



The impact of caloric availability on eating behavior and ultra-processed food reward

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ABSTRACT

The food environment has changed rapidly and dramatically in the last 50 years. While industrial food processing has increased the safety and stability of the food supply, a rapid expansion in the scope and scale of food processing in the 1980's has resulted in a market dominated by ultra-processed foods. Here, we use the NOVA definition of category 4 ultra-processed foods (UPFs) as they make up around 58% of total calories consumed in the US and 66% of calories in US children. UPFs are formulated from ingredients with no or infrequent culinary use, contain additives, and have a long shelf-life, spending long periods in contact with packaging materials, allowing for the absorption of compounds from those materials. The full implications of this dietary shift to UPFs on human health and disease outcomes are difficult, if not impossible, to quantify. However, UPF consumption is linked with various forms of cancer, increased cardiovascular disease, and increased all-cause mortality. Understanding food choice is, therefore, a critical problem in health research. Although many factors influence food choice, here we focus on the properties of the foods themselves. UPFs are generally treated as *food*, not as the highly refined, industrialized *substances* that they are, whose properties and components must be studied. Here, we examine one property of UPFs, that they deliver useable calories rapidly as a potential factor driving UPF overconsumption. First, we explore evidence that UPFs deliver calories more rapidly. Next, we examine the role of the gut-brain axis and its interplay with canonical reward systems, and last, we describe how speed affects both basic learning processes and drugs of abuse.

1. Introduction

The food environment has changed dramatically and rapidly in the last 50 years. Industrial food processing has increased the safety and stability of the food supply; however, a rapid expansion in the scope of food processing in the 1980's has resulted in a market dominated by ultra-processed foods (Monteiro & Cannon, 2019). Given the novelty, levels, and variety of food processing available in our food supply, it is perhaps unsurprising that a definition for these food products is still hotly debated. Some definitions focus on the food's hedonic or sensory properties (Fazzino, Rohde, & Sullivan, 2019), while others focus more on the level of industrial processing and additives (Monteiro, 2009; Monteiro et al., 2018; Poti, Mendez, Ng, & Popkin, 2015). Here, we use the NOVA definition of category 4 ultra-processed foods (UPFs) as they make up around 58% of total calories consumed in the US and 66% of calories in US children (Monteiro et al., 2018; Neri et al., 2022; Steele et al., 2016). By definition, these foods contain substances with no or infrequent culinary use and often contain additives (emulsifiers, colorants, sweeteners) that themselves have effects on metabolic health (Bhattacharyya, O-Sullivan, Katyal, Unterman, & Tobacman, 2012; Dalenberg et al., 2020; Monteiro et al., 2018). UPFs are formulated to

have a long shelf-life and, therefore, spend long periods in contact with packaging materials, allowing for the absorption of compounds from those materials that have also been associated with increased type 2 diabetes risk (Hwang, Lim, Choi, & Jee, 2018). The full implications of this shift to UPFs on human health and disease outcomes are difficult, if not impossible, to quantify. However, UPF consumption is linked with various forms of cancer, increased cardiovascular disease, and increased all-cause mortality (Juil, Vaidean, Lin, Deierlein, & Parekh, 2021; Micha et al., 2017; Romaguera et al., 2021; Schnabel et al., 2019).

Understanding food choice is, therefore, a critical problem in health research. Although many factors influence food choice (Drewnowski, 1997), here we focus on the properties of the foods themselves. UPFs are generally treated as *food*, not as the highly refined, industrialized *substances* that they are, whose properties and components must be studied. Here, we examine one property of UPFs: that they deliver useable calories rapidly as a potential factor driving UPF overconsumption. First, we explore evidence that UPFs deliver calories more rapidly. Next, we examine the role of the gut-brain axis and its interplay with canonical reward systems, and finally, we describe how speed affects both basic learning processes and drugs of abuse.

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2. Food processing alters caloric availability

For the calories in foods to be accessible for use by the body, several physiological processes must occur. First, they must be broken down and removed from the natural matrices present in food (Edwards et al., 2015). Next, the macronutrient must pass through the gastrointestinal tract into the bloodstream (Livesey, 1995). From the bloodstream, carbon containing substrates are routed to organs, including the brain, for use. The speed of this process is dependent on the bioaccessibility of nutrients—described here as nutrient uptake, interactions between nutrients in the food, and interaction with the gastrointestinal tract. Interestingly, foods with similar macronutrient content can yield different caloric payoffs after ingestion based on the ease with which calories are extracted from these foods (Carmody, Weintraub, & Wrangham, 2011; Mandalari et al., 2008; Traoret et al., 2008).

The Atwater system, a common system used to estimate this energetic payoff, assigns set values for calories derived from each macronutrient category (Atwater & Benedict, 1902). Although there have been adjustments proposed to the system since its creation (Watt & Merrill, 1975), this system of determining caloric content tends to overestimate macronutrient digestibility and caloric availability, especially in foods high in dietary fiber or protein (Baer & Novotny, 2019; Capuano, Oliviero, Fogliano, & Pellegrini, 2018; Carmody et al., 2011; Novotny, Gebauer, & Baer, 2012). Diets high in UPFs tend to lack adequate dietary fiber and protein (Martini, Godos, Bonaccio, Vitaglione, & Grosso, 2021). Food processing itself can also alter bioaccessibility. Extensive milling produces flours that are easier to digest (Edwards et al., 2015) and processed peanut items like peanut butter or peanut oil release more calories than whole peanuts (Traoret et al., 2008). For almonds, the release of fat is dependent on the amount of slicing and crushing performed prior to consumption by subjects (Mandalari et al., 2008). Simply cooking increases caloric availability, in both low- and high-fiber foods (meat and sweet potato), likely by decreasing the amount of digestion resistant fiber (Carmody et al., 2011). But, a meal consisting of multi-grain bread and cheddar cheese increases energy expenditure (thermic effect of food) more than one of white bread and “cheese product” (Barr & Wright, 2010). While the effects of basic forms of food preparation such as crushing, boiling, baking, and fermentation on food matrices have been well studied individually, the impacts of their combination or the industrial processes involved in formulating UPFs are less well understood (Sensoy, 2014). More detailed studies in humans are needed to understand their effects on both nutrient availability, food choice, and food reward.

3. Post-ingestive signals rapidly reach the brain and drive food reward

3.1. Modulation of the hypothalamus and mesocorticolimbic structures

To examine how altered nutrient availability might bias food choice, we must consider how this information is relayed to and interpreted by regions of the brain that govern food intake. One of the most important and well-studied central regulators of food intake is the hypothalamus (Watts, Kanoski, Sanchez-Watts, & Langhans, 2022). Structurally, the hypothalamus is organized such that axonal projections are both received and sent to higher-order brain regions, allowing for integration of sensory information (Azevedo, Ivan, Friedman, & Stern, 2021). Thus, the hypothalamus serves as a gatekeeper or control center for sensory information integration (Gouveia, de Oliveira Belez, & Steculorum, 2021). Two types of neurons within the arcuate nucleus of the hypothalamus form the primary feeding behavior-related centers, integrating signals of both acute hunger and satiety as well as chronic regulation of whole-body energy balance and nutrient availability (Gouveia et al., 2021). Hunger and fasting activate agouti-related protein (AgRP) neurons to promote food-seeking and consummatory behaviors, and pro-opiomelanocortin (POMC) neurons are activated in positive energy

balance to promote fasting and subsequent regulation of body weight (Chen & Knight, 2016).

The role of homeostatic control over these neurons via hormonal activity (i.e., leptin and ghrelin), neurotransmitters (e.g., serotonin; Donovan & Tecott, 2013), and incretins (e.g., GLP-1; Holst, 2013) has been recognized for at least the last two decades, but only within the last decade has advancement in technological approaches allowed for investigation of *in vivo* acute regulation of activity (Chen & Knight, 2016). These *in vivo* studies, with the technological ability to monitor neuronal activation on a time scale of seconds rather than minutes or hours, revealed that anticipatory food cues inhibit AgRP and activate POMC neurons (Betley et al., 2015; Chen, Lin, Kuo, & Knight, 2015; Chen & Knight, 2016; Gouveia et al., 2021; Mandelblat-Cerf et al., 2015; Su, Alhadeff, & Betley, 2017). These findings highlight the importance of signaling speed and demonstrate the dynamics of acute signals integrated with slower homeostatic mechanisms that influence hypothalamic involvement in consummatory behaviors.

Infusions of nutrients directly into the gut result in AgRP neuron inhibition (Beutler et al., 2017; Su et al., 2017), and interestingly, repeated exposure potentiates the response in a manner that is proportional to caloric content but indiscriminate of macronutrient source (Beutler et al., 2017; Su et al., 2017). However, the signaling pathways by which caloric intake influences hypothalamic response differ by macronutrient source. Inhibition of AgRP neurons by lipid infusion requires vagal signaling from the duodenum; this vagal signaling is correlated with a reduction in later feeding and is needed for changes in fat consumption (Goldstein et al., 2021; Ritter & Taylor, 1990). Conversely, vagotomy does not affect the ability of intragastric glucose to decrease AgRP neuron activity (Goldstein et al., 2021). Rather, the splanchnic nerve and its connections to the hepatic portal vein are necessary for hypothalamic and AgRP neuron response to intragastric glucose (Goldstein et al., 2021; Schmitt, 1973). Whether UPFs made up of combinations of fat and simple carbohydrates, that therefore use separate but complementary signaling pathways to reach the hypothalamus, result in greater inhibition of AgRP neurons has not been investigated. However, these studies do demonstrate peripheral signals of caloric availability rapidly change neural activity.

3.2. Influence on brain reward, learning, and motivation circuitry

The hypothalamus does not exist in isolation as a central regulator of food intake. Rather, it is densely reciprocally connected with many other nuclei. Here, we focus on its connection with nuclei making up the canonical brain “reward system.” The “reward system” is a dopaminergic pathway composed of several mesocorticolimbic structures, including the ventral tegmental area (VTA), striatum, amygdala, and prefrontal cortex (Cox & Witten, 2019). AgRP neuron activity may act through negative valence signaling to influence reward learning and motivated behaviors (Betley et al., 2015), and interconnectivity between the hypothalamus and dopaminergic targets has been hypothesized to integrate homeostatic and reward information to guide eating behavior (Hsu, McCutcheon, & Roitman, 2018; Kelley, Baldo, & Pratt, 2005). These same dopaminergic mesocorticolimbic circuits are a critical mediator of motivation, reward, reinforcement, and associative learning (Schultz, 2007). Central to this circuit is the striatum (Cox & Witten, 2019; Mogenson, Jones, & Yim, 1980). VTA neurons primarily project to the nucleus accumbens (NAc; ventral striatum), and substantia nigra (SNc) projections primarily innervate the dorsal striatum, though there are exceptions (Cox & Witten, 2019). The striatum projects back to a broad area of midbrain dopamine neurons, regulating dopamine release across both ventral and dorsal striatum (Cox & Witten, 2019; Haber, 2014; Haber & Knutson, 2010). These reward areas are interconnected with hind-, mid-, and forebrain projections that regulate homeostatic functions and goal-directed behaviors, including food-seeking (Hsu et al., 2018). Thus, regulation of dopamine release across the mesocorticolimbic circuit is complex and highly integrated.

Central to reinforcement learning hypotheses of dopamine function is the encoding of a reward prediction error, which is supported by dopamine-dependent neuroplasticity where a repeat of actions or associations with stimuli that unexpectedly produced a reward are encouraged (Glimcher, 2011). Schultz and colleagues' (Schultz, Dayan, & Montague, 1997) seminal work mapped reward prediction onto dopaminergic neuron activity. After primates were conditioned to receive a juice reward following a stimulus, these neurons spiked in activity following the stimulus, but not the reward (Montague, Dayan, & Sejnowski, 1996; Schultz et al., 1997). Similarly, when the reward was omitted, the authors observed a pause in firing, lending further support to the prediction error hypothesis (Montague et al., 1996; Schultz et al., 1997). However, learning can occur without increases in dopamine (Flagel et al., 2011). In a study conducted by Flagel et al. (2011), only a stimulus that acted as an incentive rather than a predictive stimulus was able to elicit changes in striatal dopamine. This example lends support to an alternative hypothesis of dopamine function, that it instead underlies incentive motivation. We do not propose to provide an exhaustive review of the role of dopamine function in motivated behavior, but rather seek to highlight the importance of dopamine signaling in reinforcement learning and motivation as these pathways relate to encoding ingestive and post-ingestive signals.

Most experiments probing the function of dopamine in reward learning have used sweet taste as the primary reward. Taste has been called the gatekeeper to our internal environment, providing essential information on qualities of soon to be ingested foods (Breslin, 2013). Briefly, to reach the brain, taste is carried on the 7th (facial), 9th (glossopharyngeal), and 10th (vagus) cranial nerves and converges on the nucleus of the solitary tract (NTS) of the hindbrain (Breslin, 2013). In primates, afferents of NTS projection neurons go on to innervate the ventral posterior medial nucleus (VPM) of the thalamus (Scott & Small, 2009). However, in rodents, this pathway bifurcates at the NTS with one pathway going to the pontine parabrachial nucleus (PBN), which in turn innervates the VPM and another targeting the amygdala and hypothalamus (Scott & Small, 2009). From the thalamus, taste information is relayed to primary gustatory cortex (insula), orbitofrontal cortex (OFC; often named secondary gustatory cortex), and subcortical areas like the amygdala complex. These terminal fields then project back to the thalamus, striatum, PBN, and midbrain (Breslin, 2013; Carleton, Accolla, & Simon, 2010). Through these projections, taste is able to rapidly (~1–2 s) alter striatal dopamine efflux (Canchy, Girardeau, Durand, Vouillac-Mendoza, & Ahmed, 2021), Table S2 for review of timescale).

Although orosensation can act as a primary reward and increase striatal dopamine efflux, post-oral signaling can support behavior changes in the absence of taste. For example, mice that lack sweet taste receptors (Trmp5^{-/-} or Tas1r2^{-/-} and Tas1r3^{-/-}) still show a robust preference for glucose-paired flavors (Ackroff, Yiin, & Sclafani, 2010; Araujo et al., 2008; Sclafani, Marambaud, & Ackroff, 2014), and intragastric infusion of lipid emulsions evokes a striatal dopamine efflux and conditions licking behavior of an empty drinking spout in mice (Ferreira, Tellez, Ren, Yeckel, & de Araujo, 2012; Tellez, Medina, et al., 2013). Numerous rodent studies have shown that flavor-nutrient conditioning results from intragastric, intraduodenal, or intrajejunal infusion of nutrients (Ackroff et al., 2010; Drucker & Sclafani, 1997; Sclafani & Ackroff, 2012). Even caloric availability can guide preference. In the studies manipulating cooking described above, naive rodents would consume equal amounts of raw and baked sweet potatoes; however, after exposure to the caloric consequence of the foods, the rodents developed preferences for the cooked sweet potatoes (Carmody et al., 2011). Human studies have shown that preferences are developed for flavors paired with maltodextrin, a long-chain glucose polymer less detectable by sweet taste receptors in humans, but not flavors paired with non-nutritive sweeteners (Yeomans, 2012; Yeomans, Leitch, Gould, & Mobini, 2008).

The above studies demonstrate caloric sensing in the gut can change behavior and preference; however, the circuitry and mechanisms

involved are not fully understood. Many studies (outlined below) have observed rapid changes in neuronal activity following intragastric infusion of calories, indicating involvement of neural, rather than hormonal, signaling in nutrient reward (Small & DiFeliceantonio, 2019). Fat and carbohydrate seem to have separable peripheral pathways that lead to increases in striatal dopamine efflux (Small & DiFeliceantonio, 2019). The ability of intragastric lipids to evoke increases in striatal dopamine is dependent on vagal signaling through a proliferator-activated receptor α specific-mechanism, and activation of a right nodose ganglion-hindbrain-substantia nigra-dorsal striatum pathway (Tellez, Medina, et al., 2013).

The role of the vagus in glucose sensing is more complex. Some studies have shown vagal contributions are not essential to drive dopamine efflux in the striatum following intragastric infusion of glucose (Tellez, Ren, et al., 2013), which agrees with studies demonstrating the vagus is not needed for flavor nutrient conditioning to glucose (Qu, Han, Niu, Tong, & de Araujo, 2019; Sclafani & Lucas, 1996). However, others report an effect of vagotomy on sucrose-dependent changes in VTA activity (Fernandes et al., 2020). Striatal efflux of dopamine following intragastric infusion of glucose is dependent on glucose metabolism, as infusion of 2-deoxy-D-glucose (2-DG), which disrupts glucose utilization, abolishes the rise in dopamine (Zhang, Han, Lin, Li, & de Araujo, 2018). Accordingly, alpha-methyl-D-glucopyranoside (MDG), which is transported by the sodium glucose transporter (SGLT1), but is not metabolizable, does not condition a flavor preference over glucose (Zhang et al., 2018). However, SGLT1 activation by MDG is sufficient to condition a preference over non-nutritive sweeteners, such as saccharin (Zukerman, Ackroff, & Sclafani, 2013) and acesulfame potassium (Tan et al., 2020). Intragastric MDG also leads to increased activity in the caudal NTS, a target nucleus of the vagus (Tan et al., 2020). So, while SGLT1 activation seems to play a role in preference and in modulating NTS firing, there is perhaps another sensing mechanism downstream of glucose metabolism. This in combination with redundant signaling from the splanchnic nerve could perhaps reconcile the above conflicting findings on the role of the vagus in glucose sensing.

Just as with hypothalamic responses, there are few data on how macronutrient combinations common in ultra-processed foods may alter dopaminergic responses. There is evidence that participants over-value foods containing fat and carbohydrates, potentially due to the convergence of signals from the periphery onto a common dopaminergic target (DiFeliceantonio et al., 2018; Perszyk et al., 2021; Small & DiFeliceantonio, 2019). While there is evidence an ultra-processed milkshake containing fat and sugar increases striatal dopamine on post-oral time-scales, we do not have data from single macronutrients or from minimally processed foods for comparison (Thanarajah et al., 2019). Most intragastric infusion studies in rodents use glucose as a carbohydrate stimulus, Intralipid as a fat stimulus, and protein liquids such as Proteinex (Goldstein et al., 2021; Han et al., 2018; Qu et al., 2019; Tellez, Medina, et al., 2013), but there are no studies on macronutrient combinations or foods (either ultra- or minimally-processed).

4. The role of speed in learning

Whether through vagal or other mechanisms, nutrient information is relayed from the gut to the brain and influences both homeostatic brain systems and those that govern reward, learning, and motivation, leading to changes in behavior. This integration of nutritive signals with the canonical reward network likely serves the essential function of providing information tying the sensory experience of food intake to its later nutritive consequences. From a teleological perspective, linking caloric value with the hedonic response of liking could reinforce preference for a particular food and lead an organism to seek out that food. This concept is often referred to as flavor nutrient conditioning or flavor nutrient learning (Myers, 2018, for recent review). Supporting its essential survival function, flavor nutrient learning can be acquired

rapidly and only requires a single trial (Ackroff, Dym, Yiin, & Sclafani, 2009). It can be reasoned that if flavor nutrient learning is essentially a Pavlovian conditioning process by which a conditioned stimulus (CS), in this case the smell and taste of food, is paired with an unconditioned stimulus (US) of nutrients in the gut, it must follow similar principles of Pavlovian conditioning. The one most pertinent to the discussion here is that conditioning is more effective the more closely coupled in time a US is to the CS.

Temporal congruency, or that for learning to occur events must occur closely in time, was held as a central principle in learning theory until Rescorla (1967) demonstrated that although congruency did support some forms of conditioning, instead *contingency*, the US reliably followed the CS was the most important factor governing learning acquisition. Contingency has since been the dominant theoretical framework; however, there are many instances where the influence of temporal contiguity can be observed (Balsam, Drew, & Gallistel, 2010). Most pertinent to this discussion are studies of trace-conditioning, where the spacing between CS and US is explicitly manipulated. In these studies, when the delay of US is plotted against trials to acquisition, a near linear relationship is observed, whereby increased CS-US spacing impairs learning and decreased CS-US spacing enhances learning speed (Balsam & Gallistel, 2009; Gallistel & Gibbon, 2000). In another trace conditioning paradigm, short CS-US intervals lead to more vigorous anticipatory responding, though both short and long intervals lead to learning (Balsam et al., 2010). Similarly, when there are multiple CSs, the CS closest in time to the US gains more motivational value (Tindell, Berridge, Zhang, Peciña, & Aldridge, 2005). This effect can also be observed in early conditioned taste aversion studies, where rats that experienced a longer passage of time from saccharin consumption to irradiation (to produce malaise) displayed a blunted taste aversion to saccharin compared to those who experienced the events more closely in time (Barker & Smith, 1974). Broadly, these findings demonstrate the importance of time between the CS and US to support both learning and potentially the motivational value of the cue. Applied to flavor nutrient learning, this could mean faster acquisition for flavors that deliver their associated US rapidly as well as higher motivation for these flavors. We see some hints that these processes may be affecting human food choice behavior from studies demonstrating that foods with a higher glycemic index, and thus a high rate of glucose absorption, show a greater potential for addictive-like eating behavior (Schulte, Avena, & Gearhardt, 2015, 2017) and elicit greater NAc and striatal responses (Lennerz et al., 2013) compared with foods providing lower glycemic loads.

The importance of speed of reward receipt has also been extensively studied within the framework of delay discounting (Ainslie, 1975; Mazur, 1997). Humans and animals value immediate rewards over those that are delivered at a later date with rewards becoming less and less valuable (“discounted”) the further in time they are delivered in a hyperbolic function (Vanderveldt, Oliveira, & Green, 2016). This discounting of delayed rewards has been proposed as a reason food reinforcers are often chosen over what should be a more valuable drug reinforcer (Lenoir, Serre, Cantin, & Ahmed, 2007; Tunstall, Riley, & Kearns, 2014; Tunstall & Kearns, 2014). In a powerful example of this effect, delaying both saccharin and cocaine rewards led rats who once preferred saccharin to prefer the cocaine reward (Canchy et al., 2021).

5. The importance of speed in reward: parallels in studies of drug use

The most convincing evidence that the kinetics of reward delivery changes behavior comes from drugs of abuse literature. Drugs of abuse are powerful reinforcers because they activate the same reward pathways evolved for natural rewards described above (Avena, Rada, & Hoebel, 2008; Crisicelli & Avena, 2016; Di Chiara, Acquas, Tanda, & Cadoni, 1993). Therefore, we can hypothesize the mechanisms and pathways that underlie vulnerabilities exploited by drugs with fast pharmacokinetic profiles may also be exploited by foods with fast “nutrikinetic”

profiles (van Duynhoven et al., 2012). Route of administration is a major early pharmacokinetic determinant of abuse potential; drugs taken in ways that reach the brain faster have a higher abuse and addiction potential, known as the “rate hypothesis” (Greenblatt, Shader, Divoll, & Harmatz, 1981; Hatsukami & Fischman, 1996; Jones, 1990). Similarly, for people using substances with faster routes of administration (i.e., inhalation, intravenous injection, and snorting) addiction is not only more likely but also more severe (Barrio et al., 2001; Budney, Higgins, Bickel, & Kent, 1993; Carpenter, Chutuape, & Stitzer, 1998; Ferri & Gossop, 1999; Gossop, Griffiths, Powis, & Strang, 1992; Hatsukami & Fischman, 1996; Rawson, Gonzales, Marinelli-Casey, & Ang, 2007). The importance of the speed of administration can also be shown through sobriety aids like nicotine patches. Nicotine patches do not support addictive use as cigarettes do because they slowly deliver nicotine, rather than delivering it rapidly (Fiore, Smith, Jorenby, & Baker, 1994).

Given that route of administration plays a key role in behavioral changes and subjective experiences relevant to the progress of addiction, researchers have sought to understand the key neurobiological mechanisms affected by speed. These studies often rely on altering the rate of drug infusion. For example, Samaha and colleagues (Samaha, Mallet, Ferguson, Gonon, & Robinson, 2004), varied the rate of cocaine infusion from 5 to 100 s and found faster infusions led to greater psychomotor sensitization. Similar findings hold for nicotine (Samaha, Yau, Yang, & Robinson, 2005). Later studies demonstrated that although faster infusion rates resulted in psychomotor sensitization, they produced increases in drug-seeking or -taking behavior inconsistently (Crombag, Ferrario, & Robinson, 2008; Schindler, Panlilio, & Thorndike, 2009). However, experiencing these faster rates does lead to vulnerability to relapse (Wakabayashi, Weiss, Pickup, & Robinson, 2010).

These same studies report both behavioral and brain effects of rapid or slow drug infusion. The medial prefrontal cortex, orbitofrontal cortex, and nucleus accumbens core and shell were all more active, as measured by cFos expression, after a fast (5s) cocaine infusion (Samaha et al., 2004). Fast infusions of nicotine, as compared to slower ones, elicited altered cFos expression across the striatum (Samaha et al., 2005). These changes persist even 45 days after the last cocaine experience, with rats that had experienced the fast infusion rate showing a blunted striatal response to acute cocaine challenge as well as a vulnerability to reinstatement (Wakabayashi et al., 2010). These findings can inform our hypotheses of expected behavioral and brain changes to be observed when studying foods that deliver calories more rapidly, especially long-term changes and changes after diet modification or periods of abstinence from certain foods.

In humans, parallel behavioral findings have been observed. Abreu, Bigelow, Fleisher, and Walsh (2001) intravenously injected habitual cocaine using participants with cocaine at varying speeds and found that ratings of “high” and “liking” were greater when cocaine was injected more rapidly. It should be noted the same was not found for users of opioids when hydromorphone was infused rapidly. These cocaine findings were later replicated (Nelson et al., 2006). Other studies that varied opioid infusion rate report subjective ratings of “high” and “liking” increasing with increased rate of infusion, this time using morphine (Marsch et al., 2001). Parallels between rise in drug plasma levels and subjective high have been observed in participants given a single pentobarbital bolus over the same dose given more slowly (de Wit, Bodker, & Ambre, 1992).

Parallel neurobiological findings are more difficult to interpret. Volkow and colleagues (Volkow et al., 2000) found that while varying the route of administration of cocaine (smoked, snorted, or intravenous) did alter the subject effects of the drug, there was no correlation with positron emission tomography (PET) measures of dopamine transporter (DAT) blockade. Another similar study, however, reports the time course of DAT blockade in the striatum as measured by PET to be correlated with subjective “high” (Volkow et al., 1997). Blockade of the dopamine transporter is a major way by which cocaine increases dopamine in the synapse. Brain levels of radiolabeled methylphenidate

as measured by PET have been reported to be both related to and unrelated to subjective high (Volkow et al., 1995, 1996). The lack of consistency in these human studies is likely due to a host of factors, from low participant numbers given the cost and radiation load associated with PET imaging to the varied genetic background and drug history of human participants in comparison with experimentally bred and housed rodents. However, these studies do point to a lack of understanding of the neurobiological underpinnings of the rate hypothesis in humans, despite its behavioral effects being well-characterized. Studies that address this gap, for both food and drugs, will provide important insight into how these systems integrate signals that occur over different delays and timescales.

6. Conclusions and future directions

UPFs make up an ever increasing proportion of daily caloric intake of both US adults and children (Neri et al., 2022; Steele et al., 2016). Compared to their ubiquity in our modern food environment, there is a dearth of information on how individual components of UPFs affect eating behavior and reward processes. Here, we propose one potential driver of UPF preference is their ability to deliver useable calories rapidly. Gut-derived signals do not act in isolation, however. As stated above, orosensory components are extremely important for supporting food intake. Sweetness, for example, can support intake without caloric consequence in rodents (Holman, 1969; Sclafani, 1995; Sclafani & Lucas, 1996) and as evidenced by the popularity of “diet” sodas and beverages. It should be noted that while “diet” drinks are popular, they represent just 32% of adult sweetened beverage consumption, with the rest coming from caloric sweeteners (Piernas, Ng, & Popkin, 2013). Furthermore, the appetitive effects of nonnutritive sweeteners are short-lived in rodent models (Sclafani & Ackroff, 2004). A theoretical framework that incorporates the interactions between oral sensation and post-oral signals would provide a fuller explanation of the current data and consumer trends. While some laboratories have begun these studies (Dalenberg et al., 2020), further careful experiments testing the synergistic effects of oral sensation and post-oral consequences, particularly in humans, are needed.

More broadly, experiments designed to parse individual macro and micronutrient components and food processing steps common in UPFs are necessary to determine their effects on metabolism, brain, and behavior. Foods that contain macronutrient combinations of fat and carbohydrate are valued higher calorie-for-calorie than foods that contain either macronutrient source alone (DiFeliceantonio et al., 2018; Perszyk et al., 2021). It is hypothesized that this overvaluation arises from peripherally separate, but centrally converging, post-oral signaling, resulting in greater dopamine efflux relative to either macronutrient alone (Small & DiFeliceantonio, 2019). While we have evidence that fat and carbohydrate combinations increase dopamine in the human striatum at post-oral timescales (Thanarajah et al., 2019), we do not have data on single macronutrients for comparison. Oppositely, work in rodents has tended to isolate each macronutrient and we have little or no data on macronutrient combinations (Beutler et al., 2017; Goldstein et al., 2021; Su et al., 2017). Experiments that test how macronutrients, including protein, individually and in combination contribute to reinforcement would provide a fuller understanding of the effect of UPFs on reward systems.

Ultra-processed foods are extremely complex. They consist of refined ingredients, additives, and flavors in combinations and doses not previously encountered in our evolutionary history. Here, we examine the impact of one aspect of ultra-processed foods, that they deliver calories rapidly, and summarize the pathways UPFs might exploit to lead to their preference. However, this feature is likely part of a larger interplay between speed of delivery, macronutrient content, and taste that leads to an overall preference for these foods. Experiments designed to test each of these components; their impact on physiology, brain, and behavior; and theoretical frameworks that allow for these interactions

are necessary steps to improving our understanding of food reward and how it applies to our modern food environment.

Ethical statement

The attached manuscript contains a narrative review and did not collect any new data that would be subject to ethical or regulatory approvals.

Declaration of competing interest

The authors declare no conflicts of interest.

Data availability

No data was used for the research described in the article.

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