Physiology of energy homeostasis: Models, actors, challenges and the glucoadipostatic loop

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Abbreviations

AgRP, agouti-related peptide; BSS, behavioral satiety sequence; AMPK, AMP-activated protein kinase; ARC, arcuate nucleus; BDNF, brain-derived neurotrophic factor, CART, cocaine and amphetamine regulated transcript; CCK, cholecystokinin; CfD, cafeteria diet; CNS, central nervous system; DIO, diet-induced obesity; DIWL, diet-induced weight loss; DMH, dorsomedian nucleus; DMV, dorsal motor nucleus of the vagus; DR, diet resistant; EB, energy balance; EE, exergy expenditure; EH, energy homeostasis; EI, energy intake, EIEE, exercise-induced energy expenditure; FFA, free-fatty acids; GLP-1, glucagon-like peptide 1; IMI, intermeal interval; LH, lateral hypothalamus; MCH, melanin concentratin hormone; NPY, neuropeptide Y; NEAT, non-exercise activity thermogenesis; nREE, non-resting energy expenditure; NAcc, nucleus accumbens; NTS, nucleus tractus solitarius; OXM, oxyntomodulin PAL, physical activity level; POMC, pro-opiomelanocortin; PP, pancreatic polypeptide; PPGD, preprandial glucose decline; PVN, paraventricular nucleus; REE, resting energy expenditure; SCN, suprachiasmatic nucleus; SNS, sympathetic nervous system; SPA, spontaneous physical activity; SF-1, steroidogenic factor 1; TEE, total energy expenditure; VMH, ventro-medial hypothalamus; VTA, ventral tegmental area; WAT, white adipose tissue.

Abstract

The aim of this review is to discuss the physiology of energy homeostasis (EH), which is a debated concept. Thus, we will see that the set-point theory is highly challenged and that other models integrating an anticipative component, such as energy allostasis, seem more relevant to experimental reports and life preservation. Moreover, the current obesity epidemic suggests that EH is poorly efficient in the modern human dietary environment. Non-homeostatic phenomena linked to hedonism and reward seem to profoundly impair EH. In this review, the apparent failed homeostatic responses to energy challenges such as exercise, cafeteria diet, overfeeding and diet-induced weight loss, as well as their putative determinants, are analyzed to highlight the mechanisms of EH. Then, the hormonal, neuronal, and metabolic factors of energy intake or energy expenditure are briefly presented. Last, this review focuses on the contributions of two of the most pivotal and often overlooked determinants of EH: the availability of endogenous energy and the pattern of energy intake. A glucoadipostatic loop model is finally proposed to link energy stored in adipose tissue to EH through changes in eating behavior via leptin and sympathetic nervous system activity.

1. Introduction

Homeostasis is the tendency of an organism to maintain a stable internal state. It is a more neutral and descriptive concept than control or regulation [1], that need to determine the operator and the regulated value [2] to achieve balance. In the case of energy homeostasis (EH), this supposes that the energy balance (EB) between the energy supplied and dissipated is stable. For some authors, this means that energy stores are kept constant throughout the lifespan. The worldwide epidemic of increased obesity in humans [3] shows that this is not the case, at least during the dynamic phase. Actually, EH is often used to describe the mechanism by which an organism not only fulfills its energy needs, but also reduces or induces input (intake) when output (expenditure) decreases or increases, respectively. If energy needs are efficiently supplied when environmental conditions are appropriate, experimental and epidemiological data show that the reduction of energy intake (EI) is not sufficient to preclude increased energy storage when energy expenditure (EE) is low e.g., low physical activity level (PAL), leading to fat deposition and obesity. Mechanisms of EH seem to be poorly efficient against excessive EI in individuals [4]. One hypothesis is that in certain dietary environments and with certain behaviors, excess EI relative to total EE (TEE) is necessary to maintain energy supply due to impaired mobilization of energy stores.

In the concepts of homeostasis by Claude Bernard [5] or Walter Cannon [6] there was the notion than outside of a given interval of stability, life was not possible. Neither of them imagined a fixed programmed value but only a response adapted to an external stimulus [7]. However, homeostasis was reactive and not anticipative. Most of the models were based on the satisfaction of basic needs, such that the response of the organism to the low availability of a specific need for an "element" resulted in the stability of the dependent body variables, either by a behavioral (research of the required "element") or physiological (cascade of effects leading to the compensation of this missing "element") response. The opposite was expected when the "element" was provided in excess. This theory is now challenged, supporting a large excess of EI without apparent behavioral or physiological responses leading a large proportion of humans, notably in recent history, to store much more energy than they need. This may either be interpreted as a failed EH or maybe it is an incorrect understanding of what is EH. It must be remembered that overweight and obesity conditions did not exert any negative selective pressure on humanity during most its history.

2. Modelizing and discussing energy homeostasis

2.1. Input and output of energy homeostasis

EH must not be represented by a simple input / output model. Between the two lies a very flexible energy storage compartment which is the target of many physiological factors (Figure 1). A long history of experimental studies conducted in animal models has explored these factors. In rats confined in a laboratory or in animals and humans during growth, more than homeostasis, we should use the term homeorhesis [8], the phenomenon by which the internal state is maintained, not in the initial state but in the state of its normal trajectory through time. Control groups of rats usually gain weight and fat mass during the experimental periods. Thus, when the interventional groups are compared to their control pairs to determine whether homeostasis occurred, what is tested is not homeostasis *per se*, but homeorhesis.

2.2. The set-point theory

The set point theory [9] supposes that a regulated hypothalamic body weight or white adipose tissue (WAT) mass would be defended against voluntary (e.g., dieting) or involuntary (e.g., fluctuating availability or composition of food) changes. This would make EH an ancillary mechanism to fat mass regulation as proposed by Kennedy [10] in his lipostatic model. He proposed that fat mass was regulated at the hypothalamic levels so that it remains constant in varied environmental conditions and provides the necessary energy substrates. Kennedy was the first to link adipose tissue (called "fat depots") to satiety. This was an innovative and promising concept that was even interpreted as the existence of a adipocyte-derived factor acting on eating behavior [11]. The theory would be confirmed several years later, notably with the discovery of leptin. This direct afferent link was demonstrated with the observation that adipocyte size may alter food intake [12]. However, the results of surgical lipectomy have challenged the theory that fat mass was tightly regulated, showing that fat pads restoration displayed large variations according to their localization [13] and to the composition of provided food, being only effective with a high-fat diet [14]. Interestingly, leptin is not involved in this restored process [15]. The restoration of fat mass after lipectomy was hypothesized to be the consequence of reduced sympathetic nervous system (SNS) activity and consecutive reduction in TEE and lipolysis more than increased EI [16]. Importantly, another lipostatic approach was proposed by Jacques Le

Magnen, based on the fatty acid utilization during the rest period (daytime in rats) of the fatty acids stored during the active period (nighttime in rats) [17]. Overeating in the active period was associated with increased fat synthesis and followed by reduced food intake and increased lipolysis in the rest period. Therefore, a more flexible metabolic model was therefore proposed and experimentally supported [18], in which fat mass stabilization was achieved when the mean respiratory quotient reached the mean food quotient i.e., the proportions of fat and carbohydrate metabolized by the organism reached those in the diet. Thus, more than energy *per se*, the macronutrient content and individual potential oxidative capacities, would be a prerequisite for accurate EH. EH could be considered as a stochastic value with some possibility to be predicted with an expected accuracy if enough determinants are known. The major challenge to date is to accumulate the exhaustive inventory of these determinants. Although the set point theory is strongly contested [2,7] to this date it is a theoretical framework used by many authors [19].

2.3. Alternative models to homeostasis

One hypothesis is that EH is not centered on the stability of energy stores or the equilibrium between energy needed and supplied, but on the availability of energy over the various periods of energy disposal during the circadian cycle. This would explain why some dietary or sedentary habits lead to apparently inconsistent EI, and an excess of energy stored in the form of fat mass, due to a weak stimulation of fatty acid disposal. The allostasis concept in which the body "anticipates needs and prepares to satisfy them before they arise" [20] seems to fit more to observations in the domain of EH. A predictive model [21], in opposition to a reactive model, is not only better adapted to the irregular availability of energy substrates, but avoids the unpleasant consequences of energy deficit such as prolonged hunger [22]. It has been shown that rats adapt to meal omission by rapidly switching from a reactive (increase of the next meal size) to an anticipatory (increase of the previous meal size) strategy when conditioning is possible using external e.g., time of day [23] or nutritional, e.g., odor or savor [24] cues. Thus, food intake, and therefore EH, must be considered as Pavlovian conditioning [25] with sensory characteristics of foods and the environmental cues associated with food intake, as conditioning factors. To this day, most of the models of EH are unfortunately based on a response to a shortage of energy and not to

cues signaling a necessary anticipatory behavior. Moreover, the behavioral components of EI are too much overlooked.

2.4. The role of pattern of energy intake in energy homeostasis

Energy exchanges are not a continuous but a sequential process. If TEE is relatively constant on a daily scale, bouts of EE, most often due to physical activity, are however spread during the circadian cycle. Similarly, energy is provided through macronutrients in the form of food in a specific entity called a meal. A meal is not simply an eating period, but has several temporal, behavioral and even biological characteristics (see below, in the Glucose section). In rats, a behavioral satiety sequence (BSS) is even used to define a meal [26]. Some authors have defined non-meal eating (snacks) as having some missing criteria of the BSS [27]. In humans, meals are most often defined on purely cultural criteria (breakfast, lunch, dinner) and snacks as intermeal eating, but some biological and behavioral characteristics have been proposed such as initiating eating with a low or no-hunger feeling [28]. For heuristical purposes, a meal should be considered as a physiological process of energy supply. There are some reasons to suspect that snacks contribute to excess EI and may impair EH [29]. When eating in the absence of hunger (EAH) was studied, it was positively associated with weight gain in adolescents [30] and normal-weight women [31]. The supposed benefit of snacking on satiety and EH [32,33] uses the social or quantitative definition of snacks, confusing the putative benefits of meal frequency with snacks [34]. According to definitions used for snacks, their effects on EH are discrepant [35]. Our team has repeatedly found that snacks, defined as eating in a no-hunger state, exerted poor satiety effects and were not compensated for at the next meal and therefore added extra-energy to total EI [28,36,37]. However, the consequence on 24-h EB is not known. Since conditioning on an arbitrary cue can trigger eating [38], it is possible that permanent food solicitation may initiate EAH.

In free meal conditions, EI response to varying availability or energy content of food, occurs mainly through the modification of intermeal intervals (IMI) and not meal size [39]. Thus, satiety (duration of the IMI) and not satiation (size of the meal), seems to be the main component of EI involved in EH [40]. This role in the homeostatic response to diets inducing obesity has been highlighted in a study where after a phase of weight gain, rats fed a highly palatable diet decreased their eating frequency that became much lower than in rats maintained on chow [41]. This was shown in diet-induced obesity (DIO) compared to diet

resistant (DR) or chow fed rats [42], and further confirmed when separating meals and snacks based on BSS characteristics, with a decrease in meal but not snack frequency [27]. Similarly, in humans, switching from 4 to 3 meals per day led to increased fat mass after 30 days [43], confirming that longer IMI (lower meal frequency) is rapidly associated with higher fat mass. This confirmed older studies conducted in free-living conditions showing that children switched on a low meal frequency increased their fat mass compared to children on a high meal frequency [44]. Moreover, individuals with a high meal frequency showed a reduced risk of obesity [45] an improved efficiency in adapting EI to manipulation of foods and maintaining EH [46]. The supposed fat mass-increasing effect of high eating frequency, for example in postmenopausal women [47], is based (and biased) on a definition of eating not discriminating between meals and snacks (any drink, sugar-containing or not, consumed without any food was even considered as an eating episode). Moreover, in randomized controlled trials comparing eating frequency, eating episodes are not defined [48].

In rats, it was demonstrated that during the passive period, animals used fatty acids stored during the active period to delay IMI and therefore reduce meal frequency [17]. In humans, spontaneous initiation of meals is a prerequisite to explore the role of eating patterns in EI and EH. Using this procedure, our team has found that dietary [49,50] and pharmacological [51] interventions that enhance fat availability to metabolism, increased satiety i.e., length of the IMI. The mechanism would involve the sparing-glucose effect of fat oxidation [52], known as the Randle cycle [53,54], that may delay the next meal onset. However, the ratio between the oxidized proportion of dietary fat and the increase in IMI is small [49], leading to fat storage [55].

3. A brief description of the actors involved in energy homeostasis

Multiple substrates, hormones, neurotransmitters and brain neurons [56] were found to exert an action on EH through their effects on EI and/or EE, and new molecules are constantly discovered [57]. An exhaustive analysis and discussion of their putative involvement in EH would exceed the authorized length of this review. However, it is important to schematically distinguish six components (Figure 2).

The first component is the beam of afferent hormones and neurons linking the peripheral system to the CNS [58]. Most studied were 1) the adipokines leptin [59] and adiponectin [60], 2) the pancreatic hormones insulin [61], amylin [62] and pancreatic polypeptide

(PP)[63], 3) gut hormones such as the anorexigenic cholecystokinin (CCK), glucagon-like peptide 1 (GLP-1), oxyntomodulin, peptide tyrosine tyrosine (PYY) [64–66], and the orexigenic ghrelin [67], and 4) the vagal neurons [68].

The second component is the hypothalamus, the brain area where peripheral messages induce homeostatic responses altering EI and EE [69,70]. Most of the afferent pathways converge on the arcuate nucleus (ARC) where are localized neurons synthetizing the orexigenic neuropeptide Y (NPY) and agouti-related peptide (AgRP) as well as the anorexigenic pro-opiomelanocortin (POMC)-derived α melanin stimulating hormone (αMSH) and cocaine and amphetamine regulated transcript (CART)[71]. Projections are sent 1) from the NPY/AgRP neurons to NPY receptors (NPY1, NPY2 and NPY5) in the orexin and melanin-concentrating hormone (MCH) neurons of the lateral hypothalamus (LH) leading to increased EI, and 2) from the POMC/CART neurons to the melanocortin receptors (MC3R/MC4R) localized on the paraventricular nucleus (PVN) leading to decreased EI. Moreover, AgRP acts as a natural antagonist of MC3R and MC4R, inhibiting the orexigenic action of αMSH [72]. Other target of the POMC/CART neurons is the ventromedial hypothalamic nucleus (VMH), activating neurons synthetizing the anorexigenic brain-derived neurotrophic factor (BDNF) [73]. The VMH also exerts a potent stimulating effect on SNS activity [74].

The third component is the brainstem and notably the nucleus tractus solitarius (NTS), receiving contributing to reduced EI through the interaction between leptin and gut hormones (e.g., GLP-1) with AMPK as intermediate, [75] integrating blood-borne and vagal mediated messages from periphery [76].

The fourth component is the reward system consisting of: 1) the mesolimbic dopamine system and more specifically the ventral tegmental area (VTA) and the nucleus accumbens (NAcc), where schematically the hedonic and reward response to eating are established based on previous experiences [77], and 2) the opioid system in specific subregions of the ventral pallidum (VP)[78] and the NAcc (the hotspots) [79], specifically involved in the reward of highly palatable food [80] and the support of the "liking" versus "wanting" theory [81] according to the implication of the hedonic component in the reward-induced motivations to eat [82]. Lastly, the amygdala, through its connection with the LH, is crucial for conditioning processes i.e., associating food to cues [83].

The fifth component is the cognitive frontal and cortical system, notably the prefrontal cortex (PFC) and anterior cingulate cortex (ACC)[84], involved in decision making, self-control and executive functions that were found to differ between non obese and obese status of the individuals [85].

All of these brain areas are highly interconnected [82] and EH must be considered as resulting from an integrative process involving all of these aforementioned brain and peripheral actors [84]. For example, ghrelin [86] and amylin [87] have been shown to interact with the dopamine mesolimbic system.

The sixth component, often overshadowed by the directly altered EI effect of these factors, is the neuronal efferent pathway represented by the SNS. This is all the more important since as we will see, its role exceeds the modulation of EE but may also strongly influence the effects of all the previous factors on EI [88].

4. Energy homeostasis challenges

Conditions challenging EH represent potential sources of knowledge about its mechanism of action. Among them, four are particularly interesting due to their relevance to contemporary situations in humans.

4.1. Exercise

Studies showed that when shifted from inactivity to exercise on a treadmill, rats did not increase their EI but decreased it and lost weight [89], thus challenging the concept of EH. It was not before reaching 60 min of daily exercise that EI reached a higher level than when they were inactive [90]. The homeostasis interval was estimated between 1.7-1.8 and 2.2 x REE [91]. These results raise two complementary interpretations: 1) "no-exercise" leads to a positive energy balance resulting in gain weight, and 2) under a certain volume of activity, exercise-induced energy expenditure (EIEE) is not compensated. The possible contribution of low PAL to human obesity [92,93] has received some support and is consistent with the hypothesis that under a threshold level of PAL, EH is impaired.

In obesity, exercise induces only modest weight-loss [94] but results in a decrease in fat mass and an increase in fat-free mass [95], showing the mobilization of energy stored in the WAT. Considering the role of exercise in EH only through the consequences on EE is erroneous. Although even in very active individuals EIEE may only account for 15 to 30% of TEE [96,97],

exercise leads to profound metabolic changes [98] that alter substrate metabolic partitioning between oxidation and storage [99]. One mechanism of these exercise-induced benefits in EH would actually be through its effects on TEE [100] and free fatty acid (FFA) release from the WAT [101], both being potentially mediated by SNS activity [102] leading to increased fat oxidation as soon as in the post-exercise period [103].

As in rats, EIEE is weakly compensated in humans [104,105] at least in the short-term. The mechanisms of this absence of efficient energy compensation is still unclear but the involvement of gut peptides, specially GLP-1, PP and PYY [106] and also acylated ghrelin [107,108] have received some experimental support. Importantly, when individuals are free to initiate their meal following an exercise session, an increased IMI has been reported [109–111]. The post-exercise increase in FFA disposal may contribute to this effect [112] notably through increased SNS activity during exercise [113] and an improved catecholamine response in the WAT [114].

4.2. Cafeteria and high-fat diets

The fact that rats can drastically increase their EI without apparent need and become obese when either high-fat [115] or highly varied, palatable and high-energy density foods [116] are provided i.e., cafeteria diet (CfD), suggests that EH can be easily overridden with a simple modification of dietary environment. This excess EI and consequent body weight gain greatly varies both across strains [117] and between substrains [118] of rats, some showing no tendency to overeat and to gain weight (illustrating accurate EH) whereas others showing various levels of gain weight, some reaching high level of obesity (illustrating failed EH). Interestingly, variety constantly leads to weight gain whereas less varied but high-fat diets produce obesity only in DIO rats [119]. High-energy density of the CfD is not the culprit since variety with low-energy density foods can yield a similar and even greater level of overeating and weight gain [120–122]. The increased EI effect of variety has been verified in human studies [123,124] and may represent a major factor of failed EH and obesity [125]. This has led some authors [126] to propose that EI is not only driven by homeostatic but also by non-homeostatic mechanisms, mainly related to hedonism and reward [127]. The eating triggering-power of the environment is a potential disturbance factor, free choice being one of the main causal factors of the obesogenic power of a high energy-density diet [128]. These results indicate that EH is easily impaired or, more neutrally, switched to a new

equilibrium, by dietary conditions such as variety and palatability. This supports the potential role of the hedonic reward system to alter EH toward a non-homeostatic EI [127].

Interestingly, when metabolic characteristics of DIO compared to DR rats were analyzed, the most often reported results were a reduced SNS activity and a lower efficiency to oxidize fat [129], associated with increased insulin levels [130]. This difference in the capacity to oxidize dietary and stored fats in rats is in common with human diet induced obesity [18].

4.3. Overfeeding

A recent systematic review [131] concluded that overfeeding leads to a 7 to 18% increase in TEE, allowing ~25% of excess energy to be dissipated [132]. This suggests that the efficiency for EE to realize EH is limited. Among the components of TEE, REE represented only a small part (~one fourth) of overfeeding-induced increase [132]. EIEE was reported to display 38 to 50% of the increase in EE [132–134], integrating spontaneous physical activity (SPA) as a potent actor of EH. Non-exercise activity thermogenesis (NEAT), such as fidgeting, posture, and the physical activities of daily life, represented the largest part of the increased EE and was found to be closely linked to overfeeding-induced fat storage [133]. No reduction in EI was observed during the days following an overfeeding period [134,135]. However, in real life conditions, when subjects are back in their pre-overfed dietary environment, they return to their initial body weight after several months [136]. It is not known whether this is the consequence of a physiological process or of the complex interaction between social, cultural and biological parameters. Moreover, age seems crucial since young (~24 yr) but not elderly (~70 yr) men were reported to lose all the accumulated weight gain during the overfeeding period after 46 days [137]. On the mechanistic side, SNS activity has again been proposed as the candidate to explain differences in altered EH [138], limiting energy storage in increasing EE.

4.4. Weight-loss

Relapses after diet-induced weight loss (DIWL) are relatively frequent (~50% at year 1) [139,140]. Factors leading to weight regain are beginning to be clearly determined including: decreased PAL, increased percentage of dietary fat, and dietary disinhibition [141–143]. The reduction in REE after DIWL strongly depends on the type of tissue lost i.e., decreased energy needs if more fat-free mass is lost, but is constantly higher than that predicted by

tissue loss. Called adaptative thermogenesis, this phenomenon represents a factor limiting further weight loss [144], explaining ~50% of the less than expected weight loss results [145]. In a study [146], 10% of body weight lost in lean and obese individuals obtained with a low-energy diet, was associated with a 10 to 15% decline in REE. The proportion of fat mass lost showed a high variability between individuals and between initial BMI categories e.g., 63.7 ± 27.5% and 83.6 ± 23.8% in lean and obese subjects, respectively [146]. This was associated with a 20% increase in skeletal muscle work efficiency that could account for ~75% of the decline in non REE [147]. There are various causative factors: a decrease in the glycolytic to oxidative enzyme activity ratio [148], a change in muscle fiber structure [149] and a decrease of SNS activity [150]. The higher than expected reduction in TEE after a DIWL would have no impact on regain if EI decreased accordingly. However, an increased motivation to eat was described using subjective (questionnaires) and objective (meal intake) tools after a 10% body weight reduction [151]. Excessive EI relative to energy needs after DIWL suggests that the energy consumed to maintain body weight is not sufficient to preclude an activation of the orexigenic system. With eating behavior being subjected to a learning process linking EI to the post-prandial effects and energy needs [24,152], the conditions are therefore not fulfilled for a satisfying flux of energy precluding the body to search for more energy. Allowing EI mechanisms of EH to operate seems to be important, since an *ad libitum* low-fat diet leads to an improved maintenance of DIWL compared to a fixed energy similar diet [153]. Interestingly, exercise has been shown to improve maintenance of weight loss [154,155] in increasing EE but also in changing substrate partitioning in favor of fat oxidation [156].

5. The glucoadipostatic loop

From the various results reported after previously described EH challenges, it appears that the capacities for stored or consumed fatty acids to reenter in the oxidative cycle is crucial to preventing weight gain. The main determinants of these capacities are the SNS, glucose, insulin and leptin. To be exhaustive, the role of some intestinal hormones will be briefly summarized and the influence of the circadian rhythmicity.

5.1. Sympathetic nervous system

The role of SNS activity in EH is well known [157] and its dense and heavily interconnected network with brain areas such as the ARC, the VMH and the DMH has been extensively described [158]. Importantly, WAT receives SNS innervation from the CNS [159] that increases adipocytes lipolysis [160] and inhibits fat cell proliferation [161]. Visceral and subcutaneous adipose tissues do not completely share the same circuitry [162]. SNS activity has been implicated in the impaired EH associated with obesity [163]. Low muscle [164] and total [165] SNS activity was proposed as a risk factor to developing obesity on a westernized diet after studying the weight gain outcomes in Pima Indians. This led to the MONA LISA (for Most Obesities kNown Are Low In Sympathetic Activity) theory [166]. Once obesity is established [167] or even after modest weight gain [168], muscle sympathetic nervous system (MSNS) activity is higher but WAT SNS activity is lower [169], potentially reducing lipolysis and fatty acid release [170] for supplying energy needs. This may contribute to the apparent discrepancy between EI and energy stores, the latter being not available at the predicted level due to low adipose SNS activity and high insulin levels. Moreover, SNS activity reduces glucose-induced insulin secretion [171] and this action has been considered the onset of metabolic deleterious consequences of the decreased SNS activity induced by high-fat diets [172].

5.2. Glucose

The contribution of glucose to EH has been proposed by Mayer [173] in the conceptual framework of the glucostatic theory, making this energy substrate the main intermediate of the short-term EH in triggering meal onset. This was given experimental support in rats [174] and in humans [175], each meal being preceded by a short preprandial glucose decline (PPGD) [176]. A PPGD was shown to discriminate between meals (EI motivated by hunger) and snacks (EI initiated with low or no hunger feeling) [28]. Thus, glucose is a satiety and not a satiation factor in the sense that it is involved in initiating and not in terminating a meal. The more this PPGD will be postponed, for example by fat oxidation, the longer will be the duration of the IMI as it was demonstrated with various dietary or pharmacological interventions [49,51].

The involvement of glucose in the different areas of the brain controlling energy is ubiquitous. In a classic paper, Oomura et al. [177] reported that in the LH, neurons could be inhibited by glucose (GI neurons) and that in the VMH, neurons showed a dose-dependent

increased excitation in response to glucose (GE neurons) [178]. The role of these GI and GE neurons on food intake was rapidly documented in rats and monkeys [179,180]. In the ARC, orexigenic NPY/AgRP neurons were found to be GI neurons [181] whereas anorexigenic POMC/CART neurons were found to be GE neurons [182]**.** Consistently, GE neuron activity is inhibited by orexigenic neurotransmitters (NPY, orexins) [183] and stimulated by anorexigenic neurotransmitters (POMC, α-MSH) [184]. Importantly, the VMH contains GE and GI neurons [185] and it was shown that food intake was associated with an increased glucose level in the VMH [186]. Thus, consistent with the glucostatic theory, glucose appears to be a pivotal modulator of the action of factors from the afferent pathways in orexigenic and anorexigenic neurotransmitter synthesis and action [187]. For example, orexin synthesis requires a fall in plasma glucose [188]. The actions of glucose-sensing neurons needs the intermediate of glucokinase [189] and the metabolic sensor AMP-activated protein kinase (AMPK) [190]. Moreover, glucose is a potent activator of EE through its effect on the beta-1 adrenergic receptor of the SNS [191]. An impaired glucose response in the hypothalamus has actually been established in DIO rats [192] and obese humans [193].

One hypothesis is that glucose modulates the action of the peripheral actors on the brain areas in charge of EH, with regard of the required concentrations of glucose in the blood. Since it does not completely overlap with the glucostatic theory, it has been renamed the glucoadipostatic hypothesis [194]. In a holistic perspective, it is reasonable to hypothesize that the presence of glucose in the integration of messages provided by multiple neuro-hormonal actors, would represent a safety system for the body.

5.3. Leptin

The role of the adipokine hormone leptin in EH is relatively complex [59]. Since its administration reduces body weight and more specifically fat mass via decreased food intake, it was considered as regulating WAT [195] and called a "satiety" factor [196]. An effect on satiety should mean an increased length between meals and not a reduced meal size. This was confirmed in a study comparing leptin and fenfluramine [197]. Leptin is the main actor of an afferent path linking WAT and the brain, in particular the hypothalamic areas involved in food intake and EE [198–200]. In EH terms, leptin may serve as a hormonal factor leading the body to rely more on stored energy and less on EI. In this mechanistic mode, any change in EI or EE would be followed by an opposite change driven by leptin to

maintain a null EB. Fat mass increases leptin levels and will have two complementary and consistent actions in the CNS: 1) to decrease exogenous sources (food intake) and 2) to increase endogenous sources of energy.

Targets and circuitry for the action of leptin on food intake in the CNS are partially known. In the ARC, leptin stimulates anorexigenic POMC and CART expression [201] and inhibits orexigenic NPY and AgRP expression [202]. In the LH, leptin inhibits orexigenic orexin [203]. In the VMH, leptin activates steroidogenic factor 1 (SF-1) and reduces the orexigenic effect of a high-fat diet [204]. In the NTS, leptin acts synergistically with GLP-1 and CCK to decrease food intake [205]. In the mesolimbic dopamine system and in particular the VTA [206–209], leptin decreases the hedonic response to foods in rats [210] and in humans [211], adding a role of this hormone in the increased-intake effect of food palatability. Lastly, via its inhibiting action on orexin, a neurotransmitter that stimulates arousal, alertness and locomotor activity [212], leptin also modulates SPA. These actions on VTA and orexins were shown to be interrelated and contribute to EH [213].

The mechanism for increasing endogenous sources of energy is less well established. Leptin leads to increased FFA release from WAT possibly via a direct action on adipocytes [69] but much more importantly by increasing SNS activity [170,214] in the ARC [215]. This increased adipocyte lipolysis is also mediated by its direct [216] and SNS-induced [217] inhibitory effect on insulin secretion, demonstrated with changes in physiological concentrations [218].

In the dynamic phase of obesity this mechanism fails, although leptin levels increase proportionally to weight gain [219]. Thus, "something" overrides the homeostatic function of leptin. However, this does not occur for all individuals and this heterogeneity suggests that there are vulnerability factors to this environmentally-induced impaired leptin function in EH. Hitherto, administrating leptin to obese humans without leptin deficiency has resulted only in modest weight loss [220–224]. Actually, leptin replacement exerts a significant physiological effect only when circulating leptin levels are low [225]. Correspondingly, it has been found that leptin administration inhibited all the changes observed after DIWL: decreased levels of TEE [226], increased skeletal muscle work efficiency, decreased nREE and SNS activity [227], reduced satiation [151], hyper-response to visual cues [228].

Altogether, this suggests that leptin would not only be an afferent hormonal intermediate in a WAT-CNS axis leading to reduce EI via its action on homeostatic (ARC, LH, VMH, PVN) and

non-homeostatic (VTA, NAcc, amygdala) brain areas, but also act in a loop with the SNS as an efferent pathway [229], adding endogenous substrate availability, notably FFA.

5.4. Insulin

The role of insulin in energy homeostasis must be considered differently in periphery (i.e., vascular, muscular and visceral) and in the CNS (more specifically the areas involved in EH). In periphery, its classic effects on glucose uptake by insulin-dependent tissues lead to hypoglycemia, hunger, and EI, increasing the number of meals for low doses and both size and number for the highest doses [230]. On the opposite, infusing insulin intravenously to rats during a nocturnal fast led to reduced EI on the subsequent day and this was interpreted as a centrally effect of insulin reducing intake [231]. It had actually been shown that insulin stimulated the GE neurons in the VMH in presence of glucose, but inhibited them when administrated alone, whereas on LH, insulin increased neuron activity in a dose-dependent relation [232]. Further studies clarified this action. Insulin stimulates the GE neurons in the ARC when glucose levels are low, leading to decreased release of orexigenic neurotransmitters and therefore reduces intake, and has no effect when glucose levels are elevated [184]. Insulin receptors are expressed in POMC neurons and insulin administration enhances POMC synthesis [233], and therefore reduces EI and increases EE. Moreover, insulin reduces NPY expression [234]. This latter action seems to be essential for EH as shown recently with animal models lacking insulin signaling in NPY neurons [235]. Thus, similarly to leptin, insulin has been considered as an adiposity signal [236]. Note that the cell signaling of insulin and leptin is often common in POMC [237] and NPY [238] neurons. Moreover, insulin was shown to reduce activity of dopamine neurons in the VTA [239] and, again similarly to leptin, at low doses the reward potential of food [240]. Importantly, insulin administration in the mediobasal hypothalamus has been reported to inactivate hormone-sensitive lipase and suppresses lipolysis [241], suggesting an efferent action of central insulin in reducing fatty acid disposal for peripheral metabolism probably via a decrease in SNS activity. This led these authors to propose a "Yin and Yang" concept of insulin and leptin opposed actions on the WAT [242].

5.5.Intestinal hormones

Several intestinal hormones have been reported to be involved in EH, and more specifically in eating behavior [66]. They have firstly been considered as nutrient censors and to have mainly an action on postprandial satiety [65]. We will constrain our review to cholecystokinin, ghrelin, GLP-1 and PYY, which have shown the most documented involvement in EH.

5.5.1 Ghrelin

Ghrelin is a hormonal acylated-protein principally secreted in the stomach [243] sending its afferent messages directly *via* 1) the bloodstream where it crosses the blood-brain barrier [244] and reaches the ARC [245] and 2) the vagal afferent to the NTS [246]. In the ARC, ghrelin stimulates the synthesis of NPY and AgRP [247] and opposes leptin effects in inhibiting POMC neurons [245], consistent with its orexigenic effect [248]. However ghrelin also exerts actions in several brain areas involved in reward such as ventral tegmental area (VTA) and the nucleus accumbens (NAcc) [249], in memory such as the amygdala [250] and the hippocampus [251] and in seeking behavior such as the olfactory bulb [252]. After being described, ghrelin was rapidly proposed as initiating meals [253] and this hypothesis seemed confirmed with subjects spontaneously eating [254]. It was moreover shown that ghrelin decreased satiety (meal frequency) and had no effect on satiation (meal size) [255]. The role in meal initiation was questioned by experiments in rats showing that ghrelin was entrained by habitual meal pattern [256,257] suggesting the importance of conditioning in its observation. The higher postprandial ghrelin levels in individuals who had anticipated a meal [258] and the fact that ingesting food was not even necessary for its postprandial levels to decrease, suggested a strong conditioning involvement [259]. Ghrelin may represent a signal for the anticipation of feeding due to conditioning potential of environmental cues [260], improving the adaptation of EI to energy requirements by learning processes based on internal cues, circadian factors and external cues associated with food [261]. Ghrelin could therefore contribute to enhance the power of appetizing human food environment to trigger intake and reduce the IMI. Last, ghrelin may contribute to increase fatty acid storage in adipocytes [262] and decrease fatty acid oxidation [263], by an action on the CNS, hypothetically mediated by the SNS [262].

5.5.2. CCK

CCK is a peptide hormone secreted by the upper intestine (duodenum and jejunum) in different amounts according to macronutrient composition [264,265]. It is released in bloodstream as soon as 10 min after eating onset and peaks at 60 min [266], remaining elevated until 7 hours [267]. CCK is present in various forms (with 8, 22, 33, 39 and 58 amino acids) all sharing a same heptapeptide carboxyl terminus supposed to carry the bioactivity [268]. The octapeptide CCK8 was the most often used in experiments. The anorexigenic role of CCK via satiation (meal size) was documented long ago [269] as was the fact that CCK33 but not CCK8 increased satiety (IMI) [269]. In the brain, CCK binds to CCK-A and -B receptors [270] and exerts actions in 6 hypothalamic and 2 hindbrain (DMN and NTS) sites [271]. Its anorexigenic effect requires the integrity of the vagal pathway [272]. CCK8 was also shown to inhibit the orexigenic effect of ghrelin though its action in the ARC [273] and to more than two-fold increase the insulin transport in the brain [274]. However in overweight and obese individual, CCK8/33 increase was not associated with any alteration in meal size either after a high-CHO or a high-fat meal [265]. Importantly, CCK58 is the most abundant in humans [275] and was found to also increase satiation and satiety whereas CCK8 only altered satiation [276,277].

5.5.3. GLP-1

GLP-1 belongs to the incretins family [278,279] and is released prostprandially by the small intestine and the colon, with great differences according to the nutrient content of the meal [280] and in particular glucose [281]. It binds to GLP-1 receptors in various brain regions such as the ARC, the NTS, and the PVN, resulting in decreased EI, notably through its effect on the CRH [282]. This anorexigenic effect has been described either with intracerebroventricular [283] or peripheral [284] administration. The effect with peripheral administration seems to require the vagal afferent [285]. Its kinetics is characterized by a short early phase (10–15 min) followed by a longer second phase (30–60 min) [281]. The main role of GLP-1 is to increase glucose-induced insulin secretion [286]. This may lead to modulate the PPGD-induced meal initiation but this has never been explored. Its effect on EI was documented with a reduced satiation at the meal following administration [287] but the effect is much more potent when administrated with PYY [288].

5.5.4. PYY

PYY, and more specifically its endogenous isoform PYY_{3-36}, is also released postprandially by the lower intestine (distal intestine, colon and rectum [289]) and binds to various Y receptors in the hypothalamus, the vague and the brainstem [290]. Its main effect is anorexigenic and has been shown at physiological doses in humans [291]. As for GLP-1, this action requires the integrity of the vagal afferent [285]. This action may be mediated partly by inhibiting NPY secretion with important interaction between them for this effect to be operant [292] as is its additive interaction with GLP-1 [288,293]. Its kinetics, with an appearance at 15 min, a peak at 90 min after meal onset and a prolonged high blood levels until 180 min [289], and its observed effects [288,293,294], are in favor of a role in the next meal satiation more than on satiety, but it may indicate a contribution to the subjective satiety between two meals [294].

5.6. Leptin and glucose interaction: the glucoadipostatic loop

From all the elements described above, it seems that an adaptation of the glucoadipostatic hypothesis [194] and the neuro-adipose connection [295] can be proposed. It overlaps these models since the role of glucose is pivotal, but extends their mechanisms to a loop with an efferent axis represented by the SNS activity. The leptin-SNS loop was previously described but without involving eating behavior [242]. Figure 3 is a graphical representation of this loop. Leptin, in enhancing fatty acids disposal released by adipocytes through the stimulation of the SNS activity and the reduction of the glucose-induced insulin secretion, may postpone the PPGD and increase satiety, here considered as the delay before the meal initiation. Moreover, glucose potentiates the stimulating effect of leptin on the ARC neurons. This loop requires a spontaneous eating behavior to operate, a situation rarely satisfied in the social environment of everyday life. Moreover, with time, this mechanism switches to an adaptation of meal size based on conditioning processes and learning. Intestinal hormones may participate to this loop in modulating the interval until the next meal (satiety) and the amount eaten during this meal (satiation) according to the composition and the amount of the previous meal.

5.7. Modulation of the glucoadipostatic loop by the diurnal rhythms

As stated in the Introduction, the circadian periodicity of eating behavior was extensively explored by Jacques Le Magnen and his various collaborators. They showed in rats that

sustained high insulin levels and fat synthesis during their active period were followed by a reduced EI during their passive period due to higher lipolysis, fatty acid oxidation, and longer intervals between meals [17,39,296]. They even showed that in lean and obese-stable rats, the circadian rhythm was characterized by a high and low glucose tolerance in the active and passive periods, respectively, this being not found in VMH-lesioned rats [297]. This provided a support to the role of SNS in this diurnal metabolic-induced eating behavior pattern. VMH is strongly involved in this phenomenon since its lesion definitively abolished glucose and insulin circadian patterns but only temporarily eating behavior one [298]. All the actors of this glucoadipostatic loop, and more largely, of EH, follow a diurnal rhythm. A circadian clock is situated in the suprachiasmatic nucleus (SCN) [299] and synchronizes circadian oscillators (peripheral clocks) localized in most organs and in every cell. This allows an anticipatory behavior and improves the metabolic efficiency as shown by the obesogenic effects of desynchronization such as in shift work [300], chronic jet lag [301] or even unusual meal patterns like regular breakfast skipping [45]. In rats, an inverse relation between SNS activity and food intake was reported, with a decrease effect of insulin on SNS activity when administrated in the VMH. Interestingly, in the SCN, insulin decreased SNS activity only during the rest period (high SNS activity and low EI) but increased it during the active period (low SNS activity and high EI) [302], making of insulin a pivotal actor of this circadian mechanism. This diurnal pattern is essential to maintain EH as shown recently in mice who accumulated fat depots when food was restrained to their rest period even when exercise was added [303].

6. Conclusions

Although the concept of homeostasis is not fully adapted to the anticipative characteristics of constant energy disposal, it is still used to describe the adaptation of energy supply to needs. To maintain a persistent EE with intermittent EI, the brain relies on a diversity of afferent neuro-hormonal messages with glucose and insulin as modulators. Energy stored in the WAT provides substrates when food is not available or between meals and requires efficient SNS activity. Adaptation of EI to changes in food availability or composition relies mainly on the delay between meals before conditioning i.e., learning. Learning processes are based on the association of the energy content of food and its postingestive effects, with hedonic and reward effect acting as an enhancer or moderator. This system is perfectly

appropriate in the environmental conditions that humans encountered during most their history. However, in contemporary conditions it appears that 1) the sedentary body fails to mobilize fat from the WAT to the level needed, leading to reliance on EI, 2) the social constraints do not authorize satiety i.e., length of the interval until the next meal is initiated, to modulate EI, 3) the constant availability, abundance and diversity of highly palatable foods overstimulates the hedonic and reward systems and overrides their physiological role, leading to non-homeostatic intake, and 4) the constant variety of foods precludes efficient conditioning of eating behavior to post-ingestive effects and energy supply, 5) sustained high insulin levels impair the re-enter of fatty acids in the metabolism to participate to satiety. A model based on a glucoadipostatic loop seems relevant to the current knowledge about the reactive and anticipative adjustment of EI and its frequent failure to maintain energy stability.

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Legends

Figure 1. Schematic representation of the 3 components of energy homeostasis: energy intake, energy expenditure and endogenous energy stores. The three group of factors modulating energy stores are described. Note that in this homeostatic model, the anticipative capacity of the allostatic model is missing. CNS, central nervous system; EH, energy homeostasis; PA, physical activity; REE, resting energy expenditure; TEF, thermic effect of food;

Figure 2. Schematic representation of the afferent neuro-hormonal actors and their relations with brain areas involved in energy intake and expenditure. The currently known functions and the main involved neurotransmitters are summarized in the text. ARC, arcuate nucleus; CCK, cholecystokinin; DMH, dorsomedian nucleus; GLP-1, glucagon-like peptide 1; LH, lateral hypothalamus; NAcc, nucleus accumbens; NTS, nucleus tractus solitarius; OXM, oxyntomodulin, PAL, physical activity level; POMC, pro-opiomelanocortin; PP, pancreatic polypeptide; PPGD, preprandial glucose decline; PVN, paraventricular nucleus; REE, resting energy expenditure; SNS, sympathetic nervous system; SF-1, steroidogenic factor 1; SPA, spontaneous physical activity; TEE, total energy expenditure; VMH, ventro-medial hypothalamus; VTA, ventral tegmental area.

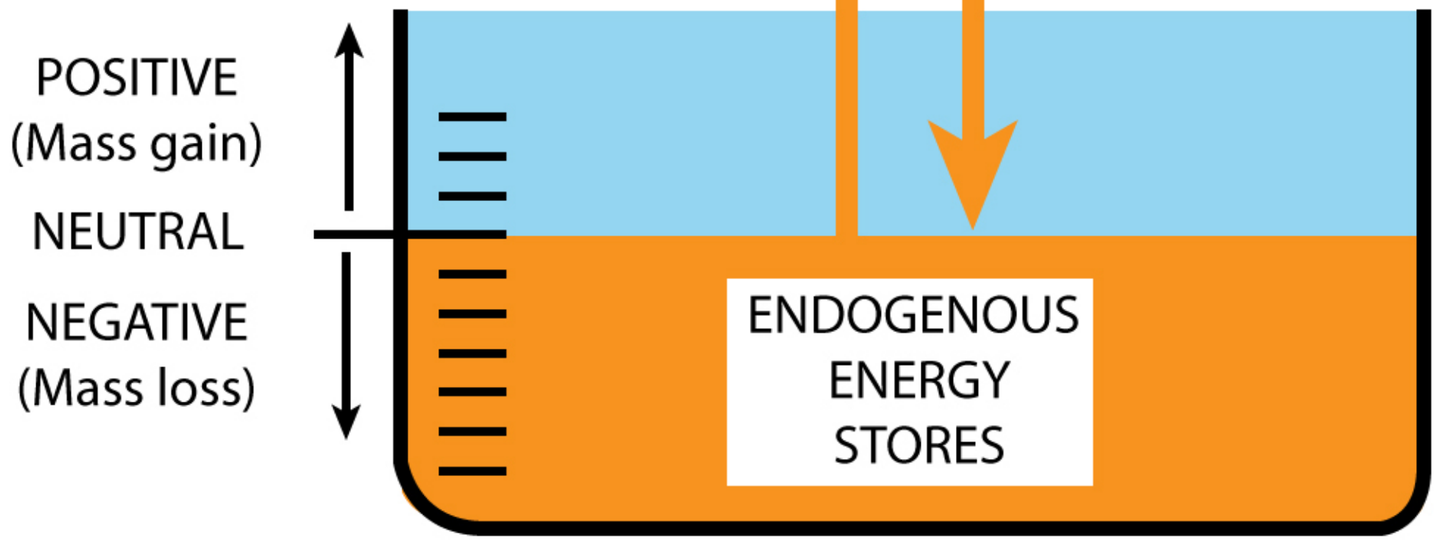
Figure 3. The glucoadipostatic loop. Energy intake (EI) has been found to exert its energy homeostastic role by modulating the duration of intermeal intervals (IMI) i.e., satiety. Each meal is preceded and initiated by a preprandial glucose decline (PPGD). ① If energy was exclusively provided by glucose, the duration of the IMI would only depend upon the glucose absorbed in the duodenum and released by the liver (not shown). ② The release of free fatty acids by adipocytes adds substrates to total oxidation, spares glucose and delays the PPGD and the onset of the next meal, increasing the duration of the intermeal interval. Glucose-induced insulin secreted in the bloodstream will reduce adipocyte lipolysis and limits the increase of the intermeal interval. ③ Leptin secreted by adipocytes reaches the hypothalamus via the bloodstream, where it stimulates neurons synthetizing anorexigenic neurotransmitters (not shown) and sympathetic nervous activity (SNA). This action is modulated by local glucose levels. The sympathetic nervous system will 1) reduce glucose-

induced insulin secretion and its inhibiting effect on adipocyte lipolysis, 2) directly stimulate the release of fatty acids by adipocytes, enhancing their contribution to total substrate oxidation and their glucose-sparing effect, leading to increase the intermeal interval. This homeostatic response requires that meals are spontaneously initiated and that no intermeal intake alters the sequence. The anticipation, conditioning and reward processes are therefore possible, based on the postingestive duration of the IMI (satiety) of the food consumed at the meal.

ENERGY BALANCE

TOTAL ENERGY EXPENDITURE
(REE, TEF, PA)

ENERGY INTAKE
(carbohydrate, fat, protein, alcohol)



GLUCOSE, HORMONES, NEUROTRANSMITTERS, VAGAL NERVES	SUBSTRATE OXIDATION	SYMPATHETIC NERVOUS SYSTEM
Afferent modulators of energy homeostasis through the transmission of peripheral messages to the CNS and the translation in 1) eating behavior (energy intake) and 2) thermogenesis and spontaneous physical activity (energy expenditure)	Adaptative metabolic component of energy homeostasis through oxidative pathways and nutrient partitioning	Efferent modulator of energy homeostasis through the neural transmission of CNS messages and the consecutive increased disposal of endogenous energy

BRAIN

PREFRONTAL CORTEX

HYPOTHALAMUS

LH

VMH

DMH

ARC

PVN

NAcc

Amygdala

VTA

REWARD SYSTEM

BRAINSTEM

NTS

Leptin

Ghrelin

PYY

PP

Insulin

OXM

Amylin

CCK

GLP-1

Adiponectin

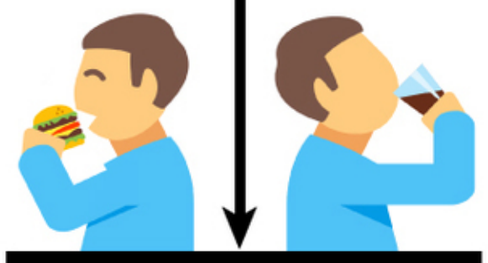
+

-

TOTAL ENERGY EXPENDITURE
(REE, TEF, PA)

+

-



FOOD INTAKE

CHO

FAT

PROTEIN

Taste

VAGUS NERVE

Ghrelin

Stretching

Leptin

CCK

STOMACH

PYY

OXM

GLP-1

SMALL INTESTINE

COLON

Insulin

PP

Amylin

PANCREAS

Leptin

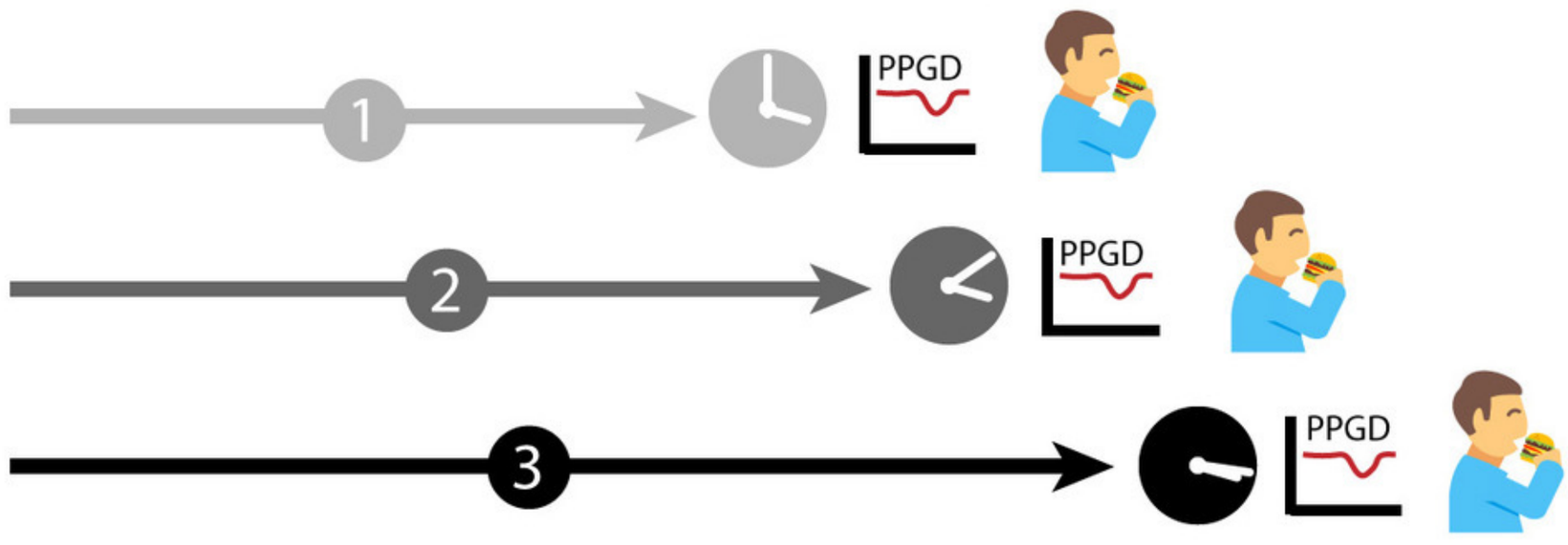
Adiponectin

ADIPOSE TISSUE

LIVER

PORTAL VEIN

INTERMEAL INTERVAL (SATIETY)



TOTAL SUBSTRATE OXIDATION

- Glucose
- Free fatty acids
- Insulin
- Leptin
- Inhibition
- Stimulation