loop. Their corresponding proteins accumulate in the cytosol, where they are post-translationally modified and form heterodimers that translocate to the nucleus, where they negatively regulate the activity of BMAL1 and CLOCK. This loop takes about 1 day (i.e., 24 h) to complete and equips every nucleated cell with its timekeeping system controlling metabolic processes needed in a time-of-day-dependent manner. In addition, several metabolic pathways are integral components of the circadian machinery and provide substrates and/or co-substrates for epigenetic regulators [48]. CLOCK itself is an acetyltransferase protein regulating circadian rhythmicity by utilizing acetyl-CoA to mediate BMAL1 acetylation [49]. Moreover, the circadian transcriptional activators regulate NAD^+ levels via transcriptional regulation of *Nampt* in the salvage pathway. NAD^+ levels regulate SIRT1 deacetylase activity [50] and thus form a feedback loop comprising transcriptional regulation, metabolic control, and epigenetic modification. Other metabolic pathways mediating circadian transcription via the molecular clock include the end-product in the hexosamine biosynthesis pathway UDP-GlcNac, which is the substrate for the post-translational modification *O*-GlcNacylation [51] as well as methionine metabolism-regulating methylation [52]. Hence, the molecular clock is bidirectionally coupled with metabolism by regulating metabolic processes that communicate back with the clock via epigenetic mechanisms.

As described earlier, the metabolism is controlled by interorgan intercommunication allowing organ-specific circadian clocks to synchronize metabolically. For instance, maladaptive behaviors (e.g., feeding on a high-fat diet) disrupt [53] while physical activity rewires temporal metabolic interorgan coordination [54]. Transgenic mouse models have been used to dissect the specific contributions of the clocks in various tissues to the regulation of systemic metabolism. For instance, liver-specific *Bmal1* knockout results in systemic hypoglycemia [55]. Furthermore, the hepatic clock integrates feeding cues to control local transcriptional rhythms [56] as well as buffering untimely food intake to protect the rewiring of transcriptional rhythms in other organs [57]. Muscle-specific clock knockout results in muscular insulin resistance [58]. In mice with constitutional deletion of *Bmal1*, transgenic reconstitution of the clock to both liver and muscle, but not to either of these organs alone, is sufficient to rescue glucose tolerance when feeding rhythms are forced [59]. Finally, the gut microbiome is a well-established player in the regulation of circadian metabolic rhythms [60]. The circadian system is thus a complex interplay between behaviors, the microbiota, and genetically encoded clocks.

The role of the clocks in metabolically active organs has been thoroughly studied in the context of metabolism. However, the brain clock, including the central pacemaker in the suprachiasmatic nucleus, is sufficient to drive the rhythms of most circulatory metabolites and to restore glucose tolerance independent of any peripheral clocks [61]. The systemic metabolic oscillations are likely to be driven by feeding–fasting rhythms; however, the restoration of glucose tolerance in mice with only the central clock is probably also regulated by neuronal communication with peripheral organs, as time-restricted feeding alone was shown to be insufficient to fully restore glucose tolerance [59]. Supporting this notion, the lack of another component of the circadian clock, *Rev-erb*, in mouse GABAergic neurons resulted in insulin resistance without influencing eating or locomotor rhythms [62]. These results suggest that the clock system in the brain plays an important role in the regulation of metabolic homeostasis. Circadian neuronal signaling to peripheral organs is a poorly studied area. One unexplored possibility is that brain–body communication is gated by molecular clocks in

the autonomic and sensory nervous systems, forming, with the organs and the brain, ascending and descending regulatory paths. Taking these findings together, the metabolic system is timed, and the timekeepers are the molecular clocks that, in a tissue-specific manner, suffice in and/or necessitate the regulation of various metabolic pathways (Figure 3).

Environment and higher brain functions in metabolic control

It is well established that the environment has an impact on metabolic health. For instance, access to bicycle lanes increases physical activity [63] and an abundance of fast-food restaurants is associated with higher body weights [64]. However, the relationship between the environment and metabolic control is more complex than that. The notion that obesity is the result of mechanisms that evolved to store extra energy in times of abundance to survive times of

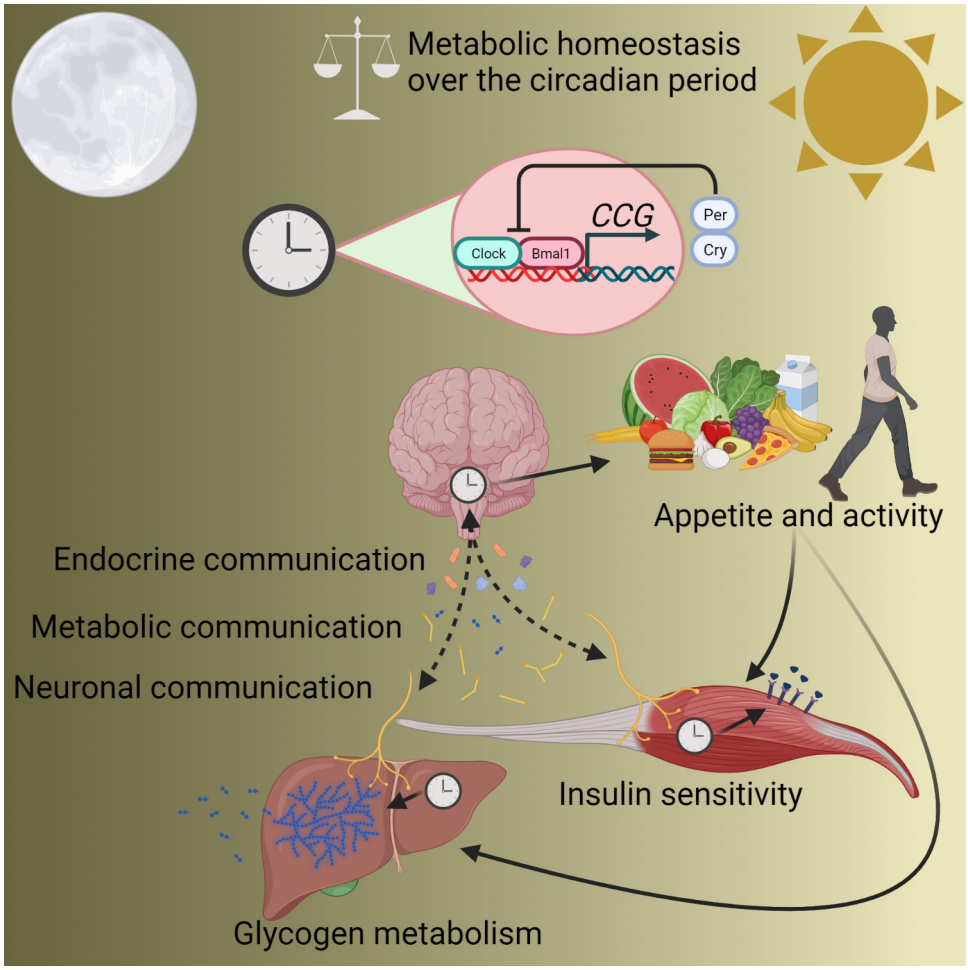

Figure 3. An overview of the temporal coordination of metabolism between organs. The genetic molecular clock, comprising the transcriptional activators BMAL1 and CLOCK and their repressors, the PERs and CRYs, is represented by an analog clock. The central clock in the brain communicates with clocks in peripheral organs through endocrine, metabolic, and neuronal signals to coordinate systemic metabolism with behavior. The clocks in peripheral organs are crucial for some metabolic functions locally, including glycogen metabolism mediated by the liver clock and insulin sensitivity mediated by the muscle clock. Figure created using BioRender (www.biorender.com).

famine may not be sufficient to explain metabolic disease in the context of modern times. Although the environment is a known, strong predictor of behavior and the prevalence of obesity [65], the association between environment and body mass index (BMI) is stronger in populations of low socioeconomic status [66]. Further, an individual's food choices and physical activity level are positively correlated with the parents' education level [67]. Finally, socioeconomic status, including household education level, influence higher brain functions [68], an aspect which is often overlooked as a contributing factor in the pathophysiology of metabolic disease.

The involvement of higher brain regions in the vulnerability to obesogenic environments is supported by an association between BMI and cognitive function [69]. A causal relationship linking metabolic dysfunction to cognitive decline is supported by longitudinal studies demonstrating that insulin resistance precedes perturbations of memory [70]. The underlying mechanisms are not fully understood but may involve extracellular vesicle signaling from WAT to the brain [71]. Conversely, evidence suggests a causal link back from cognitive function to the regulation of metabolic homeostasis. For instance, associative learning linking hypercaloric foods to reward is impaired in women with obesity [72], thus increasing the risk of unhealthy eating in an obesogenic environment. Interestingly, cognitive stimulation in the home environment has been shown to predict the incidence of childhood obesity independent of other socioeconomic factors [73], suggesting that higher brain functions contribute to the regulation of energy balance. A comparison between the association of appetite-regulating hormonal levels and prefrontal cortex activity in weight loss maintenance suggests that the latter is a better predictor of weight-regain prevention [74].

The building of societies that promote physical activity and healthy food habits is undoubtedly an effective strategy to prevent and potentially reverse the rise of the obesity pandemic and related metabolic diseases. At the same time, considering and including cognitive approaches in therapy might improve the efficacy of current treatments.

Concluding remarks

Although body weight homeostasis is indeed achieved via a balance between energy intake and expenditure, the mechanisms enabling this regulation, and its disruption, are complex and multifactorial. There are many gaps in our knowledge that remain to be filled (see Outstanding questions). The brain is in constant communication with metabolic organs via the endocrine and peripheral nervous systems. Specialized neurons integrate interoceptive signals with external information from the environment to adjust energy management. This communication is timed by genetically encoded clocks in both the brain and the periphery to ensure interorgan coordination and proper physiology. Perturbations to this system – promoted by the obesogenic environment – ultimately result in misalignment between behaviors (food intake and physical activity) and tissue functions (e.g., WAT lipid storage/release, liver macronutrient supply, muscle macronutrient uptake, pancreatic hormone release), which manifest in metabolic disorders (Box 1). Interrogation of the circuits connecting the brain to the organs has been hindered for a long time because of the secluded and scattered anatomical location of peripheral ganglia and the lack of tools to access them. Now, newly developed viral vectors allow us to map the circuitry enabling brain–body communication with unprecedented precision. From a preclinical point of view, the next challenge is to devise tools to specifically manipulate the activity of the neurons forming these circuits and infer their function. In the clinical context, the elucidation of brain–body mechanisms involved in metabolic homeostasis will provide the healthcare system with novel approaches to identify the patient-specific cause of disease as well as appropriate personalized therapies.

Outstanding questions

How does vagal and somatosensory innervation of peripheral organs control systemic metabolic homeostasis?

To what extent do molecular clocks coordinate brain–body metabolism?

What is the contribution of extrahypothalamic brain nuclei to metabolic health?

Are there therapeutic approaches targeting brain–body communication that can be used to prevent and treat metabolic disease?

Box 1. Brain–body communication in disease

An outstanding question that remains to be answered is how brain–body communication contributes to the pathophysiology of metabolic disease. Because these morbidities are multifactorial, it is challenging to infer causality. However, we can speculate, based on our current knowledge, the complex cascade of factors and events that lead to pathophysiological conditions. The environment, engagement in shift work, and socioeconomic status are some of the external factors that contribute to obesity and its comorbidities [65,69,75]. These factors may perturb brain functions and interfere with homeostatic processes [76] and circadian rhythms, leading to overeating outside mealtimes. Excess caloric intake at the wrong time of day challenges the body's energy storage capacity and causes hypertrophy of adipose tissue. Endocrine and sensory signals communicate the altered energy state to the brain, further impinging on mental health. Prolonged exposure to aberrant internal stimuli (e.g., high circulating leptin or insulin levels) may promote resistance. Without negative feedback (e.g., satiety signals), caloric intake further increases. The inability to store the extra energy in the WAT – which has now reached its maximum capacity – results in ectopic lipid accumulation, insulin resistance, hyperinsulinemia, and eventually metabolic disease [77]. Lack of insulin signaling in the brain is communicated back to the periphery via the descending autonomic nervous system [28], further disrupting the systemic metabolism and worsening the disease state, in a vicious loop.

More tools to help patients 'break' these vicious loops are required. The recent development of GLP1 analogs such as semaglutide and the refinement of vagus nerve stimulation approaches shows that harnessing the ability to control body–brain signals is crucial to reverse metabolic disease [32,78]. However, less invasive, more economical, and more long-lasting approaches are needed. In this regard, we believe that elucidating the role of the 'extrahypothalamic brain' will lead to groundbreaking discoveries and their translation into novel approaches to treat metabolic disturbances. To achieve sustained metabolic homeostasis longitudinally, more interdisciplinary efforts are needed.

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Declaration of interests

No interests are declared.

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