Cell

Food for the Brain

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Diet is a major issue facing humanity. To combat malnourishment and diseases associated with overnutrition, both research and technological breakthroughs are needed.

It is 2015, the world population is approaching 7.5 billion, and there are nearly a billion malnourished people (Food and Agriculture Organization of the United Nations). At the same time, developed countries are experiencing catastrophic increases in metabolic syndrome, obesity, diabetes, and cardiovascular disease, all likely related to diet.

Can science help us develop better ways to feed ourselves? This, of course, is a complex question with many potential answers—from innovations in agricultural sciences and crop production, to changes in livestock farming, to implementing and enforcing broad changes in the sustainable use of land and marine resources. Much has been written and debated on each of these topics. I believe that real change will require breakthrough disruptive technologies and transformational changes in policy—mere incremental improvements are unlikely to change the food system, or our eating habits, in a timeframe that matches the challenge.

In this brief Essay, I will consider three attractive opportunities in my own field that may help provide solutions to these challenges: (1) understanding our brain circuits controlling appetite for sweet; (2) developing ways of producing intrinsically palatable, novel protein-rich nutrients in a low cost, self-sustainable, renewable, high-capacity platform; and (3) elucidating the links between our diet, the microbiome, gut-brain circuits, and metabolism. Ultimately, it may be possible to prevent disease through our diet.

Our Love for Sugar

Sugar (originally from sugarcane) was first produced in New Guinea some 10,000 years ago (Smith, 1995), and brought to Europe as crystalized "honey powder" from the Indian Territories by the armies of Alexander the Great, and later, as "sweet salt," by crusaders returning from the Holy Land. By 1800 the average American consumed approximately 7 pounds of sugar a year (Elliott, 1917). Today, the average American consumes over 100 pounds of added sugar annually (USDA, 2014) (Figure 1), and according to the Centers for Disease Control, more than 1 in 4 people in the US have metabolic syndrome (Ervin, 2009). By point of comparison, Americans consume ~50 pounds of beef annually.

Our craving for sugar is likely rooted in brain circuits dedicated to reward the recognition of high-energy food sources—a mechanism essential for animals in the wild, and most certainly critical in our own evolutionary trajectory, but terribly misused and abused by humans today (in essence by hijacking this pathway for our own pursuit of pleasure) (Lutter and Nestler, 2009, Volkow et al., 2011, Nieh et al., 2015).

Sweet compounds are detected by specific taste receptor cells on our tongue and palate epithelium; sweet-sensing cells send hardwired, appetitive, consummatory signals to our brain (Yarmolinsky et al., 2009). These circuits permit the identification of energy-rich food sources, and their association with a highly positive (i.e., rewarding) brain state. Remarkably, animals can develop a strong preference for sugars completely independently of the taste system, so that even in the absence of a functional taste signaling pathway, they still acquire a strong drive to consume sugar (de Araujo et al., 2008; Sclafani and Ackroff, 2015). Defining the sugar-selective elements of this circuit may provide valuable strategies to modify our sugar-craving eating habits and help combat obesity and associated metabolic disorders. For example, by identifying the sensors that detect the (taste-independent) sweet stimulus and transfer that information to the brain it may be possible to modulate our "hunger" for sugar.

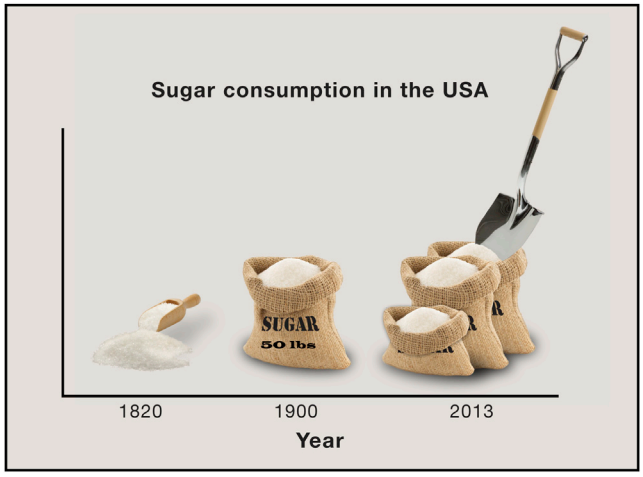

Figure 1. Increase in Sugar Consumption in the USA
Americans consumed approximately 7 pounds of sugar in 1820, 50 pounds in 1900, and over 100 pounds in 2013.

Protein Food

Proteins are regularly produced in significant amounts both for pharmaceutical and

industrial uses, with current technologies being adequate for many "niche" needs (e.g., industrial enzymes and protein-based therapeutics) (Wurm, 2004). There are a number of efforts at producing plant-derived meat substitutes and artificial meat (for example Beyond Meat http://beyondmeat.com/, Modern Meadow http://modernmeadow.com/, Impossible Foods http://impossiblefoods.com/, Cultured Beef http://culturedbeef.net/; see links for details); these are creative approaches that provide high-value, technologically intense alternatives to animal meat products. However, the kind of technology that addresses world needs would have to be simple, sustainable, easily transferable, inexpensive, and with a low carbon footprint. It takes thousands of liters of water, and tremendous amount of energy to produce just 100 g of beef protein (this includes the water and fuel needed to grow the animal feed, to process it and to transport it (Mekonnen and Hoekstra, 2012). Of note, over 60% of the grain produced in the USA is used to feed livestock (Cassidy et al., 2013). Not surprisingly, producing 1 calorie of animal protein requires 10 (or more) times the amount of fossil fuel required to produce 1 calorie of plant protein.

I believe we need to dramatically reduce our consumption of animal meat, but also harness the power of synthetic biology toward the production of alternative protein-rich food sources (for example by producing protein that may have inherently beneficial properties, and formulating them as an inexpensive, appetizing food product). However, this will require technology that scales-up biosynthetic efficiency by at least 2–3 orders of magnitude. Best-of-class current technologies yield about 0.2–1.0 g of protein per liter (Zhu, 2012); to make this proposal a viable strategy we would need to efficiently produce at least 100-fold more, and do so in a cost effective way. In this context, it would also be highly preferable to have the protein product itself exhibit intrinsic sensory properties that make it highly palatable (for example in texture and taste). Given that taste receptors can be selectively activated by amino acids, peptides, and proteins (Nelson et al., 2002), this might be an attainable goal.

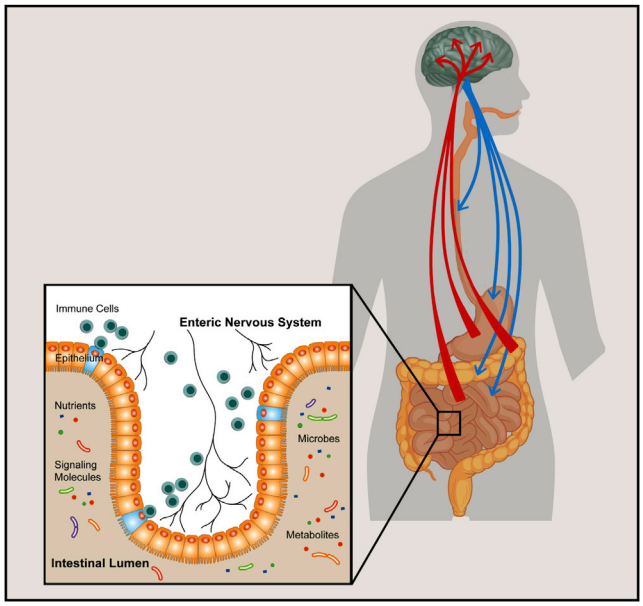

Figure 2. Interplay between the Gut, Microbiome, and Brain
The gut-brain axis is a bidirectional neural signaling system connecting the gastrointestinal system (and other internal organs) to the brain. For illustration purposes, nerve fibers are shown freely contacting the gut epithelia, and no other tissue is shown on the basal side of the gut epithelia (i.e., lamina propia).

The Microbiome-Gut-Brain Axis

Our diet modifies the microbiome, and the microbiome modifies our diet. Although not generally presented as such, this statement underscores the link between the microbiome and human physiology (Sekirov et al., 2010). Indeed, it is now evident that gut microbes impact what the human host is capable of extracting from its diet, from nutrients to bioactive signaling molecules. Understanding the biological interactions between our diet and our intestinal microflora provides an immense opportunity to improve the nutritional value of food and human health. We have many examples, including recent studies in which gut microbiota are transferred between mice with vastly different metabolic states, and in doing so changing the new host's metabolism (Vijay-Kumar et al., 2010). In this brief perspective, however, I want to highlight a related, but very distinctive link to the gut: the gut-brain axis (Figure 2).

Our gut is innervated by some 300 million neurons (a mouse brain has ~100 million neurons) that monitor and inform the brain about our internal physiological and metabolic state (Furness, 2012). I envisage this "information highway" between our gut and our brain as offering unprecedented "access" to brain centers involved in metabolic, physiological, cognitive, and emotional states. Unraveling the role of these gut-brain circuits could change the way we think about food, nutrition, and human physiology.

In this issue of *Cell*, leading researchers review and confront a wide range of questions dealing with food, physiology, and human health—from advances in crop production, to exploiting the physical and chemical properties of food ingredients to create new sensory experiences in flavor (taste, odor, texture, temperature, and presentation), to new insights into mother-child metabolic imprinting, to transformative advances in the control of cholesterol metabolism. This is an exciting time in science. This collection of papers provides a window into recent advances and future opportunities.

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