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Review

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Nutrient-Based Appetite Regulation

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Regulation of appetite is dependent on crosstalk between the gut and the brain, which is a pathway described as the gut-brain axis (GBA). Three primary appetite-regulating hormones that are secreted in the gut as a response to eating a meal are glucagon-like peptide 1 (GLP-1), cholecystokinin (CCK), and peptide YY (PYY). When these hormones are secreted, the GBA responds to reduce appetite. However, secretion of these hormones and the response of the GBA can vary depending on the types of nutrients consumed. This narrative review describes how the gut secretes GLP-1, CCK, and PYY in response to proteins, carbohydrates, and fats. In addition, the GBA response based on the quality of the meal is described in the context of which meal types produce greater appetite suppression. Last, the beneficiary role of exercise as a mediator of appetite regulation is highlighted.

Key words: Diet, Vagus nerve, Nucleus tractus solitarius, Energy intake, Weight loss, Education

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INTRODUCTION

Blunted appetite regulation is a hallmark of an advanced obesogenic state that hinders weight loss harder.[1] The link between food intake and the drive to eat is the gut-brain axis (GBA), where appetite is regulated. The GBA is interconnected in the medulla of the brainstem, where the nucleus tractus solitarius (NTS) receives the vagus nerve (VN) afferent fibers input originating from the gut.[2] For context, the gut is comprised of the stomach, small intestine, and large intestine. Distension and secretion of hormones elicited by food intake in the gut[3] cause a signal that is received by the afferent branch of the VN. This signal is transmitted by the VN to the NTS,[4] where subsequent upper brain regions (superior to the brainstem) are stimulated to suppress appetite and induce meal termination.[2,5] A representation of GBA signaling to the brain is presented in Fig. 1.

In contrast, during a fasted state, the GBA can stimulate the VN to increase the desire to eat.[6] Although the GBA is tightly regulated, there is evidence suggesting that people with obesity have a dysregulated GBA that predisposes them to greater food cravings and increased food intake due to a lack of appetite regulation.[7,8] For optimal appetite regulation, fully functional neurotransmitter activity is required. For example, dopamine can promote cravings that lead to eating, while it is also required to induce the feeling of "reward" that is required to suppress appetite.[5,7,9] Because dopamine has a potent role in regulating eating behavior, downregulation of its prefrontal cortex receptors that is driven by overstimulation of reward-like behaviors is a major factor of a dysregulated GBA.[10-13] In the context of food intake, stimulation of the GBA and subsequent NTS signal and dopamine release differ based on the type of nutrient consumed. Because the GBA has many interrelated mechanisms to correctly regulate appetite,[5,14] the scope of this narrative review is to describe the connection between the GBA and nutrient intake while elaborating how nutrient type can affect appetite regulation.

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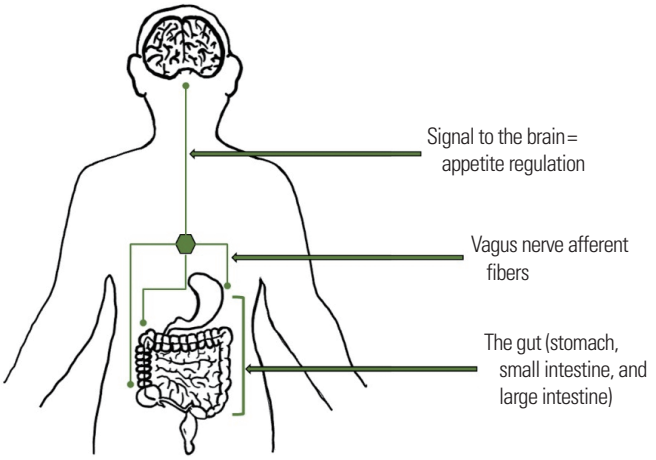

Figure 1. Illustration denoting the connection between the gut and brain through vagus nerve afferent fibers that subsequently signal appetite regulation once stimulated.

BASICS OF ENERGY INTAKE AND SIGNALING FOR APPETITE REGULATION

We briefly described modulation of appetite controlled by the GBA. However, appetite and hunger are not the same. Appetite refers to the cephalic (upper brain regions) regulation of eating,[15] whereas hunger is a process or physiological drive that aims to initiate eating and is signaled by an array of physiological stimuli, such as the "growling and emptiness of the stomach", a decrease in blood glucose, and an increase in ghrelin concentration.[16-19] Based on these definitions, appetite can be experienced at any point, whereas hunger is experienced only under fasted conditions. Herein, throughout this review, we will only describe GBA responses as they relate to appetite (drive to eat).

A common weight loss approach is to follow a hypocaloric diet that restricts overall nutrient intake. From an energy balance point of view, such an approach is logical and practical because consuming fewer calories than what is expended daily should lead to weight loss over time. However, this paradigm regularly contradicts itself, because a hypocaloric diet can lead to a reduction in energy expenditure. This concept is referred as the metabolic set point,[20] where the body reduces the nonessential energetic demands to prevent energy deficiency and meet metabolic demands. Therefore, maintaining the weight loss achieved via a hypocaloric diet can be difficult. The challenges to sustaining a hypocaloric diet to achieve weight loss are related to the physiological abilities of our body to respond to energy intake. In essence, regardless of meal size, the GBA is not capable of sensing or determining caloric intake at a given meal.[21] In contrast, meal content (macro and micronutrients) is the primary mediator of GBA stimulation. For example, a sugar-based snack might have the same caloric content as a protein-based snack. However, the protein-based snack will produce greater satiety signaling and reduce food intake in comparison to the sugar-based snack.[22] That is why the nutrient content rather than the caloric intake, in combination with the stretching of gastrointestinal walls, determines the ability of the cells in the gut to secrete appetite-regulating hormones. Herein, a dysregulated GBA that cannot adequately sense the hormonal secretions from the gut will have a blunted capability to regulate appetite[23,24] and can be associated with hedonic eating and promote an obesogenic state.

MACRONUTRIENT DIFFERENCES IN GUT-BRAIN AXIS SIGNALING

Protein intake

High consumption of protein or amino acids is a good method to reduce total energy intake by increasing satiety in comparison to that gained from carbohydrates and fats.[25,26] Based on this, it is expected that the GBA can effectively sense the intake of protein and inhibit appetite accordingly. Specifically, when protein is consumed, enteroendocrine cells located in the small intestine secrete cholecystokinin (CCK),[27] glucagon-like peptide 1 (GLP-1),[28,29] and peptide YY (PYY).[28-30] These three are defined as anorexigenic (appetite suppressant) hormones. When CCK is released, the nearby region of the small intestine that holds the VN afferents receives the signal from CCK when it binds to its CCK type 1 receptors (CCK_1).[31,32] When CCK binds to CCK_1, the GBA mediates the passage of a satiety signal from the gut to the brain and suppresses appetite to help reduce food intake. Similarly, GLP-1 and PYY have the same effect of binding to their receptor located in VN afferents and producing an anorexigenic signal.[33]

Although the overall effect of protein intake is an anorexigenic response, the composition of the protein molecules is important. For example, the satiating effects of protein intake can be further increased by consuming proteins that contain specific amino acids

like arginine,[34,35] lysine,[35] and glutamic acid.[35] Compared to other amino acids, these have shown a greater ability to produce an anorexigenic response.[35] This is an important consideration because it exemplifies how not only macronutrient type, but also quality in terms of composition are important. Leucine is an amino acid often thought to be a major precursor of an anorexigenic response. However, it is speculated that leucine acts differently than other amino acids, which produce an anorexigenic response by stimulating the GBA.[36] In contrast, leucine stimulates protein synthesis and growth that are only possible if there is sufficient energy available. Therefore, it indirectly inhibits appetite by signaling that there are enough nutrients to synthesize proteins but does not react to nutrient type.[35,37,38] More research is warranted to better understand how specific amino acids affect appetite regulation.

Carbohydrate intake

In contrast to protein intake, carbohydrates have a lower capability to stimulate the secretion of CCK.[39] Furthermore, a carbohydrate-rich meal has a lower duration in its satiety-inducing effect compared to a protein-based meal. In part, the difference is attributed to gastric emptying, where carbohydrates can be digested faster than proteins.[39,40] Therefore, from a satiety point of view, CCK will signal the GBA for longer and promote a longer satiety response when consuming protein rather than carbohydrates. Furthermore, a carbohydrate-rich meal elicits lower secretion of both GLP-1 and PYY and a shorter anorexigenic state compared to a protein-based meal.[41] On this basis, if CCK, GLP-1, and PYY are secreted to a lesser extent under a carbohydrate-rich meal, then it is expected that long-term intake of a diet that favors carbohydrates would not be ideal to maintain good appetite control.

Carbohydrate is a broad term. A carbohydrate-rich meal implies that, from a given meal, the majority of the macronutrient content is allotted to carbohydrates and a lesser extent to proteins and fats. Therefore, a carbohydrate-rich meal yields a high concentration of its glucose building block upon digestion. As such, a food that has a high glycemic index is used to describe a carbohydrate-rich meal that has a low anorexigenic action.[39] However, similar to the way amino acids determine the quality of proteins,[42] the quality of carbohydrates is attributed to their digestibility. Digestible carbohydrates are metabolized into glucose,[43] while non-digestible carbohydrates have minimal to no contribution to blood glucose and help to increase the bulk of food in the colon and to slow digestion.[44] In the colon, non-digestible carbohydrates undergo fermentation, causing the release of short-chain fatty acids (SCFA).[45] When produced, SCFA bind to nearby receptors that elicit secretion of GLP-146 and PYY.[46,47] Even though SCFA does not promote the release of CCK because their carbon chains are too short,[48] SCFA help to maintain an optimal GBA functionality by increasing the availability of enterocytes[45] that help to reduce gut permeability. Well-controlled gut permeability prevents leakage of pro-inflammatory molecules that can trigger systemic inflammation and reduce the functionality of the GBA.[49,50] Thus, simple carbohydrates (digestible) should be limited and complex carbohydrates (non-digestible) should be prioritized to maximize gut health and appetite suppression. Non-digestible carbohydrates remain longer within the gut and, like with protein intake, will induce a longer satiety response than digestible carbohydrates.[51] In contrast, abundant consumption of digestible carbohydrates (those high in glycemic index) is associated with inability to regulate appetite, obesity, and other comorbidities,[52] further warranting the need to prioritize non-digestible carbohydrates during meals.

Fat intake

As with protein and carbohydrate intake, consuming fat elicits the secretion of CCK, GLP-1, and PYY. However, a chronic high fat intake is associated with a reduced satiety effect by secretion of CCK[53,54] and GLP-1.[55] In contrast, PYY has shown the opposite response to a high-fat meal, where a high fat intake increases its secretion and effect.[56,57] As such, with a high-fat diet, PYY can promote satiety, but the roles of CCK and GLP-1 will be limited. Importantly, like carbohydrates, fat can be categorized based on its molecular type. The two main categories of interest are saturated fats and polyunsaturated fats. For simplicity, saturated fats are considered "bad" for health, whereas polyunsaturated fats are generally considered "good" for health.[58,59] As an example, consuming fried foods would primarily contribute saturated fats, whereas consuming avocados would primarily contribute polyunsaturated fats. In this context, a high intake of saturated fats is associated with excess eating and high blood glucose,[58] along with metabolic derangements.[60]

Another aspect to consider is that availability of CCK, GLP-1,

and PYY is associated with other factors. For example, in mice fed a high saturated fat diet, CCK concentration was chronically high after 18 weeks. However, the increase in CCK was not associated with an appetite regulatory response but, instead, to excess liver damage due to excess fat metabolism[61] and hepatic cancer.[62] Similarly, at the onset of type 2 diabetes, both a high-fat meal and a high-carbohydrate meal showed no increase in PYY postprandially,[63] suggesting that the GBA is not regulating feeding responses normally. In contrast, consuming a meal that has been artificially sweetened causes no change in GLP-1,[64] suggesting that long-term consumption of foods that distribute nutrients abnormally could chronically affect how the GBA regulates appetite by eliciting inadequate secretion of CCK, GLP-1, and PYY. However, novel evidence in gut physiology has demonstrated that GBA activity can differ based on the population of enteroendocrine cells irrespective of the type of nutrient intake. In other words, the ability for the GBA to regulate appetite, irrespective of gut hormones, is to some extent determined by the speed at which the VN is stimulated.[65] As such, fast signal conductivity is critical within the GBA, which is why enteroendocrine cells in the gut are now known as neuropod cells.[66,67] Therefore, the GBA not only relies on adequate gut hormonal release to regulate appetite, but also in the sensing of nutrients and subsequent signaling to the VN afferent fibers.

EXERCISE AND APPETITE REGULATION

The appetite regulatory response to exercise is extensive and intricate,[68] but this narrative review focuses on a few basic aspects. In general, frequent engagement in exercise improves appetite regulation by increasing the availability of CCK, GLP-1, and PYY.[69] Depending on the intensity of exercise, adaptation of appetite-suppressing hormones can differ.[70] In addition, the positive body composition changes attributed to exercise adaptations, i.e., reduced fat mass and increased fat-free mass, are associated with increased availability of appetite-regulating hormones.[69,71-73] Therefore, frequent engagement in exercise is recommended to improve satiety and overall appetite control. An overall summary of recommendations for improved appetite control is presented in Fig. 2.

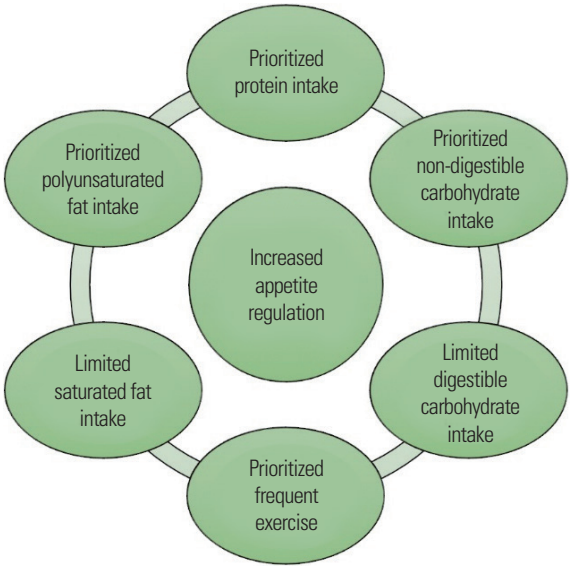

Figure 2. Summary of recommendations that aim to improve appetite regulation.

CONCLUSION

The process of appetite regulation is complex and multifactorial, and this review aimed to facilitate the understanding of this topic based on effects of nutrient type on the GBA and appetite regulation. A diet that contains adequate amounts of protein, non-digestible carbohydrates, and polyunsaturated fats is important to promote the availability of CCK, GLP-1, and PYY, which are critical to controlling appetite. Combining that type of diet with frequent exercise would be an effective approach for improving appetite regulation and body composition, which will provide long-term health improvements.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Study concept and design: JMM; analysis and interpretation of data: all authors; drafting of the manuscript: all authors; and critical revision of the manuscript: all authors.

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