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NEW DIRECTIONS IN MODELLING DYSREGULATED REWARD SEEKING FOR FOOD AND DRUGS

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Abstract

Behavioral models are central to behavioral neuroscience. To study the neural mechanisms of maladaptive behaviors (including binge eating and drug addiction), it is essential to develop and utilize appropriate animal models that specifically focus on dysregulated reward seeking. Both food and cocaine are typically consumed in a regulated manner by rodents, motivated by reward and homeostatic mechanisms. However, both food and cocaine seeking can become dysregulated, resulting in binge-like consumption and compulsive patterns of intake. The speakers in this symposium for the 2021 International Behavioral Neuroscience Meeting utilize behavioral models of dysregulated reward-seeking to investigate the neural mechanisms of binge-like consumption, enhanced cue-driven reward seeking, excessive motivation, and continued use despite negative consequences. In this review, we outline examples of maladaptive patterns of intake and explore recent animal models that drive behavior to become dysregulated, including stress exposure

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and intermittent access to rewards. Lastly, we explore select behavioral and neural mechanisms underlying dysregulated reward-seeking for both food and drugs.

Keywords

animal models; compulsive; binge; behavioral economics; habitual; addiction; binge eating disorder; obesity; maladaptive; cocaine; orexin; punishment

Introduction

A large number of individuals worldwide are afflicted by binge eating or substance use disorders. However, successful pharmacotherapies remain limited, particularly for stimulant use disorder (1-3), despite many preclinical studies using animal models as a means to identify the neural mechanisms underlying these diseases. This may partially be due to animal models that have inadvertently focused on regulated food or drug consumption that is motivated by reward and/or homeostatic mechanisms. In contrast, binge eating and drug addiction are characterized by dysregulated reward seeking, with diagnostic criteria that includes over-consumption (e.g., bingeing, escalation), lack of control over consumption, and compulsive patterns of intake. Therefore, it is essential that behavioral neuroscientists develop and utilize behavioral models that specifically focus on dysregulated reward seeking. In this review, we discuss the parallels between food and drug seeking in terms of evidence of dysregulated patterns of intake, paradigms that drive the emergence of these dysregulated patterns, and the potential behavioral and neural mechanisms underlying dysregulated reward seeking.

1.0 Maladaptive patterns of reward seeking

1.1 Binge-like consumption

A widely distributed neurocircuitry throughout the brain regulates appetite in a highly sophisticated manner to ensure energy balance (4). When food intake is driven by hedonic or reward-based processes, satiety signals can be overruled and maladaptive patterns of intake can emerge, such as bingeing and escalation. The terms ‘binge’ and ‘escalation’ are both used to describe excessive intake or overconsumption (in a within- or between-subject comparison). While ‘escalation’ indicates an increase in daily intake over a longer access period (e.g., 6 or 24 hours) and typically involves intermittent intake during this access period, ‘binge’ indicates an increase in intake over a brief access period (e.g., 1 hour) and is typically characterized by continuous intake. However, the lengths of time used to define the access periods for binge or escalation vary across substances and studies.

In animal models, binge-like patterns of consumption of sugar have been associated with features of addictive behavior such as escalation of intake, consuming more than intended, increased anxiety-like behavior (e.g., ultra-sonic distress vocalizations), and somatic signs of withdrawal upon cessation of access (5). Furthermore, rats prone to diet-induced obesity show addiction-like behavior towards high-fat high-sugar food, including binge-like consumption and escalation of intake, and show addiction-like synaptic changes at nucleus

accumbens synapses that resemble those of rats who have self-administered drugs of abuse (6). Likewise, in the case of alcohol and drugs, consumption can escalate over time and become binge-like in nature. Binge eating and binge drinking share several important features including, by definition, preoccupation with and excessive consumption of the substance.

Although regulated patterns of cocaine intake are commonly observed with limited daily access to cocaine self-administration, dysregulated patterns are observed during continuous or long access. With limited access, rats typically self-administer cocaine in a stable manner that appears guided by satiety, with rats displaying consistent pauses after each infusion, modulating inter-infusion intervals according to dose, and achieving a consistent concentration of cocaine in the brain (7-10). However, with continuous or long access to cocaine self-administration, a dysregulated pattern emerges that is not directly guided by satiety, with rats displaying escalation of intake, alternating periods of bingeing and abstinence, and increased variability in inter-infusion intervals (11-13). Recent work has observed similar binge- and burst-like patterns of cocaine intake when rats have intermittent access to cocaine self-administration (discussed in more detail below), and this dysregulated pattern is strongly associated with enhanced addiction-like features such as increased motivation, relapse, escalation, and continued use despite negative consequences (14-18). Further, this pattern of cocaine consumption is more reflective of the temporal patterns of use in humans (reviewed in (19)).

1.2 Enhanced cue-driven seeking

Research from the past 20 years demonstrates that addictive behaviors are characterised by attentional biases towards reward-related stimuli (for review see (20). For example, when regular drinkers are exposed to the sight or smell of an alcoholic beverage or smokers are asked to hold a lit cigarette, they react with increased physiological arousal and subjective craving (see (21, 22). These processes have long been thought to be important in the maintenance of addictive behaviors and key precipitants of relapse. Reward-related cues have been proposed to acquire incentive-motivational properties which therefore have the capacity to alter the ways in which the cues themselves are attended to and perceived (23). It has been proposed that, through classical conditioning, reward-associated stimuli elicit the expectancy of reward availability, and this causes both attentional bias for these stimuli and subjective craving (24).

In binge eating and addiction disorders, and in animal models of these disorders, reward-associated cues can acquire enhanced motivational properties. For example, obesity-prone rats show enhanced conditioned approach toward food cues, as well as enhanced cue-triggered food seeking during a Pavlovian-to-instrumental transfer (PIT) task, in which instrumental responding is invigorated in the presence of a conditioned stimulus previously paired only non-contingently with food reward (25, 26). Similarly, repeated exposure to stimulants enhances the motivational properties of conditioned stimuli and facilitates expression of PIT for food rewards (27). Recent work shows that cocaine-exposed rats display maladaptive responding in a PIT task, such that the conditioned stimulus drives instrumental reward seeking (i.e., lever pressing), even when expectancy for food reward is

high and the conditioned stimulus should drive conditioned approach behavior instead (i.e., going to food cup), as is observed in non-cocaine-exposed rats (27). Finally, the ability for conditioned stimuli to drive reward-seeking behavior for drugs or sucrose 'incubates' with increasing periods of time during the first several weeks of abstinence and becomes stronger (reviewed in (28)).

1.3 Continued use despite negative consequences

A key characteristic of substance use disorder and disorders associated with dysregulated eating is continued behavior despite negative outcomes (29). For example, chronic cocaine use is associated with a range of negative health outcomes – particularly cardiovascular outcomes – as well as an increased risk of criminal prosecution, loss of employment and financial stress (30, 31). Eating disorders have the highest mortality rate of any psychiatric illness (32) and there are a range of consequences associated with compensatory vomiting (dental/oral cavities), as well as the feelings of disgust and discomfort associated with food overconsumption (29). In animal models of drug use, this phenomenon can be modeled by pairing drug delivery with an aversive outcome, such as footshock (33-36). Some rats exhibit a resistance to footshock-induced suppression of drug seeking, and thus might represent a population 'vulnerable' to developing dysregulated drug-seeking (36-38). Similarly, rats exhibit individual differences in intake when alcohol is adulterated with the bitter tastant quinine, and extended access to alcohol promotes quinine-resistance across the population (for review, see (39)). Finally, with feeding behavior, palatable food seeking is typically suppressed by presentation of a cue previously predictive of footshock; however, this cue-suppression of feeding is not observed in rats following extended access to a so-called 'cafeteria diet' consisting of high fat, high salt, and energy-dense foods (40) or following binge-like intake of sucrose (41).

1.4 Excessive motivation

Substance use disorder is often conceptualized as a syndrome of dysregulated motivation, evidenced by intense drug craving and compulsive drug seeking (as above; (42)). Similarly, eating disorders associated with excessive food intake (e.g. binge eating, obesity) likely reflect excessive motivation for palatable foods, including heightened craving elicited by food cues and contexts (also discussed above). Conventional studies have typically measured drug/food motivation using a progressive ratio schedule of reinforcement; however, this procedure is susceptible to differences in drug pharmacokinetics (making 'motivation' difficult to compare across reinforcers) and shifts in baseline consumption (tolerance) (43). To this end, behavioral economics has emerged as a powerful quantitative tool for measuring the motivational component of drug/food reward distinct from baseline intake (33, 43, 44). This approach examines the consumption of a reinforcer at several prices within a single session, where price is altered either by increasing the fixed ratio (FR) requirement to earn a reward (this approach is typical for food pellets), or by maintaining a FR1 schedule but progressively reducing the amount of reinforcer delivered across the session (e.g. for liquid food reward or intravenous drug infusions) (43, 45). By applying an exponential demand equation to consumption data (46), it is then possible to derive demand intensity (Q_0), which is an estimate of consummatory behavior under unrestricted conditions (baseline intake), as well as demand elasticity (α), which is an index of how rapidly consumption

decreases with increasing price, such that high demand elasticity (high α values) reflect lower motivation to 'work' to maintain the preferred level of intake (and conversely, lower α values reflect higher motivation) (33, 43). Importantly, for most drugs and palatable foods, demand intensity and elasticity are orthogonal (43, 47), meaning that the motivational index (α) is not influenced by differences in baseline drug or food intake, thus eliminating any confound of tolerance (in the case of drugs of abuse) or higher body weight (for both drugs and food). Consistent with demand elasticity being an index of drug motivation, α correlates with several measures of craving and punishment-resistant responding, and paradigms that promote addiction-like behaviors are associated with significant reductions in demand elasticity (increased motivation) (33, 47). Moreover, behavioral economic measures determined via a hypothetical purchasing task are altered in patients with substance use disorder and obesity (48-50), further highlighting the utility of this approach for studying dysregulated motivation in clinical pathology.

The transition from controlled to dysregulated drug and food intake has often been attributed to a shift in baseline consumption ('tolerance'). Indeed, in their seminal paper examining the development of cocaine addiction in rats, Ahmed & Koob (12) posited that the loss of control over drug intake, evidenced by a steady escalation of intake across repeated extended access sessions, reflected an upward shift in the 'hedonic set point' for cocaine. Similarly, animal models of binge eating and obesity often promote a phenotype characterized by a progressive increase in the total caloric intake across time (29, 51). Consistent with this view, increased drug use is a key diagnostic criterion for substance use disorder, and binge eating disorder is characterized by a perceived 'loss of control' over how much food is eaten (52). However, recent animal studies utilizing behavioral economics approaches, which can discern between preferred baseline intake (Q_0) versus the motivation to maintain this level of intake (α), have provided a much more nuanced understanding of the extent to which shifts in hedonic/satiety set points contribute to dysregulated behaviors.

With respect to drugs of abuse, self-administration paradigms that promote persistent changes drug motivation (e.g. intermittent access, see Section 2.1 below) are characterized by dramatic decreases in demand elasticity (α) (17, 18). Consistent with this, demand elasticity (α) predicts a range of motivated drug behaviors, including punished drug responding and heightened relapse propensity, whereas demand intensity (Q_0) does not (33, 47). In contrast, paradigms that promote shifts in the 'hedonic set point' (i.e. tolerance), including the long access model in which rats are given extended (typically 6–12h/day) continuous access to drug (12), promote persistently increased demand intensity (Q_0) without drastic changes in demand elasticity (18, 47). In clinical populations, both demand elasticity and intensity have predictive value with respect to addiction severity and outcomes. Low demand elasticity (high motivation) for drug is linked to poorer treatment outcomes and a greater likelihood of polydrug abuse (53, 54). In contrast, high demand intensity (Q_0) is a strong predictor of 'real world' drug use and consumption (53, 55). Similarly, demand intensity and elasticity predict different aspects of dysregulated food behavior in humans; demand intensity (Q_0) and elasticity (α) are both correlated with body mass index (BMI), whereas only demand intensity is correlated with dietary restraint and hunger for energy-dense snacks (56). Together, these studies indicate that different

components of dysregulated food/drug seeking are differently regulated by the hedonic/satiety setpoint for the rewards vs. the motivation to achieve/maintain this satiety level.

2.0 Drivers of maladaptive patterns of reward seeking

There has long been interest in developing preclinical rodent models that promote the endophenotypes reflective of dysregulated food and drug seeking (29, 57). Such approaches have been instrumental for the identification and characterization of neural systems that contribute to substance use and eating disorders. Conventional approaches to promoting dysregulated behavior have typically focused on providing animals extended access to drugs of abuse or palatable food – these approaches are reviewed in detail elsewhere (57, 58). Here, we focus on novel approaches that have gained significant traction in both the drug and food literature over recent years, including the intermittent access model and stress exposure models.

2.1 Intermittent access

Conventional animal models of food and drug addiction have focused on increasing the amount of consumption in order to induce an addicted-like state (12). Emerging evidence, however, indicates that the development of dysregulated seeking is more critically linked to the temporal pattern of food and drug intake (15, 17), rather than total consumption, such that stronger addiction-like behaviors are observed following intermittent access to a reinforcer. Schedules of intermittent access vary across reinforcers and paradigms, but typically involve extended periods of access to food/drug on select days (e.g. every other day), brief access to drug/food in daily sessions (e.g. repeated 5 min bins of drug availability), or a combination of both, as outlined below.

In the case of food, rats given intermittent and brief access (30min; 2–3x week) to sweetened fat (vegetable shortening and sugar) exhibit greater escalation of fat intake compared to control rats with daily access (59, 60). Interestingly, rats on this schedule restrict their standard chow intake on non-access days to compensate for their binge-like intake of sweetened fat (51), and escalation of sweetened fat intake can be further exacerbated by caloric restriction prior to access sessions (59, 60). Similarly, rats given restricted daily access (12h) to a sucrose solution exhibit greater escalation and binge-like intake compared to those with unrestricted access (24h) (61).

In the case of drugs of abuse, Zimmer et al. (62) first described a novel model of intermittent cocaine self-administration, whereby rats are given brief (5 mins) access to cocaine every 30mins during 6h sessions, resulting in a spiking pattern of brain-cocaine levels across the session. The authors argued that this pattern of intake better recapitulates human drug intake patterns compared to the more conventional long-access model, in which rats are given unrestricted access to cocaine over extended periods (6–12h). Using a behavioral economics approach, Zimmer et al. reported that intermittent access to cocaine was associated with higher Pmax levels, which reflects the highest price to maintain preferred cocaine intake on a behavioral economics schedule, as compared to continuous access for a long (6h) or short (1h) duration, and thus provided the first evidence indicating that the pattern of cocaine intake, rather than the amount, may determine the development of addiction-like behaviors.

Subsequent studies reported that intermittent access to cocaine increases the potency of cocaine at the dopamine transporter, resulting in increased release and uptake of dopamine in nucleus accumbens (63, 64), The intermittent-access model has gained significant traction in the years since, with several studies now showing that intermittent access to cocaine promotes greater escalation of cocaine intake, more profound and persistent decreases in demand elasticity (higher motivation) for cocaine, as well as higher levels of punished responding and cued/drug primed reinstatement, compared to other models, including the canonical long (extended) access model (16-18, 47, 65); similar effects are observed for the commonly abused opioid, fentanyl (66). Notably however, a recent study reported that rats with a history of intermittent access to cocaine exhibit a preference for a lever that facilitates social interaction over a cocaine-paired lever, and will achieve 'voluntary abstinence' under this schedule to a similar extent as rats that underwent long access cocaine sessions (67) (for other studies utilizing choice paradigms in the context of addiction, see (68-73)). Thus, the intermittent and long access models may be comparable in promoting select addiction-relevant endophenotypes. The intermittent-access model also leads to a bingeing or burst-like pattern of drug taking, with nearly all cocaine consumption taking place in first 60–90 sec of each 5-min drug period (17, 74, 75). In male rats, the intermittent access model appears to have the most pronounced addiction-promoting effects in rats with low trait drug-seeking behavior. For example, rats prone to attributing incentive salience to discrete reward cues (sign trackers; STs) exhibit stronger baseline addiction behaviors compared to those that are goal-directed (goal trackers; GTs); following the cocaine intermittent access paradigm, these differences are eliminated, with GTs behaving more like STs (17). Similarly, rats with high baseline demand elasticity for cocaine (low willingness to work to maintain intake) are most prone to the addiction-promoting effects of the intermittent access paradigm (47). Overall, however, females appear more vulnerable to the effects of intermittent access, exhibiting extended burst-like cocaine intake patterns during the first 2–3 min of each access bin and exaggerated changes in demand as compared to males (65).

Intermittent access is also a feature in 3-criteria models of addiction (76, 77), in which rats are tested for the expression of behaviors resembling core diagnostic criteria for addiction, including persistence of responding during a signaled period of cocaine nonavailability, motivation for drug as assessed on a progressive ratio schedule, and persistence of responding for drug when paired with an aversive outcome (footshock). Individual rats are considered 'positive' for an addiction-like criteria if their score falls within the top 1/3rd of the distribution across all rats, and thus rats that are positive for each of the 3 criteria are considered an 'addicted' subpopulation. In this approach, the persistence of responding criteria is generally assessed by allowing rats to self-administer drug in sessions with three longer drug-available periods (e.g. 40 mins) separated by shorter time outs (e.g. 20 mins) (14, 76); thus, this schedule likely also promotes spiking patterns of brain-cocaine concentrations, albeit with different regularity compared to the Zimmer et al. model (78). Using this schedule, Belin et al (14) observed that burst-like self-administration of cocaine (5-infusion bursts with short-spaced intervals, but no overall difference in infusion number) was predictive of developing addiction criteria. These data indicate that bingeing patterns of intake may contribute to neuroadaptations that promote addiction (14).

These findings for cocaine largely parallel those from the alcohol literature, where it was reported almost 50 years ago that rats given homecage access to alcohol on an every-other-day schedule exhibited greater intake and preference for alcohol compared to those given continuous access over the same period (79). Variants to the every-other-day model, including a Monday-Wednesday-Friday schedule of alcohol access, as well as the so-called drinking-in-the-dark paradigm whereby access is given daily during the 12h active (lights off) period, have also been shown to reliably promote robust escalation of alcohol intake in both rats and mice (80–82). Overall, these findings indicate that the pattern of intake (binges and bursts), and not escalation of total intake, is necessary for the enhanced motivation that is indicative of addiction.

2.2 Stress

In modern society stress is typically the most common negative emotion experienced by individuals. It is well established, in both pre-clinical and clinical studies, that stress and negative affect can precipitate overeating behavior, as well as relapse to drug taking (83-85). Evidence also suggests that individuals who experience elevated levels of negative affect and increased impulsivity may be at risk for comorbid eating and drinking problems (86). Animal models that utilize stress to precipitate food and drug seeking behavior have strong face validity in this regard. Indeed, administration of glucocorticoids has been shown to stimulate drug taking and palatable food consumption in animal models (87, 88). Although stress has been demonstrated to drive reinstatement of drug seeking in both operant and conditioned place preference paradigms (reviewed in (89)), several studies showed that acute footshock stress does not reinstate food or sucrose seeking (90, 91). A more recent study by Chen and colleagues (92) reported that footshock reinstates palatable food seeking in female rats with a history of high-fat-high-sugar diet in the homecage during adolescence, indicating that stress may drive maladaptive reward seeking in particular.

Historically, studies of stress-induced binge eating have involved paradigms that use physical stressors such as tail pinch or footshock (e.g.(93)); however, these types of acute stressors often require a history of dietary restriction and have reduced face validity as compared to psychological stressors such as social stress or frustration (93, 94). Recently a model of psychological stress-induced binge eating was reported in female mice that did not require a history of caloric restriction (83), which circumvents this issue. Anversa and colleagues showed that female mice without any history of food restriction will consume up to 1.4g of highly palatable food (Reese’s and chocolate drops) in a 15min period when exposed to an acute frustrative episode. This is more than 50% of their daily chow intake in a 15min period and is 70% more than control mice that are given the same opportunity to consume the highly palatable food reward without the stressful experience (83).

Interestingly, while acute uncontrollable stress seems to sensitize animals to future insults, behavioral control over stress has the converse effect and promotes resilience against future insults, even uncontrollable stress (95). Uncontrollable stress (acute or chronic) has been shown to increase vulnerability to maladaptive behavior, including increased use of habitual response strategies (96, 97), impairments to medial prefrontal cortex (PFC) (98, 99), and sensitized reward/motivation for drugs (100-102). Conversely, previous experience with

behavioral control over stress has been shown to be protective in adult rats, promoting resilience over future uncontrollable stress through engagement of medial PFC (103, 104). Imaging studies in humans support this notion, showing that greater neural flexibility in ventromedial PFC was associated with active coping responses to acute stress, whereas lower flexibility in ventromedial PFC predicted binge alcohol intake and emotional eating (105).

3.0 Mechanisms underlying dysregulated reward seeking

3.1 Orexin (hypocretin) and motivation for drug and food

Several brain structures and neurotransmitter systems have been identified as playing differential roles in regulating demand intensity vs. elasticity for drugs of abuse and palatable foods. One such system that has received substantial recent attention is the hypothalamic orexin (hypocretin) system, to the point that there is currently significant interest in the development of orexin-based therapies designed to treat substance use disorders and a range of eating disorders characterized by dysregulated intake (106-108). Orexin peptides A and B are produced by a small (~4000 in rat) population of neurons in caudal hypothalamus that influence a broad range of behavioral and physiological processes via their actions at orexin receptors 1 and 2, which are distributed throughout the brain (109-112). A role for orexins in feeding was noted upon their discovery, with the observation that central infusions of the peptides promoted feeding in sated rats (*orexis* being the Greek word for appetite) (109). A general role for orexins in reward a was first demonstrated by Harris et al. (113), who reported that orexin neurons exhibit robust activation in response to a drug/food-paired context and that the magnitude of this activity was proportional to rats' drug and food-seeking behavior.

In the 15+ years since, a significant body of evidence has amassed strongly implicating orexin signaling in drug-seeking behavior across all drugs of abuse tested, particularly under circumstances where high levels of motivation are required to earn a drug reward (for review see (114)). Many of these studies, however, relied on self-administration schedules that are dependent on drug dose, pharmacokinetics and baseline shifts in consumption (e.g. FR5, progressive ratio), making it difficult to identify precisely which behavioral factors the orexin system underlies (114). To this end, more recent studies utilizing the behavioral economics procedure have made it possible to more clearly dissect the orexin system's role, with data arising from these studies broadly pointing to a specific role for orexin neurons in mediating drug valuation rather than baseline intake. For example, following intermittent access to cocaine or fentanyl, rats exhibit a persistent decrease in demand elasticity (α) for cocaine (higher drug motivation), but no change in Q_0 values. These behavioral effects are paralleled by an increase in the number of orexin-immunoreactive neurons (18, 66), which is causally linked to rats' motivation for cocaine, as demand elasticity (α) is normalized following shRNA-mediated knockdown of orexin-expressing neurons while baseline intake remains unaffected (18). Similarly, rats with higher endogenous levels of orexin-immunoreactive neurons exhibit lower demand elasticity (α; higher motivation) values compared to rats with lower orexin levels, but do not differ with respect to their baseline cocaine intake (Q_0;(115)). The link between increased orexin cell numbers and drug

exposure has been replicated across several species, including mice and zebrafish, and drugs of abuse, including alcohol and morphine, although these studies have not directly examined the causal role of these increases in demand intensity vs. elasticity (116-118). Nonetheless, increased orexin cell numbers are also observed in human opioid users (116), suggesting that this phenomenon is of clinical significance. Following the transition to an intermittent access-induced 'addicted state', rats also exhibit hyperactivity of orexin neurons in response to drug-associated contexts (18), pointing to enhanced orexin system function (both in terms of numbers and activity) underlying dysregulated reward seeking in addiction. Currently, it remains unclear if orexin system function is upregulated only in response to drug-associated stimuli, or if this reflects a persistent enhancement of function regardless environmental conditions; the latter may explain in part the high comorbidity of sleep dysregulation of addiction, as the orexin peptides play an important role in maintaining wakefulness (119, 120).

Studies utilizing orexin 1 receptor antagonists generally support a role for the orexin system specifically in mediating demand elasticity (α) for drugs of abuse, although there are some exceptions. For example, systemic blockade of orexin 1 receptor signaling increased demand elasticity (α; reduced motivation) for cocaine following both short- and intermittent-access self-administration conditions, without affecting demand intensity (Q_0; (18)) – a finding that aligns with several demonstrations that orexin 1 receptor antagonists reduce high- (FR5, progressive ratio) but not low- (FR1) effort responding for cocaine (121, 122). However, one study reported that FR1 responding for cocaine is reduced by orexin 1 receptor blockade following long access to cocaine, indicating a potential role for orexin signaling in demand intensity following extended cocaine intake (123, 124), however as noted above, fixed ratio schedules of reinforcement are not optimized to disentangle preferred brain-drug concentrations and motivation to maintain them. Similar results were observed for fentanyl, with orexin 1 receptor antagonists increasing demand elasticity (reduced willingness to exert effort to maintain drug intake) without affecting demand intensity (125). In the case of the short-acting synthetic opioid remifentanil, however, orexin 1 receptor antagonists both increase demand elasticity and reduce demand intensity (126-128), and blockade of either orexin 1 and 2 receptors reduces low-effort (FR1) responding for heroin (129, 130). The reason(s) why the orexin system is uniquely involved in baseline intake of remifentanil and heroin are not clear and warrant further investigation, but may involve orexins' actions at ventral pallidum (VP), as local infusions of SB reduce Q_0 for remifentanil (127, 128); it is not known if this role extends to other drugs of abuse (e.g. cocaine) or if VP represents a locus where orexins uniquely act to regulate opioid intake (although note that orexins also act in VP to mediate sucrose 'liking' (131)). Together with evidence that orexin 1 receptor antagonists are also extremely effective at reducing relapse behavior across all drugs of abuse tested, these data have prompted interest in the potential utility of orexin-based therapies for the treatment of substance use disorder. Notably, two dual orexin receptor antagonists are currently FDA approved for the treatment of insomnia (suvorexant and Lemborexant), raising the interesting possibility that these compounds could readily be repurposed for substance use disorder (106-108). Indeed, one study reported that suvorexant is effective at reducing several relapse-related indices in patients with cocaine use disorder,

including cocaine craving (132), and several other studies in opioid-using populations are ongoing (107).

Similar to drugs of abuse, studies examining the role of orexin in feeding behavior have typically utilized behavioral procedures that do not permit examination of demand intensity vs. elasticity indices. Indeed, the majority of these studies involve either free or low-effort access to palatable food, which promotes an escalation of intake across sessions, in combination with pharmacological agents to block orexin signaling. In general, blockade of orexin 1 receptor signaling is highly effective at reducing binge-like intake of a range of palatable foods, including chocolate, sucrose, saccharine and fructose, and these compounds are also effective at suppressing cue-induced reinstatement of extinguished food seeking (133-140). Interestingly, just as drugs of abuse increase the number of orexin-expressing neurons in hypothalamus, chronic exposure to palatable foods is associated with higher orexin numbers (141), although to date a causal role for this increase in food-related behaviors has not been tested. Although several studies have utilized the behavioral economics paradigm to examine demand for foods that are typically associated with dysregulated eating (142-144), only one study to date has utilized this procedure to examine orexin system function. In this study, demand values were examined for low-fat palatable, high-fat palatable, and chocolate sucrose in male and female rats. When demand intensity (Q_0) was adjusted for bodyweight, female rats were found to have higher baseline intake across all food types, but did not differ with respect to their willingness to exert effort to maintain their preferred level of intake (demand elasticity;(45)). Systemic administration of an orexin 1 receptor antagonist had the greatest effects on demand intensity, significantly reducing baseline intake across all food types in both male and female rats. Orexin 1 receptor antagonism also increased demand elasticity (decreased motivation) for low-fat palatable and chocolate sucrose pellets (and a trend was observed for high-fat palatable foods), indicating that the orexin system might be involved in mediating both the hedonic setpoint for palatable food, as well as the motivation to maintain preferred food intake levels. Importantly however, to date no study has examined whether paradigms that promote dysregulated feeding behaviors, such as intermittent/restricted access to palatable foods (51, 59, 61), alter demand intensity or elasticity for food and the potential role for the orexin system in these processes. Nonetheless, as with drugs of abuse, there is significant current interest in the use of orexin-based therapeutics for treatment of eating disorders characterized by high intake, such as binge eating disorder, with a number of clinical trials currently ongoing (e.g. ClinicalTrials.gov Identifier: NCT04753164).

3.2 Loss of control over habitual behavior

Enhanced habit formation has been heavily implicated in dysregulated reward seeking for drugs and food (145, 146). In particular, a loss of control over habits has been theorized to play a key role in addiction behaviors (147-153). While goal-directed behaviors are flexible and performed in direct pursuit of the reward outcome, habitual behaviors are automatic, less flexible, and performed in response to conditioned stimuli (discrete, environmental, or interoceptive). It is important to note that excessive goal-directed behavior has also been implicated in drug addiction (154-156), with supporting evidence that includes the presence of excessive reward motivation in drug addiction and binge eating (as discussed above).

Here, we review the evidence that increased habitual behavior is involved in dysregulated reward seeking, and explore roles for striatal and cortical systems in this process.

Many studies have shown increased habitual responding after exposure to drugs or acute/chronic stress (reviewed in (153)). Increased habit formation has also been observed in obese individuals with binge eating disorders as compared to those without, and in rats prone to binge eating (146, 157-159). However, it is not clear that this increased habitual responding is necessarily maladaptive, or that it is the underlying mechanism of compulsive or dysregulated reward seeking. Habitual behavior is insensitive to changes in the *value of the outcome*, such that reward seeking assessed under extinction seeking is unaffected following devaluation via satiety (160, 161). However, habitual behavior is generally sensitive to changes in the *outcome*, such that reward seeking is reduced after experiencing the devalued outcome in the satiated state (151, 162, 163) or, presumably, introducing a negative consequence (e.g., footshock). Habits become maladaptive when they persist despite conditions that should normally elicit goal-directed control over behavior.

In the context of dysregulated drug and food seeking, reduced flexible control over habits has been associated with neuroadaptations in dorsomedial striatum (DMS) and dorsolateral striatum (DLS), which directly guide goal-directed and habitual responding, respectively (164, 165). Recent studies support a connection between dorsal striatum and maladaptive responding. In rats self-administering alcohol, continued seeking of alcohol despite footshock was associated with greater dependence on DLS to drive alcohol seeking (166). Selective ablation of fast-spiking interneurons in dorsal striatum reduced both punished alcohol responding and escalated consumption (167), while disruption of cholinergic signaling in DMS promoted habitual sucrose responding and maladaptive eating in mice (168). However, habitual behavior is not necessarily prerequisite for punishment-resistant cocaine seeking in rats (156), and chemogenetic inhibition of DMS direct-pathway neurons was found to have no effect on high-risk addiction behaviors, including cocaine self-administration despite footshock, enhanced cocaine motivation, or responding during drug-unavailable periods (169). Therefore, dorsal striatum systems alone may not explain dysregulated reward seeking.

Reduced flexible control over habits might stem from impairments in the PFC systems that influence striatum signaling (148-151, 153, 170-175). Reduced PFC gray matter has been reported in individuals with stimulant dependence, and PFC ischemia has been shown with cocaine exposure in rodents (176, 177). The medial PFC is involved in top-down control and behavioral flexibility, including adaptive responding to conflict and stress (reviewed in (178, 179)). Accordingly, in rats, punishment-resistant cocaine seeking has been associated with hypofunction of pyramidal neurons in PFC (180, 181). Likewise, experimental disruption of the prelimbic region of PFC increased punished responding for cocaine and sucrose (180, 182, 183) and impaired the ability to withhold responding (184, 185), while optogenetic stimulation of prelimbic PFC decreased punished responding for cocaine in rats (180). Finally, in a mouse model of food addiction, continued responding for chocolate pellets despite footshock was associated with increased expression of dopamine D2 receptors in prelimbic PFC (186). Although some studies have shown that inhibition of medial PFC projections specifically to nucleus accumbens enhanced punished responding for chocolate

food and alcohol (186, 187), another showed that inhibition of this pathway reduced punished responding for alcohol (37). Therefore, further investigation is still necessary to determine the exact role of prelimbic PFC projections to dysregulated reward seeking.

While medial PFC may play an important role in top-down control over compulsive behavior, there is evidence that orbitofrontal cortex (OFC) may instead be associated with promoting compulsive behavior. In drug users tested after their last cocaine use or during craving, the OFC was hypermetabolic in proportion to the intensity of craving (188). However, gray matter reductions in OFC have been observed with obesity and cocaine addiction (189-191). In rats, methamphetamine self-administration despite footshock was associated with increased activity in an OFC-DMS circuit and decreased activity in a PL-ventral striatum circuit (192). Similarly, in mice responding for optogenetic self-stimulation of dopamine neurons, continued responding despite footshock was associated with the strengthening of lateral OFC connections to dorsal striatum (193). Although repeated hyperstimulation of lateral OFC to dorsal striatum caused compulsive grooming behavior in mice (194), stimulation of medial OFC to ventral striatum suppressed compulsive grooming behavior (195), perhaps pointing to different roles for medial vs. lateral OFC.

Altogether, these data indicate that loss of control over habitual behavior plays an important role driving dysregulated consumption of food and drug rewards. Therapeutic treatment options will likely need to address how to restore flexible control over maladaptive habits. A recent study in humans explored ways to restore flexibility over habitual responding, using well-established associations between green/red and go/no-go, and found that introducing monetary reward to enhance motivation helped to disrupt the prepotent habitual responses to green/red colors (196). This type of performance-contingent feedback may be a useful tool in restoring goal-directed flexibility and may be a critical component underlying the success of contingency-management therapeutic programs (197, 198).

3.3 Enhanced incentive motivation from cues

Drug- and food-related cues have the capacity to elicit craving and increase consumption. It may be that people who are more susceptible to the motivational effects of cues have a higher risk of developing maladaptive patterns of consumption. Moreover, with repeated consumption it may be that drug and food cues acquire enhanced incentive salience through a classical conditioning process in vulnerable individuals, thus enabling and facilitating more problematic consumption patterns. In support of this, cocaine-associated stimuli have been shown to drive dopamine release in the dorsal striatum in individuals with cocaine addiction, and the level of cue-induced dopamine correlates with self-reports of craving (199). In rats that are susceptible to junk-food diet-induced obesity, enhanced cue-induced responding was observed even prior to the development of obesity, indicating that enhanced cue-driven motivation may be an important contributor to the development of obesity, rather than a consequence (26). These rats show lower expression of mu opioid receptor mRNA expression in striatal hedonic ‘hot-spots’, indicating that enhanced cue-induced ‘wanting’ was not explained by enhanced sucrose ‘liking’. In comparison, a downregulation of striatal dopamine D2 receptor mRNA was observed following exposure to a junk-food diet regardless of the development of obesity (26).

The nucleus accumbens is critically involved in the ability of reward-associated cues to exert a general motivational influence on responding (200). Neurons in the nucleus accumbens fire in response to such reward-associated cues that have acquired value through pairing with reward (201, 202), and PIT is affected by lesions of the core subregion (203). Accordingly, several studies have shown that neuroadaptations in the nucleus accumbens may underlie enhanced cue-driven reward seeking. Selectively-bred obesity-prone rats show enhanced cue-triggered food-seeking in a PIT task as compared to their obesity-resistant counterparts, and show increased expression of calcium-permeable AMPA receptors in the nucleus accumbens core (25). Similarly, increased expression of calcium-permeable AMPA receptors in nucleus accumbens has been shown to play a critical role in the incubation of cue-induced cocaine seeking after long-term withdrawal from cocaine self-administration (reviewed in (204, 205)), revealing parallels between the processes leading to obesity and addiction. In addition to triggering enhanced motivation, cue-induced activity in nucleus accumbens may drive stronger stimulus control of habitual responding, which is performed in response to conditioned stimuli. In support of this, contextual cues associated with methamphetamine or alcohol have been shown to enhance expression of habitual behavior (206, 207).

3.4 Gene expression changes in striatum

As highlighted in the sections above, there has been a significant shift towards modelling humanised addiction traits in animal models. This parallels a growing appreciation that vulnerability to dysregulated reward-seeking is multifactorial and engages distinct, albeit frequently-overlapping, circuits including systems that control goal-directed behavior, development of habits, motivation, value attribution and stress (155, 208, 209).

Studies employing addiction phenotyping using the 3-criteria model (described in detail in Section 2.1) (76) have primarily focused on hypothesis-driven mechanisms such as a loss or enhancement of synaptic plasticity in ventral striatum, or changes in dopamine receptor levels. For example, Kasanetz et al. (77) showed that long-term depression (LTD) is suppressed in the nucleus accumbens core of rats classified as 3-criteria animals. Brown et al.(6) showed a similar LTD impairment in rats prone to obesity, the extent of which predicted the degree of ‘addiction-like’ behavior observed towards highly palatable food. Moreover, trait impulsivity has been linked to increased propensity for the development of an ‘addiction’ phenotype to both cocaine (210) and food (211); impulsive animals display lower dopamine D2/3 receptor availability prior to cocaine self-administration and addiction phenotyping (212, 213), and changes in striatal dopamine receptor expression are linked with punishment-resistant food consumption in rats and obesity in humans (40, 214).

While these studies have identified a consistent pattern of dopamine signalling changes, how these changes manifest and are sustained across the addiction cycle including into withdrawal remains unclear. Furthermore, how changes affecting other neurotransmitter systems and associated signalling pathways is also an important consideration (215). Accordingly, the Dayas laboratory to assess gene expression changes in the dorsal and ventral striatum using a modified version of the 3-criteria addiction phenotyping procedure (216-220). These studies have primarily focused on genes involved in synaptic plasticity

(LTP and LTD) as well as dopamine signalling. An initial study reported significant suppression of gene expression in addiction-prone rats as compared to resilient animals in genes encoding activity-regulated-cytoskeletal protein (Arc), glyceraldehyde 3-phosphate dehydrogenase, dopamine receptor D1a, dopamine receptor D2, Gria1, Gria2, metabotropic glutamate receptor 1 (Grm1), metabotropic glutamate receptor 5 (GRM 5), mechanistic target of rapamycin (mTOR), phosphatidylinositol-3-kinase (PI3K), protein kinase C (PKC) and cGMP-dependent protein kinase II (PRKG2)(216). A notable feature of these findings was the similarity of gene expression changes in the dorsal and ventral striatum. Further, rather than large increases in gene expression, the data revealed a more subtle downregulation of gene expression. These findings are consistent with electrophysiological studies reporting a loss of LTP and LTD in parts of the striatum, most notably in nucleus accumbens. Indeed, Kasanetz et al. reported that only animals that were classified as vulnerable displayed enduring impairments in LTD (77).

To understand how these gene expression changes might be manifest and be sustained, Dayas and colleagues performed targeted qPCR for microRNA (miRNA) with known or predicted binding with candidate mRNAs. Specifically, these studies examined the role of non-coding regulatory miRNAs, which are~22 nucleotides in length and bind to the 3’ end of target mRNAs where they can act to inhibit translation and/or cause post-transcriptional gene silencing (221). Because of the importance of regulatory RNAs in synaptic plasticity, including regulation of mRNAs trafficked to synapses to control synaptic protein expression, miRNA expression profiles were assessed in the striatum of addiction-vulnerable versus resilient rats after the animals had completed a full ‘addiction cycle’, including testing for relapse-like behavior (219). These studies identified changes in ‘networks’ of miRNA involved in synaptic plasticity. Using bioinformatics, miR-431 was identified as a candidate for the regulation of the reductions in dorsal striatal Arc identified in a previous study (216); the expression of miR-431 was increased in the DMS and DLS of addiction-vulnerable animals, and luciferase assays revealed that miR-431 regulates Arc expression *in vitro.* miR-181a was also significantly increased in the DLS of addiction-vulnerable animals, and pathway analyses predicted likely interactions with molecules linked to Grm5 and calcium GluA2Rs. Finally, miR-101b was significantly increased in both the DLS and DMS, and is predicted to target addiction-relevant signalling pathways including MAPK1, PRKC, PP2a and genes encoding the guanine nucleotide-binding proteins.

In parallel studies using this addiction phenotyping model, Dayas et al. made more restricted striatal dissections, and found that expression of miR-212 in DMS was significantly lower in addiction-vulnerable animals post-relapse. Kenny and colleagues were the first to identify that miR-212 expression *increased* during extended access to cocaine self-administration –a model of loss of control over cocaine taking (222). They reported that viral-mediated over-expression of miR-212 in dorsal striatum during the drug-taking phase significantly reduced escalation of cocaine taking and returned pro-drug seeking molecular adaptations to control levels, whereas knockdown of miR-212 substantially increased cocaine consumption (222). To gain further insight into the biological significance of miR-212 changes across the addiction cycle, Dayas and colleagues applied a Bayesian modelling average approach, which integrated 23 separate drug-taking/seeking indices during early self-administration (e.g. burst responding, responding during non-drug available period, etc), to identify

relapse-prone rats early in the addiction cycle (i.e. prior to protracted abstinence) (220). Consistent with the original findings from Kenny and colleagues (222), miR-212 levels were increased in the DMS of vulnerable animals following self-administration, but not following extinction and relapse testing (220). Taken together these data suggest that miR-212 expression is increased during cocaine consumption to counteract drug-induced neuroadaptations, but over time, this protective mechanism is exhausted in addiction-vulnerable individuals. Future work is needed to determine the consequences of miR-212 alterations on electrophysiological properties and plasticity in the direct and indirect pathways of the basal ganglia. Answering these questions may guide the development of strategies to restore control over pathological habits wherever they emerge symptomatically, even beyond addiction.

These studies also identified that miR-137 displayed an opposite pattern of expression in the dorsal striatum compared to miR-212 of vulnerable animals post-relapse (220). Bioinformatics and functional analyses link miR-137 with synaptic plasticity relevant signalling pathways including LTD (223, 224). In preliminary studies, the Dayas lab has tested whether miR-137 gain of function affects addiction behaviors. Lenti-viral mediated over-expression of miR-137 in dorsal striatum had no major effect on levels of cocaine consumption but significantly increased indices of addiction including signaled non-drug-available levels of responding and cocaine-seeking under progressive ratio testing. Remarkably, relapse-like behavior, assessed 6 weeks after viral-transduction, was substantially increased by miR-137 over-expression. The focus now turns to understanding the cellular and molecular actions mediated by miR-137 to promote habit-based plasticity in the dorsal striatum. Of note, the role of miRNAs in dysregulated food-seeking behavior is, at present, entirely unexplored. Future research in this area would determine whether common changes in gene expression exist between maladaptive forms of reward-seeking for both drug and food.

Conclusions

Maladaptive patterns of reward seeking can emerge in a parallel manner for both food and drug rewards, and include binge-like intake, enhanced cue-driven seeking, continued use despite negative consequences, and excessive motivation. As reviewed here, there are likely multiple mechanisms that underlie these patterns of dysregulated reward seeking. Arguably, one of the main obstacles in identifying new therapeutic treatments is factional disagreements over the primary drivers of the maladaptive behavior that characterizes binge eating and substance use disorders. Here, we attempt to recognize, and encourage greater acceptance of, the multifactorial nature of addiction and to encourage future research to focus on commonalities in the underlying molecular/cellular substrates across drugs of abuse and non-drug rewards such as food.

An important factor emerging from recent research is the observation of significant individual differences in the risk for developing addiction-like behaviors in animals. Studies that determine riskvulnerable phenotypes across different stages of the addiction cycle are likely to reveal engagement of distinct brain circuits and molecular adaptations at temporally specific phases of the addiction cycle (e.g., binge/intoxification, withdrawal, and

relapse). Further, these studies are likely to reveal individual differences in the mechanisms underlying maladaptive behaviors, indicating that there are multiple pathways to developing dysregulated reward-seeking behavior. Understanding the circuits and mechanisms engaged across the addiction cycle and across individuals will be crucial to identifying therapeutic strategies designed to treat dysregulated reward seeking in binge eating and substance use disorders.

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Highlights

- Under certain circumstances, animals exhibit maladaptive patterns of intake for food and drugs
- We review recent animal models of stress exposure and intermittent access to rewards
- We also explore neural and behavioral mechanisms underlying dysregulated reward seeking