Review

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Protein-dependent regulation of feeding and metabolism

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Free-feeding animals often face complex nutritional choices that require the balancing of competing nutrients, but the mechanisms driving macronutrient-specific food intake are poorly defined. A large number of behavioral studies indicate that both the quantity and quality of dietary protein can markedly influence food intake and metabolism, and that dietary protein intake may be prioritized over energy intake. This review focuses on recent progress in defining the mechanisms underlying protein-specific feeding. Considering the evidence that protein powerfully regulates both food intake and metabolism, uncovering these protein-specific mechanisms may reveal new molecular targets for the treatment of obesity and diabetes while also offering a more complete understanding of how dietary factors shape both food intake and food choice.

Protein as an essential, regulated nutrient

The maintenance of health and fitness requires that organisms procure sufficient nutrition by negotiating a complex nutritional landscape in which food availability and quality can be unreliable. Energy density, macronutrient balance, and procurement cost are often in competition, and organisms must adaptively change their behavior and metabolism during periods of nutrient restriction. It is well accepted that an intricate neuroendocrine network detects energy restriction and coordinates adaptive changes in feeding behavior, energy expenditure, and metabolism. However, when considered in the context of a natural environment, it seems likely that food intake is driven by more than only the number of calories (energy content) in the diet. This review will specifically focus on the hypothesis that dietary protein intake is regulated independently of other dietary macronutrients (carbohydrate and fat) as well as total energy intake. Unlike the regulation of energy homeostasis, there has been little progress in defining a neuroendocrine mechanism governing 'protein homeostasis', despite a large and compelling literature indicating that variations in dietary protein or amino acid content produce profound changes in feeding behavior and metabolic health [1].

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Behavioral responses to dietary protein

The experimental manipulation of dietary protein substantially alters feeding behavior, metabolism, and growth. Studies focusing on the impact of dietary protein on feeding behavior have led to three general conclusions: (i) diets with severe amino acid imbalance or that are devoid of a single essential amino acid reduce food intake and produce a learned avoidance of the imbalanced diet, (ii) high protein (HP) diets tend to suppress food intake acutely, and promote reductions in fat mass but maintenance of lean mass chronically, and (iii) moderately low protein (LP) diets increase food intake and protein selection, while extremely LP diets can reduce food intake. A brief overview of these

Glossary

Activating transcription factor 4 (ATF4): a transcription factor that induces the expression of stress response genes as part of the integrated stress response. ATF4 is downstream of GCN2/eIF2α and is activated by amino acid restriction.
AMP-activated protein kinase (AMPK): a kinase that is activated by cellular energy restriction that functions as a metabolic switch to coordinate diverse cellular responses to nutrient restriction.
Anterior piriform cortex (APC): an area of the cortical brain that is classically associated with olfaction, but which is essential for the anorexia induced by deprivation of a single essential amino acid.
Cholecystokinin (CCK): a gut-derived hormone that reduces food intake in response to food ingestion.
Corticotropin-releasing hormone (CRH): a neuropeptide, mainly produced in the hypothalamus, that is associated with the response to various stressors.
Eukaryotic initiation factor 2α (eIF2α): a cellular protein that is phosphorylated by a variety of upstream kinases in response to cellular stress, including GCN2. eIF2α phosphorylation leads to the inhibition of cellular protein synthesis as well as to the specific activation of the integrated stress response.
Extracellular signal-regulated kinase (ERK): a kinase that serves as a primary intracellular signaling molecule mediating the cellular response to a variety of growth factors.
Fibroblast growth factor 21 (FGF21): a nutritionally regulated hormone which induces a broad range of beneficial metabolic effects.
General control nonderepressible 2 (GCN2): a serine/threonine kinase that is activated by essential amino acid restriction and which phosphorylates eIF2α to inhibit cellular protein translation and induce a series of cellular stress responses.
Geometric framework: a state-space modeling method that has been used to model the interacting effects of macronutrient intake on physiological endpoints.
Glucagon-like peptide 1 (GLP1): a gut-derived hormone that reduces food intake in response to food ingestion.
Mammalian target of rapamycin (mTOR): a kinase that coordinates diverse cellular responses to variations in nutrient availability and growth factor signaling.
Melanocortin 4 receptor (MCR4): receptor expressed on neurons within the brain associated with regulation of body weight, food intake, and energy expenditure.
Peptide YY (PYY): a gut-derived hormone that reduces food intake in response to food ingestion.
Thyrotropin-releasing hormone (TRH): a neuropeptide associated with the regulation of thyroid hormone, but which also acts on diverse neural systems.
Ribosomal protein S6 kinase β1 (S6K1): a kinase which phosphorylates ribosomal protein S6 in response to upstream activation by mTOR, coordinating the effect of growth factors and nutrients on cell growth.

behavioral responses is provided for perspective, and the reader is referred to several recent reviews which cover this field in more depth [1–6].

Effects of HP and LP diets

HP diets suppress food intake over the short term, with protein being the most satiating macronutrient per calorie [3,4,7]. A large number of clinical studies indicate that HP diets promote weight and adiposity loss by reducing food intake, maintaining fat free mass, and increasing energy expenditure [8]. For these reasons the maintenance of protein intake but reduction of energy intake is a central focus of many weight-loss strategies [4,9]. Similar data exist for rodents, although some studies describe a waning of the anorectic effect over time due to adaptive increases in amino acid metabolism [10–13].

Fewer studies have focused on the response to a LP diet, and the effect seems to be dependent on the degree of protein restriction and the physiological state of the animal. Rats and mice exhibit hyperphagia in response to moderately LP diets [14–16], but will abandon this approach and spontaneously reduce food intake if the protein content is extremely low [17]. Recent studies have focused on this same question in humans. Interestingly, several studies indicate that moderate restriction of protein triggers adaptive changes in food intake and preference [18–20], whereas other studies involving more severe protein restriction have shown no effect on food intake [4,21].

Protein selection and amino acid imbalance

There exists a large body of data indicating that a wide range of species will self-select between diets that are high and low in protein to meet protein requirements [1]. Although there is debate as to whether this self-selection produces a precise regulation of protein intake, work utilizing the geometric framework (see Glossary) to model the interacting effects of all three macronutrients strongly suggests that species as diverse as fish, insects, rodents, and pigs seek to consume a specific protein:carbohydrate target, and will prioritize protein over energy [22,23]. The ability to select for protein also appears to be sensitive to physiological status because protein selection increases in response to periods of increased protein demand, such as during periods of rapid growth [23,24].

Evidence also supports selection based on the composition of individual amino acids, not only total protein. Rats rapidly detect and readily avoid diets that are deficient in a single essential amino acid [6], will specifically select the missing amino acid over other non-restricted amino acids in a choice test, and appear to be able to distinguish between minute changes in dietary amino acid content [25,26]. While diets that are completely devoid of a single amino acid induce aversion and are incompatible with life, a more moderate restriction of a single amino acid increases food intake and actually extends lifespan. The most compelling evidence for this effect comes from work focusing on methionine restriction, which increases food intake and energy expenditure, improves lipid metabolism and insulin sensitivity, and increases lifespan [27–30]. These data suggest that moderate restriction of a single amino acid produces a different physiological response compared to the complete deprivation of that amino acid.

While dietary protein clearly exerts a profound effect on feeding behavior, metabolism, and growth, at issue is whether these effects represent a specific, physiologic regulation of protein intake (i.e., protein homeostasis). While the evidence suggests that protein and energy are independently balanced, we currently have a poor understanding of the mechanisms that might contribute to such a protein-specific response. Below we discuss the potential mechanisms underlying protein-dependent regulation of food intake and metabolism.

Potential mechanisms underlying protein intake and selection

As with any nutrient, the identification, consumption, digestion, absorption, and utilization of amino acids is a complex process. Information regarding dietary protein intake or protein status could be transmitted to the brain in a large number of ways, including via taste (umami), neural or endocrine signals from the gastrointestinal (GI) tract, hormones generated by liver or skeletal muscle based on amino acid availability or metabolism, or finally a direct brain effect of circulating amino acids. Delineating the role of these individual pathways is a daunting task, and indeed it seems likely that multiple signals participate in this process. Three mechanisms have been most predominately linked to the response to dietary protein: (i) direct effects of amino acids in the brain, (ii) gut-derived neural or hormonal signals, and (iii) other endocrine signals, namely fibroblast growth factor 21 (FGF21). We discuss their contribution to the response of the organism to amino acid imbalance and to HP and LP diets (Figure 1).

Direct effects of amino acids on the brain

As mentioned above, diets that are completely devoid of a single amino acid reduce food intake and induce a learned aversion. There is very strong evidence to suggest that the detection of this imbalance is mediated by the depletion of the limiting amino acid and the resulting activation of the serine/threonine kinase general control nonderepressible 2 (GCN2) within the brain anterior piriform cortex (APC) [6,31–33]. GCN2 is a conserved amino acid sensor that couples amino acid availability to protein synthesis [34–36], and therefore its activation in the APC provides a molecular mechanism for brain detection of amino acid restriction. However, to date this APC-centric mechanism has not been connected to the regulation of food or protein intake in other settings, although GCN2 has been linked to the metabolic effects of single amino acid deficiency on the liver [36–39]. Whether GCN2 similarly contributes to more moderate restriction of single amino acids or general dietary protein restriction remains unclear, but this distinction is important considering the divergent feeding response to complete deficiency (hypophagia) versus modest restriction (hyperphagia). Finally, a separate brain signaling system has been implicated in the response to a leucine-devoid diet, although in this case the primary endpoint is the induction of energy expenditure. These studies suggest that leucine deprivation influences ribosomal protein S6 kinase β1 (S6K1) signaling and regulates