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Food as a Hormone

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Abstract

Nutrient substrates derived from food can activate intracellular signaling cascades to regulate metabolic health.

Diet has an enormous impact on many aspects of our health, yet scientific consensus about how what we eat affects our biology remains elusive. This is especially true with respect to the ongoing debate about obesity. While many in the scientific community focus on how high-fat diets can lead to increased body weight (1), others assert that we should blame processed carbohydrates (2). Is it possible that this focus on macronutrients (i.e., fats, proteins, and sugars) is misplaced?

Much of the recent public discourse about the interaction between food and metabolic health relies on two basic approaches (see the figure). One is nutritional epidemiology, in which populations of people who eat different foods are compared with regard to indices of health such as body weight, with a goal of determining which diets are more or less “healthy.” The other is biochemistry, in which the goal is to determine how different macronutrients are processed to yield energy. Despite valuable information provided by these two approaches, neither has resulted in a translatable scientific basis for recommending diets that improve metabolic health or reduce body weight for a large percentage of the affected population, perhaps because considering food only in terms of its macronutrient content overlooks the complexities of how food interacts with our bodies.

A growing body of evidence suggests an alternative perspective. That is, circulating substrates derived from food have specific direct and indirect actions to activate receptors and signaling pathways, in addition to providing fuel and essential micronutrients. Ultimately food can be considered as a cocktail of “hormones.” A hormone is a regulatory compound produced in one organ that is transported in blood to stimulate or inhibit specific cells in another part of the body. Hormones exert their effects on target tissues by acting on cell-surface receptors to alter activity through intracellular signaling cascades or via nuclear receptors to regulate gene transcription. Although food is not produced in the body, its components travel through the blood, and nutrient substrates can act as signaling molecules by activating cell-surface or nuclear receptors.

As an example, nutritional epidemiology has touted the benefits of eating omega-3 fatty acids to protect against cardiometabolic syndrome and weight gain (3). Yet simple biochemistry cannot satisfactorily explain why omega-3 fatty acids should lead to benefits compared to other fatty acids. Omega-3 fatty acids bind to and activate the cell-surface

receptor GPR120 (4), which is expressed in important metabolic tissues including adipose tissue and muscle. Reduced GPR120 signaling is associated with inflammation, weight gain, and impaired glucose control in both mice and humans (4, 5). Thus, to generate the full spectrum of beneficial effects on vascular disease risk, ingested omega-3 fatty acids are not simply processed to generate energy, but additionally act via GPR120 in key tissues to improve metabolic endpoints.

Whereas activating GPR120 appears to protect against weight gain, other lipid-activated receptors exert the opposite effect. Peroxisome proliferator-activated receptor γ (PPAR γ), for example, is a nuclear receptor that is activated by a variety of fatty acids and regulates transcription of genes important for lipid and glucose metabolism. Increasing PPAR γ activity with pharmacological agonists enhances lipid storage in adipose tissue, and also acts in the brain to cause hyperphagia, dual actions that promote accretion of body fat (6–8). Consistent with this, reducing PPAR γ activity in the brain decreases consumption of high-fat diets, thereby blunting weight gain (6, 8). These studies lay the groundwork for understanding how components of high-fat diets cause overconsumption and weight gain by activating specific fatty acid receptors in the brain.

In addition to acting directly on these specialized fatty acid receptors, there is evidence that some dietary fatty acids also modify the actions of classical hormones. For example, the stomach-derived hormone ghrelin increases food intake and weight gain by binding to its receptor, growth hormone secretagogue receptor (GHSR). However, for ghrelin to signal effectively, a fatty acid must first be attached to the peptide as a side chain. Different fatty acid side chains derived from different dietary fats change the ability of ghrelin to increase food intake (9). These fatty acid side chains come from ingested food rather than from adipose tissue (10). In this way, specific dietary components can exert hormone-like metabolic effects by physical interaction with a peptide hormone.

Fatty acids are not the only direct source of “hormones” in our food; certain amino acids can also activate signaling pathways. The most-studied are the branched-chain amino acids including leucine, which activates the mammalian target of rapamycin (mTOR) pathway. mTOR is a serine-threonine kinase that regulates cell-cycle progression, growth, and insulin action (11). Leucine directly activates the mTOR pathway in the central nervous system to reduce food intake and body weight (12, 13).

Food components also interact with gut flora to induce indirect signaling cascades within the body. For example, nondigestible complex carbohydrates, including dietary fiber, are metabolized by the gut microbiota and fermented to short-chain fatty acid (SCFA) end products—mainly acetate, propionate, and butyrate (14). These SCFAs bind to and activate cell-surface receptors free fatty acid receptor 2 (FFAR2) and FFAR3 to alter host metabolism. For example, FFAR2 and 3 are expressed on entero-endocrine L cells that produce the incretin hormone glucagon-like peptide-1 (GLP-1). Stimulation of L cells with SCFA induces GLP-1 secretion, but this effect is diminished in the absence of FFAR2 or, to a lesser extent, FFAR3 (15). Acetate and propionate also activate FFAR2 on adipocytes to increase expression of the weight-reducing hormone leptin. In this way, specific dietary

carbohydrates, modified by the gut microbiota, can signal at specific receptors to alter whole-body energy and glucose metabolism.

Viewing food as a hormone could substantially influence how we make dietary recommendations to promote health or treat specific diseases. Rather than using only nutritional epidemiology to identify what healthy people consume, we may be able to design diets from the bottom up—based on their ability to alter signaling pathways in specific tissues that we know are linked to metabolic disease. In addition, this framework suggests that the argument over whether fat or sugar is to blame for the increasing incidence of obesity may be misguided. Macronutrients are classified by their energy-yielding biochemical properties, not by their ability to activate receptors in a manner similar to that of a hormone. It may be more productive to examine the signaling properties of a given diet to understand whether it will promote weight gain or weight loss. Identifying these food- and food metabolite–receptor interactions will provide new opportunities to understand the relationship between what we eat and diseases including obesity.

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Figure 1. Making sense of what we eat

Nutritional epidemiology and biochemical approaches, focusing primarily on the relationship between macronutrient consumption and metabolic outcomes, have not provided a translatable scientific basis to recommend diets that improve metabolic health for a broad range of people. Alternatively, understanding our diets as a collection of signaling molecules, having hormone-like actions via cell-surface and nuclear receptor signaling, may provide new insights into the relationship between what we eat and metabolic disease. Moreover, this framework may eventually allow us to make dietary recommendations from the bottom up—based on the ability of specific foods to alter relevant signaling pathways.