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Rats acquire stronger preference for flavors consumed towards the end of a high-fat meal

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HIGHLIGHTS

► Rats learn to prefer cue flavors followed by the postingestive effects of fat.
► In a high-fat meal consisting of two flavors, rats learn stronger preference for the flavor occurring later in the meal.
► This differs from prior patterns seen with glucose.
► This suggests the postingestive reward generated by fat is of relatively slow onset, and potentially different from glucose.

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ABSTRACT

Rats learn to prefer flavors associated with postingestive effects of nutrients. The physiological signals underlying this postingestive reward are unknown. We have previously shown that rats readily learn to prefer a flavor that was consumed early in a multi-flavored meal when glucose is infused intragastrically (IG), suggesting rapid postingestive reward onset. The present experiments investigate the timing of postingestive fat reward, by providing distinctive flavors in the first and second halves of meals accompanied by IG fat infusion. Learning stronger preference for the earlier or later flavor would indicate when the rewarding postingestive effects are sensed. Rats consumed sweetened, calorically-dilute flavored solutions accompanied by IG high-fat infusion (+ sessions) or water (− sessions). Each session included an "Early" flavor for 8 min followed by a "Late" flavor for 8 min. Learned preferences were then assessed in two-bottle tests (no IG infusion) between Early(+) vs. Early(−), Late(+) vs. Late(−), Early(+) vs. Late(+), and Early(−) vs. Late(−). Rats only preferred Late(+), not Early(+), relative to their respective (−) flavors. In a second experiment rats trained with a higher fat concentration learned to prefer Early(+) but more strongly preferred Late(+). Learned preferences were evident when rats were tested deprived or recently satiated. Unlike with glucose, ingested fat appears to produce a slower-onset rewarding signal, detected later in a meal or after its termination, becoming more strongly associated with flavors towards the end of the meal. This potentially contributes to enhanced liking for dessert foods, which persists even when satiated.

1. Introduction

Food intake is guided by the various taste and flavor properties of foods. Some food constituents, particularly sugars and fats, promote intake because of predominantly unlearned positive responses to their sensory properties. But the much broader range of complex flavors and odors in food become liked or disliked primarily through experience. Perception of a food's flavor always precedes its postingestive consequences, allowing animals to learn when particular flavors reliably predict either beneficial or aversive postingestive events and then use these associations to guide subsequent food selection and meal size.

One influential type of associative flavor-postingestive consequence learning is flavor–nutrient conditioning. In this Pavlovian-like process, a taste or flavor (CS) of a food is followed by the post-oral physiological effects of macronutrients (US) contained in the food (see reviews [1–4]). This flavor–nutrient association can powerfully alter subsequent reactions to the CS flavor. If an initially-neutral flavor is followed by caloric consequences (especially of glucose but also other carbohydrates, fats, proteins, or even ethanol) rats can learn to preferentially select that flavor and consume larger amounts of it, often treating the CS flavor itself as if it has become more hedonically positive [5–7].

Procedurally, flavor–nutrient learning can be measured in experiments where two distinctive flavors that are similar in initial attractiveness are given to subjects in different training sessions, but with one flavor providing nutritional consequences and the other not. With experience, increased intake of the nutrient-paired flavor relative to the unpaired flavor, and preferential intake of the former in a direct choice

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between the two (even when the nutrient is no longer present) are typical results showing that flavor evaluation is based on learned associations with nutrient consequences, rather than mere familiarity [8]. Experiments in which flavor consumption is accompanied by direct intragastric or intraduodenal nutrient infusion (versus water infusion) show that subjects are associating the cue flavor with the nutrient's postingestive properties rather than its inherently rewarding taste (e.g., sweetness). Animals may also associate cue flavors with a meal's satiating effects, which sometimes results in a net decrease in subsequent intake when that effect opposes the intake-promoting effects of learning [9,10]. This is still consistent with the idea that flavor evaluation is altered by associative experience with postingestive nutrient consequences.

Preference learning can be acquired in as little as a single flavor–nutrient pairing [11,12], and learned preferences are especially persistent once they are acquired [11,13]. In this manner, food selection is steered towards nutrient-rich foods not only by unlearned positive responses to nutrient tastes themselves but also by learned responses to whatever flavors in an animal's food environment tend to co-occur with nutrients. Thus in humans' modern environment of flavor-enhanced, energy-dense, processed foods, Pavlovian conditioned responses to flavors associated with caloric density may maladaptively encourage selection and overconsumption of obesity-promoting foods.

The present experiments are concerned with the psychobiological mechanisms of flavor–nutrient learning with high-fat food. Although rats learn to alter their preference and intake of flavors associated with different macronutrients, a variety of evidence shows that fats are somewhat less effective than carbohydrates as a postingestive US, even when equated for caloric density. First, preferences for fat-paired flavors are learned more slowly. Preference is learned with as little as a single flavor + nutrient pairing for glucose but requires several pairings for corn oil [12]. Second, even after extensive experience, fat-based preferences often remain weaker than carbohydrate-based preferences. Rats trained with one CS flavor paired with IG carbohydrate and a different CS flavor with equicaloric IG corn oil learn to prefer both flavors versus an unpaired control flavor, but typically still prefer the carbohydrate CS flavor over the fat CS flavor in a direct choice [14,15]. Third, in studies of conditioned meal size effects, flavor + fat learning requires more training exposures than flavor + carbohydrate learning when equated for caloric density [16], and flavor + fat learning requires a more calorically dense fat stimulus to be effective [10]. Thus the postingestive US effects of fat are generally considered less effective than carbohydrates in producing learned responses to cue flavors.

Since the precise physiological identity of the postingestive events acting as the US for flavor–nutrient conditioning is unknown (see reviews [4,17,18]), investigating these cross-nutrient differences may help identify the underlying physiological signals involved. There are a number of potential explanations for why fat is a less effective US than carbohydrate. First, in the course of a meal fat may be slower to produce the relevant postingestive reinforcing stimuli. As a form of Pavlovian conditioning, flavor–nutrient learning should be sensitive to the temporal contiguity between CS (flavor) and US (postingestive events), so a slower-onset postingestive US should be more difficult to associate with the preceding flavor. Second, there actually may be a number of distinct physiological signals generated at different time points during and after a meal, arising from different sites of action, that have additive or synergistic effects at reinforcing preference for the CS flavor. Fat may stimulate a smaller subset of these reward pathways than carbohydrates. Third, analysis of flavor–nutrient learning should also consider the possible general influence of the prandial rise in circulating glucose on immediate attention and information processing (e.g., [19,20]). A meal high in glucose or rapidly digested glucose-containing saccharides should be most effective at stimulating this attentional effect, making the flavors of a glucose meal more perceptually salient and memorable when delayed postingestive effects of nutrients subsequently arise. It is important to note the three potential explanations outlined above are not mutually exclusive.

Our recent work has been focused on the timing of onset of the critical postingestive US events, using a behavioral paradigm to determine at what point after meal initiation rats detect the onset of nutrient reward acting post-orally. This strategy involves training rats in sessions wherein they consume 'meals' of distinct CS flavor cues paired with intragastric (IG) nutrient infusion, except that some CS flavors are always encountered early in the meal and other flavors only late in the meal. For comparison purposes each rat also experiences meals with other flavors paired with IG water. If, as has been an implicit assumption in much flavor–nutrient research (e.g., [1]) the postingestive US effects of a meal are only detected after a relatively long delay, the strongest preference learning should accrue for the flavor routinely encountered towards the end of the meal, because of the closer temporal contiguity between that CS flavor and the US onset. Similarly, retroactive interference would further inhibit learning about the early flavor. But contrary to this prediction, we have shown [21] that when flavors are paired with IG glucose, rats acquire a strong preference for the early-occurring flavor in addition to the late flavor. Moreover, rats' learned responses to the early flavor were qualitatively different from their responses to the late flavor. Learned responses to the early flavor were expressed only when rats were hungry, whereas learning about the late flavor was not state dependent, and was exhibited regardless of whether rats were hungry or recently satiated.

We have argued [21] that this reveals two fundamental facts about the mechanisms of flavor–nutrient conditioning, at least when glucose is the US. First, the strong preference for the early flavor shows that some rewarding effects of the US are detected rapidly, within the first several minutes of the meal in progress. If postingestive reward arose only late in a meal or afterwards, temporal contiguity effects (e.g., trace decay and retroactive interference) should minimize or prevent learning about the early flavor. This conclusion is also consistent with the recent findings by Sclafani's lab that mice that are accustomed to drinking saccharin while being infused IG with water will accelerate their intake within minsutes the very first time the IG infusion is switched to glucose or Intralipid [22]. Thus a fairly immediate effect of intragastrically infused nutrient can enhance appetitive motivation. We have recently replicated this "immediate appetition" effect in our lab using rats in a somewhat different protocol (Myers, Taddeo, and Richards, submitted).

Second, our prior results suggest that nutrients in a meal generate multiple, distinct US signals at different time points, supporting qualitatively different learned responses to the early and late flavors. For instance, there may be a rapid-onset signal generated by preabsorptive chemosensation in the proximal intestines, and a late-onset signal generated by metabolic byproducts or satiation factors later in the prandial sequence. Ordinarily in a meal of only one food, that flavor would come to be associated with both the early- and late-onset USs. Our recent findings suggest that a putative rapid-onset US produces state-dependent conditioning, and a separate delayed-onset US produces state-independent preference, potentially helping explain why "dessert" foods remain attractive when encountered during satiety.

The notion of multiple USs is consistent with several facts about the behavioral organization of flavor–nutrient conditioning. The conditioned response pattern has several dissociable behavioral/motivational components. Conditioning can separately influence appetitive and consummatory phases of meal patterning [23,24], acceptance and preference responses [6,13,25], and hedonic and non-hedonic aspects of flavor evaluation [7,26–29]. Postingestive nutrient effects can act to separately condition both intake-promoting preference responses and intake-suppressing satiation responses [9,10]. There is some evidence that the rewarding effectiveness of post-absorptive infusion sites (e.g., hepatic portal) may be modulated by whether or not there is also pre-absorptive nutrient stimulation (see [4]). Some neural and pharmacological manipulations (such as PBN lesions or surgical deafferentation at the celiac-superior mesenteric ganglia [30,31]) can significantly attenuate the strength of conditioning without blocking it altogether.