Amino acid-dependent regulation of food intake: is protein more than the sum of its parts?

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Free-feeding organisms utilize a wide variety of internal and external cues to guide feeding behaviour. While internal cues related to energy stores are certainly important regulators of intake, it is evident that food intake is governed by more than simply the need to consume calories. One powerful example of energy-independent regulation of food intake is the effect of dietary protein (Morrison et al. 2012). High protein preload supresses subsequent food intake to a greater extent than isocaloric carbohydrate or fat preloads, and high protein diets have been shown to suppress food intake in several settings (Davidenko et al. 2013). Protein-dependent feeding is also evident when individuals overconsume diets that are moderately low in protein, self-select between diets that vary in protein content to meet a specific protein target, avoid diets that are severely imbalanced in amino acid composition, and seek out amino acids that are otherwise deficient in the diet (Morrison et al. 2012). These data collectively indicate that both protein quantity and quality can have a profound impact on food intake, and suggest that organisms simultaneously balance the need for energy with the physiological need for protein.

Yet despite the behavioural evidence supporting a regulation of protein intake, the physiological and metabolic mechanisms governing this process are unclear. One particular issue is the fact that protein actually represents a mixture of over 20 amino acids, of which a subset must be consumed in the diet for survival. While glucose is the common currency for energy, there is no single molecule that represents ‘protein’ in the body, and as such it remains unclear whether all amino acids are sensed equally, or instead whether some amino acids are more important than others. In other words, if protein is more satiating, which amino acids specifically contribute to this effect? Similarly, if one eats for protein, what is being selected for specifically?

In this issue of The Journal of Physiology, Jordi and colleagues (Jordi et al. 2013) systematically compare individual amino acids for their ability to suppress food intake following intragastric infusion. The results clearly demonstrate that individual amino acids do not act the same. Of the 20 amino acids tested, only three (glutamate, lysine and arginine) significantly suppressed food intake, with the remaining amino acids producing smaller but still variable effects. This suppression of food intake was accompanied by effects on gastric secretion and gastric emptying, as well as the activation of neurons within area postrema (AP) and the nucleus of the solitary tract (NTS). Interestingly, intravenous amino acid infusion was sufficient to reproduce the anorectic effects, suggesting that increases in circulating amino acids may be key to the sensing mechanism.

Taken together, these results suggest that select amino acids may act as unique signals within the gut, and the ability of intravenous amino acid infusion to reproduce the anorectic effect suggests that these amino acids may also act directly in the brain. This possibility is consistent with previous work demonstrating that leucine signalling in the brainstem is sufficient to suppress food intake (Blouet et al. 2012), although it is interesting that leucine had no effect in the current work. Importantly, the increases in cFos in the AP and NTS implicate these brainstem regions as potential mediators of the anorectic effects of intragastric amino acid infusion, prompting the authors to focus more closely on their role in amino acid detection. The AP is well described as a key site for the detection of blood-borne signals, while the NTS receives an array of visceral sensory information via vagal afferents. Thus signals related to amino acid intake could reach the brainstem via either of these pathways. To test these possibilities, the authors chose to independently lesion the AP and vagal afferents. Interestingly, the results indicate that the individual amino acids act via different pathways, with lesions of the AP blocking the anorectic effects of intragastric glutamate and arginine (but not lysine), while capsaicin-dependent lesions of vagal afferents only blocked the anorectic effects of lysine. The conclusion that lysine requires vagal afferents while arginine and glutamate require the AP is extremely interesting, but these data also beg the question of why these amino acids would act via fundamentally different mechanisms.

Despite the interesting implications, the manuscript is not without its limitations. Due to the large number of amino acids involved in the initial screen, the authors were forced to test their efficacy at only a single, somewhat arbitrary dose. Whether other amino acids might also regulate food intake at higher doses is therefore unclear. It is also unclear to what extent these three amino acids mediate the anorectic effects of protein intake in general. It seems unlikely that just three amino acids are sufficient to reproduce the full effect of protein, and the manuscript falls short of directly testing the role of these amino acids in the context of a normal diet. For instance, would protein sources relatively deficient in one or more of these amino acids be less satiating, or would supplementing diets with these amino acids reduce food intake? Lastly, the divergent responses to AP and vagal lesions raise questions regarding the relative roles of these structures in responding to a mixed amino acid load, and the extent to which these brain areas mediate the impact of dietary protein in general.

Adequate consumption of protein is essential for survival, yet how organisms balance protein quantity and quality against other nutritional priorities remains an elusive question. Dietary protein exerts substantial effects on both food intake and metabolism, and tapping into the underlying regulatory mechanism represents fertile ground for identifying novel approaches to the treatment of obesity and metabolic disease. The work described here indicates that individual amino acids may play unique roles in these processes, highlights arginine, glutamate and lysine as nutrient signals, and implicates vagal afferents and the area postrema as mediators of their detection. Future experiments are now required to define how these effects fit within the larger scheme of nutrient homeostasis.

References

