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Selective breeding for differential saccharin intake as an animal model of drug abuse.

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Selective breeding for differential saccharin intake as an animal model of drug abuse

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A positive relationship between the consumption of sweetened dietary substances (e.g. saccharin and sucrose) and drug abuse has been reported in both the human and other animal literature. The proposed genetic contribution to this relationship has been based on evidence from behavioral, neurobiological, and linkage studies in heterogeneous and homogeneous animal populations. Initial work in several laboratories indicated that rodents that are selected for high alcohol consumption also display an increased preference for sweets compared with low alcohol-consuming animals. More recently, Sprague–Dawley rats have been selectively bred based on high saccharin (HiS) or low saccharin (LoS) consumption, and these lines represent an ideal opportunity to determine whether a reciprocal genetic relationship exists between the consumption of sweetened substances and self-administration of drugs of abuse. The purpose of this review is to examine a series of studies on the HiS and LoS rats for drug-seeking and drug-taking behavior using laboratory animal models that represent critical phases of drug abuse in humans. The data support the hypothesis that sweet consumption and drug self-administration are closely related and genetically influenced. Other characteristics of HiS and LoS rats are discussed as possible mediators of the genetic differences such as activity, impulsivity, novelty reactivity, stress, and emotionality. The interaction of sweet preference with biological variables related to drug abuse, such as age, sex, and hormonal influences, was considered, as they may be additive vulnerability factors with consumption of sweet substances. In the studies that are discussed, the HiS and LoS lines emerge as ideal addiction-prone and addiction-resistant models, respectively, with vulnerability or resilience factors that will inform prevention and treatment strategies for drug abuse. *Behavioural Pharmacology* **19:435–460 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Vulnerability to drug addiction is a complex behavioral phenomenon with both genetic and environmental influences (Nestler, 2000; Vanyukov and Tarter, 2000; Crabbe, 2002; Kreek *et al.*, 2005a, b; Uhl, 2006). Despite several well-known phenotypic risk factors for drug abuse and related impulse control disorders, effective predictors of risk that may be useful in prevention and treatment have remained elusive. Several lines of research in both humans and laboratory animals have revealed a positive relationship between the consumption of sweetened dietary substances (e.g. saccharin and sucrose) and drug abuse. In laboratory animal studies, selection of rats for high and low intake of sweetened substances predicts subsequent drug self-administration (Carroll, 1993, 1999; Gosnell and Krahn, 1998; Levine *et al.*, 2003a, b). Similarly, alcohol (Gosnell and Krahn, 1992; Kampov-Polevoy *et al.*, 1995, 1997, 2001), amphetamine (DeSousa *et al.*, 2000), cocaine (Janowsky *et al.*, 2003), nicotine (Pomerleau *et al.*, 1991), and opioid (Weiss, 1982) abusers or those with positive family histories of alcohol abuse (Kampov-Polevoy *et al.*, 2001, 2003) have been shown to prefer higher concentrations of sweets than nonabusers. However, the relationship between preference for sweets and drugs of abuse also depends on the tastants or dietary macronutrients used, and they are not always consistent (Bogucka-Bonikowska *et al.*, 2001; Scinska *et al.*, 2001; Levine *et al.*, 2003a, b). Furthermore, as there are many other factors related to sweet preference (Dess and Minor, 1996; Dess, 2000), the causative nature of sweet preference and its interaction with addiction remains unclear (Kranzler *et al.*, 2001; Hirsch, 2002). Selective breeding for a behavioral trait is a powerful technique for revealing underlying mechanisms influencing pathological behavior such as drug addiction.

Alcohol preference has also been shown to predict sweet consumption. In studies of inbred rodents (McClearn and Rodgers, 1959; Belknap *et al.*, 1993) and selectively bred rodents (Sinclair *et al.*, 1992; Li *et al.*, 1993; Kampov-Polevoy

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et al., 1995) rodents bred or bred or selected for high alcohol preference consumed more sweet solution than those showing lower alcohol preference. The link between sweets and other drugs of abuse (e.g. stimulants and opioids) has not been as closely examined, although alcohol-naive offspring of rats bred for alcohol intake are more susceptible to nicotine self-administration and reinstatement than offspring of rats that do not prefer alcohol (Le *et al.*, 2006). This suggests that rats selectively bred for alcohol preference may have a proclivity not only for sweet substances, but other addictive drugs. The seemingly robust and reciprocal relationship between sweet intake and drug self-administration has inspired a series of studies with rats that were selectively bred for high saccharin (HiS) and low saccharin (LoS) intake (Dess and Minor, 1996) at Occidental College (Los Angeles, California, USA). The Occidental HiS and LoS rat lines were initially bred to study whether LoS rats were a suitable model of enhanced stress and emotionality and if they would consume less of other flavors such as quinine as they did saccharin (Dess and Minor, 1996). Rats from the HiS LoS lines have been used predominantly in feeding research by Dess and colleagues, but two studies indicated HiS and LoS line differences in ethanol (HiS > LoS) consumption (Dess *et al.*, 1998) and ethanol withdrawal severity (LoS > HiS) (Dess *et al.*, 2005). However, whether these genetic effects extended beyond alcohol consumption to other drugs of abuse and different routes of administration, and the specificity of the pleiotropic effects (e.g. sweet preference, taste reactivity, novelty reactivity, impulsivity, etc.) were not known. Another study using the Occidental HiS and LoS rats showed that HiS rats acquired intravenous (i.v.) cocaine self-administration more rapidly than LoS rats (Carroll *et al.*, 2002). Later, a second breeding program for HiS and LoS rats from the Occidental HiS LoS progenitors began, at the University of Minnesota, Minneapolis, Minnesota USA (Perry *et al.*, 2006a), to specifically study laboratory animal models of drug abuse. These Minnesota studies extended the research from ethanol to other drugs (e.g. cocaine, heroin), to the i.v. route of self-administration, to other phases and aspects of drug abuse, and to the interaction of HiS and LoS phenotypes with other factors controlling drug abuse.

The HiS and LoS rats were of particular interest because the HiS rats not only consumed more saccharin than LoS rats, they consumed large quantities of saccharin (Dess, 2001). This form of excessive consumption also occurs in outbred rats offered access to a sucrose solution (Rada *et al.*, 2005; Avena *et al.*, 2006, 2008a, b), and the neurochemical consequences of this behavior are similar to those seen with drug abuse. Bingeing on sweet liquids in rats can be used to model behavioral disorders in humans, such as binge-eating disorder; thus, it serves as a model of one of the key elements of addictive behavior, escalating, out-of-control use (Ahmed and Koob, 1998, 1999; Koob and Le Moal, 2005). It was hypothesized that the HiS and LoS lines would represent addiction-prone and addiction-resistant laboratory models, respectively. The HiS and LoS rats also allow us to determine whether reciprocal genetic factors influence consumption of sweet substances and drug abuse liability, and how other major variables affecting drug abuse interact with this reciprocal relationship.

Our initial goal in working with the HiS and LoS lines was to study the importance of this behavioral phenotype, the excessive consumption of sweetened liquid (vs. water), as a major factor that would predict the initial development and progression of drug abuse through critical phases (acquisition, escalation, relapse, treatment) that characterize the etiology of drug addiction in humans. The rationale for these studies was that if a major factor related to drug abuse is better described and understood in terms of its mechanisms and its generality, rational strategies for prediction, prevention, and treatment of drug abuse could be developed. A related goal was to discover other major variables that covaried with the excessive intake of sweet substances and to examine their cumulative influence as predictors of drug abuse.

Selectively breeding laboratory animals based on differential phenotypes has been critical to our understanding of genetic susceptibility to drug abuse (Nichols and Hsial, 1967; George and Goldberg, 1989; George, 1991; Crabbe and Phillips, 1993; McBride and Li, 1998; Nestler, 2000; Crabbe, 2002). According to this method, only the individuals most strongly expressing the phenotype of interest in a population are mated, and following several generations of selective pressure, the frequency of genes underlying the selected phenotype are increased, resulting in diverging lines. For example, selectively bred lines have been developed for ethanol-related hypnotic (McClearn and Kakihana, 1981), hypothermic (Crabbe *et al.*, 1987a), locomotor (Crabbe *et al.*, 1987b), and withdrawal effects (Wilson *et al.*, 1984; Crabbe *et al.*, 1986) as well as ethanol preference (Eriksson, 1968a, b; Li and Lumeng, 1977). Selective breeding in rodents has also been extended to the ataxic effects of diazepam (Gallaher *et al.*, 1987), analgesic effects of opiates (Belknap *et al.*, 1987), sensitivity to psychostimulants (Smolen and Marks, 1991; Marley *et al.*, 1998), and to the locomotor effects of nicotine (Smolen and Marks, 1991; Smolen *et al.*, 1994). The selective breeding process invariably reveals accompanying phenotypic changes that, when properly controlled for, can be attributed to the pleiotropic effects of the genes underlying the selected phenotype. For example, the consistent finding of high or low sweet intake in the animals selected for high or low alcohol consumption, respectively, has led to a hypothesis suggesting pleiotropic effects of the genes underlying intake of alcohol and

sweet substances (Li *et al.*, 1993; Kampov-Polevoy *et al.*, 1995, 1999; McBride and Li, 1998).

Objectives

This review has several objectives. First was to strengthen the awareness of commonalities between drug-motivated and food-motivated behaviors. Extensive literature has emerged in the last decade to suggest common reward mechanisms between preferred foods and psychoactive drugs. Morbidity and mortality due to drug abuse (e.g. tobacco) and excessive food consumption (e.g. obesity) are responsible for the top two causes of death yearly in the United States, cancer and heart disease. In view of the recent obesity epidemic, a better understanding of the relationship between drug-motivated and food-motivated behaviors may inform us about strategies gained from studying drug abuse that would lead to solutions for overeating as well (Volkow and Wise, 2005). Second, selective breeding has been useful for a better understanding of other psychiatric disorders; thus, breeding for HiS and LoS consumption may enhance our existing models of drug abuse, and advance our knowledge of addictive behavior in general. As such, HiS and LoS rats represent an ideal model to determine whether reciprocal genetic factors (i.e. pleiotropic effects) influence intake of sweetened substances and drug self-administration. Third was to apply sensitive models of the key phases of drug abuse that have been developed in our laboratory and others, including initial 'acquisition' of drug self-administration in drug-naive animals, 'maintenance' of self-administration under conditions of short daily access, 'escalation and dysregulation' of intake with extended access to the drug, 'extinction (abstinence)', drug 'withdrawal' effects, and 'reinstatement (relapse)' of drug-seeking behavior in rats differing in vulnerability to cocaine-seeking behavior (HiS vs. LoS). The fourth objective was to discuss alternative explanations, other characteristics of the HiS LoS lines (aside from saccharin intake) that are related to the differences in drug-seeking and drug-taking behavior. For example, in the breeding process other phenotypes emerged, such as reactivity to novelty, stress, and impulsivity, and it may be that these factors that are related to drug abuse as they are to saccharin intake. Finally, the fifth objective was to examine the interaction of sweet preference or aversion in the HiS or LoS rats, respectively, and drug-related behavior with other variables (e.g. age, sex, and hormonal status) that also have a significant influence on drug abuse. If other major vulnerability factors in drug abuse are correlated with the HiS and LoS phenotype, they could combine to produce additive vulnerability.

Commonalities among drugs, food, and other rewards

Recent evidence indicates significant overlap, on both behavioral and neurobiological levels, among various forms of addiction, ranging from drug abuse to pathological eating, exercise/activity, and gambling (Kelley and Berridge, 2002; Levine *et al.*, 2003a, b; Pelchat *et al.*, 2004; Ahmed, 2005; Volkow and Wise, 2005; El-Guebaly *et al.*, 2006). Behavior directed toward seeking natural rewards (e.g. food, activity) and other rewards (e.g. drugs, gambling) is motivated by positive reinforcement such as consumption, hedonic value, wanting, and liking, as well as negative reinforcement, such as relief from stress, craving, and withdrawal effects. The pleasurable effects of food and other natural rewards, as well as food cravings and withdrawal effects provide powerful motivation for compulsive drug-seeking and food-seeking which can sometimes lead to pathological results (Avena *et al.*, 2008a, b). Sweet preference in humans has been linked to mood altering effects and impaired control over ingestion of sweet substances (Kampov-Polevoy *et al.*, 2005). Identifying and understanding the key features that underlie addiction could lead to behavioral and pharmacological treatments that inhibit the positive and negative reinforcing effects that sustain these motivated behaviors. Some of the key features comprising addictive behavior with drug and nondrug rewards are (i) early initial use, (ii) escalation and dysregulation of intake, (iii) increased motivation to consume, (iv) difficulty abstaining, and (v) risk of relapse after exposure to stimuli related to the addictive behavior (Ahmed, 2005).

Similarities among drug and nondrug rewards have been reviewed extensively [*Nature Neuroscience*, 8(11), 2005; *Physiology and Behavior*, 86(1–2), 2005; Levine *et al.*, 2003a, b; Pelchat *et al.*, 2004; Ahmed, 2005; Volkow and Wise, 2005], and evidence is rapidly accumulating to indicate that drugs of abuse have many neurobiological effects that are the same as those found with nondrug rewards such as food, sex, and exercise. For example, all of these substances and events increase extracellular dopamine (DA) in the mesolimbic reward pathways (Volkow and Wise, 2005). In addition, the hallmark features of drug addiction such as sensitization (Avena and Hoebel, 2003a, b; Vitale *et al.*, 2003; Gosnell, 2005), escalation of intake (Colantuoni *et al.*, 2001, 2002; Lattanzio and Eikelboom, 2003; Corwin and Hajnal, 2005; Corwin, 2006; Avena, 2007; Avena *et al.*, 2008a, b), and withdrawal effects (Colantuoni *et al.*, 2002; Stoffel and Craft, 2004), and relapse (Shalev *et al.*, 2006; Ghitza *et al.*, 2006, 2007; Avena *et al.*, 2008a, b) have recently been reported with behaviors motivated by rewarding substances such as food and sucrose.

Many other parallels between food and drug reward exist; for example, just as withdrawal is not necessary for drug craving, hunger is not necessary for food craving (Pelchat *et al.*, 2004), whereas cross tolerance (D'Anci *et al.*, 1996) and cross-dependence (Colantuoni *et al.*, 2001) have been observed between sugars and drugs of abuse. A recently published study showed that when rats were allowed exclusive choice between i.v. cocaine and

saccharin-sweetened drinking water, 94% of the animals showed a preference for the saccharin (Lenoir *et al.*, 2007). Similarly, when saccharin and i.v. cocaine were available concurrently in an earlier study (Carroll *et al.*, 1989), there was a negative correlation between intake of cocaine and saccharin, such that intake of one increased as the other decreased, suggesting that they were substitutable for each other. Woods (1991) provides an excellent discussion of how food and drugs have similar biological effects such as physiological and behavioral tolerance, and how both food and drugs may disrupt homeostatic mechanisms, as others have discussed for drugs of abuse (Koob and LeMoal, 2006, 2008).

Several types of rewards such as drugs, foods, sex, and exercise result in activation of neurotransmitter action in similar brain areas. Brain structures that show activation during drug and alcohol craving include amygdala (Childress *et al.*, 1999), anterior cingulate (Childress *et al.*, 1999, 2000), orbital frontal cortex (Wang *et al.*, 1999), insula (Wang *et al.*, 1999; Garavan *et al.*, 2000), hippocampus (Schneider *et al.*, 2001), and caudate (Hommer, 1999). Intake of palatable foods (Rada *et al.*, 2005; Avena *et al.*, 2008a, b) and psychostimulant drugs (Rouge-Pont *et al.*, 1995; Cadoni *et al.*, 2003) modulate concentrations of extracellular DA in the nucleus accumbens (NAc) of rodents. Substantial evidence for the role of DA in feeding-related behaviors has been presented (Carr, 2007). Intake of palatable foods or psychostimulant drugs increases concentrations of extracellular DA in the NAc in food-restricted rats (Rouge-Pont *et al.*, 1995; Cadoni *et al.*, 2003), and food restriction decreases DA transporter activity (Zhen *et al.*, 2006). In addition, sweet tastants (Hajnal *et al.*, 2004) and drugs of abuse (Di Chiara and Imperato, 1988) stimulate DA signaling in the ventral striatum. Electrophysiological studies also show that ethanol activates sensory-neural substrates that are involved in the taste of sugar (Lemon *et al.*, 2004), and these substrates have been linked to reward circuits in the central nervous system (Hajnal *et al.*, 2004). Recent studies indicate that the intake of highly palatable foods leads to the activation of the midbrain and striatum (Carr, 2002, 2007; Carr *et al.*, 2003), brain structures implicated in response to drugs of abuse and development of drug addiction (Nestler, 2005; Hyman *et al.*, 2006; Hyman, 2007). Finally, recent imaging studies show similar neuroadaptations in the brains of obese and cocaine-addicted individuals (Wang *et al.*, 2004, 2006; Volkow and Wise, 2005).

Although the mesolimbic DA system is most frequently attributed to reward function, other DA functions and other transmitter systems are involved (Wise, 2004). For example, endogenous opioid systems also underlie the rewarding effects of palatable foods (Zhang *et al.*, 1998, 2003; Yeomans and Gray, 2002; Pecina *et al.*, 2006). Sucrose, when taken in excess by rats, produces opioid mRNA levels similar to morphine-dependent rats (Spangler *et al.*, 2004). Gamma amino-butyric acid neurons that inhibit DA systems are inhibited by μ opioids that also modulate intake of palatable foods. This results in disinhibition of the DA system and increased DA release in the Nac. Similar complex actions occur with glutamate and corticotropin releasing factor (Koob *et al.*, 2004). Furthermore, genetic mapping of quantitative trait loci for saccharin consumption in inbred alcohol preferring and nonpreferring lines overlaps with quantitative trait loci (chromosome 3) for alcohol consumption (Foroud *et al.*, 2002).

Selective breeding and psychiatric disorders

Several selectively bred rodent lines have been developed to model psychiatric illness and disorders of the central nervous system. For example, selective breeding for differential responses to the anticholinesterase agent diisopropyl fluorophosphate in, the Flinders sensitive line and Flinders resistant lines, and selection for differential hypothermic responses to the 5-HT agonist 8-OH-DPAT, the high DPAT sensitive and low DPAT sensitive lines, have been useful for modeling depression, discovering potential antidepressant drugs, and characterizing the relationship between mood disturbances and drug abuse (Overstreet, 2002). The Fischer 344 (F344) and Lewis (LEW) inbred strains of rats have been useful models of genetic factors in drug abuse, particularly the psychostimulants. They differ (LEW > F344) in several aspects of drug abuse including acquisition of cocaine (Kosten *et al.*, 1997; Ranaldi *et al.*, 2001; Kruzich and Jinlei, 2006), and morphine (Martin *et al.*, 1999) self-administration, maintenance of drug self-administration (George, 1991; Haile and Kosten, 2001), reinstatement of drug-seeking behavior after extinction (Kruzich and Jinlei, 2006), development of behavioral sensitization to cocaine (Kosten *et al.*, 1994), and the LEW strain consumes more alcohol than F344 (Suzuki *et al.*, 1988a, b) and other outbred Wistar rats (Marinelli *et al.*, 2003). The LEW strain also has fewer D2-like DA receptors (Flores *et al.*, 1998) and lower basal levels of DA metabolism than the F344 strain (Strecker *et al.*, 1995). Compared to F344, LEW rats have higher magnitudes of cocaine-induced increases in extracellular DA in the NAc core following lower doses of cocaine and in the NAc shell after higher doses (Cadoni and Di Chiara, 2007). Behavioral responses to psychoactive drugs such as emotion, fear, stress, and conditioning effects related to the drugs (see review by Kosten and Ambrosio, 2002) have also been reported in F344 and LEW rats. The F344 and LEW rats parallel the LoS and HiS rats, respectively, showing an inverse relationship between reactivity to aversive tastes (F344 > LEW) and drug self-administration (LEW > F344) (Roma *et al.*, 2006).

The first selectively bred lines of interest to the field of drug abuse originated during the 1940s and 1950s. Rats

were selectively bred for high (UChB) and low (UChA) oral alcohol preference, and these lines continue to be propagated (Mardones *et al.*, 1953; Mardones and Segovia-Riquelme, 1983; Tampier and Quintanilla, 2005). Four additional high and low alcohol-drinking rodent lines were subsequently developed: (i) Alko (Finland) alcohol-accepting and alcohol nonaccepting lines, (ii) the Indiana University preferring (P) and nonpreferring lines (Eriksson, 1968a, b, 1971), the (iii) high alcohol drinking and low alcohol drinking lines (Li *et al.*, 2001), and (iv) the Sardinian preferring and nonpreferring lines (Colombo *et al.*, 1995; Agabio *et al.*, 1996). These four lines have been investigated thoroughly and are reviewed elsewhere (Nestler, 2000; Vanyukov and Tarter, 2000; Crabbe, 2002).

History of selective breeding for high saccharin and low saccharin rats

The Occidental (Occidental College) HiS and LoS lines originated with the incidental discovery of a male rat (Holtzman Sprague–Dawley, Indianapolis, Indiana, USA) that did not voluntarily consume a saccharin (0.1% w/v) solution (Dess and Minor, 1996). Most rats from genetically heterogeneous populations voluntarily consume large quantities of this solution when given the opportunity; thus, identifying a rat with little or no voluntary saccharin intake was uncommon. Dess and colleagues used this male and another male that was an avid saccharin drinker as the LoS and HiS founding males, respectively. Each founder was then mated with several female rats that displayed average saccharin intake to initiate the HiS and LoS lines. Subsequently, the phenotypic trait used for the HiS versus LoS selection was the saccharin phenotype score. To derive a saccharin phenotype score a two-bottle preference test was conducted over 48 h. During the first 24-h period, one water bottle is given, and the consumption over that 24-h period is used as the total 24-h water intake measure. During the second 24-h period, two bottles are offered, one containing a saccharin (0.1% w/v) solution and the other water (Dess and Minor, 1996), and the saccharin intake is used in the following equation used to calculate the saccharin phenotype score:

$$\text{Saccharin phenotype score} = \frac{\text{24-h saccharin intake (ml)} - \text{24-h water intake (ml)}}{\text{body weight (g)} \times 100}$$

Dividing by body weight ($\times 100$) controls for differences due to sex, age, or other factors. Positive and negative scores indicate saccharin intake, respectively, above and below normal daily water intake levels; a score of 0 indicates saccharin intake equal to normal daily water intake levels. Saccharin phenotype scores tend to range from about 12 to 50 for groups of HiS rats and 0 to 20 in LoS male and female rats (Dess and Minor, 1996; Carroll *et al.*, 2002, 2007a, b; Dess *et al.*, 2005, unpublished; Perry *et al.*, 2007a, b; Anker *et al.*, unpublished). Table 1 summarizes saccharin phenotype scores from studies conducted with groups of the HiS and LoS rats over the last 12 years. The line difference emerged by generation 3 (Dess and Minor, 1996); it stabilized quickly, and it has remained stable for the last 10 years in both the Occidental College laboratory (Dess *et al.*, unpublished) and the University of Minnesota laboratory.

Saccharin phenotype scores are shown separately for groups of males and females in Table 1 for groups of HiS and LoS males and females by generation for a number of studies conducted in both laboratories. Over 30 generations, LoS adult males typically have the lowest scores ranging from 0.3 to 20.2, LoS adult females are next ranging from 1.2 to 21.2, HiS males rank next highest ranging from 11.3 to 35.2, and HiS females are highest with scores ranging from 20 to 52.7. The last two lines of Table 1 show means of the group scores calculated separately from the rows above for Occidental rats (Dess) and the University of Minnesota rats (Carroll). Although group size was not accounted for, the means are quite similar across institutions. The rank ordering of the scores is the same for both labs, but three of the four group means are lower for the Carroll lab than

Table 1 Mean saccharin phenotype scores in groups of HiS and LoS adult rats

Females		Males			
HiS	LoS	HiS	LoS	Generation	Reference
38.1	10.1	16.3	4.1	3	Dess and Minor (1996)
34.0	2.4	–	–	19–20	Dess *et al.* (2000)
51.0	2.2	35.2	5.7	18	Dess *et al.* (2000)
38.6	1.2	–	–	19–20	Dess *et al.* (2000)
27.8	10.7	11.3	0.3	17–20	Carroll *et al.* (2002)
49.5	7.8	–	–	25–26	Dess *et al.* (2005) (Exp. 1)
52.7	9.4	32.9	4.8	27, 29	Dess *et al.* (2005) (Exp. 2)
35.9	14.2	–	–	20–23	Perry *et al.* (2006a)
32.9	17.6	17.9	5.7	20–23	Perry *et al.* (2006) Unpublished
43.5	1.8	29.7	11.2	20–23	Carroll *et al.* (2007a)
35.0	3.7	–	–	20–23	Carroll *et al.*, (2007b)
–	–	16.6	5.0	20–23	Perry *et al.* (2007a) (adults)
		23.8[a]	20.2[a]		Perry *et al.* (2007a) (adolescents)
50.5	21.2	20.4	10.9	21–23	Perry *et al.* (2007b) (food)
23.5	9.6	12.8	4.0	21–23	Perry *et al.* (2007b) (cocaine)
31.0	18.5	12.8	11.6	22–23	Anker *et al.* (in press)
20.0	7.9	12.5	4.9	22–23	Anker *et al.* (in press)
45.2	1.4	25.8	1.3	20	Dess (2008) Personal Communication
46.7	3.9	30.0	0.4	30	
44.1	5.1	31.5	6.1	10–30	Mean of groups from Dess Lab[b]
35.1	10.1	18.8	4.7	17	Mean of groups from Carroll Lab[b]

Anker, Carroll, and Perry studies (excluding 2002) used rats bred at the University of Minnesota.
–, not tested; HiS, high saccharin; LoS, low saccharin.
[a]Tested with 0.25% saccharin (all others 0.1% vol/vol).
[b]Means across studies, males and females.

the Dess lab. This may be due to the use of older (90–120 days) rats in the Carroll lab (because the i.v. catheter is easier to implant and maintain in larger rats) than those used by Dess and coworkers, who tend to use 60–80-day-old rats. In fact, a comparison of adult and adolescent males (Perry *et al.*, 2007a) in Table 1 shows elevated saccharin phenotype scores in adolescents versus adults. The influence of age on saccharin phenotype score is discussed in more detail in a later section. With the exception of these two adolescent groups, all the studies in Table 1 have been conducted with adult rats. The difference could also be due to the cocaine exposure before saccharin testing in the Carroll lab rats, versus the Dess lab rats that involve food reward or tastants as saccharin testing typically follows other experimental manipulations. There is evidence from Perry *et al.* (2007b) and Anker *et al.* (unpublished) that food-exposed rats consistently have higher saccharin phenotype scores than cocaine-exposed rats, and this is consistent with the Dess (food) versus Carroll (cocaine) lab differences.

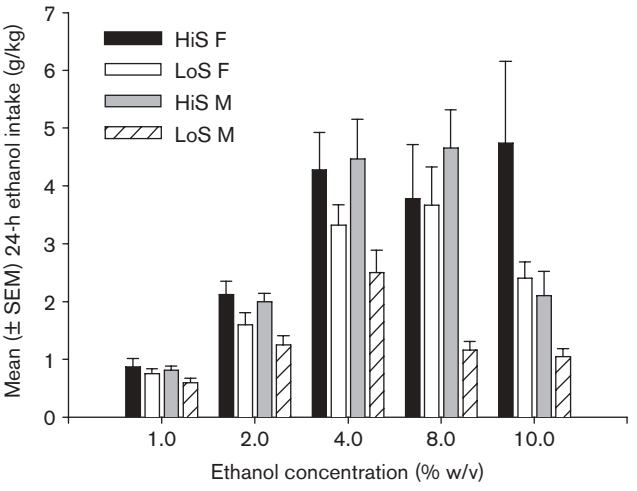
For the purpose of this review, outbred lines are defined as populations comprised of animals that have been mated to animals with a genetic relationship no closer than their second cousin; that is, no sibling, half-sibling, or first cousin matings (Phillips *et al.*, 1989). The HiS and LoS colony established at the University of Minnesota was from generations 17 to 18 of the Occidental HiS and LoS rats, and other rats from those generations had been used in the second study outlined in Table 1 (Carroll *et al.*, 2002). The HiS and LoS rats have since been propagated at the University of Minnesota according to established breeding techniques (Phillips *et al.*, 1989) and selection criteria (Dess and Minor, 1996). The outbred status of the HiS and LoS lines has been maintained through occasional (every four to six generations) mating with rats derived from the same stock as the original founders (Harlan Sprague–Dawley, formerly Holtzman).

As accumulating evidence concurs that there is increased sweet preference in animals selectively bred or selected for high (vs. low) alcohol intake (George, 1991; Li *et al.*, 1993; McBride and Li, 1998), HiS and LoS rats represent an ideal model to determine whether reciprocal genetic factors (i.e. pleiotropic effects) influence sweet and alcohol consumption. Accordingly, Dess *et al.* (1998) measured both voluntary and forced alcohol consumption in male and female HiS and LoS rats from generations 11 to 12. A two-bottle choice test was used to assess the voluntary consumption of five concentrations of alcohol (1, 2, 4, 8, and 10% w/v) in the presence of a second bottle containing water. After the voluntary drinking component, a 21-day forced-exposure period was conducted, in which all animals were allowed to consume only alcohol (10% w/v) during 24-h periods. Dess *et al.* (1998) identified robust differences between HiS and LoS rats during both the free-choice and forced-consumption tests. HiS rats consumed significantly more alcohol than the LoS rats in both conditions, though the difference in forced consumption was more marked for males. Figure 1 shows 24-h alcohol consumption across all concentrations tested. At most concentrations HiS rats exceeded LoS rats within the male and female groups, and females consumed more than males at the two highest concentrations. Furthermore, the average alcohol consumption in the HiS rats approached 4 g/kg, an amount close to a typical selection cutoff to be considered as a high alcohol consuming animal. These initial findings support the hypothesis that common genetic influences underlie saccharin and alcohol intake.

Intravenous drug self-administration in high saccharin and low saccharin rats

The following studies were undertaken to extend the findings from the Dess *et al.* (1998) alcohol study to (i) a different route of drug administration (i.v.), (ii) drugs of abuse from different pharmacological classes, and (iii) several phases of drug abuse. Several other considerations exist in beginning this line of research with i.v. drug self-administration. First, an i.v. self-administration paradigm was used because it diminishes taste factors that may complicate the interpretation of data from oral alcohol consumption studies. According to this paradigm, drug administration is contingent upon one or more lever presses on an 'active' lever or another operant response (e.g. nosepoke) performed by the animal. Drug is considered to have rewarding effects if the occurrence of the lever-press behavior subsequently increases. Greater responding on the active versus the inactive

Fig. 1



Mean 24-h ethanol intake (g/kg) as a function of ethanol concentration for female and male HiS and LoS rats. Across all concentrations tested, HiS rats consumed significantly more alcohol than their LoS counterparts ($P<0.05$). Adapted with permission from Dess *et al.* (1998). HiS, high saccharin; LoS, low saccharin.

lever (responses produce no drug deliveries) suggests that the contingency between the active lever and drug delivery has been established, and drug self-administration is not interfering with operant performance through increased or decreased arousal or activity. Second, the acquisition of both i.v. cocaine and heroin self-administration were examined in HiS and LoS rats to determine whether saccharin phenotype differences extended across other drug classes. Third, potential differences between the HiS and LoS lines were examined as a function of the phase of drug abuse. Several phases of drug abuse have been modeled in animals, and are discussed in this review, including: acquisition, maintenance, escalation, dysregulation, extinction (abstinence), and reinstatement (relapse) of extinguished responding. These preclinical models and phases of drug abuse have been reviewed in detail elsewhere (Carroll and Campbell, 2000; Carroll and Perry, 2008). The following sections describe the performance of HiS and LoS rats under a variety of behavioral tests representing key phases of drug abuse. Table 2 summarizes the phenotype effects (HiS vs. LoS) for males and females by phase, behavioral task, and self-administered drug.

Drug-seeking behavior over several phases of drug abuse in high saccharin and low saccharin rats

The HiS and LoS rats have been studied over several phases of drug abuse that occur in humans to determine whether drug-seeking and drug-taking behavior is more sensitive to these phenotype differences during particular phases of drug abuse. The following phases are discussed: acquisition, maintenance, escalation/dysregulation, extinction, withdrawal, and reinstatement.

Acquisition of intravenous cocaine and heroin self-administration in high saccharin and low saccharin rats

The acquisition of i.v. cocaine (0.2 mg/kg) and heroin (0.015 mg/kg) self-administration was first examined using an automated procedure (autoshaping) to quantify objectively the initiation of drug taking in both male and female HiS and LoS rats from generations 17 to 20 (Carroll *et al.*, 2002). The autoshaping procedure is a sensitive method to explore the effects of individual differences during the acquisition phase, including subtle environmental and genetic variables (Campbell and Carroll, 2000; Carroll *et al.*, 2004). According to this procedure, there are two daily components, (i) autoshaping (6 h/day) and (ii) self-administration (6 h/day). During autoshaping, a predetermined number of drug infusions (10/h) is automatically delivered to the animal at random intervals. Before each infusion, the retractable lever is extended into the cage for 15 s, and during this time the animal can receive a cocaine (0.2 mg/kg) infusion immediately, if it makes one lever press, or it can receive the infusion automatically at the end of the 15 s period, whichever occurs first. During self-administration, the retractable lever remains extended, and each response is reinforced by an infusion of drug according to a fixed-ratio 1 (FR 1) schedule of reinforcement. All

Table 2 Summary of results from studies on selectively bred HiS and LoS rats and drug-related behavior

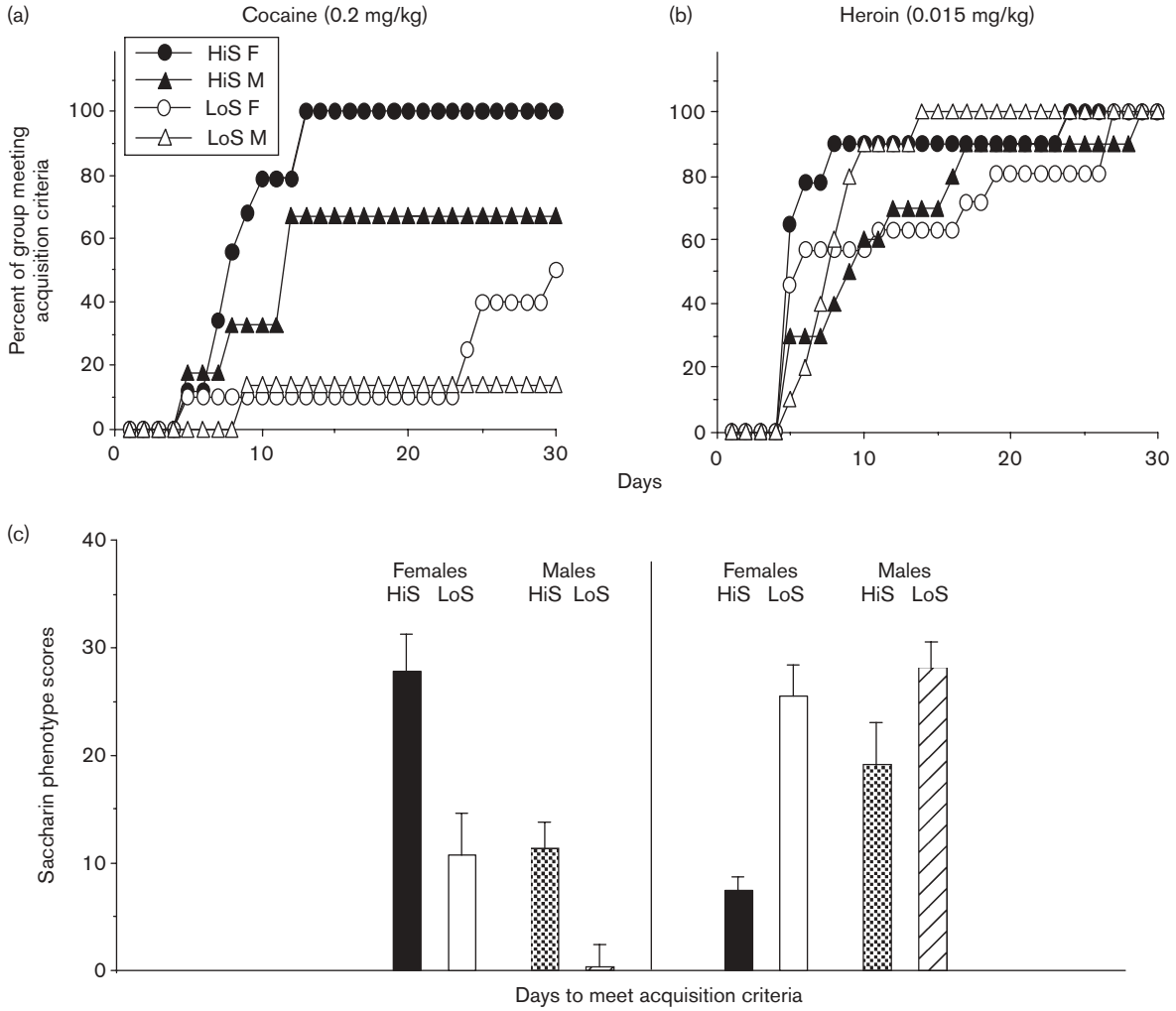
Behavioral model	Drug	Phenotype effects	Sex differences	Reference
Acquisition	Cocaine	HiS>LoS	M only	Carroll *et al.* (2002)
	Heroin	HiS>LoS	M only	Carroll *et al.* (2002)
	Ethanol	HiS>LoS	Intake (g) F<M	Dess *et al.* (1998)
Maintenance	Cocaine	HiS=LoS	F=M	Carroll *et al.* (2007a,b)
		HiS>LoS	F only	Perry *et al.* (2006a,b)
	Heroin	HiS>LoS	F>M	Carroll *et al.* (2002)
	Ethanol	HiS>LoS	Intake (g) F<M	Dess *et al.* (1998)
			Intake (mg/kg) F>M	Dess *et al.* (2005)
Escalation	Cocaine	HiS>LoS	F only	Perry *et al.* (2006a)
Pre-FR 1		HiS>LoS (ShA)	F only	Perry *et al.* (2006a)
Post-FR 1		HiS>LoS(LgA)	F only	Perry *et al.* (2006a)
Dysregulation of dose	Cocaine	HiS>LoS	F only	Carroll *et al.* (2007b)
Delay discounting (impulsive choice)	Food	(Impulsivity) HiS>LoS	(Impulsivity) F>M	Perry *et al.* (2007b)
		(Intake) HiS>LoS	(Intake) F<M	
	Cocaine	(Impulsivity) HiS=LoS (Intake) HiS>LoS	(Impulsivity) F>M (Intake) F>M	Perry *et al.* (2007b)
Go/No-go (Impaired inhibition)	Cocaine	HiS>LoS (go, no go)	F>M (go, no go)	Anker *et al.* (in press)
	Food	HiS=LoS (go, no go)	F=M (go, no go)	
Extinction	Cocaine	HiS>LoS	F only	Perry *et al.* (2006a)
Reinstatement	Cocaine	HiS>LoS (15 mg/kg)	F only	Perry *et al.* (2006a)
Withdrawal	Ethanol	HiS<LoS	F only	Dess *et al.* (2005)
Locomotor activity	–	HiS=LoS	F=M	Perry *et al.* (2007b)
		HiS < LoS	F only (HiS)	Carroll *et al.* (2007a)
Cocaine-induced locomotor activity	Cocaine	HiS>LoS	F>M (HiS)	Carroll *et al.* (2007b)
Cocaine-induced locomotor sensitization	Cocaine	HiS>LoS (F)	F>M	Carroll *et al.* (2007b)

F, female; HiS, high saccharin; LgA, long access (6 h); LoS, low saccharin; M, male; ShA, short access (2 h).

animals were given 30 days to meet an acquisition criterion of 100 infusions per day for five consecutive self-administration components. The use of an autoshaping model to capture the drug acquisition phase has face validity because a human's first exposure to a drug may come with little or no response cost; however, subsequent drug access may entail increased behavioral cost (e.g. money, dealing) (Campbell and Carroll, 2000).

Results from this study identified clear differences between HiS and LoS rats in the acquisition of cocaine self-administration (Fig. 2a). HiS rats of both sexes initiated cocaine self-administration more rapidly than their respective LoS counterparts, and a greater percentage of HiS rats met the criterion for cocaine acquisition compared to LoS rats. In contrast to these results, no overall differences were found between HiS and LoS rats with respect to the percent of groups that acquired heroin self-administration at the end of 30 days. While there were no significant phenotype differences, female HiS and LoS rats acquired heroin self-administration more rapidly than their male counterparts up to day 5, but they had reached the same levels by the other days that were compared (10, 15, 20). The dose of heroin (0.015 mg/kg) used, however, may have been too high to detect robust individual differences, as all rats quickly met the acquisition criterion (Fig. 2b). Dose-ranging pilot work in these animals indicated that a lower heroin dose (0.0075 mg/kg) did not result in self-administration in the autoshaping paradigm. These findings indicate that HiS rats were more vulnerable than LoS rats to initiate cocaine-taking but not heroin-taking behavior, and female

Fig. 2



Acquisition (percent of group meeting acquisition criteria for i.v. cocaine (a) and heroin, (b) self-administration, for HiS and LoS male and female rats), the data are plotted for the 30 days allowed for acquisition. (c) Saccharin preference scores and days to meet acquisition criteria for cocaine self-administration for the HiS, LoS, male and female groups. Reprinted with permission from Carroll *et al.* (2002). HiS, high saccharin; LoS, low saccharin.

rats were more vulnerable than males to acquire cocaine and heroin self-administration, regardless of saccharin phenotype. Figure 2c compares the saccharin phenotype scores taken at the end of the experiment and the number of days to meet the acquisition criteria in the HiS, LoS, female, and male groups self-administering cocaine. An inverse relationship was found between saccharin score and days to acquire indicating that saccharin consumption is a predictor of rate of acquisition of cocaine self-administration.

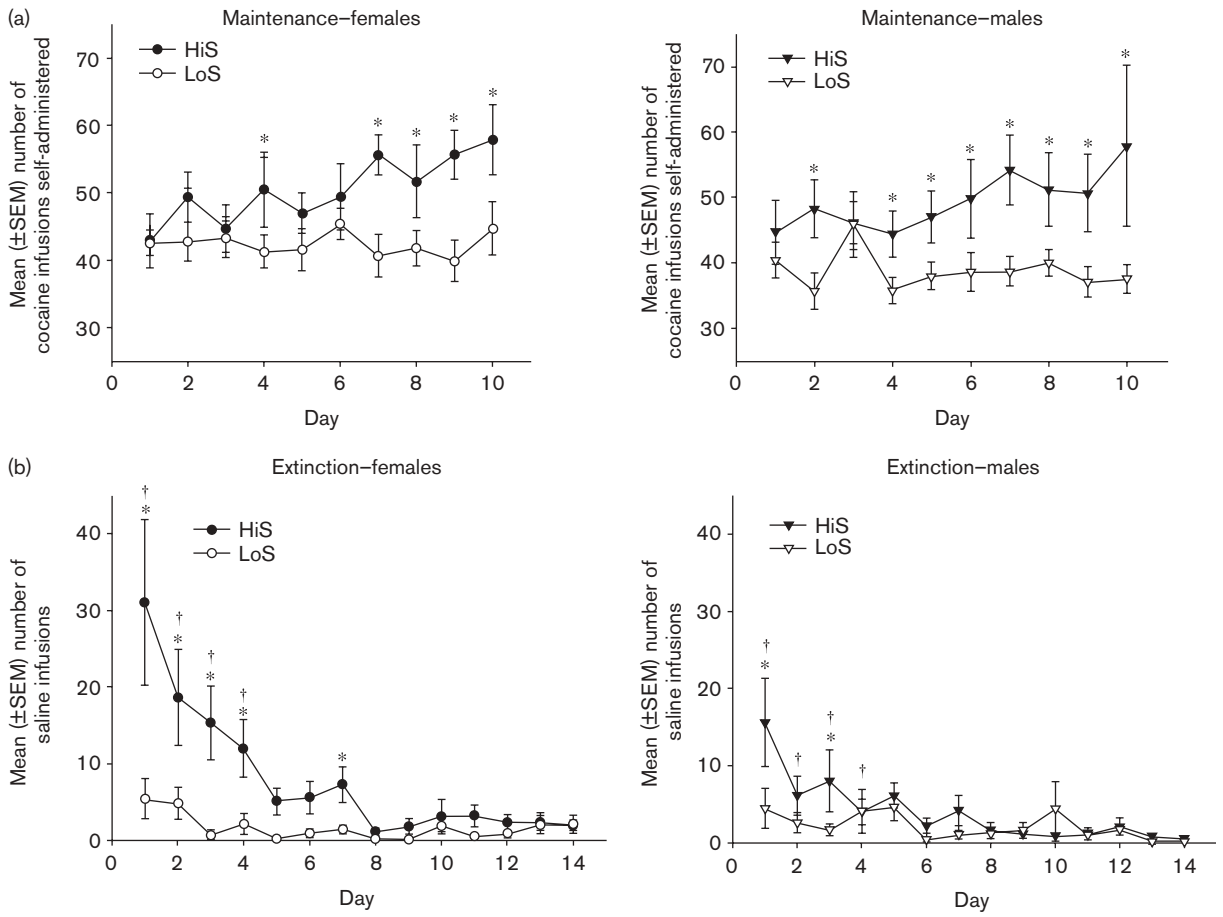
Maintenance of intravenous cocaine self-administration in high saccharin and low saccharin rats

Typically, increases in drug self-administration level off after acquisition with cocaine and other stimulants; however, with opioids, long-term increases may occur due to tolerance (Carroll and Campbell, 2000). The maintenance phase is typically defined as a time when drug self-administration has stabilized at relatively constant daily levels, and it is usually studied during short access (ShA) (e.g. 1-h, 2-h) sessions often under FR or progressive ratio (PR) schedules.

Fixed-ratio schedules

Figure 3a shows that in a study in which rats were trained to acquire cocaine (0.4 mg/kg) self-administration under an FR 1 schedule, HiS female (left panel) and male (right panel) rats earned significantly more infusions than LoS females and males, respectively, on many days during a 10-day short-access (2-h) maintenance period (Perry *et al.*, 2006a). Similarly, in another experiment in the same study, HiS (vs. LoS) rats self-administered more cocaine during 2-h sessions (FR 1), before an escalation period (Perry *et al.*, 2006a). A postescalation retest of infusions during the 2-h sessions (FR 1) in these rats revealed no differences between HiS and LoS groups (Perry *et al.*, 2006a). A ceiling effect could have obscured phenotype differences after escalation, as both groups may have reached maximum amounts of cocaine intake under FR 1 schedule.

Fig. 3



Maintenance and extinction of cocaine self-administration during consecutive daily 2-h sessions. (a) Mean cocaine infusions self-administered by HiS and LoS female and male rats over a 10-day maintenance period. (b) Mean infusions over a 14-day extinction phase that followed the maintenance phase. *HiS>LoS, †females>males ($P<0.05$). HiS, high saccharin; LoS, low saccharin.

Progressive ratio schedules

Owing to the large phenotype differences identified in the cocaine acquisition study (Carroll *et al.*, 2002), a PR schedule was subsequently used in HiS and LoS rats to assess their motivation to self-administer drug under increasing response requirements. A PR schedule systematically increases the response requirement that a subject is required to complete (according to an exponential function, e.g. Roberts *et al.*, 1989) to receive each sequential reinforcer. Eventually, if the response requirement becomes so great that the animal ceases responding, the last ratio requirement achieved is designated the break point, and it is considered a reflection of the reinforcing effectiveness of the drug (Richardson and Roberts, 1996; Stafford *et al.*, 1998).

In the first study with cocaine and heroin (Carroll *et al.*, 2002), it was hypothesized that HiS rats would reach greater break points for cocaine than LoS rats; however, no differences were found between the HiS and LoS cocaine groups, suggesting their motivation to respond for cocaine did not differ at the dose examined. However, there were marked differences between heroin groups (HiS > LoS). These data suggest that complex, multidimensional changes, may occur when rats are bred for HiS and LoS intake. For example, HiS and LoS rats differed in their acquisition of cocaine self-administration behavior (HiS > LoS), but they were equally motivated to respond for cocaine under a maintenance phase. These differences in behavior during the acquisition and maintenance phases may be due to the influence of factors other than reward, such as novelty reactivity, emotionality, stress, or impulsivity, which will be discussed later, but they highlight the importance of studying different drugs and several phases of drug abuse.

Escalation of intravenous cocaine self-administration in high saccharin and low saccharin rats

Escalation is a transition phase in drug self-administration that occurs when regular, steady rates of drug use during maintenance accelerate to binge-like, dysregulated, out-of-control use when access is extended (e.g. 5–12 h). This switch from controlled to escalated use is considered a hallmark of drug addiction (Ahmed and Koob, 1998, 1999; Koob and LeMoal, 2005). The escalation phase can be studied in laboratory animals using a model developed by Ahmed and Koob (1998). Under this procedure, one group of animals are allowed to self-administer drug for a long (5–12 h) duration, whereas a control group has drug access during shorter daily sessions (e.g. 1 or 2 h) for the same number of days. The short access (ShA) group typically maintains stable intake or increases only slightly over several weeks; however, the long access (LgA) group shows a marked pattern of escalation of intake over the same amount of time. Usually there is a significant linear trend in the data, such that drug intake during the last few days is often significantly higher than during the first few days in the LgA group.

Escalation has also been shown to be greater in females (vs. males) (Roth and Carroll, 2004), when estrogen levels are high and progesterone levels are low (Larson *et al.*, 2007), and in high impulsive (HiI) versus low impulsive (LoI) rats (Anker *et al.*, unpublished). Escalation has been shown for the self-administration of several drugs such as cocaine (Ahmed and Koob, 1999; Paterson and Markou, 2003; Roth and Carroll, 2004), methamphetamine (Kitamura *et al.*, 2006), and heroin (Lenoir and Ahmed, 2007) delivered i.v. in rats, and phencyclidine (PCP) (Carroll *et al.*, 2005) delivered orally in rhesus monkeys. Escalation does not occur for nicotine self-administration (Paterson and Markou, 2004). Another aspect of the escalation studies is to compare drug intake during a ShA period that occurred before LgA to ShA intake that occurs after the escalation period, using the same reinforcement schedules to determine whether escalation produced an enduring increase in ShA drug self-administration.

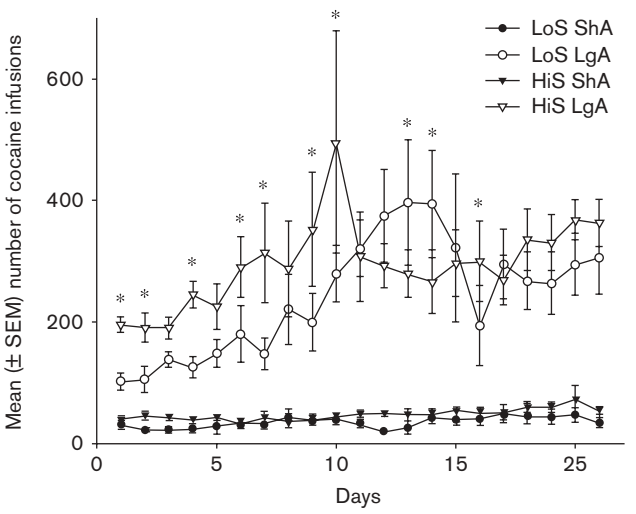
The escalation paradigm was used to compare female HiS and LoS rats, given either ShA or LgA to i.v. cocaine infusions for 21 days (Perry *et al.*, 2006a). An abbreviated acquisition procedure was used, and during the 21 days, the ShA (2-h) groups' intake remained stable, and there were no HiS–LoS differences (Fig. 4). However, during LgA (6 h), the HiS group escalated its cocaine (0.4 mg/kg) intake more rapidly than the LoS group (Fig. 4, Table 2). When comparing cocaine intake in HiS and LoS rats under the preescalation and postescalation conditions, HiS rats exceeded LoS in the ShA groups preescalation, and postescalation in the LgA groups (Table 2). Thus, HiS rats (vs. LoS) showed elevated cocaine intake before, during, and after escalation of cocaine self-administration.

Regulation/dysregulation of intravenous cocaine self-administration in high saccharin and low saccharin rats

Another method of modeling escalation of drug intake as a marker of the shift from drug use to abuse concerns a procedure in which an animal is allowed to select the dose of each infusion over LgA sessions (e.g. 5 h) (Lynch *et al.*, 1998, 2000; Lynch and Carroll, 1999). The animal is trained to respond on two levers that each lead to a cocaine infusion. The infusion time (dose) increases after responses on one lever and decreases after responses on the other lever, yielding nine discrete doses (0–1.6 mg/kg) advancing in 0.2 mg/kg steps. When responding on the increasing or decreasing dose lever reached a maximum (1.6 mg/kg) or minimum (0), respectively, that dose is delivered until a response on the other lever changes the dose. Using this method, Lynch *et al.* (2000) found that, at the four lowest possible cocaine doses

(0, 0.2, 0.4, 0.6 mg/kg) and the highest dose (1.6 mg/kg), HiS rats obtained significantly more infusions than LoS rats, suggesting that cocaine was more rewarding for HiS than LoS rats. An alternative hypothesis might be that higher levels of cocaine intake resulted in more hyperactive or stereotyped behavior, expressed as response perseveration at the dose-decreasing lever, as HiS rats responded nearly twice as much as LoS rats when they reached the 0 dose. Regulation of the self-administered dose was defined as a high correlation between the previous dose self-administered and the subsequent delay before responding for the next infusion (postinfusion interval). When HiS and LoS female rats were compared using this dose self-selection task, HiS rats were less precise (lower correlation) in their regulation than LoS rats. HiS rats had shorter interinfusion intervals (consumed cocaine faster) and lower correlations between dose size and interinfusion interval than LoS rats, resulting in higher cocaine intake overall for the HiS rats (Fig. 5b) (Carroll *et al.*, 2007b).

Fig. 4



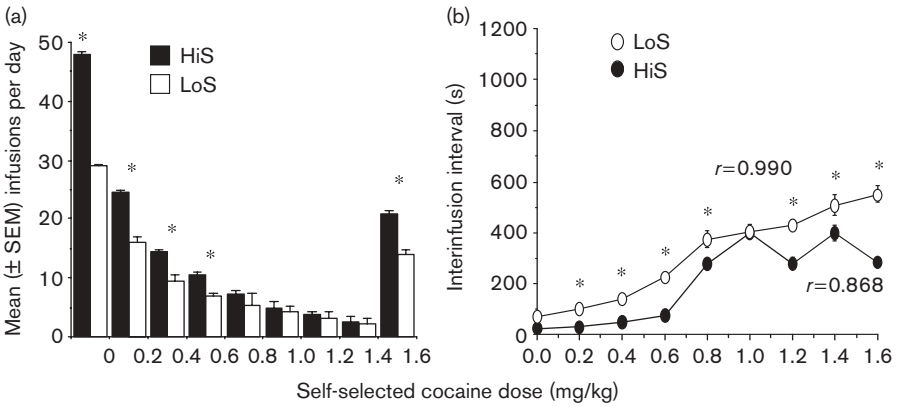
Escalation of cocaine self-administration. Mean cocaine infusions over a 21-day period when HiS and LoS female and male rats had short (ShA) access (2-h) or long (6-h) access (LgA) to cocaine (0.4 mg/kg) infusions. Reprinted with permission from Perry *et al.* (2006a). *HiS LgA>LoS LgA ($P<0.05$). HiS, high saccharin; LoS, low saccharin.

Extinction (abstinence) and reinstatement (relapse) of drug-seeking behavior

Despite efforts to reduce or stop drug abuse, maintaining abstinence remains a major challenge to sustained recovery. Animal studies indicate that the perseverance of drug use that leads to failure in achieving abstinence may be influenced by genetic and environmental factors. For example, rats that have a predisposition to initiate drug abuse and maintain high levels of drug-reinforced behavior, such as females (vs. males) (Lynch and Carroll, 2000) or high impulsivity (HiI) versus low impulsivity (LoI) (Carroll *et al.*, unpublished; Perry *et al.*, 2008a), and high wheel-running versus low-wheel-running (Larson and Carroll, 2005), show elevated levels of drug-seeking in animal models of relapse. The laboratory reinstatement paradigm is modeled after the human condition whereby when drug use ends, there is a period of drug nonavailability. However, when environmental and/or drug cues that were previously associated with drug taking are introduced, they trigger drug-seeking behavior.

In the rat studies, a method modified from that developed by De Vries *et al.* (1998) is used to model relapse in humans. Rats are first trained to self-administer the drug i.v., and after a maintenance phase of 10–14

Fig. 5



Cocaine dose regulation. (a) Mean number of infusions in HiS and LoS rats as a function of self-selected cocaine doses. *HiS>LoS ($P<0.05$). (b) Mean interinfusion interval(s) after self-selection of a range of nine cocaine doses. r=correlation between dose selected and subsequent interinfusion interval ($P<0.05$). *LoS>HiS ($P<0.05$). Reprinted with permission from Carroll *et al.* (2007b). HiS, high saccharin; LoS, low saccharin.

days, the drug is replaced by saline, and behavior subsides and reaches low levels. Subsequently, there is a cue-primed or drug-primed reinstatement phase when drug-paired cues, or an experimenter-administered drug or saline-priming injection is given, and responding on the operant device (e.g. lever) that was previously associated with drug is monitored. When this procedure was used to compare HiS and LoS rats that had been trained to self-administer cocaine (0.4 mg/kg), there were no HiS–LoS group differences in the rate of acquisition of cocaine self-administration or the mean number of infusions self-administered during the 2-h acquisition sessions (Perry *et al.*, 2006a). However, during the 10-day maintenance phase, HiS rats had significantly more infusions than LoS rats on 5 (females) or 8 (males) of the 10 days during the maintenance period (Fig. 3a, Table 2).

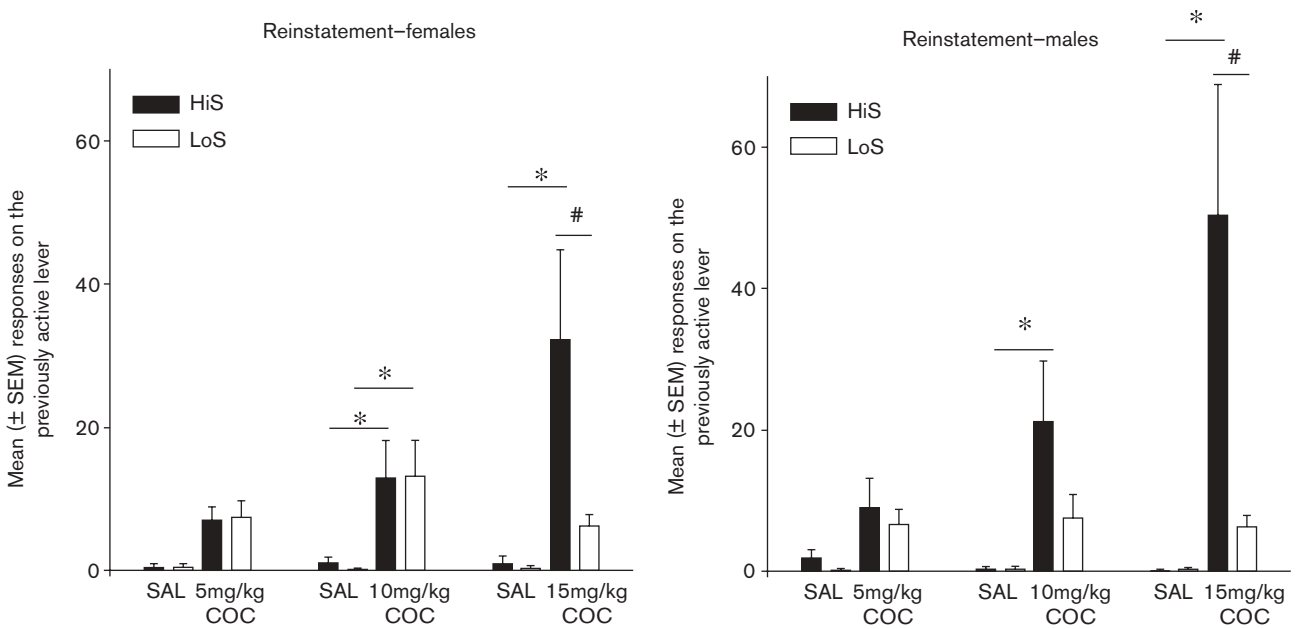
Figure 3b shows that during the 14-day extinction period, HiS female rats' infusions (left panel) started at approximately 30 saline infusions and declined to near 0 by day 8. In contrast, the LoS group started at about five infusions and decreased to 0 by day 3. The HiS female group's infusions were significantly greater than LoS group's over 5 of the first 7 days of extinction. HiS males (right panel) started extinction at about 16 saline infusions; whereas, the LoS males started at five saline infusions. HiS males had more responses than LoS males on 2 of the first 3 days of extinction. The HiS females were more resistant to extinction than HiS males; however, the LoS females and males showed similar rates of extinction, and all groups did not differ on the 1st 6 days of extinction.

After the extinction period, saline and cocaine-priming injections (alternated) were administered before the session for 6 days. Figure 6 shows that the HiS groups were also significantly higher than LoS groups in responding during reinstatement following a 15 mg/kg intraperitoneal-priming injection of cocaine; however, there were no saccharin phenotype differences after lower priming doses (5 or 10 mg/kg) of cocaine or saline. No sex differences were observed in reinstatement in this study, possibly due to ceiling effects in HiS rats and floor effects in LoS rats. However, previous studies have indicated greater reinstatement responding in female than male rats (Lynch and Carroll, 2000; Perry *et al.*, 2008a).

Reinstatement (relapse) of food-seeking behavior

In support of the notion that drug abuse and palatable food seeking are similar addictive behaviors (Lenoir *et al.*, 2007; Avena *et al.*, 2008a, b), the drug reinstatement model (used for drugs) has also been applied to food, to provide an animal model of relapse to palatable food-seeking (Shalev *et al.*, 2006; Ghitza *et al.*, 2007) and sucrose-seeking (Grimm *et al.*, 2007) behavior. Using a procedure similar to that described above, Ghitza *et al.* (2007) found that noncontingent pellet delivery reinstated pellet-seeking behavior, whereas Shalev *et al.* (2006) reported that an injection of yohimbine, a

Fig. 6



Reinstatement of cocaine-seeking behavior in female and male HiS and LoS rats after saline or cocaine (5, 10, 15 mg/kg intraperitonealy) priming injections. *saline vs. cocaine, #HiS vs. LoS ($P<0.05$). Reprinted with permission from Perry *et al.* (2006a). HiS, high saccharin; LoS, low saccharin.

pharmacological stressor, reinstated food-seeking in food-restricted rats previously trained to respond for food reward. These findings are similar to earlier data showing an enhancement of drug-seeking behavior following a stressful event (Erb *et al.*, 1996; Brown and Erb, 2007). These results provide further parallels between the food-motivated and drug-motivated behaviors.

The results from the extinction/reinstatement phases, as well as all of the other phases described above, indicate that HiS and LoS rats have distinct drug-seeking and drug-taking profiles and suggests that a proclivity for sweets is robustly associated with excessive drug-seeking and drug-taking behavior. This has important implications for drug addiction prevention and treatment efforts in humans as well as for understanding interactions between drug and food (obesity, binge eating disorder) addictions.

Drug withdrawal effects in high saccharin and low saccharin rats

Although genetic factors, individual differences (e.g. age, sex, sweet preference), and environmental factors account for drug abuse vulnerability during several phases of drug abuse, drug withdrawal effects have seldom been modeled in the laboratory with groups differing in their susceptibility to drug abuse. This is an important aspect of drug addiction that needs further attention because factors related to the initiation of a withdrawal period are key to successful treatment, and the relationship between withdrawal severity and subsequent relapse may be predictive of sustained abstinence or resumption of the addictive behavior.

Initial work has been done with HiS and LoS rats and their responsivity to ethanol withdrawal (Dess *et al.*, 2005). Female rats were given only ethanol (11% vol/vol) to drink for 14 days (vs. water in control groups). All rats were subsequently examined using an acoustic startle test followed by an ethanol reinstatement test. The startle test is considered a measure of negative emotionality that would be expected during a withdrawal state. LoS ethanol-withdrawn rats had greater acoustic startle amplitude and greater prepulse inhibition of startle than LoS water-only rats; whereas, HiS ethanol-withdrawn and water-only rats did not differ. These results indicate a greater withdrawal effect in the LoS (vs. HiS) group. During ethanol reinstatement, LoS rats also showed a lower preference for ethanol than HiS rats. Thus, several measures indicated than LoS rats displayed a negative aversive state consistent with withdrawal effects, despite having consumed amounts similar to the HiS rats during the initial 14 days of forced exposure.

As reported in human subjects (Grillon *et al.*, 1997), the results from the HiS and LoS rats showed an inverse relationship between voluntary drug consumption and withdrawal severity effects. Voluntary ethanol consumption is lower in LoS rats (Dess *et al.*, 1998, 2005), and they show more severe withdrawal as measured by acoustic startle than HiS rats (Dess *et al.*, 2000, 2005). These results are in agreement with those of Metten *et al.* (1998) and Chester *et al.* (2002, 2003) who found that low-alcohol preferring genotypes had higher withdrawal severity scores than high alcohol preferring genotypes. Rats selectively bred for low alcohol-drinking also showed increased intracranial self-stimulation thresholds during ethanol withdrawal (indicating greater withdrawal-induced dysphoria) compared with those bred for high levels of ethanol drinking (Chester *et al.*, 2006).

These results are also consistent with recent findings from rhesus monkeys. Generally, females self-administer more PCP than males when body weight is taken into account (Carroll *et al.*, 2005); however, males showed more severe and a longer duration of withdrawal effects (a disruption of a food-reinforced operant task) than females (Perry *et al.*, 2006b). This sex difference was consistent with the results of a study of morphine withdrawal in rats in which males showed greater physical withdrawal signs than females (Cicero *et al.*, 2002). Male rats also showed more withdrawal from ethanol, measured by seizure susceptibility and recovery time (Devaud and Chadda, 2001) and greater anxiety in social situations (Varlinskaya and Spear, 2004) and in the elevated plus maze (Gatch and Lal, 2001). In contrast, in other studies comparing sex, females showed more physical signs of withdrawal (e.g. convulsions, weight loss) than males when access to pentobarbital (Suzuki *et al.*, 1985) or methaqualone (Suzuki *et al.*, 1985) was discontinued, but others have found no sex differences in operant responding during PCP withdrawal (Wessinger and Owens, 1991; Wessinger, 1995). This pattern is also apparent in adolescents. That is, compared with adults, adolescents self-administered more nicotine (Levine *et al.*, 2003a), alcohol (Brunell and Spear, 2005; Doremus *et al.*, 2005), cocaine (Perry *et al.*, 2006b), and amphetamine (Shahbazi *et al.*, 2008), and they showed reduced withdrawal severity (Doremus *et al.*, 2003; O'Dell *et al.*, 2004; Brunell and Spear, 2005). Overall, most of the studies to date support an inverse relationship between amount of the drug self-administered and withdrawal severity. Thus, HiS and LoS rats offer a reliable model of addiction-prone and addiction-resistant behavior during the withdrawal phase.

Other characteristics of high saccharin and low saccharin rats that may offer alternative explanations for line-related differences in drug-related behaviors

Drug abuse and consumption of sweet substances could be mediated by a third factor, or behavioral trait, that has the same effect on drug abuse and sweet consumption.

Examples of such behaviors might be sensitivity or reactivity to novel events, locomotor activity, drug-induced locomotor activity and sensitization, impulsivity, stress, emotionality, and taste reactivity. In additon, there are endogenous variables such as sex and age that are related to drug abuse and other behavioral traits. This section will focus on some of these behavioral traits (other than saccharin intake) that vary in HiS and LoS rats and have an influence on drug abuse vulnerability.

Novelty reactivity

The proclivity for drug abuse and its relation to sweet preference may be an example of a more general construct by which increased reactivity to any novel rewarding substance, behavior, or event predicts drug abuse (i.e. a novelty-seeking or risk-taking trait). For example, excessive wheel running in rats predicts higher levels of i.v. cocaine self-administration and reinstatement of cocaine-seeking behavior after drug access has terminated (Larson and Carroll, 2005). Others, however, have found that although saccharin intake was positively related to subsequent alcohol intake, locomotor response to novelty was not associated with subsequent alcohol intake (Koros *et al.*, 1998). This suggests that selection for high-novelty and low-novelty-induced activity is a fragile phenomenon that may appear to be related to the HiS LoS phenotypes with some tasks but not with others. Furthermore, these behavioral measures may be predictive of drug use in some phases but not every phase of addiction. Indeed, there is lack of consensus regarding the nature of the relationship between locomotor activity in a novel environment and subsequent vulnerability to drug of abuse (Mitchell *et al.*, 2005). Some clinical findings support the hypothesis that novelty reactivity and sweet preference are related as vulnerability factors in drug abuse. For example, it has been shown that high novelty seeking increases risk of alcoholism in sweet-preferring individuals but not in sweet-nonpreferring individuals (Kampov-Polevoy *et al.*, 2003). In addition, Grucza *et al.* (2006) showed that novelty seeking is strongly associated with alcohol dependence in subjects with a parent diagnosed with alcohol dependence, and low novelty seeking may protect against the familial risk of alcoholism.

Locomotor activity

Another possible explanation for the higher rates of drug-seeking and drug-taking behavior in HiS (vs. LoS rats) may be that HiS rats have higher innate levels of activity. Locomotor activity was compared in HiS and LoS rats using a circular open field apparatus with four motion sensors, similar to that initially reported by Piazza *et al.* (1989). In one study, LoS males and females exceeded HiS males and females on day 1 (first exposure to novel chamber), but there were no differences in locomotor activity on day 2 (Perry *et al.*, 2007b), suggesting line differences in response to novelty but not activity. In a subsequent study, when intraperitoneal injections of saline were given to HiS and LoS rats immediately before the activity measures in the same apparatus, activity was higher in LoS (vs. HiS) male rats (Carroll *et al.*, 2007a) which is consistent with the novelty reactivity (Perry *et al.*, 2007b) described above and with reports of running-wheel activity in LoS versus HiS rats (Dess *et al.*, 2000) (LoS > HiS). These results may be explained by greater reactivity to the stress of an injection or an absolutely or relatively novel open field apparatus or running wheel in LoS versus HiS rats.

Drug-induced locomotor activity and locomotor sensitization

Drug-induced locomotor activity and drug-induced sensitization of locomotor activity have been hypothesized to predict susceptibility to subsequent drug-seeking and drug-taking behavior (Piazza *et al.*, 1989, 2000; Robinson and Berridge, 2001, 2003; Ferrario *et al.*, 2005). Exceptions to these findings, however, have been noted (Phillips and Di Ciano, 1996; Ben-Shahar *et al.*, 2004; Ahmed and Cador, 2006). In a recent study with HiS and LoS rats, novelty reactivity and cocaine-induced locomotor sensitization were compared in males and females using the circular open-field apparatus described above (Carroll *et al.*, 2007a); the rats received five saline or cocaine injections each separated by several days, and the last one by 2 weeks.

The results showed that HiS rats were higher than LoS rats, and females exceeded males on cocaine-induced activity measures (Table 2). In addition, there was a weak sensitization effect in cocaine-induced locomotor activity in HiS females when activity after injection 5 was compared with activity after injection 1. These results suggest HiS and LoS rats are differentially responsive to cocaine-induced locomotor activity and sensitization (which are considered to be markers of drug-seeking behavior), and these results (HiS > LoS) are consistent with cocaine-seeking behavior during several phases of addiction, as described above (Table 2). Thus, using drug-induced locomotor activity and sensitization as a predictor of drug abuse was validated by HiS and LoS rats that have a preestablished propensity for (HiS) or against (LoS) drug-rewarded behavior. These results also suggest that saccharin phenotype and sex have additive effects on cocaine-induced locomotor activity and sensitization.

Stress and emotionality

The HiS and LoS rats were originally bred to study the relationship between emotionality and eating (Dess, 2001). These lines of rats were selectively bred to produce offspring that drank large or small amounts of saccharin and subsequently to determine how they differed in the realm of emotion and stress. One study compared HiS and LoS rats in the response to acoustic startle (Dess *et al.*, 2000), as past studies have indicated

that increased startle amplitude is a measure of negative emotional reactivity (Lang *et al.*, 1990). The results from this experiment indicated that startle amplitude was higher in LoS rats. In other studies, stress markedly decreased food intake in LoS but not HiS rats (Dess and Minor, 1996), and stress induced a stronger analgesic response in LoS rats (Dess *et al.*, 2000). Thus, initial work indicated that LoS rats had a more negative emotional state and greater vulnerability to stress than HiS rats. Restricted feeding also made LoS rats more susceptible to wheel-running (activity-induced anorexia) than it did in HiS rats (Dess *et al.*, 2000). Elevated locomotor activity, as discussed earlier, with studies involving the open field, running wheel, and saline injections has also been interpreted as an expression of stress or emotion. For example, high locomotor activity in a novel environment is also commonly used as a behavioral measure of stress reactivity that is thought to be a predictor of stimulant abuse (Piazza *et al.*, 1989, 2000; Gingras and Cools, 1997) as well as a predictor of subsequent alcohol intake (Koros *et al.*, 1998).

The relationship between taste and emotion seen in LoS rats has parallels in humans. Work with humans supported the findings with laboratory animals and showed that sensitivity to saccharin's bitterness predicted overactivity in highly arousable female dieters (Craig *et al.*, 2003). For example, differential reactivity to sweet and bitter tastes has been associated with several psychiatric disorders such as depression (Amsterdam *et al.*, 1987), alcoholism (Pelchat and Danowski, 1992; Kampov-Polevoy *et al.*, 1999) and posttraumatic stress disorder (DeMet *et al.*, 1998). Thus, taste perception is not only a marker for drug abuse vulnerability, but a number of other psychiatric disturbances. In college students who were highly arousable, stress enhanced their perception of bitter and sweet, and for those who scored low on trait pleasure, stress made saccharin more bitter and less sweet (Dess and Edelheit, 1998).

Taste responses

Early work with rats that were selected for intake of sweet substances served as an important model for defining factors such as responses to tastes that predict subsequent drug use. Initial studies of the interaction between sweet intake and subsequent alcohol intake became a well-characterized animal model of the genetic relationship between sweet preference and vulnerability to drug abuse that is presented in this review. The following two studies are indicative of this relationship and demonstrate that saccharin intake can predict subsequent drug-taking behavior in heterogeneous populations. Gosnell and Krahn (1992) examined saccharin intake as a predictor of alcohol intake by separating Wistar rats into low, intermediate, or high intake groups. Their voluntary oral alcohol intake was then assessed using a two-bottle choice test under both food-restricted and free-feeding conditions. They found that when food was restricted, there was no relationship between voluntary saccharin and alcohol intake; however, when alcohol intake was assessed under free-feeding conditions, the high intake group consumed significantly more alcohol than the low intake group.

These findings were extended by Bell *et al.* (1994) to determine whether saccharin intake predicted the operant self-administration of alcohol. Again, Wistar rats were separated into low, intermediate, or HiS groups based on 3 days of voluntary saccharin intake. Subsequently, each group was required to lever press for access to alcohol, and alcohol consumption was measured across several FR requirements and alcohol concentrations. They found that the rank-order of the three saccharin groups (i.e. high > intermediate > low) remained the same throughout 25 of the 32 conditions examined. These findings suggest that voluntary saccharin intake can be predictive of subsequent alcohol intake in several rodent populations using both voluntary consumption and operant self-administration paradigms. The alcohol and saccharin relationship, however, is sensitive to other factors such as feeding condition (Gosnell and Krahn, 1992) and response requirement, or the cost of the drug (Gahtan *et al.*, 1996).

Eating and taste have also been extensively studied in the selectively bred HiS and LoS rats (Thiele *et al.*, 1997; Dess, 1993, 2000, 2001; Dess *et al.*, unpublished). HiS rats consume more of a variety of palatable substances such as sugars, saccharin, polycose, and salt than LoS rats; however, LoS rats do not consume less food or water overall than HiS rats. Compared to their HiS counterparts, LoS rats are more responsive to bitter components of taste mixtures and ethanol, whereas they are less responsive to sugars. Within lines, females often consume more sweet substances than males when adjusted for body weight (Table 1). Similarly, work with HiS and LoS female (F) and male (M) rats and the various forms of drug self-administration (e.g. oral, i.v.), the different drugs used (e.g. cocaine, ethanol, heroin), over most of the phases of drug abuse that have been modeled, has consistently yielded a rank ordering of drug-taking and drug-seeking (HiSF > HiSM > LoSF > LoSM) that reflects the rank ordering of saccharin phenotype scores. In addition, similar absolute values and general rank ordering of the saccharin phenotype scores were reproduced when the HiS and LoS female and male groups of rats that have been tested with other tastants such as, sucrose, sucrose quinine mix, sodium choride, and polycose. Thus, the HiS LoS selective breeding resulted in a differentiation of responses to a wide variety of tastes in addition to saccharin for which they were selectively bred, and the rank-ordering of these taste phenotype scores matched the rank ordering of drug-seeking and drug-taking behavior under most conditions. Interest-

ingly, line differences involving aversive tastes seem to be strictly limited to LoS rats' greater finickiness about bitter taste components of complex tastes, with the lines equally likely to reject purely bitter solutions (sucrose octaacetate, quinine) and sour citric acid alone or in sucrose solution. This pattern of results is consistent with greater sensitivity of LoS rats to signals for toxicity in complexly flavored foods (Scott, 1987) and greater responsiveness of HiS rats to potential rewarding qualities of ingestables.

Overall, HiS rats are more sensitive to the rewarding effects of drugs and specific tastes (sweets, salt) and LoS rats are more sensitive to the aversive taste qualities in complex flavors and the aversive effects of oral and i.v. drugs. Thus, the way rats respond to food is very similar to the way they respond to drugs. For example, HiS rats prefer sweets and have a greater avidity for drugs than LoS rats; whereas, LoS rats are less responsive to sweet tastes than HiS rats, they have less drug consumption than HiS rats, and they show greater withdrawal effects (aversive consequences of drug use) than HiS rats. Similar findings have also been reported in inbred rat lines. For example, LEW and F344 rats show a similar dissociation between reward reactivity (LEW > F344) and responsiveness to the aversive aspects (F344 > LEW) of drugs (Kosten and Ambrosio, 2002; Kruzich and Jinlei, 2006).

Many questions remain about the precise nature of the interaction between sweet consumption and drugs of abuse. In particular, the decreased taste and smell sensitivity shown in humans following short-term or long-term ingestion of alcohol complicates any conclusions regarding the relative importance of each factor (Meisch, 2002). One possibility is that increased sweet preference in some drug abusers (vs. nonabusers) results from a decreased taste sensitivity (Maier *et al.*, 1994; Kranzler *et al.*, 2001). Taste differences are well known to occur in human and nonhuman populations. For example, humans can be classified as either nontasters, tasters, or supertasters on the basis of their sensitivity to 6-n-propylthiouracil (PROP), a bitter substance (Bartoshuk, 1979, 1993). Individuals that were classified as supertasters, based on responses to PROP, perceived alcohol and sweet substances, including saccharin, to be stronger than nontasters. Taste (sweet) preference, however, has been shown to be related to the genetic risk for alcoholism on the basis of family history and the current alcohol-drinking status of the individual (Kampov-Polevoy *et al.*, 2001, 2003).

Impulsivity

An expanding body of clinical literature indicates that drug abusers are more impulsive than nonusers or previous users (Bickel and Marsch, 2000; De Wit and Richards, 2004). Results from animal studies not only concur with this correlational evidence, but they have provided prospective accounts whereby rats selected for high (HiI) and low (LoI) impulsive behavior subsequently exhibited elevated drug-seeking and drug-taking behavior (Poulos *et al.*, 1995, 1998; Perry *et al.*, 2005, 2008a; Dalley *et al.*, 2007). Connections are beginning to emerge between impulsivity, sweet consumption, and drug abuse. For example, impulsivity for sucrose is also associated with higher levels of sensitization to the stimulating effects of ethanol (Mitchell *et al.*, 2006). Saccharin intake (HiS) and impulsivity (HiI) are both predictive of drug-seeking and drug-taking behavior, but they are not necessarily correlated or predictive of each other. They, however, may have a similar influence on vulnerability to drug abuse. For example, when saccharin phenotype scores were compared with a measure of impulsivity (mean adjusted delay, MAD), the result was that there was no significant correlation (Perry *et al.*, 2007a). When saccharin phenotype scores were compared after the completion of other experiments in HiI and LoI male and female rats, there were sex differences (F > M) but no HiI–LoI phenotype differences (Perry, Anker, Carroll, unpublished data). In humans, Vaidya *et al.* (2004) studied the relation between sucrose preference and impulsivity in adolescents and adults. Personality measures of impulsivity were not correlated with sucrose preferences. The interaction between impulsivity and drug abuse in laboratory animals and humans has been extensively reviewed elsewhere (Evenden, 1999; De Wit and Richards, 2004; Mitchell, 2004; Carroll *et al.*, unpublished; Perry and Carroll, unpublished); thus, the following sections will focus on impulsiveness for food and drug reinforcement as it applies to HiS and LoS rats. Two main methods of assessing impulsivity were used: impulsive choice (delay discounting task) and impaired inhibition (Go/No-go task).

Delay discounting

To examine possible links between a proclivity for saccharin intake, impulsive behavior, and sex, male and female HiS and LoS rats were evaluated on a delay-discounting task using either 'food' pellets or i.v. 'cocaine' as the reinforcers (Perry *et al.*, 2007a). The delay-discounting task is a measure of impulsive choice in which the subject chooses between a small-immediate and a large-delayed reward. In this study, an adjusting delay procedure was used that allowed rats access to two levers. Responding on one lever, under an FR 1 schedule, resulted in one 45 mg food pellet, and responding on the other lever (FR 1) resulted in three or six pellets after a delay. The delay started at 6 s and increased by 1 s after each response on the delay lever; however, the delay decreased by 1 s after each response on the immediate lever. This allowed the animal to titrate its delay interval, and the starting delay for each subsequent day was the last delay of the session on the day before. The daily mean MAD at the end of the 30 choice trials (3-h

session) each day served as an index of impulsivity. The experiment was repeated in separate groups with a choice between a small-immediate (0.2, 0.4, or 0.8 mg/kg) or large-delayed (3 × small immediate) cocaine delivery.

In the food-reinforced groups HiS rats were more impulsive than LoS rats (lower MADs), and LoS females were more impulsive than LoS males. HiS rats also earned more food pellets than LoS rats, but males earned more food than females. In contrast, there were no saccharin-phenotype or sex differences in impulsive choice (MAD) for cocaine; however, HiS rats earned more cocaine infusions than LoS rats, and females self-administered more cocaine than males. Thus, impulsivity, saccharin intake, and female sex are positively related to drug self-administration; however, saccharin phenotype, impulsivity, and sex are dissociable depending upon the type of reward (drug vs. food). It is possible that the higher cocaine intake in HiS (vs. LoS) rats and females (vs. males) lowered impulsivity, yielding no saccharin phenotype or sex differences. Others have shown differential effects of amphetamine on MADs for food based on rearing environment (Perry *et al.*, 2008b). The elevated drug intake and impulsivity in HiS versus LoS rats was not due to higher levels of locomotor activity, as locomotor activity did not differ in a comparison of HiS and LoS female rats in a circular open-field apparatus (Carroll *et al.*, 2007a). Similar results have been reported for mice that differed in delay discounting for sucrose (Mitchell *et al.*, 2006).

Another line of evidence suggesting similarities in HiS and LoS rats and HiI and LoI rats, respectively, comes from several parallel studies conducted at different phases of drug abuse using procedures similar to those used with HiS and LoS rats (Table 3). For example, HiI female and male rats acquired cocaine self-administration faster and in greater numbers per group that LoI females and males, respectively (Perry *et al.*, 2008a) (Table 3). Similarly, HiI rats escalated their cocaine self-administration; whereas, LoI rats did not (Carroll *et al.*, unpublished), and HiI rats that showed escalation had significantly more cocaine infusions during 2-h access after escalation than during 2-h access before escalation (Carroll *et al.*, unpublished) (Table 3). These findings were consistent with the HiS rats' performance post-escalation versus preescalation (Perry *et al.*, 2006a) (Table 2).

The selected HiI and LoI rats also differed in a reinstatement paradigm (Perry *et al.*, 2008a) (Table 3). For example, during maintenance, HiI and LoI groups did not differ until the last 2 days when LoI exceeded HiI rats. A similar finding occurred during extinction when LoI rats responded more than HiI rats on 5 of the 14 days. In contrast, HiI rats showed more reinstatement responding than LoI rats, but only at the highest cocaine-priming dose (15 mg/kg), which was consistent with HiS and LoS rats, respectively. Overall, there are many similarities in HiS LoS selectively bred rats and HiI and LoI selected rats on several measures suggesting that excessive intake of sweet substances may be a reflection of impulsive behavior. The differences in maintenance and extinction, however, emphasize that these behavioral phenotypes have dissociable elements in their drug-seeking behavior. It is possible that HiI rats have less sensitivity to the effects of cocaine, and/or to the drug-associated cues.

Go/No-go

The study described above has also been applied to another measure of impulsivity (impaired inhibition) using a Go/No-go task in HiS and LoS male and female rats self-administering i.v. cocaine and food (Anker *et al.*, unpublished). Different groups of rats were tested with 0.4 mg/kg i.v. cocaine, or food pellets as the reinforcer during the 'Go' condition. Three 45-min Go components were present when lever pressing was reinforced by cocaine or food under an FR 1, 3, or 5 schedule, and these

Table 3 Summary of results from studies on rats selected for high impulsivity (HiI) and low impulsivity (LoI)

Behavioral model	Drug	Selection task	Results	Sex differences	Reference
Acquisition	Cocaine	Delay discounting	HiI>LoI	F=M	Perry *et al.* (2008a)
	Cocaine	5CSRT	HiI>LoI	M only	Dalley *et al.* (2007)
	Ethanol	Delay discounting	HiI>LoI	M only	Paulos *et al.* (1995)
Maintenance	Cocaine	Delay discounting	(Responses) HiI > LoI (M), HiI < LoI (F)	(Responses) F>M (LoI)	Perry *et al.* (2008a)
			(Infusions) HiI=LoI	(Infusions) F>M	
		5 CSRT	HiI>LoI	M only	Dalley *et al.* (2007)
Escalation pre-FR1	Cocaine	Delay discounting	HiI>LoI, HiI=LoI	F only	Carroll *et al.* (in press)
Post-FR1			HiI=LoI Post>Pre (HiI)		
Pre-PR			HiI=LoI		
Post-PR			HiI>LoI (0.8 mg/kg)		
Escalation	Cocaine	Delay discounting	HiI>LoI	M only	Dalley *et al.* (2007)
Extinction	Cocaine	Delay discounting	(Responses) HiI<LoI	(Responses) F>M (LoI)	Perry *et al.* (2008a)
			(Infusions) HiI=LoI	(LoI infusions) F=M	
Reinstatement	Cocaine	Delay discounting	HiI>LoI (15 mg/kg)	F>M (15 mg/kg)	Perry *et al.* (2008a)
Locomotor activity	–	Delay discounting	HiI=LoI	F=M	Perry *et al.* (2008a)

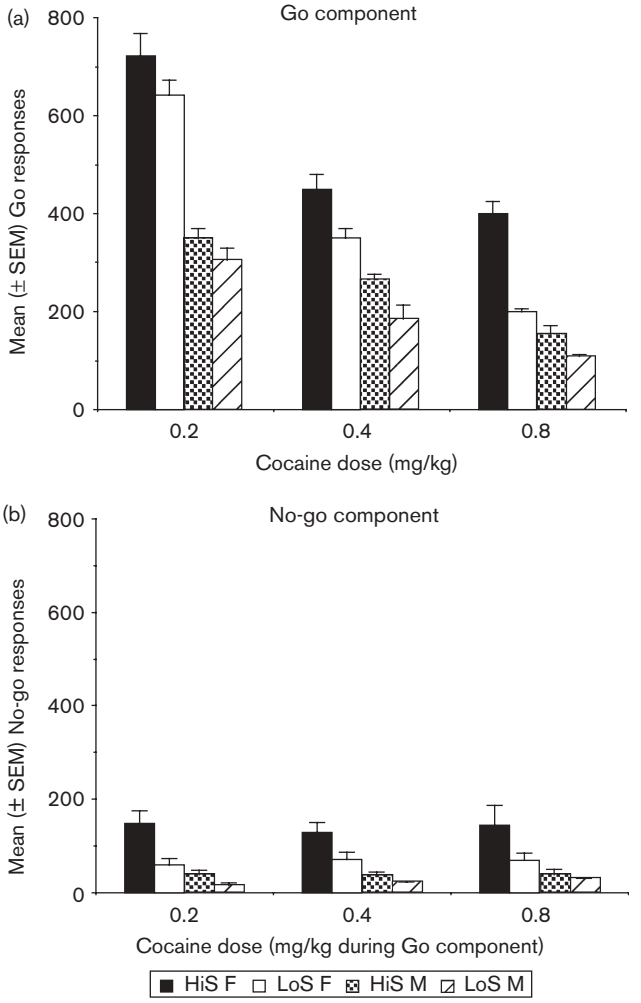
F, female; FR, fixed-ratio; M, male; PR, progressive ratio.

components were separated by two 15-min No-go components when lever responding was counted, but had no programmed consequences. Different discriminative stimuli signaled the Go and No-go components. Responding during the No-go components was used as a measure of behavioral inhibition (impulsivity).

During the Go components, under an FR 5 schedule, HiS females and males responded significantly more for cocaine than LoS females and males, respectively. Additionally, females responded more than males in both the HiS and LoS groups. This was consistent with results of an earlier study in which only one out of seven LoS male rats met acquisition criteria for cocaine self-administration (Carroll *et al.*, 2002). The No-go responding (a measure of impulsivity) was also higher in HiS than LoS rats, and females were higher than males, when the 0.2, 0.4, and 0.8 mg/kg cocaine doses were available during the preceding Go components (Fig. 7b). Thus, the Go and No-go components were sensitive to phenotype and sex differences when cocaine was the reinforcer.

No phenotype differences in the Go or No-go responses for food (Anker *et al.*, unpublished; data not shown) were found (Table 2). In contrast, there were no sex or phenotype differences in the food groups with the Go/No-go procedure, unlike delay discounting (Table 2). Thus, the 'cocaine' Go/No-go task was more sensitive to the saccharin phenotype differences than the 'cocaine' delay-discounting task (Perry *et al.*, 2007b) and delay discounting (vs. Go/No-go) was more sensitive to the saccharin phenotype when food was a reinforced than when cocaine was the reinforcer. These results suggest that higher drug-maintained responding in the HiS rats may be partially attributed to another factor, inhibitory failure, an aspect of impulsive behavior. Results during the Go components concurred with earlier studies (Carroll *et al.*, 2002; Perry *et al.*, 2007b) showing that HiS rats self-administered more cocaine than LoS rats, and females exceeded males. They also agreed with an earlier mouse study (Logue *et al.*, 1998) that used a signaled nose-poking task to define impulsivity (inability to withhold nose-poking for food rewards until signaled) in 13 strains of mice. Mice were subsequently tested with a three-bottle test with 3 and 10% (v/v) ethanol and water. The strains that were more impulsive consumed more ethanol. Similar findings have been reported recently from a study in which mouse lines selected for high (STDRHI2) and low (STDRLO2) ethanol consumption differed (STDRHI2 > STDRLO2) in a Go/No-go (but not in a delay-discounting task) for sucrose (Wilhelm *et al.*, 2007). These findings support the link between ethanol and sucrose consumption and aspects of imupulsivity, with the impaired inhibition (Go/No-go) task appearing to be more sensitive to phenotype differences than delay discounting.

Fig. 7



Go/No-go responding in HiS and LoS males and females. (a) Mean responses during three 45-min Go components when cocaine (0.2, 0.4, 0.8 mg/kg) was contingent upon lever-press responses (FR 1). (b) Responding during two intervening 15-min components when responding had no programmed consequences. Go and No-go components were signaled with different stimuli. Horizontal lines indicate phenotype and sex differences ($P<0.05$) (Anker *et al.*, unpublished). FR, fixed-ratio; HiS, high saccharin; LoS, low saccharin.

Converging evidence indicates that saccharin intake using the selectively bred HiS and LoS rats, and impulsivity using the selected HiI and LoI rats, are major factors having a strong influence on drug abuse at several key phases. A comparison of Tables 2 and 3 reveals that the saccharin intake and impulsivity variables are related in very similar ways to drug self-administration. Continued research at the behavioral and neurobiological level will reveal underlying mechanisms of these influen-

tial factors. Data from the HiS LoS rats indicate that there is a genetic component in the spectrum of individual differences attributed to these rats, and impulsivity may be one of the pleiotropic gene effects.

Interaction of the high saccharin and low saccharin phenotypes with other major factors mediating vulnerability to addictive behavior

In addition to the factors mentioned in the previous section, conditions such as age, sex, and hormonal status have been shown to strongly influence drug abuse. The following section discusses how these factors interact with the HiS and LoS phenotypes.

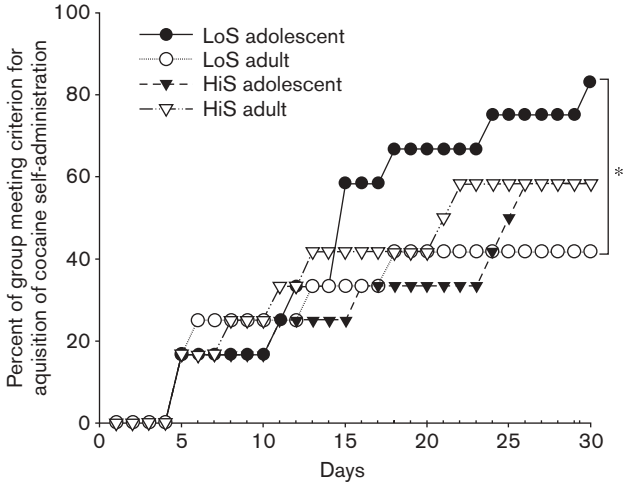
Age

Age is an important factor in vulnerability to drug abuse that has recently received increased attention. Adolescence is a critical period characterized by elevated susceptibility to drug abuse and other forms of addiction (Laviola *et al.*, 1999; Spear, 2000a, b; Chambers *et al.*, 2003; Smith, 2003; Caster *et al.*, 2005). Most drug abuse begins during adolescence (Kreek *et al.*, 2005b), and escalation of cocaine abuse is more rapid among adolescents than adults (Clark *et al.*, 1998; Chen and Kandel, 2002). Eating disorders also begin during adolescence, and there are high rates of comorbidity between drug abuse, eating disorders, and other impulse control disorders (Jonas, 1990; Bulik *et al.*, 1992; Chambers *et al.*, 2003; Kelley *et al.*, 2004). In addition, there are dramatic hormone changes that occur during adolescence, particularly increases in estrogen, which are related to elevated drug-seeking and taking (Lynch *et al.*, 2000; Carroll *et al.*, 2004; Roth *et al.*, 2004) and progesterone, that has a dampening effect on drug self-administration (Jackson *et al.*, 2006; Larson *et al.*, 2007). Changes in sweet preference have also been reported during adolescence in rats (Zucker, 1969).

Adolescent and adult HiS and LoS male rats were compared in a study of the acquisition of i.v. cocaine (0.4 mg/kg) self-administration (Perry *et al.*, 2007a). Both the HiS and LoS adolescents showed greater avidity for sweet substances than adults, as indicated by their significantly higher saccharin scores (Table 1). In addition, saccharin score was negatively correlated with the number of days to meet the acquisition criteria for cocaine self-administration. The LoS adolescent rats had a faster rate of acquisition of cocaine self-administration than LoS and HiS adults; however, age differences in HiS rats may have been obscured by a ceiling effect (Fig. 8).

In another rat study, adolescent rats drank more of the lowest and highest sucrose concentrations in a two-bottle choice test than adults (Vaidya *et al.*, 2004). Again, lack of age differences at the peak of the sucrose concentration curve may have been due to ceiling effects. Increased consumption of the sucrose solution early in the session was also an indicator of the adolescents' greater avidity for sucrose than that seen in adults. These results were consistent with those of Perry *et al.* (2007a) showing higher saccharin scores in adolescents.

Fig. 8



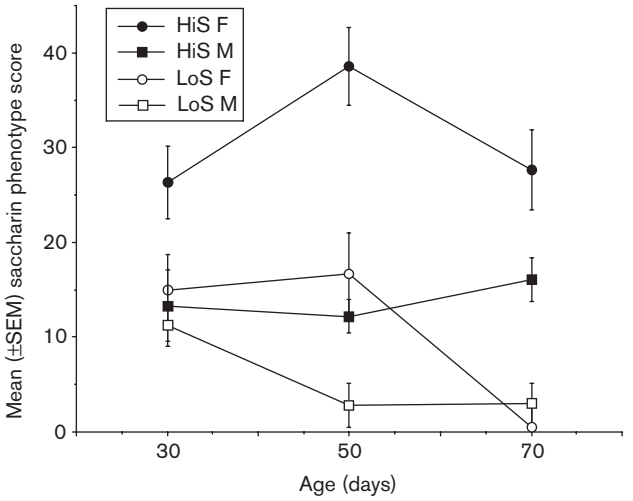
Acquisition (percent of group meeting acquisition criteria) of i.v. cocaine self-administration in HiS and LoS male adolescent and adult rats. *Adolescent > adult ($P < 0.05$). Reprinted with permission from Perry *et al.* (2007a). HiS, high saccharin; LoS, low saccharin.

An earlier study by Dess and colleagues (Dess NK and Savage B, unpublished data) compared saccharin scores in independent groups of selectively bred HiS and LoS female and male rats that were 30, 50, or 70 days of age. Age 55–60 days is often considered the end of adolescence in females and males, respectively (Spear, 2000a, b). Figure 9 shows that there was a significant main effect of age in saccharin phenotype scores. Scores at 30 and 50 days did not differ, but they were greater than at 70 days of age, and most of the difference was accounted for by the decrease with age in the LoS groups. Overall, HiS rats' scores were greater than LoS for both males and females, and females' scores were higher than males at 30 and 50 days. Together, the findings from these studies suggest that adolescence is associated with greater avidity for sweet substances.

Sex and hormonal influences

Sex influences the intake of sweetened solutions, with females showing higher intake/preference than males in both humans (Enns *et al.*, 1979; Katou and Ikawa, 2002) and rats (Valenstein, 1967; Valenstein *et al.*, 1967; Wade and Zucker, 1969). Table 1 shows that within the HiS and LoS lines, saccharin intake scores are higher in females

Fig. 9



Age effects on saccharin phenotype score. Mean saccharin phenotype scores for HiS and LoS male (M) and female (F) groups of rats that were 30, 50 (adolescent) or 70 (adult) days of age. From unpublished data collected by Dess, NK and Savage, B. HiS, high saccharin; LoS, low saccharin.

than males. This sexually dimorphic effect can be accounted for by the presence of ovarian hormones, estrogen and progesterone, but progesterone alone does not account for the effect (Valenstein *et al.*, 1967; Wade and Zucker, 1969; Gabric and Soljacic, 1975). Sweet preference also changes as a function of menstrual cycle (Bowen and Grunberg, 1990) and pregnancy (Bowen, 1992) in humans. The effect of ovarian hormones on preference for tastants in rats is complex and dependent on the type of food, caloric content, deprivation, conditioned stimuli, and specific hormonal conditions. Many studies show that estrogen produces a general anorectic effect in rats, and it decreases preference for novel flavors (Brobeck *et al.*, 1947; Wade and Zucker, 1969; Kenney and Mook, 1974; Wade, 1975; Blaustein and Wade, 1976; Flanagan-Cato *et al.*, 2001). Food intake decreases during the estrus phase of the estrous cycle when estrogen has peaked and begun to decline (Eckel *et al.*, 2000). It is, however, not known how estrogen manipulations would differ in HiS and LoS rats with respect to food intake/preference or drug self-administration.

Females also exceed males across a wide range of drug-seeking behaviors, including acquisition of drug self-administration (Lynch and Carroll, 1999; Carroll and Campbell, 2000), escalation of drug intake under extended access conditions (Roth and Carroll, 2004; Carroll *et al.*, 2005; Carroll *et al.*, unpublished), and postescalation (vs. pre-escalation) FR and PR performance under ShA (Roth *et al.*, 2004; Carroll *et al.*, unpublished), dysregulation of dose (Lynch and Carroll, 2001), binge-like patterns of intake (Morgan *et al.*, 2002), extinction (Fig. 3), and cocaine-primed (Lynch and Carroll, 2000) but not cue-induced (Fuchs *et al.*, 2005) reinstatement. As previously described, HiS rats outperformed LoS rats during many of these phases of drug abuse (e.g. acquisition, maintenance, escalation, post-escalation ShA, dysregulation of dose, extinction, and cocaine-primed reinstatement), and Table 2 indicates that there is a sex difference in drug-seeking behavior within the HiS and LoS inbred strains.

One study in which sex was compared in HiS and LoS strains involved the maintenance phase and a delay-discounting task for cocaine or food reward (Perry *et al.*, 2007a). No sex differences were found in delay discounting for 'cocaine' in either HiS or LoS rats, but the number of cocaine infusions was significantly higher for females than males in both HiS and LoS groups. In the 'food'-reinforced groups females were more impulsive than males in the LoS groups, but HiS males and females did not differ. The recent study comparing male and female HiS and LoS rats on a Go/No-go test of impaired inhibition indicated that females exceeded males at Go and No-go responding for 'cocaine' but not 'food' (Fig. 7) (Anker *et al.*, unpublished). Thus, with respect to drug self-administration, females exceeded males in cocaine infusions in both the HiS and LoS groups, suggesting that these variables do not interact on the drug self-administration measure.

A full review of the interaction between sex, hormones, feeding, and taste reactivity is beyond the scope of this review; however, the important point is that HiS and LoS lines differ in their responses to most tastes, and within these lines there are sex differences that are consistent with HiS/LoS line differences in reactivity to drugs of abuse. Thus, sex and hormonal influences are linked to taste reactivity and avidity for drug-taking and drug-seeking, and they may have an additive influence. For example, note that, in Table 1, two vulnerability factors (HiS and female) consistently yield the highest saccharin phenotype scores. Overall, the effect of sex on responsivity of HiS and LoS rats to drugs is similar to their responsivity to saccharin. HiS rats and females are more sensitive to the rewarding effects of drugs and food; whereas, LoS rats and males are more reactive to the aversive drug effects such as withdrawal (Dess *et al.*, 2005; Perry *et al.*, 2006b) and the aversiveness of bitter tastes in mixtures (Dess, 2000, 2001).

Discussion

Consumption of sweet substances is predictive of several aspects of drug-seeking and drug-taking behavior in both human and animal studies. A relationship between saccharin intake and drug-abuse vulnerability was demon-

strated for alcohol, cocaine, and heroin, through the use of the HiS and LoS rats. Differences between the lines were identified in several phases of drug abuse and across several pharmacological classes of drugs.

The HiS and LoS rats not only displayed stable, characteristic, saccharin phenotype scores across many studies, generations, and years, but importantly, they demonstrated that avidity for sweet substances is related to a wide range of behavior associated with drug abuse. The HiS rats showed elevated rates of acquisition, maintenance, and escalation of drug-taking and drug-seeking behavior compared with LoS rats. HiS rats showed greater dysregulation of cocaine dose under a behavioral schedule that allowed them to select the dose. They also exhibited more resistance to extinction (higher responding) when drug access was terminated, and elevated reinstatement responding (relapse), compared with LoS rats, after one priming injection with 15 mg/kg cocaine. In a test of impulsive choice using a delay-discounting measure for 'cocaine' reward, there was no difference between HiS and LoS, but HiS were more impulsive than LoS on a 'food' delay-discounting task. On another measure of impulsivity, Go/No-go, HiS exceeded LoS rats with 'cocaine' reward, but HiS and LoS were equal under the Go/No-go 'food' task. Thus, differences in impulsivity were generally HiS > LoS, but they differed with type of task and reinforcer (food vs. drug).

Further examination of the HiS and LoS lines with a locomotor test and cocaine-induced locomotor sensitization again revealed that HiS rats had greater cocaine-induced locomotor activity, and they became sensitized to the increased locomotor activity after repeated administration. Thus, in almost all aspects of drug abuse, HiS rats exceeded LoS rats. A notable exception was severity of withdrawal effects. Dess *et al.* (2005) showed more severe withdrawal from ethanol in LoS rats compared with HiS. This is the same exception found in a series of studies comparing male and female rats undergoing morphine (Cicero *et al.*, 2002) and ethanol withdrawal (Devaud and Chadda, 2001; Gatch and Lal, 2001; Varlinskaya and Spear, 2004), and monkeys in PCP withdrawal (Perry *et al.*, 2006b). In all aspects of drug abuse where HiS exceeded LoS, females also exceeded males, except for an opposite effect in severity of withdrawal. Males and LoS rats showed greater withdrawal severity than females and HiS rats, respectively.

Overall, these studies provide behavioral evidence for a genetic relationship between sweet intake and drug self-administration, and the robust differences between HiS and LoS rats in all aspects of drug abuse suggest that they may be excellent models representing addiction-prone and addiction-resistant genotypes and phenotypes. Many more questions regarding genetic involvement in drug abuse can be addressed using the HiS and LoS lines, such as examining how the effectiveness of behavioral and medication-based treatments, and their combination, affect addiction-prone and addiction-resistant phenotypes. Eventually, information regarding treatment for aspects of drug abuse may apply to other addictive behaviors, such as overeating, which leads to problems with obesity such as diabetes and heart disease.

In humans, the well-known connection between sweet preference and drug abuse is correlative; thus, the causative nature of this relation remains elusive. The use of laboratory animals selectively bred for high and low sweet intake, however, allows for prospective studies of many aspects of abuse and interactions with other major determinants. The selective breeding studies also reveal that other aspects of the selected lines may be related to the addiction-prone behavior. For instance, HiS rats are also more receptive of other rewarding substances in general, and they are more impulsive. In contrast, LoS rats are more reactive to the aversive qualities of substances than the rewarding aspects, and they are less impulsive and more emotional than HiS rats. It seems that the sweet intake phenotype on which the HiS and LoS rats' breeding is based is a major variable in drug abuse; however, these lines differ in other aspects that are also predictive of drug abuse, such as novelty reactivity, locomotor activity, stress reactivity, emotionality, and impulsiveness. Although a proclivity for sweet substances has emerged as a major variable predicting drug abuse vulnerability, there are other factors such as age, sex, and hormonal status that are strongly associated with drug abuse severity. These factors may combine in individuals to confer an additive vulnerability. Further genetic and neurobiological research will enable a better understanding of the genetic differences between HiS and LoS animals and how it can inform drug abuse prevention and treatment research for humans.

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