

Addicted to Food: An Interview With Bart Hoebel

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Continuing with my exploration of the intersection of psychology, health, and dietary choices in these columns, this month I present an interview with ground-breaking food researcher Bart Hoebel, a Professor of Psychology at Princeton University. Hoebel is one of the pioneers who first stimulated brain areas involved in feeding. His work illustrates the power of animal models to elucidate human behavior and shows the central role of feeding in all species. His work on the brain mechanisms controlling the pleasure evoked by feeding has contributed critical insights to our understanding of food choice and drug addiction.

Bartoshuk: What were the early years of brain stimulation research like?

Hoebel: In my graduate student days, stimulation of the lateral hypothalamus (LH) of the brain was the 8th wonder of the world to me. I would turn on the stimulating current; the rat would walk to the food dish and eat until I turned off the stimulation. How could brain stimulation cause an integrated, normal-looking passion for food? Somehow, LH neurons activate downstream cell assemblies that store sequentially coded memories and motivations that come pouring out in the form of appetite. In the posterior hypothalamus, Anthony Caggiula found it was the urge to mate that was elicited, complete with all the normal courting, approach, and copulatory behavior. The stimulation elicited a goal, not a reflexive path to it. (You can view and download a movie of stimulation-induced eating, running, or mating by request to Hoebel@princeton.edu.)

At the same time, Jim Olds was trying to stimulate arousal and learning with electrodes in the reticular formation, and he discovered electrical self-stimulation. Like his animals, my rats would press a bar 3,000 times per hour for short half second trains of electrical current. If I left the current on for 20 seconds, they did not need to press any more and instead they went to the food and started eating. My PhD thesis was a series of experiments showing that self-stimulation of the LH varied as a function of appetite that I manipulated with a gastric balloon, intragastric feeding, intravenous feeding and appetite suppressant drugs. Dave Margules and Jim Olds did the flip side with food deprivation increasing self-stimulation, and the resulting back-to-back *Science* articles launched my career (Hoebel & Teitelbaum, 1962).

Bartoshuk: I remember the days when the University of Pennsylvania was the hub of feeding studies and Eliot Stellar's theory of feeding ruled: feeding was excited by the LH and inhibited by the ventromedial nucleus. For a while, the theory was challenged and some scoffed at a LH feeding center, but I gather that passed.

Hoebel: Yes, I waited for the pendulum of understanding to swing back. We knew from local LH injection studies that there had to be cells in the LH controlling feeding behavior. Modern evidence shows the cell groups in the LH with roles in arousal, feeding, and reward. All of this leads back to the original question: Why is LH stimulation so rewarding, so natural, so appetite inducing?

We now know that feeding is controlled by a network. In network theory, nodes develop for information collection, processing, and broadcasting. I suggest that the LH be considered a “node.” If you would like to see a node in the process of being built, look at the paper from Sarah Leibowitz’s group (Chang et al., 2008), in which a mother’s high fat diet programs a baby rat’s brain *in utero*, such that extra galanin cells are born (hypothalamic neurogenesis) and migrate within the hypothalamus to create offspring with an appetite for a high fat diet. Good for rats in the wild, bad for people in our modern McDonald’s society.

Bartoshuk: The head of NIDA (National Institute of Drug Abuse), Nora Volkow, has noted that drugs of abuse “hijack” the areas of the brain that evolved to insure that eating gives us pleasure. How did your early work lead to that idea?

Hoebel: It was obvious to everyone that opioids in the brain had to be the basis for natural and drug-induced “pleasure.” It was Roy Wise who told me that dopamine was critical for this process, and his research over the years bears this out. Dopamine also plays key roles in motivation and reward, which I have always referred to collectively as reinforcement.

You ask about drugs of abuse. We showed that morphine, cocaine, amphetamine, and even nicotine all increase extracellular dopamine in the nucleus accumbens, a brain area where feeding and self-stimulation also released dopamine. Therefore, drugs act, in part, via a feeding reinforcement system. Then the question dawned on me, since these drugs are all addictive, does that mean that food is addictive too? I asked undergraduate Carlo Colantuoni to feed rats sucrose 12 hours per day to induce binge eating and then give them naloxone in a fanciful effort to precipitate opiate withdrawal. I will never forget the day he said they were shaking and chattering their teeth. I knew we had it and announced it at my presidential talk at the Society for the Study of Ingestive Behavior, saying, “remember you heard it here first.” The reaction ranged from “I don’t believe it” to curious, but were basically ho hum, because teeth chattering does not prove food addiction.

Carlo went to graduate school at Johns Hopkins, and we collaborated there to do receptor binding that revealed changes in sugar bingeing rats similar to what had been reported for rats on drugs. The plot was thickening. It was my greatest good fortune that Nicole Avena applied to Princeton as a graduate student and came to work on the problem. She now has 30 articles and reviews giving the evidence for sugar addiction and comparing sugar with fat.

The story is relatively complete and summarized as follows (Avena, Rada, & Hoebel, 2008). Rats given 10 percent sucrose and rat chow (like a soft drink for people) 12 hours per day binge on the sugar drink when they get it, and, after a month, it changes their brains in a manner that leads to the following addictive-like behavior: (1) their opioid system is altered such that naloxone or sugar deprivation causes anxiety in an elevated maze; (2) their dopamine system is sensitized, as shown by hyperactivity in response to a small dose of amphetamine; (3) worse yet, the sugar addicted rats, when deprived of sugar will drink more sugar-water than ever before if given the opportunity, and, if they are allowed to drink alcohol, they consume more than normal control rats. Thus going without sugar, i.e. “dieting,” can make the situation, the craving, worse instead of better, and sugar addiction is a gateway for alcohol abuse. Translate that to high school students, and the country has a problem that goes beyond sugar addiction to alcohol addiction.

The sugar addiction work was controversial among scientists, and thus unfindable in the peer review system. But then came new interactions with the true believers. Books abound on sugar addiction. These authors have web sites that reach and teach thousands of people how to cope with sugar addiction. As shown by the obesity rate in this country, teaching a food addict not to eat is likely harder than teaching an alcoholic not to drink or a cocaine addict to stop using cocaine. So how do they do it? All these web sites teach the food addicts to not eat sugar and flour.

Kelly Brownell at Yale held a food addiction meeting bringing together Nora Volkow and others of us with evidence of brain changes due to eating or obesity that resembled changes due to drug addiction. My former student Emmanuel Pothos has linked diet-induced obesity to deficits in mesolimbic dopamine neurotransmission. Depressed dopamine release in obese animals may cause them to compensate by eating palatable food, a stimulus that releases dopamine when laboratory chow fails. This helps explain overeating “comfort” food and ensuing obesity in some people.

Then, a Food Addiction Summit in Seattle brought together scientists and patients. Mark Gold, an avant garde advocate in the area of addiction medicine, was there, and we started a molecular research collaboration to compare the changes in brain DNA and protein expression that occur in our sugar addicted rats to those in morphine-addicted rats. Preliminary results show sugar-morphine similarities.

Bartoshuk: It has been said that you have started a new field of ingestive behavior research. What is it?

Hoebel: Nicole Avena and I have shown that daily bingeing on sugar can have the same behavioral and brain neurochemical effects as drugs of abuse (Avena et al., 2008). This launched the scientific study of food addiction, as reflected particularly in sugar addiction. It is the first solid, scientific evidence for a “natural addiction.” As such, it is exciting, both in the ingestive behavior field and in behavioral neuroscience in general.

Bartoshuk: One of the areas in your work I have always loved concerns your pioneering work on the technology of collection from (or introduction of) substances in the brain that allowed you to understand function.

Hoebel: Luis Hernandez from Venezuela was entranced with the LH self-stimulation phenomenon, and he came to my lab to work on it. We were in Israel at a conference when we ran into Urban Ungerstedt, who said he had invented microdialysis. I sent a postdoc to study with him in Sweden and bring back the technology that allowed us to make a microdialysis probe that could be implanted in freely moving rats to measure dopamine as they engaged in self-stimulation or feeding. Now we could get neurotransmitters out of nerve terminal regions in the brain as well as infuse them in. Scientists came to Princeton from around the country to learn the technique. We were able to report that brain-stimulation reward and feeding released dopamine in the nucleus accumbens, an area critical for reinforcement.

Bartoshuk: What else is new in the Hoebel lab?

Hoebel: Pedro Rada from Venezuela comes to my lab for a few months each year. Our goal is to find the yin and yang of reward and depression. After hearing Pat McGeer talk about Parkinson’s disease, I realized that if acetylcholine in the striatum acts in opposition to dopamine, causing the Parkinsonian movement disorder, acetylcholine probably acts in opposition to dopamine in the accumbens in

motivational disorder. It seemed that everyone and their uncle was studying dopamine, so we focused on acetylcholine. You know now what increases extracellular dopamine (feeding when food is novel, self-stimulation, drugs of abuse), but what releases acetylcholine? The answers turns out to be (a) aversive brain stimulation. If the stimulation releases acetylcholine, rats will actually bar press to turn off that stimulation; (b) depression in the Porsolt forced swim test. after being removed from the water, acetylcholine level rises and is still high the next day, suggesting this causes them to be depressed and give up easily again. We have discovered the nucleus accumbens is one place that Prozac and serotonin act to alleviate behavioral depression; (c) during a meal, as the eating rate slows down, acetylcholine levels in the accumbens rise, suggesting a role for acetylcholine in satiety signaling when dopamine is relatively high; (d) during withdrawal from morphine or sugar, dopamine levels fall and acetylcholine is released. Thus, low dopamine combined with high acetylcholine is a hallmark of withdrawal and the unpleasant state that it represents. Note that it is the same for drugs and sugar withdrawal.

The overall conclusion is that acetylcholine in general does the opposite of dopamine (Hoebel, Avena, & Rada, 2007). Whatever your favorite dopamine theory, consider the possibility that acetylcholine interneurons are opposing that function. This has led to the beginning of a neural model for approach and avoidance, those two basic psychological processes, so important for every animal (Hoebel, et al, 2007 and 2009).

Also, Pedro Rada used microdialysis to measure the release of neurotransmitters glutamate and GABA in our old friend the LH during a meal minute-by-minute! When rats start eating, glutamate is released and then falls off as other systems kick in to keep the meal going. I presume the glutamate signal to eat normally comes from areas such as the cortex, striatum, and accumbens. As the rats finish their spontaneous meal and eating slows down, you guessed it, GABA release peaks. This fits exactly the microinjection studies of former student Glenn Stanley, showing the role of these fast-acting amino acid neurotransmitters in the LH feeding node.

Bartoshuk: Have you retired?

Hoebel: There is no way to retire when having this much fun and excitement, opening a new field of investigation, and modeling an accumbens system that stops behavior, and I have two more graduate students doing exciting work. Miriam Bocarsly finds that high-fructose corn syrup can cause obesity. Yu-Wei Chen has discovered that interleukin, a product of the immune system that causes fever and sickness behavior, causes depression when injected in the accumbens, as measured in the forced swim test. This is intriguing as the first study showing immune system interaction with a brain mechanism that controls depression. It was a revelation to me that the immune system operates within the brain using the same neurochemicals as in the body. The future of behavioral neuroscience is full of possibilities for alleviating human suffering through an understanding of such immune-linked processes.

Bartoshuk: What is coming next?

Hoebel: Judging from our work with the Leibowitz lab cited above, a mother's diet when pregnant can program her offspring for the next generation of obese children and for children who consume excessive alcohol at puberty. Most obese adults have not inherited obesity-prone genes, their mother's diet may have imbued them with an overabundance of cells with the genes for the hypothalamic peptides that create the propensity to eat fat or drink alcohol. The obesity epidemic is not just about high-fat food and

low exercise. What is coming next is the realization that the hypothalamus can be programmed *in utero*, and this can dictate a measure of obesity and alcoholism in the next generation. This could be a self-perpetuating national problem, with huge costs in health care and untold suffering due to alcohol related accidents, unless government and industry cooperate to get a grip on it and stop the self-perpetuating cycle of obesity.