The Relationship Between Feeding and Drug-Seeking Behaviors

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Abstract

This chapter focuses on the relationship between avidity for sweet substances and drug abuse using rats that were selectively bred for high (HiS) vs. low (LoS) saccharin intake. These rats serve as genetic models for several aspects of drug abuse such as initiation, maintenance, escalation, and relapse to drug seeking. Neurobiological differences in brain areas associated with drug and food reward underlie the behavioral differences. In addition to dietary compulsions, animal models of high vs. low novelty reactivity (HR vs. LR), novelty preference (HNP vs. LNP), impulsive choice (HiI vs. LoI), impulsive action (HI vs. LI), avidity for exercise (HiR vs. LoR), and attention to reward-related stimuli, such as sign- (reward-associated stimuli) vs. goal-tracking (reward) (ST vs. GT), also predict high vs. low drug seeking, respectively. The high-performing traits have some overlap in predicting addictive behavior, but in many respects they appear to be independent predictors of addictive behavior. In contrast, rats selected for low reward seeking are more reactive to stressful or aversive events associated with drugs and less likely to engage in drug seeking. These traits provide a model of resilience to drug abuse. Segregating individual differences into reward sensitive and aversion reactive may allow for customized addiction treatment. It is hypothesized that reward-sensitive individuals would be responsive to reward-replacement therapy, such as exercise, while aversion-reactive individuals may react more to negative outcomes for drug use. Initial data indicate better treatment success in the LoS (vs. HiS) and LoI (vs. HiI) rats, yet higher drug-seeking females respond better to treatment than males. Knowledge of specific

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vulnerability factors is important to designing maximally effective prevention and treatment strategies.

Keywords

Aversive effects • Drug seeking • Feeding • Impulsivity • Novelty preference/seeking • Reward substitution • Punishment • Sweet intake • Treatment • Vulnerability

2.1 Introduction

Drug abuse and feeding are related to biological, genetic, and environmental factors that play a role in determining when drug- or food-rewarded behavior becomes out of control and manifests itself as an addiction. Drug- and food-related addictions interact such that reduction in availability of one substance leads to overconsumption of another (Carr & Cabeza de Vaca, 2013; Carroll, Holtz, & Zlebnik, 2013), and drug- and food-rewarded behaviors are mediated by overlapping brain reward circuitry. Drug addiction and excessive eating leading to obesity, and the corresponding metabolic syndrome, are among the top causes of death in the USA and an enormous cost to society. This close relationship between feeding and drug seeking (addiction) has been studied for many years and has been reviewed previously at behavioral (e.g., Ahmed, 2005, 2012; Avena, 2010; Belin, Berson, Balado, Piazza, & Deroche-Gamonet, 2011; Belin & Deroche-Gamonet, 2012; Bocarsly & Avena, 2012; Carroll, 1999; Carroll, Holtz, & Zlebnik, 2013, Carroll, Morgan, Anker, Perry, & Dess, 2008) and neurobiological levels (e.g., Carr & Cabeza de Vaca, 2013; Johnson & Kenny, 2010; Levine, Kotz, & Gosnell, 2003a, b; Olsen, 2011; Pelchat, Johnson, Chan, Valdez, & Ragland, 2004; Volkow & Wise, 2005). The present review focuses on behavioral-genetic aspects of this interaction, specifically drug-seeking behaviors in rats that are *selectively bred* to consume excessive amounts of sweet substances (see reviews by Carroll et al., 2008, Carroll, Holtz, & Zlebnik, 2013), and rats that have been *selected* for other addiction-related behaviors such as novelty reactivity, novelty preference, impulsivity, exercise, and incentive salience of drug-related stimuli (see reviews by Carroll, Anker, Mach, Newman, & Perry, 2010, Carroll, Johnson et al., 2013; Carroll, Mach, LaNasa, & Newman, 2009).

A major difference between excessive food intake and drug addiction is that food is necessary for survival, while recreational drugs are not. However, the tenacity of food and drug addiction is similar in strength, factors that initiate and maintain these self-destructive behaviors are similar, both disorders are highly treatment resistant, they readily substitute for each other, and both food and drug addiction result in similar rates of morbidity and mortality. When considering addiction using animal models, several laboratories have attempted to use addiction criteria described for diagnosing human drug abusers according to DSM-IV and DSM-5 criteria (Deroche-Gamonet, Belin, & Piazza, 2004; Vanderschuren &

Ahmed, 2013). This approach has been helpful in identifying mechanisms for disordered behavior, developing treatments, and translating animal research findings to clinical practice. In an increasing number of studies, these criteria are being applied in the design of animal models that allow us to learn more about the development of addictive behavior and interventions and treatments that will translate to applications for changing pathological human behaviors.

The goal of this chapter is (1) to briefly review seminal research on the relationship between feeding and drug seeking; (2) to examine a genetic relationship between drug-seeking behavior and feeding-related traits using rats that were selectively bred for high (HiS) and low (LoS) saccharin intake. i.e., HiS rats also eat more food, weigh more, and show more drug seeking than their low sweet-preferring (LoS) counterparts; (3) to determine how these genetic influences relate to other individual differences that predict vulnerability to drug abuse, and to recognize their commonalities and underlying neurobiology; (4) to examine differences in HiS and LoS rats' reactivity to stress and aversive events; and (5) to discuss behavioral and pharmacological treatments for drug abuse as they relate to the underlying vulnerability factors and how these factors influence treatment effectiveness.

2.2 Models of Addiction

An important guideline for studying addictive behavior in the animal laboratory is to closely model the behavior in humans. In considering hedonic overindulgence in food or binge eating as an addiction, there are similar diagnostic criteria for drug dependence and problematic food intake (Gearhardt, Corbin, & Brownell, 2009; Gearhardt, Davis, Kuschner, & Brownell, 2011), and DSM-IV criteria for substance dependence, such as binge eating or overindulgence in preferred (sweet) high-caloric foods, have been applied in the animal models. In animal studies, behavioral models have been designed to emulate DSM-IV drug addiction criteria (Deroche-Gamonet et al., 2004, Vanderschuren & Ahmed, 2013), and there are parallels to measures of the DSM-IV binge eating disorder (BED) criteria described in humans. In fact, instruments such as the Yale Food Addiction Scale (YFAS) (Gearhardt et al., 2009) that has been used to link binge eating and food addiction in humans show that nearly half of BED patients meet criteria for "food addiction" (Bocarsly & Avena, 2012; Cassin & von Ranson, 2007; Gearhardt, White, & Potenza, 2011). Drug abuse has been modeled in rats (Ahmed, 2012; Belin et al., 2011; Belin & Deroche-Gamonet, 2012; Carroll & Meisch, 2011; Jupp, Caprioli, & Dalley, 2013; Vanderschuren & Ahmed, 2013) and nonhuman primates (Foltin, 2013) using DSM-IV criteria for substance use disorders (SUD) such as (1) tolerance (Perry, Dess, Morgan, Anker, & Carroll, 2006), (2) difficulty limiting use (Perry et al., 2006), (3) excessive time spent seeking (Perry et al., 2006), (4) impaired control over use (Lynch, Arizzi, & Carroll, 2000), (5) activities given up or drug use preferred over other activities (Carroll et al., 2008), (6) continued use despite negative consequences (Holtz, Anker, & Carroll, 2013), and (7) withdrawal signs

Table 2.1 HiS vs. LoS rats and criteria for drug addiction

Criteria for addiction	HiS vs. LoS	References
Tolerance	HiS > LoS	Perry et al. (2006)
Difficulty limiting use	HiS > LoS	Perry et al. (2006)
Excessive time seeking	HiS > LoS	Perry et al. (2006)
Impaired control over use	HiS > LoS	Lynch et al., (2000)
Activities given up	HiS > LoS	Carroll et al. (2008)
Use despite punishment	HiS > LoS	Holtz, Anker, Regier, Claxton, & Carroll (2013)
Withdrawal	LoS > HiS	Dess et al. (2000, 2005); Radke, Zlebnik, & Carroll (2014)

after termination of use (Dess et al., 2000; Dess, O'Neill, & Chapman, 2005). As summarized in Table 2.1, rats that were selectively bred for sweet preference (HiS) scored higher on criteria for addictive behavior than their low saccharin-preferring counterparts (LoS), except LoS rats exceeded HiS rats on withdrawal measures. These criteria that are shown in Table 2.1, when adapted to animal models (Vanderschuren & Ahmed, 2013), include tolerance, impaired control over use, difficulty limiting use, excessive time spent seeking drug, activities given up (or replaced) by drugs, and continued use despite punishment. The HiS animals exceeded LoS in behaviors that were developed to emulate the DSM criteria that are used to describe human addiction.

To evaluate drug-seeking behavior using these criteria for drug addiction, we have used several animal models to mimic the establishment of drug use in humans and its progression through regular use to escalation and compulsive use. For example, studies have modeled *impulsive action*, inability to withhold responding for long periods of time each day, and *impulsive choice*, choosing a smaller amount of drug immediately over a larger amount after a delay, or a smaller probability of a sooner reward vs. a larger probability of a delayed reward (see reviews by Carroll & Meisch, 2011; Carroll et al., 2010).

2.3 Drug Seeking in Rats Selectively Bred for High and Low Saccharin Intake

With these models of addiction, we have pursued a line of research that allows us to address the relationship between feeding and drug-seeking behavior as it is related to genetic background by studying rats that have been selectively bred to prefer sweet substances. These rats were originally derived from the Sprague-Dawley strain, and the HiS rats eat more and weigh more than their low sweet-preferring counterparts (LoS) or outbred control rats from the Sprague-Dawley background strain (Carroll et al., 2008). Thus, the HiS rats could also serve as an animal model for overconsumption of rewarding substances, particularly sweet substances, and drugs of abuse. The rats we are reporting data on were initially selectively bred for

high (HiS) and low (LoS) saccharin intake by Dr. Nancy Dess at Occidental College in Los Angeles, CA. Progenitor rats were tested for their intake of saccharin during a 24 h 2-bottle test with water concurrently available, and their 24-h saccharin intake was compared to 24 h water intake from a previous day when only water was available in the two bottles. Rats exhibiting extremely high saccharin preferences were mated together, and rats with low saccharin preferences or saccharin aversion (less consumption than water) were mated together. Breeding continued with HiS pairs and LoS pairs, and initially Dess and coworkers studied differing levels of emotionality and taste preferences in these rats (Dess, 2001, Dess et al., 2000; Dess & Minor, 1996). Subsequently, they studied alcohol intake and found that the HiS rats exceeded the LoS rats in their consumption, but LoS rats were more affected by alcohol withdrawal effects (Dess et al., 2005).

Our laboratory obtained some of the Occidental HiS and LoS rats and demonstrated that the HiS rats also showed elevated cocaine intake compared to LoS rats during initiation of drug self-administration in drug-naïve rats and in cocaine-experienced rats under a progressive ratio (PR) schedule (Carroll, Morgan, Lynch, Campbell, & Dess, 2002). Subsequent studies extended these findings with cocaine to several phases of the addiction process (see reviews by Carroll et al., 2008, Carroll et al., 2010; Carroll, Holtz, & Zlebnik, 2013). These reviews described studies indicating that HiS rats exceeded LoS rats during initiation or acquisition of cocaine self-administration (Carroll et al., 2002), escalation of bingeing on cocaine during long (LgA) vs. short (ShA) access (Perry et al., 2006). The HiS rats also showed more resistance to extinction when cocaine was replaced with saline and reinstatement of responding (relapse) that occurred after extinction when drug access had been terminated and the rats were later given experimenter-administered priming injections of cocaine, or a stressor—yohimbine (Holtz, Anker, & Carroll, 2013; Perry et al., 2006). It has recently been shown that HiS rats similarly exhibited binge-like behaviors when given access to fat- or sugar-based substances (Yakovenko, Speidel, Chapman, & Dess, 2011).

It is important to note that when the HiS and LoS rats' drug-seeking behavior was examined in these models of drug abuse, they were saccharin naïve. Their HiS or LoS status was based entirely on their breeding history, and they were not given access to saccharin prior to drug exposure. This allowed us to verify the breeding status after the drug-seeking experiments were completed, because testing their saccharin intake to verify the HiS or LoS phenotype might interfere with their drug self-administration behavior (Carroll, Lac, & Nygaard, 1989). At least 2 weeks after the end of the drug self-administration experiments, when rats were returned to the home cage with lab chow and water freely available, they were tested for their saccharin preference score to verify their selection status, and the phenotypes were confirmed. Across many studies, on average, The HiS rats achieved a score ranging from 25.2 to 39.6 for HiS males and females, respectively, and 5.2 to 7.6 for LoS males and females, respectively (Carroll et al., 2008). An interesting result of comparing saccharin preference scores over several studies, however, was that the rats that had more access to cocaine before their saccharin testing showed lower saccharin scores (less saccharin preference) than those with less cocaine

experience (Carroll et al., 2008). Thus, the rewarding effect of prior exposure to cocaine may have produced a contrast effect and reduced the hedonic value of saccharin (see Grigson & Twining, 2002). This provided further evidence for the interaction of hedonic effects of food and drugs and addresses the DSM criteria of *other activities given up* (Table 2.1).

The selectively bred HiS and LoS rats' corresponding high and low drug seeking has also been demonstrated in outbred rats that were screened for high or low sweet intake, and they subsequently showed high vs. low drug seeking, respectively. For example, Bell, Gosnell, Krahn and Meisch (1994) separated Wistar rats into "high," "intermediate," or "low" groups based on their saccharin intake, and they found that the groups maintained their rank order on measures of alcohol consumption. Also, rats screened as saccharin/sweet likers (SL) consumed more alcohol (Gahtan, Labounty, Wyvell, & Carroll, 1996) and morphine (Gosnell, Krahn, Yracheta, & Harasha, 1998; Gosnell, Lane, Bell, & Krahn, 1995), than saccharin/sweet dislikers (SDL). Similarly, rats selected for high sucrose feeding (HSF) consumed more amphetamine and acquired cocaine self-administration faster than their low-sucrose feeding (SLF) counterparts (DeSousa, Bush, & Vaccarino, 2000; Gosnell, 2005).

The connection between avidity for dietary sweets and substance use disorders (SUD) has also been reported in human populations, such as those who abuse alcohol (Chester, Blose, & Froehlich, 2003; Kampov-Polevoy, Garbutt, & Janowsky, 1999; Kampov-Polevoy, Tsoi, Zvartau, Neznonov, & Khalitov, 2001; Wronski et al., 2007), cocaine (Janowsky, Pucilowski, & Buyinza, 2003), nicotine (Pepino & Mennella, 2007; Pomerleau, Garcia, Drewnowski, & Pomerleau, 1991), and opioids (Weiss, 1982). In these studies drug users/abusers experienced greater hedonic effects from sweets and consumed more sweets than those who do not abuse these drugs. These parallels between the selectively bred rats, outbred rats, and human self-report studies suggest that the feeding and drug-seeking behaviors are moderated by genetically mediated traits (Uhl, Drgon, Johnson, & Liu, 2009) and common neural mechanisms (Carroll et al., 2008; Holtz & Carroll, 2013).

It is also important to note that the findings of differential vulnerability to drug abuse in the HiS and LoS rats due to their selective breeding history are not unique to these sweet-preferring/non-preferring phenotypes (e.g., HiS, LoS). In recent years, there have been numerous examples of individual differences on other dimensions that correspond with high vs. low drug seeking. As Table 2.2 indicates, drug abuse liability is also predicted by novelty reactivity (Davis et al., 2008; Piazza et al., 1989), impulsive choice (Perry, Nelson, & Carroll, 2008), impulsive action (Dalley et al., 2007), shock avoidance (Fattore et al., 2009), incentive stimulus reactivity (Saunders, & Robinson, 2013), sex and hormonal conditions (Carroll & Anker, 2010), age (O'Dell et al., 2006), and exercise avidity (Ferreira et al., 2006). Similar differences have also been found across different rat strains such as Lewis and Fischer 344, which are compared for other characteristics, like differences in hypothalamic-pituitary-adrenal axis responses (Kosten & Ambrosio, 2002; O'Dell et al., 2006).

Table 2.2 indicates that high performers are also more drug abuse prone relative to corresponding low-performing individuals that are resistant to drug-seeking

Table 2.2 Risk factors for drug seeking, aversion to drugs, and response to treatment

Vulnerability	Prone	Resistant	References
Sweet intake	HiS	LoS	Carroll et al. (2008)
Impulsive choice	HiI	LoI	Carroll et al. (2010)
Impulsive action	HI	LI	Dalley et al., 2007
Novelty reactivity	HR	LR	Piazza, Deminiere, Le Moal, and Simon (1989)
Bred for novelty reactivity	bHR	bLR	Davis, Clinton, Akil, and Becker (2008)
Avoidance	RHA	RLA	Fattore, Piras, Corda, and Giorgi (2009)
Exercise	HiR	LoR	Larson and Carroll (2005), Ferreira et al., 2006
Sign/goal tracking	ST	GT	Saunders and Robinson (2013)
Sex	Female	Male	Carroll and Anker (2010)
Female hormones	Estrogen	Progesterone	Anker and Carroll (2010)
Age	Adolescent	Adult	O'Dell et al. (2006)
Lewis/Fischer	Lewis	Fischer	Kosten and Ambrosio (2002)

behavior. Some of the low performing individuals (e.g., LoS, LoI, males, and Fischer rats) have been shown to be more responsive than their high preferring counterparts to aversive effects of drugs. Differences in these lines of rats shown in Table 2.2 are not limited to drug seeking and self-administration. While these are the variables most studied, the selectively bred HiS vs. LoS rats exhibit a range of other behaviors that are associated with drug addiction, such as (1) impulsive behavior, (2) dysregulation of intake during self-selection of high vs. low drug doses, (3) and sensitization of drug-induced locomotor activity. For example:

1. The HiS and LoS rats were tested for their impulsivity of choice for a small immediate vs. a larger delayed reward using food and cocaine with a delay-discounting task for food or IV cocaine. In this task a response on one lever was rewarded by one food pellet or a small cocaine infusion after a short delay, while responding on another lever was rewarded by three food pellets or three times the dose of the cocaine infusion following a long delay. HiS rats were more impulsive than LoS rats for food on a delay-discounting task (Perry et al., 2008), and HiS rats were also more impulsive for cocaine than LoS rats on a go/no-go task (Anker, Gliddon, & Carroll, 2008), wherein they showed more no-go responding (i.e., impulsive action). HiS rats also exceeded LoS rats on another measure of impulsive action—responding that occurs during the drug infusion in a drug self-administration paradigm in which drug is available under a fixed-ratio 1 (FR 1) schedule. This ineffective responding is counted after the infusion pump begins to deliver drug, and during the infusion and the timeout period after the infusion. These ineffective responses that occur after the infusion begins are counted but have no consequences, and when they were compared, they were higher in HiS rats than LoS rats (Carroll, Holtz, & Zlebnik, 2013). Thus, food and cocaine were not only more rewarding for HiS than LoS rats, but HiS rats were more impulsive than LoS rats in their food- and cocaine-seeking behavior.

2. Another behavior that is related to drug seeking is regulation or dysregulation of drug dose, and that differs between HiS and LoS rats. For example, when rats have a choice between responding on one lever that increases the next dose of cocaine and responding on the other lever that decreases the next dose of cocaine, their ability to regulate their dose is determined by a negative correlation between the dose they received and the time before a response occurs for the next infusion. Thus, high or low doses of cocaine were not necessarily preferred and seemed to be nonsystematically chosen by the rats, but there was a very precise regulation of the amount consumed per unit of time. A comparison of HiS and LoS rats in this paradigm showed that HiS rats did not regulate their dose quite as precisely as LoS rats, and HiS rats spent more time than LoS rats perseverating on the lever that increased the dose, thereby self-administering a larger number of the highest doses than the LoS rats (Carroll, Anderson, & Morgan, 2007b; Lynch et al., 2000, Lynch & Carroll, 1999, Lynch, LaBounty, & Carroll, 1998).
3. HiS and LoS rats also showed differences (HiS > LoS) in sensitization to cocaine-induced locomotor activity, a neuronal adaptation that is thought to be related to the rewarding effects of cocaine (Robinson & Berridge, 1993). For example, HiS rats exceeded LoS rats on cocaine-induced locomotor activity and sensitization to repeated cocaine injections after five daily injections of cocaine, and when an additional injection was given 2 weeks later and compared to the first injection (Carroll, Anderson, & Morgan, 2007a).

2.4 Neurobiological Differences in HiS and LoS Rats

The consistent differences between food seeking and drug seeking between HiS and LoS rats using several measures of motivated behavior suggest that the HiS and LoS differences are related to underlying differences in neurobiology of reward circuitry. In recent research, initial attempts have been made to examine differences in neuronal activity in the HiS and LoS rats by examining c-Fos reactivity in brain areas associated with drug reward. In these studies drug-naïve HiS and LoS rats were given one injection of 15 mg/kg cocaine HCl or saline (controls) and sacrificed 20 min later. In one study several brain areas (orbital frontal cortex, cingulated gyrus 1, nucleus accumbens shell, and dorsomedial and dorsolateral caudate putamen), associated with cocaine's rewarding effects, were examined for c-Fos counts (fold change from the cocaine-treated to the saline-treated group). Results indicated that the LoS rats showed higher neuronal activity than the HiS rats in the nucleus accumbens shell and dorsomedial and dorsolateral caudate putamen. Thus, HiS rats that are more vulnerable to cocaine-seeking behavior at several phases of the addiction process than LoS rats also exhibit less neuronal reactivity compared to LoS rats, after one injection with 15 mg/kg cocaine, in brain areas associated with food and drug reward. However, since it was an experimenter-injected dose and not self-administered, and the dose was high, it is not clear whether it was having a rewarding or aversive consequence.

In another study of HiS and LoS rats, the neurobiological connection between food and drug seeking was examined by counting the number of orexin-A-positive cells in the lateral hypothalamus and perifornical areas in HiS and LoS rats that had been injected with 15 mg/kg of cocaine or saline. Orexin-A is a neuropeptide that stimulates the motivation to ingest preferred substances and mediates dopamine release that affects motivation for cocaine and other highly valued rewards, including food. Orexin-A antagonists reduce intake of highly palatable foods in rats (Bocarsly & Avena, 2012; Cason & Aston-Jones, 2013; Kotz, 2006) and humans (Cason et al., 2010), and cue-induced reinstatement of drug-seeking behavior in rats via actions in the mesolimbic dopamine system (Espana et al., 2010; Moorman & Aston-Jones, 2009; Shoblock et al., 2011; Smith, Tahsili-Fahadan, & Aston-Jones, 2010). After an injection of cocaine or saline, HiS rats had more orexin-positive cells than LoS rats, suggesting that the HiS rats had higher endogenous orexin, and this may be related to their higher motivational states for sweet substances, alcohol, cocaine, and other drugs than LoS rats (Holtz, Zlebnik, & Carroll, 2012). Initial evidence suggests that the orexin-A antagonist reduces cue-induced drug-seeking behavior (Smith, See, & Aston-Jones, 2009).

2.5 Other Individual Differences and Drug Seeking

The findings of a relationship between different feeding preferences in HiS and LoS rats and corresponding differences in drug-seeking behavior are strong evidence for an innate connection between feeding and drug-seeking behavior. However, recent reports have also revealed a wide array of other motivated behaviors or traits that are also associated with drug abuse and eating disorders (ED), such as (1) impulsivity in humans (e.g., Dawe & Loxton, 2004) and in animal studies (Carroll et al., 2010); (2) novelty reactivity (Piazza et al., 1989), novelty preference in animals (Belin et al., 2011), or novelty/sensation seeking in humans (Kreek, Nielsen, Butelman, & Laforge, 2005), traits that are highly predictive of drug abuse; (3) physical activity (Larson & Carroll, 2005); and (4) sign vs. goal tracking in regard to attention to stimuli (incentive salience) associated with food reward (Flagel et al., 2010; Flagel, Watson, Akil, & Robinson, 2008). Some of the following examples of studies involving these vulnerability factors have used both rats selected for particular traits and rats selectively bred for those traits (see review by Carroll, Holtz, & Zlebnik, 2013).

1. *Novelty reactivity and preference*. Early studies selected rats for high (HR) vs. low (LR) novelty reactivity in a novel environment and showed that the HR rats initiated drug seeking more than the LR rats (Piazza et al., 1989). In subsequent work, similar results were found in rats selectively bred for high or low (bHR, bLR) reactivity in a novel environment (Cummings et al., 2011; Davis et al., 2008; Kabbaj, 2006; Kabbaj, Devine, Savage, & Akil, 2000). Recently, rats have been selected for novelty preference in a free-choice paradigm in which there is a choice between a familiar and novel environment, and those that are selected for the high-novelty-preferring (HNP) phenotype show more impulsive and

compulsive drug seeking compared to low-novelty-preferring (LNP) rats (Belin et al., 2011).

2. *Impulsive choice and impulsive action*. Several studies have compared high vs. low impulsive behavior determined by delay discounting (HiI, LoI) (see reviews by Carroll et al., 2010; Perry & Carroll, 2008) or with a 5-choice serial reaction time task (5-CSRTT) (HI, LI) that detects prepotent responding for food reward (Dalley et al., 2007). There is extensive evidence that rats selected for high and low impulsivity have similar propensities and disinterest, respectively, in drugs of abuse as shown in HiS and LoS rats (Carroll et al., 2010, Carroll, Holtz, & Zlebnik, 2013). For example, when HiS and LoS rats were compared on an impulsive choice measure, such as a delay-discounting task for food and cocaine, HiS rats were more impulsive than LoS rats for food (Perry, Nelson, Anderson, Morgan, & Carroll, 2007). However, under a go/no-go task for impulsive action, HiS rats were more impulsive than LoS for cocaine (Anker et al., 2008). There is extensive evidence that rats selected for high and low impulsivity have similar propensities and disinterest, respectively, to drugs of abuse as shown in HiS and LoS rats (Carroll et al., 2010); however, the sweet-preferring and impulsive phenotypes are not an expression of the same underlying factor, as HiS and LoS rats are not consistently high and low impulsive, and HiI and LoI rats do not show consistent differences in saccharin preference scores. Thus, the sweet-preferring and impulsive phenotypes are not completely overlapping, and they may represent different genetically-determined traits.
3. *Physical activity*. A propensity for physical exercise is another factor that is related to addictive behavior such as avidity for physical activity or exercise (Larson & Carroll, 2005; Olsen, 2011), and others have shown that physical activity is a genetically mediated characteristic (Bauman et al., 2012) that predicts SUD. For example, Larson and Carroll (2005) reported that rats selected for high wheel running (HiR) subsequently self-administered more cocaine than rats selected for low wheel running (LoR), and in a reinstatement (relapse) paradigm with HiR and LoR rats, Larson and Carroll (2005) also showed that HiR rats exhibited greater reinstatement of lever pressing that was previously reinforced by cocaine than LoR rats. Similarly, Ferreira et al. (2006) reported that wheel running in a heterogeneous rat population was positively related to amphetamine-induced locomotor activity, a behavior that is correlated with the initiation of drug seeking. Thus, avidity for exercise, like seeking preferred foods, predicts drug abuse in animal models.

   However, as in the case of preferred food, exercise functions as an economic substitute for drug abuse and seems to have a therapeutic function in treating drug abuse. For example, exercise reduces cocaine self-administration, and cocaine availability reduces exercise (Cosgrove, Hunter, & Carroll, 2002). Initial studies indicate that the interaction of drug seeking and exercise is likely related to common neurobiological reward mechanisms. (Zlebnik, Hedges, Carroll, & Meisel, 2013). Earlier work by Kanarek and coworkers (Kanarek, D'Anci, Jurdak, & Mathes, 2009; Kanarek, Gerstein, Wildman, Mathes, & D'Anci, 1998) indicated that exercise and drug seeking may be mediated by

the endogenous opioid system. A difficulty in considering exercise as a treatment for drug abuse, in terms of a substitute for drug addiction, is that in a small subset of individuals, too much exercise can become addictive and result in activity-induced anorexia (Davis, Kennedy, Ravelski, & Dionne, 1994). This has also been modeled in rats (Spear & Hill, 1962).

4. *Sign* vs. *goal tracking*. Another dimension of individual differences that has recently been reported to be predictive of addictive behavior involves rats selected for attention to cues associated with food reward (sign tracking—ST), or the food receptacle (goal tracking—GT). For the ST rats, stimuli associated with food reward have more incentive salience, while goal tracking rats focus their attention on the goal or food reward and its delivery receptacle (Flagel et al., 2008). These studies found that ST rats, for which stimuli associated with food reward have more incentive salience, self-administer more cocaine and show more drug-primed reinstatement of cocaine seeking compared to GT rats that focus their attention on the food reward and its delivery receptacle (Saunders & Robinson, 2011a, b; Saunders, Yager, & Robinson, 2013). Distinctions between stimulus (sign) and reward (goal) seeking in rats have not yet been associated with parallels for these attentional differences in humans, but recent studies with animal models suggest there is some overlap between impulsive and high-novelty-seeking characteristics. Thus, as discussed regarding Table 2.2, these relatively recent findings on ST and GT individuals might indicate another behavioral dimension that predicts high vs. low probability for addictive behavior. While this dimension could have some overlap with impulsive behavior, further work is needed to determine whether it is a unique trait that is predictive of drug abuse in humans and other animals.

The high performing phenotypes on all of these measures, compared with the low performing phenotypes, exhibited increased drug-seeking behavior using several models and phases of the addiction process. Thus, sweet preference is one example of several forms of nondrug reward-seeking traits that predict higher levels of drug seeking. There are other biological factors that determine vulnerability to drug abuse and predict high levels of drug seeking, such as sex (female) and age (adolescent), and these factors add to the selected or selectively bred addiction-prone phenotypes to predict even higher levels of drug-seeking behavior, or in the case of low drug preferring attributes, more resilience. Thus, avidity for palatable foods, as shown in the HiS rats, is only one example of several forms of reward-seeking traits in rats that predict high rates of drug-seeking behavior. However, sweet preference seems to be one of the strongest and most reliable traits that predict drug abuse, and it may be related to the interchangeability of food and drug addiction. Corresponding evidence has also been reported in humans with impulsivity as a predictor of drug abuse (Yi, Mitchell, & Bickel, 2010).

As indicated in Table 2.2 there are also several other strain or line differences in rats that predict drug abuse, and some have corresponding differences in feeding behavior. For example, there are rats that have been selected or bred to have high vs. low fear, anxiety, and emotionality, and these rats parallel the LoS

vs. HiS and LoI vs. HiI rats in terms of opposite relationships between aversion sensitivity and amount of drug self-administered (Holtz & Carroll, 2013). Also, Lewis (LEW) rats exhibit more drug seeking than Fischer (F344) rats, high alcohol consuming (HAC) rats consume more alcohol than low alcohol consuming (LAC) rats, and Roman high avoidance (RHA) rats consumed more ethanol compared to Roman low avoidance (RLA) rats (Guitart-Masip et al., 2006; Manzo et al., 2012) and LAC rats. However, the RLA and LAC rats have higher measures of stress reactivity, suggesting that rats that are avid drug seekers seem to be resilient to stress and aversive consequences of drug taking, while less drug addiction-prone rats are more susceptible to stress and aversive consequences of drug self-administration.

2.6 Reactivity to Aversive Events Associated with Drug Seeking in HiS and LoS Rats

Early findings by Dess and colleagues showed that while HiS rats consumed more of a variety of palatable substances such as sugars, saccharin, polycose, and salt than LoS rats, LoS rats were responsive in their aversion to bitter components of ethanol and taste mixtures (Dess, 1993, 2000; Thiele, Badia-Elder, Keifer, & Dess, 1997). Subsequent work by Dess and colleagues (2005) on the HiS and LoS rats and recent studies from our laboratory (Carroll, Holtz, & Zlebnik, 2013; Holtz & Carroll, 2013) have shown that the interaction between feeding behavior and drug seeking is more complicated than substitution of one rewarding substance (e.g., drug) for another (sweet food), and in fact, the relative reactivity to the aversive effects of ingested substances has an important role in the HiS/LoS difference in drug taking in rodent strains. Recent evidence suggests that the balance of rewarding and aversive effects is important to take into account when assessing addiction liability (Riley, 2011; Verendeev & Riley, 2013). Table 2.2 summarizes examples of high vs. low drug-abuse-vulnerable rat lines and indicates that the low drug-seeking counterparts of each pair of lines have a greater reaction to aversive events than their high reward-seeking counterparts.

While the HiS rats inform us about general vulnerability characteristics that predict drug-seeking behavior, the LoS rats provide valuable information about resilience to and avoidance of addictive behaviors involving both food and drugs. Initial work by Dess and colleagues (Dess et al., 2000; Dess & Minor, 1996; McLaughlin, Dess, & Chapman, 2011) and in our laboratory (Carroll, Holtz, & Zlebnik, 2013) indicates that LoS rats are more reactive to aversive stimuli, such as food restriction, than HiS rats. LoS rats are also more severely affected by the adverse effects of withdrawal of rewarding substances such as ethanol, glucose (Dess, O'Neill, & Chapman, 2005; Radke, Zlebnik, & Carroll 2014; Dess, Badia-Elder, Thiele, Kiefer, & Blizard, 1998; Yakovenko et al., 2011), or food (McLaughlin et al., 2011); LoS rats also react more than HiS rats to brief intermittent bursts of white noise (acoustic startle) (Dess et al., 2000), and during ethanol withdrawal, Dess et al. (2005) also used ethanol withdrawal-induced conditioned

taste aversion (CTA) as an indicator of the aversive effects of withdrawal in HiS and LoS rats, and the CTA was significantly greater in LoS than HiS male rats. These studies were expanded by examining the effects of stress (inescapable foot shock) on startle amplitude in the HiS and LoS rats, and results indicated a greater effect on startle amplitude on LoS (vs. HiS) rats (Gonzales, Carrett, Chapman, & Dess, 2008).

In a recent study, spontaneous and naloxone-precipitated morphine withdrawal effects were measured in HiS and LoS rats using elevation in intracranial self-stimulation thresholds, and LoS rats' thresholds were more elevated than HiS rats' indicating greater aversion to morphine withdrawal in LoS than HiS rats. These effects of drug withdrawal in HiS and LoS rats have recently been found with forced glucose abstinence (withdrawal) (Yakovenko et al., 2011). Rats were given extended access to glucose, and escalation of glucose intake was positively correlated with an increase in acoustic startle responding in the LoS vs. HiS rats. Similar findings with drug and glucose withdrawal in HiS vs. LoS rats are consistent with previous reports of parallel findings in studies of drug dependence, dysregulation of food intake, and food addiction (Avena, Long, & Hoebel, 2005; Avena, Rada, & Hoebel, 2006; Blumenthal & Gold, 2010).

Another approach to examining differences in HiS vs. LoS rats with regard to aversive effects has been to train rats to self-administer IV cocaine infusions and, after behavior stabilizes, to punish the cocaine-taking behavior by adding an aversive stimulus, histamine, to the cocaine solution. Thus, cocaine self-administration was punished by allowing the rats to self-administer a dysphoric consequence, histamine, during cocaine self-administration (Holtz, Anker, Regier, Claxton, & Carroll, 2013). First, a cocaine-only baseline was obtained for ten stable daily 2-h. sessions, followed by 10 days of cocaine + histamine, and subsequently, there was a 20-day return to cocaine only. Figure 2.1a indicates that both HiS and LoS rats reduced their cocaine self-administration by more than half during histamine treatment, but LoS rats were very slow to recover during the first 15 days of return to cocaine alone, while HiS rats returned to pre-histamine baselines in 3 days or less. Figure 2.1b illustrates the delay in recovery of the cocaine baseline over 2 weeks in the LoS rats. Thus, the aversive effects of punishment had similar aversive effects as stress measures that were previously discussed, in that LoS rats were more affected by aversive events than HiS rats.

2.7 Treatment Models in HiS and LoS Rats

The ultimate goal in understanding vulnerability to drug abuse, and how it relates to aberrant feeding patterns, is preventing the escalation of food or drug use by delivering treatment to those with food or drug addiction. While much has been learned about vulnerability factors, and their interactions, there are almost no clinical data on treatment in high vs. low vulnerable groups. One area that has been studied in this regard shows that addictive behavior is related to sex differences (F > M), and ovarian hormonal cycles (follicular > luteal) (see reviews

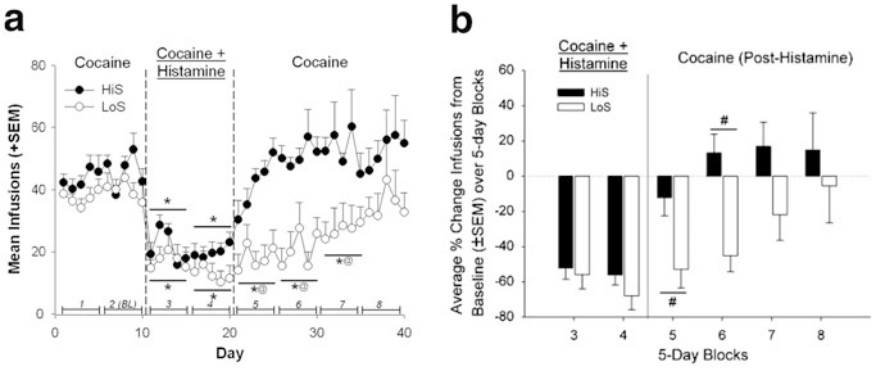

Fig. 2.1 Mean daily cocaine infusions (± SEM) are presented over 40 days in rats that were (**a**) selectively bred for high (HiS) or low (LoS) on measures of saccharin consumption or (**b**) high (HiI) or low (LoI) impulsive based on a delay-discounting task with food reward. The first 10-day period represents a stable baseline period when only cocaine (0.4 mg/kg) was available under a fixed-ratio 1 (FR 1) schedule. During days 11–20, histamine (4 mg/kg/infusion) was added directly to the cocaine syringe, and subsequently on days 21–40 only cocaine was available. Filled symbols indicate the HiS or HiI groups, respectively, and open symbols represent the LoS and LoI groups. An *asterisk* indicates a significant difference from baseline block 2 (Days 6-10), and @ indicates days when there were significant differences between the phenotypes at the $p < 0.05$ level (reprinted with permission from Holtz, Anker, et al., 2013)

by Anker & Carroll, 2010, 2011). Initial studies indicate that females exceed males during all phases of drug abuse that are modeled in the laboratory, except during withdrawal when males show more severe withdrawal effects than females (Carroll, Mach, et al., 2009), and in females withdrawal severity varies with phase of the menstrual cycle (Carroll, Johnson et al., 2013). In the few animal studies of sex differences in treatment effects, females were also more responsive to both behavioral and pharmacological treatments than males (Anker & Carroll, 2010, 2011; Carroll & Anker, 2010). In treatment of women for cigarette smoking, treatment also varies with phase of the menstrual cycle and when during the cycle the quit attempt is initiated (Allen, Bade, Center, Finstad, & Hatsukami, 2008; Franklin et al., 2007; Mazure, Toll, McKee, Wu, & O'Malley, 2011).

Much less is known about differential treatment effects with other individual differences such as HiS and LoS, HiI and LoI; however, in a few treatment studies that have recently been completed, it appears that the low drug-abuse-vulnerable phenotypes (LoS, LoI) were more responsive to treatment than their high vulnerable counterparts. For instance, as indicated in Fig. 2.2a, when HiS rats were allowed to self-administer cocaine and escalate their intake over 6-h sessions, progesterone (which functions as a $GABA_A$ modulator) treatment initially reduced cocaine infusions in LoS rats, but increased cocaine in HiS rats at the end of the 21-day escalation period (Anker, Holtz, & Carroll, 2012). Similarly as indicated in Fig. 2.2b, baclofen, a $GABA_B$ agonist, reduced cocaine infusions throughout the 21-day escalation phase in LoS rats and increased cocaine infusions during the last

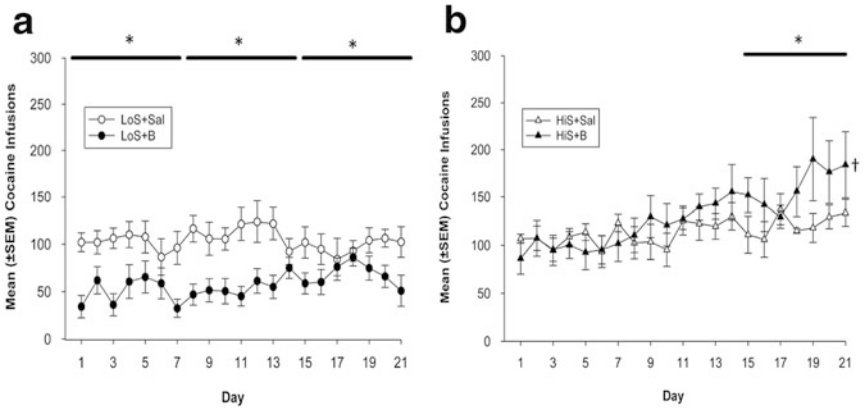

Fig. 2.2 Percent change of infusions self-administered by HiS and LoS rats are averaged into 5-day blocks and compared to the 5-day baseline average. The *hash* sign indicates phenotype differences in percent change of infusions self-administered between the phenotypes compared to baseline at the $p < 0.05$ level (reprinted with permission from Holtz, Anker, et al., 2013)

few days in the HiS rats (Holtz & Carroll, 2011). In a recent study of allopregnanolone (progesterone metabolite), treatment of HiI and LoI rats during reinstatement of cocaine seeking (relapse) primed by cocaine or caffeine, LoI rats showed a greater reduction in reinstatement than HiI rats (Regier, Zlebnik, Claxton, & Carroll, 2013). Similarly, combined exercise (wheel running) and atomoxetine had greater effects than each treatment alone and a better reduction in reinstatement responding in LoI than HiI rats. These results that indicated better treatment results in the LoS and LoI, less vulnerable groups, are in contrast with the treatment results in male and female rats and monkeys. In several studies, the more vulnerable females showed a better treatment response with both medications such as ketoconazole for heroin (Carroll, Campbell, & Heideman, 2001), or baclofen (Campbell, Morgan, & Carroll, 2002), or bremazocine (Cosgrove & Carroll, 2002) for cocaine self-administration, and behavioral interventions such as access to saccharin for phencyclidine (Cosgrove & Carroll, 2003) or exercise for cocaine (Cosgrove et al., 2002) self-administration.

The recent data reviewed here regarding the LoS rats' greater sensitivity to aversive effects of drugs and the HiS rats' greater sensitivity to the rewarding effects provides information regarding the design of customized treatment strategies for drug abuse. For example, the LoS rats responded more to histamine, which may have functioned as an aversive treatment or a negative factor that when added to the positive cocaine effect neutralized the rewarding effects of cocaine, while in the HiS rats for which cocaine's rewarding effects may have been stronger, histamine treatment was unable to reduce the rewarding effects of cocaine beyond the immediate treatment phase. In terms of translating the present animal studies to customized strategies to humans, a method used for drug addiction in humans that has been relatively successful is the community reinforcement approach (Higgins

et al., 2003), a form of contingency management whereby compliance with drug abstinence is rewarded over time by an accelerating point schedule that can be used for valuable commodities in the community (e.g., school tuition, rent, etc.), while noncompliance is punished by resetting the point contingencies. Based on the animal data, it would be hypothesized that those with lower addiction severity assessments at intake would respond better to more severe punishment (point reset) contingencies, while those with high addiction severity might have more success with a steeper point acceleration to enable nondrug alternatives to interfere with drug seeking. There is substantial evidence that nondrug alternatives interfere with drug seeking (Carroll, Bickel, & Higgins, 2001; Cason & Grigson, 2013); however, little laboratory work has been done to model treatment in differentially vulnerable groups using animals. The initial findings with HiS vs. LoS and HiI vs. LoI rats suggest that a better understanding of how vulnerability interacts with treatment receptivity might lead to optimal customized treatments for drug abusers.

Conclusion

This chapter has discussed accumulating evidence for a strong relationship between feeding behavior and drug seeking. Recent studies using DSM-IV criteria such as difficulty limiting use, increased motivation to use, and continued use despite negative consequences have shown in laboratory models with rats that there is a strong relationship between "food addiction," which may be related to DSM eating disorders, and drug addiction. Palatable food and addictive drugs, such as cocaine, are interchangeable as reward; thus, one form of maladaptive behavior may be substituted for another. In this chapter we focused on a genetic model—rats that are selectively bred to prefer and binge on sweet substances (HiS), and their low saccharin-preferring counterparts (LoS) that do not exhibit these excessive behaviors. The HiS line shows preferences for drugs of abuse and drug bingeing behavior according to the DSM criteria, while LoS rats do not; thus, these lines serve as models for a wide range of human drug users. There are related vulnerability factors such as high and low impulsivity (HiI, LoI) that show preference for and bingeing on cocaine and novelty reactive (HR, LR) selected rats that initiate drug seeking more than low reactive (LR) rats. There is also a high-novelty-preferring (HNP) phenotype that exhibits more impulsive and compulsive drug seeking compared to low-novelty-preferring (LNP) rats. The HiS and LoS rats and the other selected or selectively bred lines have unique characteristics but similar predictions for addictive behavior. There is some overlap in vulnerability factors mentioned here that can result in additive vulnerability to addiction and which allows for a wide range of vulnerability profiles that can determine severity of drug abuse, but the factors focused on in this chapter (e.g., sweet preference, impulsivity) are relatively independent. Yet, the vulnerability characteristics may be additive with each other and with age and sex as well, allowing for a wide range of vulnerability profiles that can determine drug abuse. Also, vulnerability status is a factor to consider in designing treatment strategies, as initial studies indicate that treatment outcome varies considerably in differentially vulnerable

phenotypes, suggesting that custom-designed or multiple treatments might be an important consideration for the high-vulnerability phenotypes. Initial studies with rats suggest that vulnerability status is an important determinant of treatment outcome. Since factors that determine food and drug addiction are interwoven, it is likely that treatments for drug abuse would benefit other disorders of behavioral dysregulation such as obesity.

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