RECENT ADVANCES IN ENDOCRINOLOGY

The Carbothalamus: Villain and Victim in Metabolic Care

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Abstract

The hypothalamus, through its expression and interaction with various neurotransmitters, pituitary hormones and orexigenic and anorexigenic signals, regulates appetite. Leptin and insulin, released in response to food intake, act as anorexigenic stimuli whereas ghrelin, released in fasting, is orexigenic. Imbalance in these signals can lead to disorders in appetite regulation with cardiovascular implications. Glucose, through multiple mechanisms, shows an addictive potential and interacts and affects the hypothalamic regulation of appetite and energy metabolism. The concept of Carbothalamus integrates the hypothalamic function in response to carbohydrate craving and proves opportune to identify the individual maladaptation and an approach to manage the same. This simple concept helps understand, as well as address, obesity in an easy and effective manner.

Keywords: Carbohydrates, hypothalamus, incretins, nutrition, obesity, overweight, weight

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Introduction

The hypothalamus plays a vital role in energy and glucose homeostasis with appetite regulation a function of various neurotransmitters, pituitary hormones, and signals from orexigenic and anorexigenic neurons. The hypothalamic arcuate nucleus regulates appetite, food intake, glucose and energy metabolism by sensing nutrient levels and integrating signals from hormones like insulin from the pancreas and leptin from the adipocytes. Carbohydrate craving and intake disrupt this homeostasis.

This concept, termed "Carbothalamus," encapsulates the intricate pathophysiological interaction between the thalamus and carbohydrates, highlighting their reciprocal influence and the implications for health. This model can assist in public and individual health interventions, providing a holistic approach to management.

The hypothalamus is the seat of appetite regulation.

The hypothalamus, specifically the arcuate nucleus (ARC), is vital for regulating metabolism and appetite.[1] ARC neurons release peptides like agouti-related peptide (AgRP) and neuropeptide Y (NPY) to increase hunger, while others release proopiomelanocortin (POMC) and cocaine and amphetamine regulated transcript (CART) to reduce eating. Hormones such as ghrelin from the stomach and leptin from fat cells communicate with the hypothalamus to help control appetite.

The orexigenic agouti-related peptide (AgRP)/ neuropeptide Y (NPY) neurons, promote appetite, and anorexigenic pro-opiomelanocortin (POMC) neurons, suppress it.[2] POMC neurons primarily project to the paraventricular nucleus (PVN), dorsomedial hypothalamus (DMH), lateral hypothalamus (LH), and ventromedial hypothalamus (VMH) to relay signals to extra-hypothalamic circuits about energy intake and expenditure. Lesions in PVN or VMH neurons can cause overeating, while DMH or LH damage reduces appetite.

The POMC mediates its anorexic effect via α-melanocyte-stimulating hormone (α-MSH), acting on melanocortin 3 and 4 receptors (MC3/4R). Whereas ,NPY/AgRP, orexigenic neurons, stimulate feeding and block α-MSH's action.[3] Hypothalamic nuclei connect to extra-hypothalamic regions like the nucleus of the solitary tract (NTS), ventral tegmental area (VTA), and nucleus accumbens (NAc), integrating homeostatic and hedonic feeding signals. LH neurons, including glutamate/orexin and GABAergic types, project to the VTA, influencing reward-driven feeding.[4] These circuits interact with the amygdala, hippocampus, and prefrontal cortex to regulate feeding, glucose and energy homeostasis.

Orexigenic and anorexigenic signals regulate body weight by controlling hunger and energy balance. Anorexigenic signals, like leptin and insulin, decrease food intake, whereas orexigenic signals, like ghrelin, encourage food intake. Ghrelin, released during fasting, activates AgRP/NPY neurons, promoting appetite and adiposity. Postprandial hormones like glucagon-like peptide 1 (GLP-1), peptide YY3-36 and cholecystokinin exert anorexigenic effects via

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the ARC, NTS, and other regions, with GLP-1 also reducing food reward in the VTA and NAc.[5]

The hypothalamus integrates brainstem and reward signals to regulate appetite, eating behaviour, and energy balance. Disruption of these pathways contributes to disorders such as anorexia nervosa and obesity by altering appetite and energy homeostasis.

Glucose has an addictive potential

Intermittent sugar intake in rats induces bingeing with dopamine release in the nucleus accumbens, alters receptor expression[6] and reduces enkephalin mRNA, causing withdrawal-like symptoms via decreased extracellular dopamine. Repeated exposure produces mild dopaminergic, cholinergic, and opioid effects, leading to subtle dependence and cross-sensitization with amphetamine. In humans, some exhibit addiction-like sugar responses—cravings, impaired control, persistent use—with withdrawal symptoms (headache, fatigue, irritability) on restriction, though evidence remains limited.

Protein satiety hypothesis

High-protein diets enhance satiety. The aminostatic theory (1956) states low serum amino acids promote hunger, while high levels induce satiety; protein intake raises plasma amino acids. Nefti et al. suggest this activates vagal input to the brainstem and hypothalamic satiety centres (nucleus tractus solitarius).[7] Poppitt et al.[8] showed high-protein preloads are more satiating than isoenergetic fat or carbohydrate, reducing total calorie intake and supporting weight loss/maintenance.

Mechanisms of protein satiety

High-protein diets increase energy expenditure by raising diet-induced thermogenesis (DIT) and preserving resting energy expenditure (REE). Total expenditure includes REE, DIT, and activity. DIT varies by macronutrient: fat 0–3%, carbohydrate 5–10%, protein 20–30%[9] and rises with higher caloric/protein intake. HPDs maintain REE by preventing lean mass loss; a meta-analysis showed higher REE (+142 kcal/day; 95% CI 16–269) with ~1.25±0.17 g/kg/day vs ~0.72±0.09 g/kg/day protein.[10] Increased oxygen demand from protein metabolism also enhances satiety, aiding weight loss.

High-protein diets enhance satiety via hormonal pathways: they increase anorexigenic GLP-1, CCK, and PYY from gut enteroendocrine cells, activating vagal signalling and reducing appetite,[11] while suppressing ghrelin; protein preloads lower ghrelin more than glucose, contributing to weight loss.

The aminostatic hypothesis (1956)[12] states high plasma amino acids from HPDs promote satiety, while low levels trigger hunger. HPDs raise plasma AA and satiety vs high-fat/carbohydrate diets. However, fasting AA levels poorly correlate with appetite, and postprandial AA rises do not consistently reduce hunger;[13] further research is needed on peripheral AA–CNS signalling.

HPDs promote weight loss via increased gluconeogenesis: excess AAs (not used for protein synthesis) upregulate phosphoenolpyruvate carboxykinase and glucose-6-phosphatase, raising energy expenditure and glucose, enhancing hepatic glycogen and satiety signalling. In high-protein, low-carbohydrate diets, ketogenesis increases β-hydroxybutyrate, directly promoting satiety. Although gluconeogenesis may not suppress appetite, HPDs prevent appetite increases and maintain levels similar to standard-energy medium-protein diets, while limiting intake at subsequent meals, aiding weight loss despite lower total energy intake.

Increased appetite and carbohydrate craving in hypothalamus

Bulimia involves daytime restriction, evening bingeing on palatable foods, and purging (vomiting, laxatives, excessive exercise). It is associated with low β-endorphin levels (driving sweet preference) and reduced insular μ-opioid receptor binding linked to fasting. Intermittent sugar intake repeatedly triggers dopamine release, promoting bingeing.[14] The auto-addiction hypothesis implicates endogenous opioid dependence, with bingeing and starvation increasing opioid activity; high intake of non-caloric sweeteners, cross-sensitization with amphetamine, and increased alcohol use further support this.

Carbohydrate cravings are stronger in obesity, possibly due to disrupted brain serotonin metabolism, causing preference for sugary/starchy foods even without hunger. Leptin resistance impairs satiety, increasing intake. An obesogenic environment (processed, high-calorie foods, food cues like advertisements) further drives overeating. Micronutrient deficiencies (magnesium, zinc, chromium) and inadequate sleep also increase hunger and cravings.

Clinical and Public Health Significance

Rising sugar intake correlates with obesity, with soft-drink consumption up ~500% over 50 years. High-fructose corn syrup less effectively stimulates insulin and leptin, reducing satiety and promoting weight gain. Repeated sweet-induced dopamine release in the nucleus accumbens suggests binge intake of sweeteners may foster dependence. Excess refined carbohydrates are calorie-dense and readily stored as fat; reducing them supports weight loss, improves metabolic syndrome risk (type 2 diabetes, cardiovascular disease, stroke), stabilizes glycaemia, and helps control cravings.

We propose the term “Carbothalamus” to describe the maladaptive hypothalamus in obesity, reflecting the bidirectional link between carbohydrate intake and hypothalamic/neurotransmitter activity, and a unified pathophysiology connecting diet, central regulation, and obesity.

The construct of carbothalamus reinforces the need for concerted actions to

1. Reduce carbohydrate intake
2. Modify behaviour
3. Reset the metabolic set point
4. Understand syndromic obesity
5. Appreciate possible neurocognitive adverse effects of anti-obesity medications.

This concept converts the vicious cycle of “*Increased carbohydrates leading to increased obesity*” to a virtuous cycle of “*Decreased carbohydrates leading to weight loss*”.

Identifying craving triggers (stress, boredom, habit) and practicing mindful eating (slowing, food awareness, recognizing hunger cues) help prevent overeating, promote healthier choices, and support diabetes/obesity management. Limiting carbohydrate intake aids weight control, improves health, and fosters sustainable, balanced eating patterns.

Conclusion

Carbohydrate craving and intake alter hypothalamic function; “Carbothalamus” summarizes this complex interaction. It enables individualized identification of maladaptation and non-hierarchical management, integrating with other physiological signals to expand therapeutic options and improve outcomes, underscoring its clinical relevance.

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