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Neurological Systems Regulating Energy Balance: Opportunities for Obesity Therapy

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What is already known about this subject?

Multiple factors influence the development of obesity and the relative success of different treatment options. Current non-surgical treatment options for obesity frequently have little impact, and exploratory work is needed to identify promising new avenues.

What are the new findings in your manuscript?

This workshop proceeding summarized the synergy between neurological drivers of energy regulation and the cultural, environmental and behavioral factors that differ between individuals. Emerging evidence for brainstem areas of involvement in long-term control of energy regulation was also summarized.

How might these results change the direction of research or the focus of clinical practice?

These presentations highlight the synergy between environmental factors and biology in determination of energy regulation in humans, supporting increasingly personalized treatment approaches that take into account both individual biology and behavioral/environmental constraints and opportunities.

Abstract

Physiological adaptations to intentional weight loss can facilitate weight regain. This review summarizes emerging findings on hypothalamic and brainstem circuitry in the regulation of body weight, and identifies promising areas for research to improve therapeutic interventions for sustainable weight loss. There is good evidence that body weight is actively regulated in a homeostatic fashion similar to other physiological parameters. However, the defended level of body weight is not fixed but rather depends on environmental conditions and genetic background in an allostatic fashion. In an environment with plenty of easily available energy-dense food and low levels of physical activity, prone individuals develop obesity. In a majority of individuals with obesity, body weight is strongly defended through counterregulatory mechanisms such as hunger and hypometabolism, making weight loss challenging. Among the options for treatment or prevention of obesity, those directly changing the defended body weight

would appear to be the most effective ones. There is strong evidence that the mediobasal hypothalamus is a master sensor of the metabolic state and integrator of effector actions responsible for the defense of adequate body weight. However, other brain areas such as the brainstem and limbic system are also increasingly implicated in body weight defense mechanisms and may thus be additional targets for successful therapies.

INTRODUCTION

Studies in both animals and humans have shown that the body promptly responds to intentional perturbations of body weight through underfeeding or overfeeding. For example, after food-restriction-induced weight loss of about 15% over 2 weeks, rats return to exactly the same body weight of an unrestricted control group about 3 weeks later, which is higher than at the time of restriction due to growth (1). Even more impressively, after food restriction in the Siberian Hamster during their seasonal weight loss phase, body weight returns to exactly the time-adjusted body weight of controls, suggesting that homeostatic mechanisms even incorporate a *sliding set point* (2).

In humans, intentional weight loss through dieting is carried out by millions of individuals every day and the typical outcome is the same – gaining back all the lost weight in a short period of time. Conversely, while overfeeding studies generally also show return to the original body weight, regulation is not as precise and, under certain genetic and environmental conditions and stages of life, return is incomplete (3, 4). Concerning intentional weight loss, this is reported to elicit strong counter-regulatory responses, namely hunger and hypometabolism which attenuate changes in body weight (5). What is less clear is why an abnormal body weight such as occurs in obesity and anorexia is defended, and the molecular mechanisms and brain sites that are most responsible for underlying this classical homeostatic energy balance regulation.

POTENTIAL MOLECULAR MECHANISMS

Master Sensor of Energy Fluxes in the Basomedial Hypothalamus, and Signal Integration and Orchestration of Effector Pathways

The hypothalamus has long been implicated in the regulation of body weight, (6, 7) and particularly convincing evidence has been the identification of rare human genetic variants of

these circuits that lead to dramatic elevations in body weight (8). The modern neurobiological tool kit has also allowed identification of specific neuron populations in the basomedial hypothalamus that are critical for the controls of food intake and energy expenditure. Two adjacent populations of neurons, one expressing the neuropeptides agouti-related peptide (AGRP) and neuropeptide Y (NPY) as well as the neurotransmitter gamma-aminobutyric acid (GABA), the other expressing pro-opiomelanocortin (POMC), cocaine-amphetamine-regulated transcript) CART, and glutamate, appear to constitute the master energy sensor that orchestrates control over both energy intake and expenditure to achieve homeostatic regulation of body weight/adiposity (9). The AGRP neurons seem to be mainly concerned with defending availability of nutrients for survival by stimulating foraging behavior and food intake and suppressing unnecessary energy expenditure, when active. They have been compared with the ”gas pedal” (10). In contrast, POMC neurons are primarily concerned with defending against overnutrition by stimulating satiety mechanisms and increasing energy expenditure, and have been compared with the “brake pedal” (11).

To accomplish their task, basomedial hypothalamic neurons receive an array of sensory input and project through an equally rich array of effector pathways. Major sensory inputs include hormonal and nutrient signals from the internal milieu that reach the basomedial hypothalamus through the bloodstream or neuronal pathways. Major output pathways include other hypothalamic and extrahypothalamic systems with direct access to brainstem nuclei involved in the organization of ingestive behavior, and brain nuclei driving the autonomic nervous system control of all involved organs, including white and brown fat tissue driving energy expenditure (see (12, 13) for recent review).

An Independent Role for Brainstem Circuits

A wide range of additional work has pointed to an important role of for brainstem circuits in the regulation of food intake (14), in particular for meal-to-meal regulation of energy intake. For example, chronic decerebrate rats have a transection of the neuroaxis such that the brainstem circuits are isolated from hypothalamic input, and while these animals respond to wide range of meal-related stimuli (15) they do not adjust their intake when moved from 3 to 2 meal opportunities per day to defend their body weight (16). This is something that intact rats with normal hypothalamic input do quite adeptly. Further, experiments where the gut hormone cholecystokinin was infused into free-feeding rates with indwelling intraperitoneal catheters each time a rat initiated a meal, resulted in substantial reductions in meal size. However, rats also

compensated by increasing their meal frequency such that daily food intake was not reduced and they maintained their body weight (17). Taken together, these observations are consistent with the suggestion that meal-related signals important to the short-term regulation of intake rely on brainstem circuits, while longer-term weight homeostasis relies on hypothalamic circuits (**Fig. 1**).

Support for an independent role for the brainstem circuits has come from several sources. First sodium glucose co-transporter 2 (SGLT2) inhibitors that cause glucose calories to be lost in the urine do result in small but sustained weight loss with no evidence that this has a direct or indirect impact on hypothalamic circuits (18). Second, bariatric surgery is the most effective weight loss intervention on average, and this effect cannot be easily attributed to mechanical restriction and malabsorptions since patients report being less hungry even after substantial weight has been lost (19). The strong implication is that bariatric surgery results in altered signals from the GI tract that impinge on the central nervous system (CNS) to alter food intake. Given that a wide range of observations indicate that GI signals act via brainstem circuits, one could argue that bariatric surgery can alter body weight without targeting the hypothalamus. Again, this is not a perfect argument since there are gut signals that can act in the hypothalamus. A number of studies in mice show that weight loss induced by Roux-en-Y gastric bypass (RYGP) surgery (20-22) but not vertical sleeve gastrectomy (13) require hypothalamic melanocortin signaling.

A third argument involves the evolving understanding of how glucagon-like peptide 1 (GLP-1) agonists result in sustained weight loss in rodents and humans. Clinically used GLP-1 agonists are analogues of the gut hormone GLP-1 in which the half-life has been extended. While it is tempting to think that these analogues act in the same manner as the gut hormone they are designed to mimic, this seems unlikely. Little evidence links gut-derived GLP-1 to the normal control of body weight, and increasing the circulating levels of GLP-1 by inhibiting dipeptidyl peptidase 4 (DPP4) does not result in weight loss (23, 24). Therefore, if GLP-1 agonists are not mimicking a gut signal, one possibility is that the significant reduction in weight caused by these drugs is the result of direct targeting of the hypothalamus. This remains a controversial topic particularly because local injection of GLP-1 into many brain regions can reduce food intake including within the hypothalamus. Work by one of us (RS) has pointed to CNS GLP-1 receptors as critical for the food intake and visceral illness effects of liraglutide but not its beneficial effects on glucose regulation (25). Further, David Olson's group has found that when

they deleted GLP-1 receptors from inhibitory neurons throughout the CNS, it did not alter the food intake and body weight effects of liraglutide. However, when they deleted GLP-1 receptors from excitatory neurons, liraglutide no longer could reduce food intake, body weight or produce a conditioned taste aversion. Moreover, much of the ability of liraglutide to activate the fos transcription gene in disparate portions of the CNS was lost as well. Interestingly, the only place in the CNS that expresses GLP-1 receptors in excitatory neurons and also expresses fos in GLP-1 receptor bearing neurons is in the area postrema (AP) located in the brainstem (26). This provides strong evidence that the AP is an important target for the effects of GLP-1 receptor agonists but it certainly does not eliminate the possibility that they also have actions on hypothalamic circuits that contribute to their effects (27). However, as demonstrated in GLP-1 receptor-deficient mice, neither weight loss induced by RYGB, nor vertical sleeve gastrectomy (VSG) requires GLP-1 receptor signaling (28-31).

This works raises the further question of whether it is possible to identify a system that, when targeted, has effects that are entirely restricted to the brainstem. The answer to this question is clearly yes. Growth/differentiator factor 15 (GDF-15) is a member of the transforming growth factor (TGF-beta) superfamily and has been shown to be elevated in a number of cancers (32). Importantly, the levels of GDF15 are predictive of the degree of anorexia and weight loss associated with specific tumors and blocking GDF15 reduces the anorexia associated with these tumors in rodents (33). Further, pharmacological administration of GDF15 potently reduces food intake in mice, rats and non-human primates (34). Interestingly the receptor that is responsible for these potent effects is termed GDNF family receptor alpha like (GFRAL) and is narrowly expressed exclusively in the AP and the nucleus of the solitary tract (35-39). Consequently, activation of GFRAL neurons exclusively in these brainstem areas can produce profound reductions in body weight. Interestingly, these GFRAL neurons would appear to be distinct from AP neurons that express the GLP-1 receptor and combined administration of low doses of GDF15 and liraglutide result in greater reductions in food intake and weight loss than the single agents alone (40). But again, these brainstem neurons are not required for the weight loss effects of VSG (40).

Unsolved questions. A major unresolved question is whether the defense of a body weight/adiposity set point resides in the hypothalamus, the brainstem, any other brain area, or is diffusely organized. This fundamental question will only be addressed with studies on multiple mechanistic candidates. Concerning peripheral signals, although leptin appears to be the

principal negative feedback signal for the regulation of adiposity, it is only effective in the lean state when it's circulating levels are low (41). Complete absence of leptin action, as in genetic deletions of the leptin or leptin receptor gene, is the most powerful driver of food intake. However, once leptin levels reach a certain level, the hormone seems powerless to defend against obesity (42). In addition, leptin feedback alone is unable to silence AGRP/NPY neuronal tone after a period of fasting as measured at the level of messenger RNA (mRNA) expression (43). Only refeeding for a sufficiently long duration fully normalized AGRP/NPY tone, suggesting that there are additional feedback signals to be identified among circulating nutrients and hormones.

An additional feedback signal may originate in lean mass, as supported by the argument that survival is much more likely to depend on vital organs such as the brain, gut, liver, kidneys, and muscle, which together make up for 75% of basal metabolism, than on adipose tissue. It is further supported by the strong positive association between basal metabolic rate with lean mass as well as food intake in humans (44). The search for such a feedback signal(s) from lean mass should have a high research priority. It will also be interesting to look further for a potential gravitostat signal, perhaps originating from bone (45). In addition much detail of how the homeostatic regulator competes with other survival behaviors such as fluid balance and fight and flight, and how it orchestrates effector pathways remains to be investigated.

ENVIRONMENTAL INFLUENCES ON BODY WEIGHT SET POINT

In a landmark paper published in 1976, which occurred before the obesity epidemic, Sclafani & Springer demonstrated the obesifying effects of exposing rats to a cafeteria diet (46). Not only did they demonstrate that rats rapidly developed obesity on a diet containing a palette of mostly energy-dense palatable human food items, but the ability to engage in exercise was a major modifier, significantly slowing down the process. These findings essentially foreshadowed our current understanding of the obesity crisis, that is, how an environment of almost unlimited supply of high energy-dense palatable foods combined with little opportunity to work for it is the perfect storm leading to obesity. Since then, this phenomenon has been replicated in many other animal species, from fruit flies to elephants, demonstrating its general validity. In humans, the experiment is going on globally, with increasingly large populations switching from a rural to an urban environment. As an example, the rapid transition from a mostly agricultural to an

industrial society in China is accompanied by one of the highest rates of increase in obesity and diabetes (47).

In light of the above presented powerful homeostatic regulator of body weight/adiposity, at least two questions come to mind. First, why is the powerful energy balance regulatory system not able to prevent extremes in body weight such as in obesity and anorexia? The most parsimonious answer is that the regulator was never “intended” to regulate at a fixed set point, such as a room thermostat. Rather, the regulator flexibly adapts to prevailing environmental and genetic conditions. This suggests that in an environment with plenty of food but an occasional famine, body weight set point is adaptively increased to soften the blow of famines. This interpretation is supported by the outcome of the above mentioned intentional weight loss study in Siberian hamsters, in which the body weight returns to its original trajectory after a period of food restriction (2). It is important to realize that under this scenario, the homeostatic regulator is still active and functionally responsive to environmental changes in obese subjects, but at a higher set point.

Several alternative explanations have been put forward. One is the “hypothalamic injury” hypothesis, which suggests that high-fat diet in particular causes inflammatory damage to the hypothalamus and corrupts normal functioning of the homeostatic regulator (48). Another one makes high-fat diet-induced numbing of vagal afferent satiety signaling responsible for corruption of the homeostatic regulator (49). As direct tests of these two hypotheses are difficult, neither one has been proven beyond doubt that it is at the root cause of developing obesity, and it is more likely that these two pathological processes accelerate rather than cause the development of obesity.

The other question that comes to mind is whether diet-induced, common obesity is reversible. Most studies in rodents show that diet-induced obesity is either completely or nearly completely reversible when animals are put back on normal, low-fat laboratory chow (50). Depending on the genetic background and the duration of obesity, reversibility is more or less complete. Even if not complete, all detrimental metabolic impairments are usually completely reversed (51). Because humans cannot simply be put back to the equivalent of “normal laboratory chow”, a conclusive reversal experiment has not been carried out in humans. A valid test would require turning back the entire obesogenic environment, not just food intake, and thus remains elusive. As myriads of personal experiments and many controlled studies demonstrate, intentional

weight loss without completely reversing the obesogenic environment will sooner or later fail in most individuals with obesity. This is because the body weight set point of individuals with obesity is defended and weight loss induces the powerful counter-regulatory physiological responses.

Potential Neural Mechanisms by Which the Environment Modulates Homeostatic Regulation

The key mechanism by which physiological hunger (hunger induced by lack of macronutrients) is translated into behavior is the generation of incentive motivation to find and ingest food, or in brief, the "implicit wanting" of food (52) (**Fig. 2**). It is generally agreed that "implicit wanting" is neurally-code by activity of the midbrain dopamine system with its projections to striatum, prefrontal cortex, amygdala, and hypothalamus. The dopamine system generates motivation and its downstream circuits translate it into action (53). The power of this system can be illustrated in leptin-deficient children, which continuously want to eat, even unpalatable foods, and in which the ventral striatum is hyperactive (54). Hunger and striatal activity promptly stop when leptin is administered. Thus, a shortage in nutrient supply, here signaled by zero leptin, generates wanting for food through the so-called food reward system.

Importantly, recent investigations have demonstrated rich direct and indirect reciprocal connections between the master energy sensor in the basomedial hypothalamus and the food reward system (55). These connections are likely involved in the modulation of the classical homeostatic regulator by the obesogenic environment. By directly acting on components of the reward pathway, the obesogenic environment appears to influence arcuate AGRP/NPY neurons and corrupt the energy balance set point. Thus, besides feedback from the internal milieu, it is hypothesized that AGRP neurons also receive hedonic feedback, leading to an upward shift of body weight/adiposity set point in an obesogenic environment. It can thus be said that the obesogenic environment hijacks the powerful motivational system to increase intake of palatable, high energy dense foods that are easily available.

Clearly, much of the circuitry involved in the functional links between the classical homeostatic energy balance regulator and the food reward system remains to be investigated. In addition, links to cognitive control and decision making centers that undoubtedly also play a role in the final behavioral output need to be much better characterized, both functionally and anatomically.

IMPLICATIONS FOR PREVENTION AND TREATMENT OF METABOLIC DISEASE

Given that the obesogenic environment and lifestyle are the main modifiable risk factors for obesity in genetically and metabolically prone individuals, removing the obesogenic environment would be the therapy of choice. However, this seems an unsurmountable task in the current environment. The developing of next-generation therapeutic tools based on our evolving understanding of the role of the hypothalamus and brainstem in the regulation of energy balance now seems a real possibility, and in the meantime there are a number of symptomatic treatment options that can have significant beneficial effects, particularly if tailored to each individual.

Behavioral therapy to support lifestyle changes that explicitly counterbalance known metabolic adaptations to weight loss holds promise for improving the success of lifestyle interventions for weight loss. In particular, such interventions can emphasize dietary factors such as dietary fiber (56) that increase metabolic rate to counterbalance the slight tendency for metabolism to decrease with weight loss (57). They can also facilitate increased energy expenditure for physical activity for prevention of weight regain. Energy expenditure for physical activity may decrease disproportionately to the change in body composition with weight loss (58, 59) while high levels of physical activity are associated with support for weight loss maintenance (60) Using the principle of counterbalancing known metabolic adaptations to weight loss, one of us (SBR) has reported sustained percent weight loss maintained to 12 months that is 2-3 times higher than typical in lifestyle interventions (61, 62), indicating the potential for this approach to support improvements in therapeutic care in obesity.

In addition, gastric bypass surgery is quite effective on average for patients with morbid obesity. This is remarkable for several reasons. First, this surgery does not indiscriminately reduce appetite but rather appears to change the defended body weight or body weight set point (63). Unlike weight loss induced by food restriction, which in most studies results in increased hunger and hypometabolism, weight loss induced by gastric bypass surgery appears to suppress these counter-regulatory adaptations. Consistent with this conclusion, one of us (HRB) recently demonstrated that basomedial hypothalamic AGRP mRNA expression in mice is, unlike after starvation-induced weight loss, not increased after gastric bypass-induced weight loss (22), suggesting that a new set point has been established. At present, it is unclear by what mechanisms the surgery acts on the brain to establish this new body weight set point.

Identification of this mechanism might be key for developing pharmacological tools that can eventually replace the invasive surgery. It should be noted however, that lifestyle interventions are the first line treatment for obesity, because more than a third of surgical patients regain more than a quarter of lost weight (64) and nutritional deficiencies and post-surgical complications are common (65, 66).

SUMMARY

In susceptible individuals living in an obesogenic environment, obesity is seemingly inevitable because the homeostatic regulator appears to adapt to the environment and the higher level of body weight/adiposity becomes biologically defended. Therefore, treatments that do not address the defended body weight set point are likely to be ineffective in the long-term. Evolving knowledge on neurological systems involved in the regulation of energy balance is identifying new therapeutic targets for improving methods for prevention and treatment of obesity.

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Fig. 1 Schematic diagram showing the general flow of information important for the control of ingestive behavior and the regulation of body weight.