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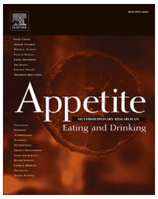

The convergence of psychology and neurobiology in flavor-nutrient learning

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ABSTRACT

Flavor evaluation is influenced by learning from experience with foods. One main influence is flavor-nutrient learning (FNL), a Pavlovian process whereby a flavor acts as a conditioned stimulus (CS) that becomes associated with the postingestive effects of ingested nutrients (the US). As a result that flavor becomes preferred and intake typically increases. This learning powerfully influences food choice and meal patterning. This paper summarizes how research elucidating the physiological and neural substrates of FNL has progressed in parallel with work characterizing how FNL affects perception, motivation, and behavior. The picture that emerges from this work is of a robust system of *appetition* (a term coined by Sclafani in contrast to the better-understood *satiation* signals) whereby ingested nutrients sensed in the gut evoke positive motivational responses. Appetition signals act within a meal to promote continued intake in immediate response to gut feedback, and act in the longer term to steer preference towards sensory cues that predict nutritional consequences.

1. Introduction

Sensory evaluation is an important influence in determining which foods to choose and how much of them to eat. It is practically self-evident that we prefer foods that “taste good,” although that's an imprecise use of the term “taste.” The complex combination of basic primary tastes plus odors, textures, and trigeminal sensations creates the experience of “flavor” (Small, 2012; Stevenson, 2009) which is a large part of what makes foods attractive and rewarding. Importantly, flavor evaluation is neither innate nor fixed. Humans (and the rodents which co-evolved with us and serve as laboratory models) are born possessing only a few general reactions to basic taste stimuli, such as a generalized liking for sweetness and dislike of bitter (Ganchrow, Steiner, & Daher, 1983; Hall & Bryan, 1981; Rosenstein & Oster, 1988). But the vast array of complex flavors in foods — the piquant zestiness of pepperoni pizza, the complex, aromatic tang of chicken tikka masala, the fruity, toothsome qualities of apple pie — take on value based on individuals' experiences with them (Capaldi, 1996; Myers, 2015; Sclafani, 2004; Yeomans, 2006). This helps explain why food preferences differ among individuals and vary so much geographically that members of different cultures enjoy foods that are unappealing or even downright revolting to outsiders. Understanding how flavor preferences are established by experience becomes increasingly important in light of the obesity epidemic, now that modern food processing brings us an array of manufactured foods with carefully engineered sensory properties and unnaturally high energy density. These learning systems may hold the key to the motivational processes driving overconsumption, but may also be used to promote choice of healthier options.

There are several ways that experience shapes flavor preference, and most of them are described in the framework of Pavlovian conditioning. A flavor can be conceptualized to act as a conditioned stimulus (CS) that, although initially arbitrary, comes to be evaluated more positively or negatively by result of its association with other biologically significant events (unconditioned stimuli, US) that occur with consumption. The powerful phenomenon of conditioned food aversions is a recognizable example for most people. When a flavor (CS) is followed by severe nausea (US), that flavor-illness association is learned and that flavor is subsequently regarded as disgusting.

While conditioned aversions had been a well-studied topic in the empirical analysis of basic learning mechanisms, Holman (1975) demonstrated that associative learning could produce strong positive reactions to flavors as well. In one experiment rats

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consumed two distinct flavors (e.g., almond and banana), one in a very sweet saccharin solution and the other in a less sweet solution. They subsequently preferred the flavor paired with higher sweetness even when it was no longer as sweet. Another experiment showed that a flavor became more strongly preferred when it was followed by delayed consumption of glucose (sweet and nutritious) compared to delayed saccharin (sweet but not nutritious). The distinction between those two experiments was crucial. Holman demonstrated two distinct types of preference learning: a flavor can become preferred by association with an already preferred taste/flavor (sweetness), or by association with nutritional consequences. These came to be called “flavor-flavor” (or, more precisely “flavor-taste”) learning and “flavor-nutrient” learning (hereafter abbreviated FNL), respectively.

These two types of learning can work independently, but may also interact with one another (Capaldi & Privitera, 2007; Warwick & Weingarten, 1994; Yeomans, Leitch, Gould, & Mobini, 2008) which presents a methodological challenge. During ordinary eating, flavor-flavor and flavor-nutrient learning can presumably both occur, either independently or in combination. If an individual shows increased preference for a flavor after consuming it in a sugary food, it's not clear whether the flavor has become associated with the rewarding taste of the sugar or with its nutritive properties, or both. An experimental method for specifically focusing on the mechanisms of FNL in lab animals was developed by Tony Sclafani, called the “electronic esophagus” method (Elizalde & Sclafani, 1990). Rats' consumption of a distinctively flavored but non-nutritive solution is accompanied by direct intragastric (IG) infusion of either a nutrient (e.g., glucose) or non-nutritive solution (water) through an infusion catheter. Intake of the solution could be monitored with an electronic lick detector interfaced to a computer that in turn controlled the IG infusion pump, enabling IG infusion to be matched to the rats' oral intake. In a typical experiment, training alternated between to two flavors (e.g., grape and cherry), with one flavor (CS+) accompanied by IG nutrient and the opposite (CS−) paired with IG water. Thus, if rats subsequently responded more positively to the CS+ flavor it reflected the learned association between that flavor and the postingestive effects of the nutrient.

The early studies using this method (Drucker, Ackroff, & Sclafani, 1993; Drucker, Ackroff, & Sclafani, 1994; Elizalde & Sclafani, 1988, 1990; Perez, Lucas, & Sclafani, 1995) demonstrated that FNL can produce two main changes in behavior. One is conditioned *preference*: in a choice between a CS+ and CS− flavor (for which the rats had been initially indifferent before training) they strongly favor the CS+. The second is increased *acceptance*: rats learn to consume larger amounts of the CS+ flavor, mainly by taking progressively larger meals. These two behavioral outcomes of FNL reflect its adaptive value for foraging animals (and ancestral humans) who ought to preferentially seek out cues signaling potential caloric advantage. The adaptive significance of FNL is underscored by the speed of acquisition and resistance to extinction (Ackroff, Dym, Yiin, & Sclafani, 2009; Drucker et al., 1994; Myers, 2007). This learning is relevant in the modern situation by helping to explain how high-calorie foods become so attractive and capable of promoting overeating.

Though at first glance some of the findings from the Sclafani group's original electronic esophagus studies may have suggested FNL as a relatively simple mechanism for shifting flavor evaluation, work that followed revealed FNL to be quite physiologically and psychologically complex, with diverse effects on food evaluation, meal size, and meal patterning. The goal of the following sections is to outline some key areas of progress in understanding FNL, including its physiological and neurobiological substrates and the ways that the learning shapes the psychological drivers of eating behavior. My intention is to focus on areas in which our understanding of the behavioral mechanisms of FNL has converged with and illuminated the search for its underlying neurobiological signals and circuitry. This work has been chiefly led by Tony Sclafani, who, along with his many trainees and collaborators, has pursued a careful and systematically organized exploration driven by three central questions:

1) What sensor (or sensors) detect the ingested/infused nutrient post-orally to generate the reward signal for FNL?
2) How is that signal conveyed to the central nervous system?
3) How is that information integrated into the central neural circuitry governing ingestive behavior to produce lasting changes in CS flavor evaluation?

2. Central circuits in FNL

I will begin with the last of those three questions, only because that's where the focus was when I joined the Sclafani lab as a postdoc in 1999. The search for central neural circuits that process flavor-nutrient associations is conceptually linked to the psychological question of how those associations impinge on the perceptual and/or motivational controls of behavior. That is, when a CS flavor becomes associated with calories, how is it perceived differently than before? Does it actually start to “taste better?” We should expect the nature of the psychological experience to provide clues to CNS pathways mediating the behavior.

This work was heavily influenced by Berridge's model (Berridge, 1996) of “wanting and liking” which emphasized the dissociability of incentive motivation (attention towards a source of anticipated reward and focused effort towards obtaining it) from hedonic evaluation (the experience of sensory pleasure). The former is generally governed by dopaminergic signaling in mesolimbic and mesocortical pathways, while the latter is attributable primarily to opioid and endocannabinoid signaling in the limbic system. Of course this model has been continually updated to reflect the interactions between the two systems, (e.g., Berridge, Robinson, & Aldridge, 2009; Castro & Berridge, 2014; Smith, Berridge, & Aldridge, 2011), but the dichotomy between liking and wanting continues to have considerable heuristic value for understanding the controls of complex, motivated behaviors.

FNL was sometimes called “hedonic shift” learning (Mehiel & Bolles, 1988; Mehiel, 1991), although it's not necessarily the case that a nutrient-paired CS+ flavor is preferred because it becomes more palatable. Stimulation of intake could instead reflect incentive motivational effects (i.e., ‘wanting’ instead of, or in addition to, ‘liking’ in Berridge's (1996) parlance). Using the taste reactivity test, which quantifies the automatic, stereotyped orofacial reactions rats exhibit in response to small intraoral infusions as the gold-standard measure of ‘liking’ (see Berridge, 2000; Grill & Norgren, 1978), we found that rats did indeed react to a saccharin-sweetened CS+ that had been paired with IG glucose as more palatable than an equally-sweet CS− flavor that had been paired with water (Myers & Sclafani, 2001a). The learned shift in CS+ palatability relative to the CS− was approximately the same as seen when shifting from 3% to 16% sugar solution. A companion study showed differences in CS+ and CS− lick microstructure consistent with CS+ palatability enhancement (Myers & Sclafani, 2001b), further indicating that FNL can influence ‘liking.’

While this may have seemed to settle the question of the hedonic nature of FNL, a follow-up study complicated that conclusion considerably. Instead of saccharin-sweetened flavors, which were initially moderately palatable and became more so with flavor-nutrient pairing, we studied rats' reactions to bitter or sour solutions which were initially unacceptable to rats. When a bitter or

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