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The neuropharmacology of relapse to food seeking: methodology, main findings, and comparison with relapse to drug seeking

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Abstract

Relapse to old, unhealthy eating habits is a major problem in human dietary treatments. The mechanisms underlying this relapse are unknown. Surprisingly, until recently this clinical problem has not been systematically studied in animal models. Here, we review results from recent studies in which a reinstatement model (commonly used to study relapse to abused drugs) was employed to characterize the effect of pharmacological agents on relapse to food seeking induced by either food priming (non-contingent exposure to small amounts of food), cues previously associated with food, or injections of the pharmacological stressor yohimbine. We also address methodological issues related to the use of the reinstatement model to study relapse to food seeking, similarities and differences in mechanisms underlying reinstatement of food seeking versus drug seeking, and the degree to which the reinstatement procedure provides a suitable model for studying relapse in humans. We conclude by discussing implications for medication development and future research. We offer three tentative conclusions:

1. The neuronal mechanisms of food-priming- and cue-induced reinstatement **are likely different** from those of reinstatement induced by the pharmacological stressor yohimbine.
2. The neuronal mechanisms of reinstatement of food seeking are **possibly** different from those of ongoing food-reinforced operant responding.
3. The neuronal mechanisms underlying reinstatement of food seeking **overlap to some degree** with those of reinstatement of drug seeking.

Keywords

Diet, Extinction; Food reward; Self-administration; Food cues; Reinstatement; Relapse; Review; Stress

I. Introduction

In the United States, a third of all adults and over 15% of children and adolescents are overweight (Ogden *et al.*, 2007). One of the major reasons for the growing number of

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overweight individuals is excessive consumption of energy-dense food (Little *et al.*, 2007). While many people attempt to control their excessive food intake, they typically RELAPSE (Box 1) to old, unhealthy eating habits within a few months (Kramer *et al.*, 1989; Peterson and Mitchell, 1999; Skender *et al.*, 1996). Longitudinal studies (Gorin *et al.*, 2004; McGuire *et al.*, 1999), retrospective studies (Byrne *et al.*, 2003; Grilo *et al.*, 1989; Kayman *et al.*, 1990), and laboratory studies (Herman and Polivy, 1975; Polivy and Herman, 1999; Torres and Nowson, 2007) suggest that this relapse is often triggered by re-exposure to palatable foods, exposure to food-associated cues (such as the smell or sight of a fast-food restaurant), or exposure to stress. For example, Gorin *et al.* (2004) and McGuire *et al.* (1999) reported that people who are re-exposed to highfat foods during dieting are more likely to relapse to their unhealthy eating habits. Byrne *et al.* (2003), Kayman *et al.* (1990) and Grilo *et al.* (1989) reported that dieters frequently attributed relapse to the occurrence of stressful life events; in the latter study, relapse was also frequently attributed to exposure to food-related cues.

Surprisingly, despite considerable evidence of relapse to unhealthy eating habits during dieting in humans, the neuronal substrates of relapse to FOOD SEEKING have rarely been studied in animal models (Fig. 1). Instead, studies on feeding in laboratory animals have focused almost exclusively on food intake and food reward (Dallman *et al.*, 2003; Figlewicz *et al.*, 2007; Hoebel *et al.*, 1989; Kelley and Berridge, 2002). Most of these studies involved home-cage feeding; a few included OPERANT SELF-ADMINISTRATION and CONDITIONED PLACE PREFERENCE (CPP) procedures. This state of affairs in feeding research sharply contrasts with that of drug-addiction research. Like relapse to unhealthy eating habits during dietary treatments, relapse to drug use in abstinent individuals during behavioral or pharmacological treatments is a major clinical problem (Carter and Tiffany, 1999; Hunt *et al.*, 1971; O'Brien and Gardner, 2005). Consequently, many investigators are currently exploring neuronal mechanisms of relapse to drug seeking in animal models (Kalivas and McFarland, 2003; Shalev *et al.*, 2002; Weiss, 2005) (Fig. 1).

Since the publication of a seminal paper by de Wit and Stewart (de Wit and Stewart, 1981), relapse to drug seeking has frequently been studied using a REINSTATEMENT procedure (Bossert *et al.*, 2005b; Self, 2004; Spealman *et al.*, 1999). In this procedure, laboratory animals are trained to self-administer drugs and are then subjected to extinction training, during which lever presses are not reinforced with the self-administered drugs. Reinstatement of ACTIVE LEVER responding (the operational measure of drug seeking) under extinction conditions is determined after manipulations such as non-contingent priming injections of the drug (de Wit and Stewart, 1981; Stretch *et al.*, 1971), exposure to cues associated with drug intake (Crombag and Shaham, 2002; Davis and Smith, 1976; Meil and See, 1996), or exposure to environmental or pharmacological stressors (Lee *et al.*, 2004; Shaham and Stewart, 1995). The reinstatement model is regarded as a suitable animal model of the clinical condition, because stimuli (acute drug exposure, drug cues, and stress) that reinstate drug seeking in laboratory animals are thought to provoke drug relapse and craving in humans (Childress *et al.*, 1986; Epstein *et al.*, 2008; Jaffe *et al.*, 1989; Ludwig and Wikler, 1974; Sinha, 2001). Issues related to the validity of the reinstatement procedure as an animal model of relapse to drug use were discussed elsewhere (Epstein *et al.*, 2006; Katz and Higgins, 2003; Shaham *et al.*, 2003) and are not addressed.

Recently, investigators have begun to use the reinstatement procedure to study neuronal mechanisms of relapse to food seeking induced by acute reexposure to small amounts of food (food priming), food-associated cues, and the pharmacological stressor yohimbine. Yohimbine is a prototypical alpha-2 adrenoceptor antagonist that increases brain noradrenaline cell firing (Aghajanian and VanderMaelen, 1982) and noradrenaline release (Abercrombie *et al.*, 1988). Yohimbine has been used in many studies as a pharmacological stressor, because it induces stress- and anxiety-like states in both humans (Bremner *et al.*, 1996b; Charney *et al.*, 1983;

Holmberg and Gershon, 1961) and non-humans (Bremner *et al.*, 1996a; Davis *et al.*, 1979; Lang and Gershon, 1963; Redmond and Huang, 1979). As mentioned above, acute reexposure to palatable foods, food-associated cues, and life stressors were reported to provoke relapse to old, unhealthy eating habits during dietary treatments (Drewnowski, 1997; Grilo *et al.*, 1989; Torres and Nowson, 2007). This correspondence between the animal model and the human condition suggests that the reinstatement procedure can be used to study the mechanisms of such relapses (see section VIIC for a discussion of this issue).

Our goal here is to review the neuropharmacology of relapse to food seeking, as assessed in the recent body of studies that have used reinstatement procedures. The reviewed studies include those that specifically explored mechanisms of reinstatement of food seeking (Fig. 1a), as well as a larger number of studies in which addiction researchers examined the pharmacological and anatomical specificity of their findings with drug-experienced rats by using rats with a history of food self-administration or food-reinforced responding (Fig. 1b). We will also discuss results from several studies in which cue-induced food seeking was assessed in a single extinction session (rather than in a conventional post-extinction reinstatement). In these studies, rats were exposed to background (contextual) cues previously associated with food availability (i.e., the self-administration chamber) and responding on the previously active lever resulted in contingent presentations of discrete cues (e.g., tone, light) that had been temporally paired with food delivery during training for food-reinforced responding. General topics we will discuss include methodological issues, similarities and differences in the neuropharmacology of reinstatement of food seeking versus drug seeking, and clinical implications of the laboratory animal studies. Table 1 provides a glossary of terms that appear in small capital letters in the text.

II. Methodological issues

Before reviewing results, we address several methodological issues that should be considered in the interpretation of data from neuropharmacological studies on reinstatement of food seeking.

A. Type of food during training

In the studies reviewed below, rats were trained to self-administer different types of food that varied across studies (e.g., regular nutritionally balanced food pellets, high-fat food pellets, sucrose pellets, sucrose solutions, Ensure, corn-oil solutions). Differences in food type can affect results from reinstatement tests in two major ways. The first is the magnitude of lever responding during the reinstatement tests induced by food priming and yohimbine, and potentially by cues. For example, we found robust food priming- and yohimbine-induced reinstatement of lever responding in rats trained to lever press for nutritionally-balanced Bio-Serv food pellets (5.5% fat), moderate-fat (25%) pellets, and high-fat (35%) pellets, but not in rats trained to lever press for fiber pellets that are largely devoid of nutritional content (Ghitza *et al.*, 2006; Nair *et al.*, 2008; Nair *et al.*, 2006). Additionally, responding for sucrose pellets was reliably reinstated by yohimbine, but only very weakly by priming with sucrose pellets (Nair *et al.*, 2006).

The type of food available during training can also influence the effect of pharmacological manipulations on reinstatement of food seeking. For example, the cannabinoid CB1 receptor antagonist SR 141716A decreased cue-induced reinstatement in rats trained to self-administer sucrose pellets (De Vries *et al.*, 2005) or mice trained to self-administer Ensure (Ward *et al.*, 2007). In contrast, SR 141716A had minimal effect on cue-induced reinstatement in mice trained to self-administer corn-oil solution (Ward *et al.*, 2007). The reasons for the unexpected differential effect of SR 141716A on cue-induced Ensure versus corn-oil seeking in mice are unknown. Results from an earlier study by Ward and Dykstra (2007), using both CB1 knockout

mice and CB1 receptor agonists and antagonists, suggest preferential involvement of endocannabinoid signaling during Ensure versus corn-oil self administration. Thus, we speculate that this signaling plays a more prominent role in forming conditioned associations between the discrete cue and Ensure and a lesser role in the case of corn oil, leading to differential effects on subsequent cue-induced reinstatement. More recently, Richards et al. (2008) reported that the hypocretin 1 receptor antagonist SB 334867 attenuated yohimbine-induced reinstatement in rats trained to self-administer a 5% sucrose solution. In contrast, in our study, SB 334867 had no effect on yohimbine-induced reinstatement in rats trained to self-administer high-fat (35%) food pellets (Nair *et al.*, 2008). We propose below that these discrepant results are potentially due to different levels of food restriction in these two studies.

B. Level of food restriction

There are no published parametric studies on the impact of different levels of food restriction on reinstatement of food seeking. However, in preliminary (unpublished) studies to determine the experimental parameters for our reinstatement studies with food, we found that the effects of both food priming and yohimbine on reinstatement are substantially weaker and more variable in rats given unlimited access to regular rat chow than in rats that were food restricted to 20 g/d (about 75–80% of their regular daily Purina Rat Chow intake).

Level of food restriction may also modulate the effects of pharmacological agents on reinstatement of food seeking; this may be due to alterations in basal mRNA levels of feeding-related peptides following food restriction. For example, food restriction elevates basal levels of preprohypocretin (the precursor for hypocretin), neuropeptide Y, and melanin-concentrating hormone (Qu *et al.*, 1996; Sakurai *et al.*, 1998). These alterations may account for the discrepancy mentioned above between two studies using a hypocretin 1 receptor antagonist: in our study (Nair *et al.*, 2008), the rats were restricted to about 65–70% of their free-feeding ration, whereas in the study by Richards *et al.* (2008), the rats were food sated.

C. Priming and cue manipulations

In the studies to be reviewed below, food priming manipulations differed. In some studies, the priming stimulus was the noncontingent delivery of a small number (1–5) of 45 mg pellets just prior to or during the first minute of the test session (Dias *et al.*, 2004; Duarte *et al.*, 2004; Ghitza *et al.*, 2006; Shaham *et al.*, 1997a). In other studies, the priming stimulus was the noncontingent delivery of a pellet every 1–3 min during the entire test session (Anderson *et al.*, 2008; Sun *et al.*, 2005) or parts of the session (first 10–20 min) (Anderson *et al.*, 2006; McFarland and Kalivas, 2001; Nair *et al.*, 2008) Footnote 1. While both food priming manipulations reliably reinstate food seeking, we suggest using the former manipulation in future studies to allow more uniform comparisons across studies. A potential interpretation issue is that when food pellets continue to be delivered during the test sessions on a regular interval, the delivery of food pellets could appear from the subject's perspective to be contingent on operant responding. As discussed in subsequent sections, there is evidence that pharmacological manipulations have different effects on contingent food-reinforced responding versus noncontingent food-priming-induced reinstatement (Ghitza *et al.*, 2007; Nair *et al.*, 2008). Thus, pharmacological manipulations may have different effects on lever responding when food priming is given acutely at the beginning of the test sessions versus repeatedly during these sessions.

Footnote 1 It should be noted that in the learning literature, food-priming-induced reinstatement is also assessed in two (or more) separate daily sessions: on one or more sessions, rats are exposed to the food pellets noncontingently in the absence of the active lever; on a subsequent test day, rats are given access to the lever without the food pellets. The reinstatement observed under these conditions is significantly weaker than that observed if the test sessions include non-contingent presentation of the pellets in the presence of the active lever (Baker *et al.*, 1991). To our knowledge, there are no published studies on the neuropharmacological basis of reinstatement induced by non-contingent food priming in the absence of the active lever on the day before the test session.

Another difference among the studies reviewed below is the nature of the cue, which may be discrete, discriminative, or contextual (see glossary entries for DISCRETE-CUE-, DISCRIMINATIVE-CUE- and CONTEXT-INDUCED REINSTATEMENT). This is an important distinction, because studies with heroin and cocaine suggest that the neuronal circuits underlying reinstatement induced by these different cue types only partially overlap (Bossert *et al.*, 2005b; Bossert *et al.*, 2007; Fuchs *et al.*, 2005; Weiss, 2005). Additionally, in some of the studies reviewed below, cue-induced food seeking was assessed in a single extinction session. There is recent evidence that the neuronal substrates of cue-induced reward seeking may differ depending on whether reward seeking is assessed in a single extinction session or in a post extinction session reinstatement procedure. For example, while reversible inactivation of the ventral medial prefrontal cortex (mPFC) had no effect on cue-induced reinstatement of cocaine seeking after prolonged withdrawal from the drug (McLaughlin and See, 2003), it attenuated extinction responding in the presence of the cocaine cues (Koya *et al.*, 2009).

D. Response rates during training

As can be seen in Table 2–Table 4, the studies reviewed below used different reinforcement schedules, leading to different response rates during training. The effect of pharmacological manipulations on operant responding is dependent on baseline rates of responding, a phenomenon termed the rate-dependency effect (Sanger and Blackman, 1976). An important question, therefore, is whether the rate of responding during training leads to differences in reinstatement of food seeking.

For reinstatement of drug seeking, we have argued that the response rates during training (and extinction) are not likely a major methodological concern, because after extinction, tests for reinstatement are conducted when the response rates are low (Shalev *et al.*, 2002). For example, the effects of dopamine receptor agonists and antagonists on reinstatement of cocaine seeking appear to be independent of response rates during training (Khroyan *et al.*, 2000; Self *et al.*, 1996; Spealman *et al.*, 1999). Additionally, pharmacological manipulations (e.g. CRF1 receptor antagonism) that attenuate footshock-induced reinstatement of lever responding (Shaham *et al.*, 2000a) also attenuate stress-induced reinstatement of CPP (Lu *et al.*, 2003), a rate-independent classical-conditioning procedure.

However, there are no published studies examining the impact of response rates during training on reinstatement of food seeking; therefore, this remains an empirical question. Although response rates during training may not qualitatively alter the effect of neuropharmacological manipulations on reinstatement of food seeking, they probably will affect the magnitude of reinstatement itself. Thus, as is the case with reinstatement of cocaine seeking (Acosta *et al.*, 2008; Valles *et al.*, 2006), training rats to lever press for food on intermittent schedules of reinforcement will likely lead to higher rates of lever presses (or nose-pokes) during the reinstatement tests.

E. Type of reinstatement procedures

Reinstatement can be assessed in a within-session procedure (training, extinction, and test sessions on the same day) or a between-session procedure (training, extinction and test sessions on different days). The choice of procedure may have accounted for differences in the results of two studies (Dias *et al.*, 2004; Duarte *et al.*, 2003a) to be discussed in detail in Section 3.

F. Side effects of neuropharmacological manipulations

Any pharmacological agent or brain manipulation given prior to tests for reinstatement may have nonspecific effects (e.g., ataxia, catalepsy) that need to be distinguished from its specific effects on food seeking. We have previously argued that multiple control conditions are required to adequately address this concern (Shalev *et al.*, 2002). One commonly used but

insufficient control for nonspecific effects is to assess responses on the INACTIVE LEVER. The main problem with this approach is that baseline rates of responding on the inactive lever are typically too low to permit detection of nonspecific sedative effects. Additionally, if the experimental manipulations increase responding on the inactive lever, this may not indicate nonspecific behavioral activation, but rather response generalization, which commonly occurs during extinction (Catania, 1992).

Another important but insufficient control for nonspecific effects of pharmacological/brain manipulations is to determine their impact on active-lever pressing after extinction, but in the absence of the reinstating stimulus. This control condition assesses the effect of the 'treatment' manipulation on baseline responding, against which reinstatement induced by food priming, cues, or yohimbine is assessed. However, because response rates on the active lever are low after extinction, nonspecific sedative effects are difficult to assess. Also, even if an experimental manipulation selectively increases responding on the active lever, but not on the inactive lever, some of the increase may be due to nonspecific behavioral activation; this possibility is supported by the finding that methamphetamine does not increase low-rate baseline responding that was never reinforced (Verhave, 1958).

In our opinion, the optimal way to ascertain the behavioral specificity of a given experimental manipulation is by determining its effect on more than one reinstating stimulus, and possibly also on ongoing food-reinforced responding. If selective effects are observed, one can conclude with some confidence that the effect of a given manipulation on reinstatement is not due to unknown side effects. For example, the corticotrophin-releasing factor 1 (CRF1) receptor antagonist antalarmin selectively attenuates yohimbine- but not food-priming-induced reinstatement (Ghitza *et al.*, 2006), while peptide YY3-36 (PYY3-36) attenuates food priming and cue-induced reinstatement, but has no effect on yohimbine-induced reinstatement of food seeking or ongoing food-reinforced responding (Ghitza *et al.*, 2007).

G. Summary

We have outlined several methodological considerations related to the use of a reinstatement procedure to study relapse to food seeking. These include the type of food, the level of food restriction, the types of food priming and cue manipulations used, the type of reinstatement procedure used, and the need to assess the selectivity of the effects of the neuropharmacological manipulations on reinstatement. We hope that introducing these methodological issues will help readers interpret the studies described in Sections III–VI below, and will also help investigators avoid potential confounds when designing future experiments.

III. Effect of systemic injections of pharmacological agents on reinstatement of food seeking

One way to begin to investigate the mechanisms of reinstatement of food seeking is to determine how reinstatement is affected by systemic (or ventricular) injections of pharmacological agents. Results from such studies are summarized in Table 2.

A. Indirect and direct dopamine agonists

Reinstatement of heroin and cocaine seeking is known to involve the mesolimbic and mesocorticolimbic dopamine projections from the ventral tegmental area to the nucleus accumbens and prefrontal cortex, respectively (Feltenstein and See, 2008; Schmidt *et al.*, 2005). The mesolimbic dopamine system also plays an important role in regulation of food reward (Abizaid *et al.*, 2006; Avena *et al.*, 2008; DiLeone *et al.*, 2003; Wise and Rompre, 1989). These findings have led investigators to assess the effect of indirect dopamine agonists and direct dopamine receptor agonists on reinstatement of food seeking.

Indirect dopamine agonists—Dias et al. (2004) found that cocaine priming injections increased active-lever responding (the operational measure of reinstatement of food seeking) in rats after extinction of food-reinforced responding, an effect also associated with a modest increase in inactive-lever responding. However, the degree to which this finding reflects reinstatement of food seeking is unknown, because cocaine also increased lever responding in control rats for which lever presses resulted in illumination of a cue light (paired with food in the experimental group) but not in delivery of food. In other studies in rats and monkeys, food seeking was not reinstated by priming injections of amphetamine (Odum and Shahan, 2004) or cocaine (Banks *et al.*, 2007; de Wit and Stewart, 1981; Keiflin *et al.*, 2008; Weerts and Griffiths, 2003). Cocaine or amphetamine priming injections, however, did reinstate food seeking in rats previously exposed to these drugs just prior to the food-reinforced responding sessions (and not prior to the extinction sessions) (Keiflin *et al.*, 2008; Odum and Shahan, 2004). This finding is likely related to the drugs' DISCRIMINATIVE STIMULUS effects, because the drugs became reliable predictors of food availability during training. An alternative interpretation of this finding is that prior exposure to amphetamine or cocaine caused sensitization of their INCENTIVE MOTIVATIONAL (Beninger and Gerdjikov, 2004; Robinson and Berridge, 1993) effects. This possibility, however, is unlikely, because Keiflin *et al.* (2008) and Odum *et al.* (2004) found that when cocaine or amphetamine was injected after the food-reinforced responding sessions, there was no effect on reinstatement of food seeking.

Taken together, the data provide little evidence that acute priming injections of amphetamine or cocaine, which reliably reinstate drug seeking in rats (De Vries *et al.*, 1998; de Wit, 1996) and monkeys (Banks *et al.*, 2007; Spealman *et al.*, 1999; Stretch *et al.*, 1971), reinstate food seeking in drug-naïve rats or monkeys.

Direct dopamine receptor agonists

D1-family receptors: Dias et al. (2004) found that injections of the D₁-family agonist SKF 82958 reinstate food seeking. This effect, however, was weaker than the reinstatement induced by food priming and was also observed in control rats for which during training, lever presses led to cue-light presentations but not food. In another study, Duarte et al. (2003a) found that the D₁-family partial agonist SKF 38393 has no effect on reinstatement of food seeking.

D2-family receptors: In an early study, Shaham et al. (1997a) found that the mixed D₂/D₃ receptor agonist bromocriptine reinstates food seeking. More recently, Duarte *et al.* (2003a) found that food seeking can be reinstated by the mixed D₂/D₃ receptor agonist quinolorane, the preferential D₂ agonist apomorphine (also binds with high affinity to the D₁ receptor), or the preferential D₃ agonist 7-OH-DPAT. These effects occurred at high doses and were therefore likely due to direct activation of postsynaptic D₂-family receptors on non-dopaminergic neurons rather than D₂ autoreceptors, which inhibit dopamine transmission (Bunney *et al.*, 1991). In contrast, Dias et al. (2004) reported that food seeking was not reinstated by quinolorane or by 7-OH-DPAT. There are two potential reasons for the discrepant results. The first is that Dias et al. used a between-session reinstatement procedure (training, extinction, and test sessions on different days) and assessed drug effects on reinstatement 10–11 days after the last food training session, while Duarte et al. used a within-session reinstatement procedure (training, extinction, and test sessions on the same day) and assessed drug effects 30 min after the last food delivery. The second possible reason is that Dias et al. used only one dose for each drug. In general, negative results from single dose pharmacological experiments should be interpreted with caution. Taken together, the available data suggest that activation of D₂-family receptors reinstates food seeking, while a role for D₁-family receptors has not been established.

A surprising conclusion that emerges from the studies reviewed above is that while food seeking is reliably reinstated by direct activation of D2-family receptors (presumably postsynaptic), there is little evidence that food seeking is reinstated in drug-naïve rats by increasing synaptic dopamine levels by systemic injections of cocaine or amphetamine. An issue to consider regarding this discrepancy is that cocaine and amphetamine also increase brain levels of norepinephrine and serotonin (Kuczenski and Segal, 1989; Parsons and Justice, 1993; Pepper *et al.*, 2001; Rothman *et al.*, 2001). It is unlikely that the increases in brain norepinephrine levels would inhibit reinstatement of food seeking (see results discussed below of studies with yohimbine, which increases norepinephrine levels). However, there is evidence that stimulation of serotonin transmission inhibits food-taking behavior (Rothman and Baumann, 2002a, b). Thus, cocaine- and amphetamine-induced increases in brain serotonin levels may counter the actions of dopamine on D2-family receptors that lead to reinstatement of food seeking. Firmer conclusions will require studies using more selective reuptake blockers of the dopamine transporter.

B. Other pharmacological agents

Other agents whose effects on food-seeking reinstatement have been explored include hypocretin 1 (orexin A), **melanin-concentrating hormone (MCH)**, adenosine receptor antagonists (CGS 15943 and caffeine), nicotine (a nicotinic acetylcholine receptor agonist), and the cannabinoid delta-9-tetrahydrocannabinol (THC). We have assessed the effect of the alpha-2 adrenoceptor antagonist yohimbine; these data are described in section VI on stress-induced reinstatement.

Hypocretin 1—Hypocretin 1 and 2 (orexin A and B) are neuropeptides synthesized in the lateral hypothalamic and perifornical areas and are known to be involved in arousal (de Lecea *et al.*, 1998) and feeding (Sakurai *et al.*, 1998). Recently, several studies have demonstrated a role of hypocretin 1 and its receptors in reinstatement of drug seeking (Boutrel *et al.*, 2005; Harris *et al.*, 2005; Lawrence *et al.*, 2006). These findings have led to the investigation of the role of hypocretin 1 in reinstatement of food seeking.

In an initial study, Boutrel *et al.* (2005) found that ventricular injections of hypocretin 1 modestly reinstate food seeking in food-sated rats. More recently, we found that such injections strongly reinstate food seeking in food-restricted rats (Nair *et al.*, 2008). The difference in the magnitude of reinstatement between these studies may be due to the different food types used during training: high-fat in our study versus low-fat in Boutrel *et al.* (2005) study. However, a more obvious and plausible explanation is that the rats in our study, having been food restricted during tests for reinstatement, were more motivated to seek food.

It is possible but unlikely that hypocretin 1 exerted its effect in our food-restricted rats by further increasing hunger. Acute food deprivation (24 h) in food-sated rats reinstates heroin and cocaine seeking (Shalev *et al.*, 2006; Shalev *et al.*, 2003; Shalev *et al.*, 2001) and also reinstates food seeking in food-sated rats (unpublished data). However, in food-restricted rats under our training and testing conditions, omitting the daily 16–20 g ration (thereby presumably exacerbating hunger) has only a minimal effect on reinstatement of lever presses (unpublished data); therefore, it is unlikely that exacerbation of hunger *per se* can explain hypocretin 1-induced reinstatement of food seeking.

Finally, a surprising finding in our study was that systemic injections of the hypocretin 1 receptor antagonist SB 334867, at doses that significantly decreased high-fat food reinforced responding, had no effect on reinstatement induced by hypocretin 1. These data suggest that the effect of hypocretin 1 on reinstatement of food seeking may be mediated by hypocretin 2 receptors, because hypocretin 1 has similar affinity for the hypocretin 1 and 2 receptor subtypes (Smart *et al.*, 1999). This possibility can be explored by using selective hypocretin 2 receptor

antagonists (Chang *et al.*, 2007) or mixed hypocretin 1/hypocretin 2 receptor antagonists (Brisbare-Roch *et al.*, 2007).

Melanin-concentrating hormone—Melanin-concentrating hormone (MCH), a cyclic, 19 amino acid neuropeptide, is an important modulator of food intake and energy balance (Qu *et al.*, 1996; Saper *et al.*, 2002). MCH effects are mediated by MCH1 receptors (these are the functional MCH receptor type in the rodent brain) and MCH2 receptors (Chambers *et al.*, 1999; Saito *et al.*, 2001), both of which are expressed in hypothalamic and extrahypothalamic sites (Lembo *et al.*, 1999; Saito *et al.*, 2001). In rodents, ventricular MCH injections increase home-cage food intake, and this effect is reversed by MCH1 receptor antagonists; MCH1 receptor antagonists also decrease home-cage food intake (Borowsky *et al.*, 2002; Pissios *et al.*, 2006; Qu *et al.*, 1996). Based on these findings, we examined the effects of MCH on reinstatement of food seeking (Nair *et al.*, 2009). We found that ventricular injections of MCH reinstated lever responding in our food-restricted rats and this effect was reversed by systemic injections of the MCH1 receptor antagonist SNAP 94847. However, at a dose (30 mg/kg) that reversed MCH-induced reinstatement and decreased ongoing food-reinforced operant responding, SNAP 94847 injections had no effect on reinstatement induced by yohimbine, food priming, or food cues. These results indicate that MCH1 receptors are involved in food-reinforced operant responding but not in reinstatement induced by acute reexposure to high-fat food, food cues, or the stress-like state induced by yohimbine.

Adenosine receptor antagonists—Non-contingent priming injections of caffeine (an adenosine A1/A2 receptor antagonist) reinstate cocaine seeking in rats (Schenk *et al.*, 1996). Similarly, both caffeine and the adenosine A2A/A1 receptor antagonist CGS 15943 reinstate cocaine seeking in baboons (Weerts and Griffiths, 2003). Weerts and Griffiths (2003) also examined whether the effects of caffeine and CGS 15943 generalize to reinstatement of food seeking. They found that CGS 15943 only weakly reinstated food seeking at the highest dose tested, and caffeine did not reinstate food seeking at any dose tested. These findings suggest that the effect of the adenosine receptor antagonists is selective to cocaine seeking and does not generalize to food seeking.

Nicotine—Priming injections of nicotine reinstate nicotine (Chiamulera *et al.*, 1996; Le *et al.*, 2006; Shaham *et al.*, 1997a) and alcohol (Le *et al.*, 2003) seeking in rats. Shaham *et al.* (1997a) examined the generality of this effect using nicotine-naïve and nicotine-experienced rats that were trained to self-administer food pellets. Nicotine reinstated food seeking in rats with a history of nicotine self-administration, but not in drug-naïve rats. In this study, the nicotine-experienced rats were first trained to self-administer nicotine in self-administration chambers and underwent extinction and reinstatement with nicotine priming injections. Subsequently, these rats were trained to self-administer food in different chambers. Thus, unlike the results described above for cocaine (Keiflin *et al.*, 2008) or amphetamine (Odum and Shaham, 2004), the effect of nicotine priming injections on reinstatement of food seeking is independent of the pairing of drug effects with food-reinforced responding during training.

The effect of nicotine on reinstatement might be due to increased brain dopamine transmission (Di Chiara, 2000), resulting in activation of D2-family dopamine receptors (see above). However, this putative mechanism cannot account for the lack of effect of nicotine injections on reinstatement in nicotine-naïve rats, because both acute and repeated nicotine injections increase mesolimbic dopamine release (Di Chiara, 2000). One possible explanation is that other effects of acute nicotine in drug-naïve rats counteract the reinstatement inducing effect. For example, it has been shown that acute nicotine injections to drug-naïve rats disrupt operant performance, and that this effect undergoes tolerance that is independent of whether nicotine is temporally paired with the operant response (Villanueva *et al.*, 1992).

Delta-9-tetrahydrocannabinol (Delta-9-THC)—Studies using the cannabinoid 1 receptor antagonist SR 141716 and the synthetic cannabinoid agonist HU 210 indicate that brain endocannabinoid systems play an important role in the reinstatement of heroin, cocaine, and alcohol seeking (De Vries and Schoffelmeer, 2005; De Vries *et al.*, 2001; Economidou *et al.*, 2006; Fattore *et al.*, 2007). In the rat, the cannabinoid agonist delta-9-THC, the main psychoactive constituent of cannabis, increases home-cage feeding and operant food-reinforced responding (Higgs *et al.*, 2005; Koch, 2001; Williams and Kirkham, 2002). Using a lick-based drinking procedure, McGregor *et al.* (2005) showed that delta-9-THC reinstates seeking of sucrose, alcohol (beer), and “near beer,” a beer-like beverage containing less than 0.5% alcohol (the dependent measure in this study was lick rate). None of these three forms of reinstatement were observed after injections of another drug that stimulates feeding, the short-acting benzodiazepine midazolam (Cooper and Yerbury, 1986). This observation (and the finding that 24 h food deprivation did not increase seeking of “near bear” or alcohol) led McGregor *et al.* (2005) to conclude that the mechanism underlying the reinstatement of alcohol and sucrose seeking is not merely appetite stimulation. Currently, the mechanisms of delta-9-THC-induced reinstatement of sucrose (and alcohol) seeking are unknown. It should be noted that in the standard operant lever pressing (nose-poke) reinstatement procedure, delta-9-THC has no effect on cocaine or heroin seeking (De Vries and Schoffelmeer, 2005; Fattore *et al.*, 2007; Schenk and Partridge, 1999). A question for future research is whether the effect of delta-9-THC on reinstatement is reinforcer and/or procedure specific.

IV. Food-priming-induced reinstatement

Results are summarized in Table 3 (systemic injections) and Table 4 (intracranial injections).

A. Dopamine

The role of dopamine in food-priming-induced reinstatement has been investigated by examining whether dopamine receptor antagonists decrease this reinstatement and whether dopamine receptor agonists potentiate it.

Dopamine receptor antagonists—Ettenberg and colleagues used a RUNWAY REINSTATEMENT PROCEDURE to examine the effect of dopamine receptor antagonists on food-priming-induced reinstatement. In an initial study, Horvitz and Ettenberg (1988) found that systemic injections of the preferential D2-family receptor antagonist haloperidol increase run-time to the goal box or decrease food-priming-induced reinstatement. Subsequently, Chausmer and Ettenberg (1997) found that such reinstatement is also attenuated by systemic injections of the D2-family receptor antagonist raclopride but not the D1-family receptor antagonist SCH 39166. In these studies, the dopamine receptor antagonists were injected systemically 24 h prior to the runway reinstatement test. The reinstatement test was thus carried out in a drug-free state, excluding acute non-specific drug effects such as sedation. Together, these data indicate that D2 but not D1 receptors are critical for food-priming-induced reinstatement as assessed in the runway procedure.

In contrast, using the operant lever-pressing reinstatement procedure, we recently found that systemic injections of the D1 receptor antagonist SCH 23390 decrease food-priming-induced reinstatement of food seeking (Fig. 2). We used experimental procedures that were similar to those described in our previous studies (Nair *et al.*, 2008). Briefly, we trained different groups of rats under food restriction (16–20 g per day of regular Purina Rat Chow) to lever press for high-fat (35%) pellets for 9–10 days (3-h per day, every other day). After extinction of food-reinforced responding for 9–10 days (3-h session per day), we determined the effect of systemic injections of SCH 23390 injected 20–25 min prior to reinstatement of lever responding induced by food priming. Together with the previous results from Ettenberg and colleagues, these data suggest that the role of D1-family receptors in food-priming-induced reinstatement is

procedure-dependent. Alternatively, the differential findings might be due to the time interval between drug injection and reinstatement testing: no delay in our studies versus 24 h in Ettenberg's studies. A question for future research is the role played by D2-family receptors in food-priming-induced reinstatement in the lever-pressing operant reinstatement procedure.

The brain sites involved in these systemic effects have been explored in the following studies. In the runway procedure, the effect of systemic injections of D2-family receptor antagonists on food-priming-induced reinstatement was not mimicked by accumbens injections of raclopride (Chausmer and Ettenberg, 1999). In the operant self-administration procedure, accumbens injections of sulpiride (also a D2-family receptor antagonist) had no effect on reinstatement (Anderson *et al.*, 2006). These are surprising findings, because accumbens dopamine is critical for food reward (Avena *et al.*, 2008; Kelley and Berridge, 2002; Wise, 2004).

A potential brain site for the effect of dopamine receptor antagonists on food-priming-induced reinstatement is the dorsal mPFC. Sun *et al.* (2005) found that dorsal mPFC injections of the D2-family receptor antagonist eticlopride attenuate food-priming-induced reinstatement in rats trained to self-administer sucrose pellets. Sun *et al.* also found that dorsal mPFC injections of the D1-family antagonist SCH 23390 modestly attenuate food-priming-induced reinstatement, a finding that is in agreement with our results (Fig. 2).

Finally, Xi *et al.* (2006) found that systemic injections of the selective D3 receptor antagonist NGB 2904 have no effect on food-priming-induced reinstatement of lever responding in rats trained to self-administer a sucrose solution. These data suggest that the effect on food-priming-induced reinstatement of D2-family receptor antagonists, which typically bind at high affinity to both D2 and D3 receptors (Seeman and Van Tol, 1994), is likely mediated by D2 receptors. This conclusion is potentially challenged by the findings of Duarte *et al.* (2003a) that several D2-family antagonists had no effect on food-priming-induced reinstatement, as assessed by the within-session reinstatement procedure. These data, however, are difficult to interpret due to very low responding after the priming manipulation (3–5 presses/15 min test session). Under these conditions, it is unlikely that pharmacological attenuation of reinstatement of lever responding can be detected due to a floor effect. Because of this problem, these data, as well as negative data with the preferential D3 ligand BP 897 on food-priming-induced reinstatement (Duarte *et al.*, 2003b), are not included in Table 3.

Dopamine receptor agonists—Duarte *et al.* (2004) found that systemic injections of the D2-family receptor agonists quinlorane and 7-OH-DPAT potentiate food-priming-induced reinstatement. However, Feltenstein *et al.* (2007) found no such effect with systemic injections of the partial D2 receptor agonist aripiprazole. This finding should be interpreted with caution, because although aripiprazole preferentially binds to D2 receptors, it is also a partial agonist at D3 and 5-HT_{1A} receptors and an antagonist at 5-HT_{2A} receptors (Jordan *et al.*, 2002; Langlois, 2005); its effect on these other receptors may counteract its effect on D2 receptors. Finally, Duarte *et al.* (2004) also found that systemic injections of the D1-family receptor agonist SKF 38393 very modestly potentiate food-priming-induced reinstatement.

B. Glutamate

A glutamatergic pathway from the mPFC to the accumbens is critical for drug-priming-induced reinstatement of drug seeking (Kalivas and McFarland, 2003; Park *et al.*, 2002). Accumbens and ventral tegmental area (VTA) glutamate are also critical for drug priming-induced reinstatement of drug seeking (Sun *et al.*, 2005; You *et al.*, 2007). Based on these findings, the role of glutamate in food-priming-induced reinstatement has been assessed in two studies.

Peters and Kalivas (2006) found that systemic and accumbens injections of LY 379268 attenuate food-priming-induced reinstatement. LY 379268 is an agonist at group II metabotropic glutamate (mGluR2) receptors that acts centrally to decrease evoked glutamate release (Schoepp, 2001), primarily via presynaptic mGluR2 (Bonci *et al.*, 1997; Manzoni *et al.*, 1997). On the other hand, Sun *et al.* (2005) found no effect on sucrose-priming-induced reinstatement when inhibiting glutamate transmission in the VTA with kynureate, a non-selective ionotropic glutamate receptor antagonist. In this study the priming manipulation consisted of delivery of 3 sucrose pellets every 10 sec in the beginning of the test session, and additional deliveries every 3 min during the session. As mentioned in Section II, a potential interpretation issue with this manipulation is that when food pellets continue to be delivered during the test sessions on a regular interval, the subject could perceive food delivery to be contingent on lever responding.

C. Other neurotransmitters and peptides

Peptide YY3-36 (PYY3-36)—Peptide YY3-36 (PYY3-36) is a major circulatory derivative of Peptide YY (Eberlein *et al.*, 1989), a gastrointestinal-derived hormone released from intestinal L-cells after meals in proportion to caloric intake (Murphy *et al.*, 2006; Tatemoto and Mutt, 1980). PYY3-36 binds with high affinity to presynaptic inhibitory Y2 autoreceptors and with lower affinity to postsynaptic excitatory Y1 and Y5 receptors (Ballantyne, 2006; Grandt *et al.*, 1992). Systemic PYY3-36 injections decrease food intake in mice, rats, monkeys, and humans (Batterham *et al.*, 2002; Batterham *et al.*, 2007); but see Tschop *et al.* (2004) and Boggiano *et al.* (2005) for different results. We found that systemic injections of PYY3-36 decrease food-priming- and cue-induced, but not yohimbine-induced reinstatement of food seeking (Ghitza *et al.*, 2007). The systemic effect of PYY3-36 on food-priming-induced reinstatement is reversed by systemic injections of the Y2 antagonist BIIE0246, indicating that the effect of PYY3-36 is mediated by Y2 receptors. Finally, we found that the systemic effect of PYY3-36 on food-priming-induced reinstatement is mimicked by injections of PYY3-36 into the arcuate nucleus.

Opioids—Buprenorphine is a partial agonist at mu-opioid receptors and an antagonist at kappa-opioid receptors, used for treatment of opiate addiction (Vocci and Ling, 2005). Sorge *et al.* (2005) found that chronic exposure to buprenorphine (via osmotic minipumps) attenuates drug-priming-induced reinstatement of heroin and cocaine seeking (Sorge *et al.*, 2005). Following up on these results, Hood *et al.* (2007) showed that chronic buprenorphine decreases sucrose-priming-induced reinstatement of food seeking. Stewart had previously hypothesized that the priming effect of appetitive reinforcers such as drugs and food is due to restoration of the incentive motivational effects of the extinguished reward cues (Stewart, 2000, 2004). Within this framework, Hood *et al.* interpreted their data to suggest that chronic buprenorphine's attenuation of priming effects is mediated by a decrease in the motivational impact of reward-associated cues.

A question for future research is what role endogenous opioid systems play in food-priming-induced reinstatement. This is an important question because endogenous opioids have an established role in food reward (Avena *et al.*, 2008; Levine *et al.*, 1985). However, this question cannot be readily addressed in studies using buprenorphine because of its complex pharmacological effects on opioid receptors.

D. Brain sites involved in food-priming-induced reinstatement

The studies reviewed above indicate that food-priming-induced reinstatement involves glutamatergic but not dopaminergic transmission in the accumbens, and that it may also involve the arcuate nucleus. The involvement of different brain sites in food-priming-induced reinstatement was assessed by Kalivas and colleagues in order to assess the selectivity of their

experimental manipulations on cocaine-priming-induced reinstatement. They found that food-priming-induced reinstatement is attenuated by reversible inactivation of the ventral pallidum (but not the dorsal mPFC and accumbens core) with a mixture of muscimol+baclofen (GABA_A +GABA_B agonists) (McFarland and Kalivas, 2001). In a subsequent study, however, Tang et al. (2005) found that reinstatement was not attenuated by ventral pallidum injections of the mu opioid receptor antagonist CTAP. Additionally, the negative findings of McFarland and Kalivas with muscimol+baclofen in the mPFC are inconsistent with the findings of Sun et al. (2005) with mPFC injections of D1- and D2-family receptor antagonists. In reconciling these results, it is important to note that inactivation with muscimol+baclofen may not be equivalent to selective receptor antagonism (Bossert *et al.*, 2005b). For example, while McFarland and Kalivas (2001) found that cocaine-induced reinstatement was attenuated by muscimol +baclofen inactivation in the accumbens core, Anderson et al. (2003; 2006) found that it was attenuated by selective dopamine antagonism in the accumbens shell but not the core.

V. Cue-induced reinstatement

In laboratory animals, food seeking can be reinstated by three different types of conditioned cues previously associated with food delivery: discrete cues, discriminative cues, and contextual cues (see Table 1). In this section, we describe results from neuropharmacological studies on reinstatement of food seeking induced by these cues. We also review results from studies that used a single extinction session rather than the conventional reinstatement procedure. These studies are summarized in Table 3 and Table 4.

A. Dopamine

We know of three published studies in which cue-induced food seeking was subjected to manipulations of the dopaminergic system. Hamlin et al. (2006) found that context-induced reinstatement of sucrose seeking was attenuated by systemic injections of the D1-family receptor antagonist SCH 23390. Cervo et al. (2007) found that discriminative-cue-induced reinstatement of sucrose seeking was not affected by systemic injections of the preferential D3 antagonist SB 277011-A (10 mg/kg). Interpretation of the latter finding is problematic because only a single drug dose was used, and this dose actually did appear to produce a modest (non-significant) decrease in reinstatement (Fig. 4 Cervo *et al.*, 2007). Gal and Gyertyan (2006) found that haloperidol, the preferential D3 receptor antagonist SB 277011-A, and the D2 antagonist/D3 partial agonist BP 897 had no effect on initial extinction responding in the presence of sucrose cues 21 d after the last self-administration training. Together, the findings suggest that cue-induced reinstatement of food seeking involves D1-family receptors but not D2-family receptors.

B. Glutamate

An important role for glutamate transmission in cue-induced reinstatement is supported by 3 studies using the mGluR2/3 agonist LY 379268 (which decreases evoked glutamate release). Systemic injections of LY 379268 decrease reinstatement of food seeking induced by discrete cues previously paired with food pellets (Liechti *et al.*, 2007), discriminative cues previously paired with condensed sweetened milk (Baptista *et al.*, 2004), and contextual cues previously paired with sucrose solution (Bossert *et al.*, 2006). Additionally, Uejima et al. (2007) found that systemic and central amygdala injections of LY 379268 decrease the expression of INCUBATION OF SUCROSE CRAVING, the time-dependent increase in cue-induced sucrose seeking after last exposure to sucrose. In this study, systemic and central amygdala LY 379268 injections selectively decreased enhanced extinction responding in the presence of the sucrose cues 21 days after cessation of sucrose (10% solution) reinforced responding, but had no effect on extinction responding 3 days after cessation of sucrose reinforced responding. Dravolina et al. (2007) found that systemic injections of the mGluR1 antagonist EMQMCM

attenuate discriminative-cue-induced reinstatement of food (pellet) seeking. The same investigators found that this type of reinstatement was not affected by systemic injections of the mGluR5 antagonist MPEP (Bespalov *et al.*, 2005). In contrast, systemic injections of MTEP, an mGluR5 antagonist with greater selectivity for mGluR5 receptors (Cosford *et al.*, 2003), decreased discriminative-cue-induced reinstatement of lever responding for sweetened condensed milk (Martin-Fardon *et al.*, 2009). MTEP, however, had no effect on discrete-cue-induced reinstatement of food seeking (Gass *et al.*, 2009).

Potential evidence against a role for AMPA glutamate receptors in cue-induced food seeking is that viral over-expression of the GluR1 or GluR2 AMPA receptor subunits in the accumbens in rats, or genetic deletion of the GluR1 gene in mice, has no effect on extinction responding for sucrose or food pellets, respectively (Mead *et al.*, 2007; Sutton *et al.*, 2003).

There is currently no explanation for the discrepant results from studies using pharmacological agents (LY379268 and EMQMCM) versus studies using a viral vector construct or knockout mice. In our view, results from genetic manipulation studies should be interpreted with caution and should be independently confirmed by neuropharmacological manipulations, because of unknown compensatory changes that may develop over days after the viral vector manipulation or over the lifetime after constitutive gene deletion (Routtenberg, 1996).

Together, results from pharmacological studies suggest that cue-induced reinstatement of food seeking involves glutamatergic transmission. In the specific case of discrete-cue-induced reinstatement, however, it appears that mGluR5 receptors do not mediate this effect.

C. Other neurotransmitters, peptides, and receptors

Cannabinoids—Systemic injections of the CB1 receptor antagonist SR 141716A (rimonabant) attenuate discrete-cue-induced reinstatement of cocaine seeking (De Vries *et al.*, 2001), heroin seeking (De Vries *et al.*, 2003), methamphetamine seeking (Anggadiredja *et al.*, 2004), and nicotine seeking (De Vries and Schoffelmeer, 2005). Rimonabant injections also attenuate discriminative-cue-induced reinstatement of ethanol seeking (Economidou *et al.*, 2006) and context-induced reinstatement of nicotine seeking (Diergaarde *et al.*, 2008). Based on these findings, several investigators assessed the effect of rimonabant injections on cue-induced reinstatement of food seeking.

De Vries *et al.* (2005) found that rimonabant injections attenuate discrete-cue-induced reinstatement of sucrose (pellet) seeking in rats. Similarly, Ward *et al.* (2007) found that rimonabant injections (1.0 and 3.0 mg/kg) attenuate discrete-cue-induced reinstatement in mice trained to self-administer Ensure, a palatable mixed macronutrient (15 g carbohydrate, 2.3 g fat, 3.4 g protein) that maintains reliable self-administration behavior in mice (Ward and Dykstra, 2005).

Interestingly, in mice trained to self-administer a 32% corn-oil solution, Ward *et al.* (2007) found that discrete-cue-induced reinstatement was not affected by rimonabant at doses of 1.0 or 3.0 mg/kg. These investigators found that a higher dose (10 mg/kg) was effective, but this dose may have non-specific behavioral effects. In CB1 knockout mice, Ward *et al.* found modest (non-significant) attenuation of discrete-cue-induced reinstatement of Ensure seeking but not corn-oil seeking. As discussed in Section II, we speculate that this difference may be due to preferential recruitment of endocannabinoid signaling during training for Ensure-reinforced operant responding.

Serotonin—In cue-induced reinstatement of cocaine seeking, the effects of serotonergic manipulations are complex: cocaine seeking (in a single extinction test several weeks after last exposure) is reduced by either serotonin depletion or by chronic exposure to fluoxetine, a

serotonin reuptake blocker that increases synaptic serotonin levels (Baker *et al.*, 2001; Tran-Nguyen *et al.*, 1999). Discrete-cue-induced reinstatement of cocaine seeking is also attenuated by systemic injections of fluoxetine or d-fenfluramine (a serotonin reuptake blocker and releaser) (Burmeister *et al.*, 2003). Additionally, in cocaine-trained rats, Accosta *et al.* (2005) found that systemic injections of the 5-HT(1A/1B) receptor agonist RU 24969 attenuate discrete-cue-induced reinstatement of cocaine seeking, while Fletcher *et al.* (2008) and Burbassi *et al.* (2008) found that injections of the 5-HT_{2C} receptor agonist Ro 60-0175 attenuate context- and discriminative-cue-induced reinstatement, respectively. In some of these studies, the effects of the serotonergic manipulations in cocaine-trained rats were also assessed in food-trained rats.

In the study by Tran-Nguyen *et al.* (1999), serotonin depletion with the tryptophan hydroxylase inhibitor para-chlorophenylalanine (p-CPA) had no effect on extinction responding in the presence of cues previously paired with food. However, in a subsequent study, the same group found that lesions of serotonin neurons by ventricular injections of the toxin 5,7-dihydroxytryptamine (DHT) enhance lever responding in an extinction test in rats previously trained to self-administer sucrose (Tran-Nguyen *et al.*, 2001). The difference in results is probably not due to the type of lesion manipulation, because the magnitude of serotonin depletion was similar after p-CPA and 5,7-DHT injections. The difference might be due to the type of food used during training and/or the food-restriction conditions (see Section II). Specifically, in the earlier study (Tran-Nguyen *et al.*, 1999), the rats were food-restricted (1 h/d food access) and trained to lever press for regular food pellets, while in the later study (Tran-Nguyen *et al.*, 2001), the rats had free access to food during most training days and during testing, and lever pressed for sucrose pellets during training.

In two studies, cue-induced reinstatement was manipulated with 5-HT_{1A/1B} and 5-HT_{2B/2C} receptor agonists. Burbassi *et al.* (2008) found that injections of the 5-HT_{2B/2C} agonist Ro 60-0175 have no effect on discriminative-cue-induced reinstatement of sucrose seeking. Acosta *et al.* (2005) found that injections of the 5-HT_{1A/1B} agonist RU24969 attenuate discrete-cue-induced reinstatement of sucrose seeking. Because RU 24969 decreases serotonin release (Bosker *et al.*, 1997; Martin *et al.*, 1992), the finding by Acosta *et al.* (2005) may seem difficult to reconcile with the earlier finding that 5,7-DHT lesions of serotonin neurons enhance cue-induced food seeking in an extinction test (Tran-Nguyen *et al.*, 2001). However, as mentioned in Section II, the mechanisms of cue-induced cocaine seeking in a single extinction test may differ from those of cue-induced reinstatement of cocaine seeking after extinction (Feltenstein and See, 2008). Thus, a question for future research is whether the same serotonergic manipulation (5,7-DHT lesion or RU 24969 injections) would have opposite effects in the two behavioral procedures.

Together, the data suggest that, as with cue-induced reinstatement of cocaine seeking, serotonin plays a complex, not fully understood role in cue-induced reinstatement of food seeking.

Opioids—It is well-established that endogenous opioid systems are important modulators of feeding in humans and laboratory animals: opioid receptor agonists increase food intake while opioid receptor antagonists decrease food intake (Kelley, 2004; Levine *et al.*, 1985). In two studies, the effect of preferential mu opiate receptor antagonists (naloxone and naltrexone) on cue-induced reinstatement of food seeking was assessed.

Grimm *et al.* (2007) studied the effect of naloxone on the time-dependent increases in discrete-cue-induced sucrose seeking (incubation). Rats were trained to self-administer a sucrose solution and then tested either 1 or 30 days after last exposure to sucrose for reinstatement following 6 h of extinction. The results indicated that over a range of doses, naloxone decreases enhanced discrete-cue-induced reinstatement after 30 days but has minimal effect on the lower

response to cue-induced reinstatement after 1 day. The negative findings on day 1 are difficult to interpret because reinstatement on that day was very weak (~10 presses/1-h in the vehicle condition). As mentioned above, when response rates during testing are low, the effect of a pharmacological manipulation may be undetected due to a floor effect.

Burattini et al. (2008) found that discriminative-cue-induced reinstatement of sucrose (pellet) seeking was only weakly (and non-significantly) attenuated by naltrexone (2.5 mg/kg).

Together, the data suggest that mu opioid receptors are involved in discrete-cue-induced reinstatement of food seeking and incubation of sucrose craving, but may not be involved in discriminative-cue-induced reinstatement of food seeking.

Peptide YY-36—As mentioned in Section 4, we found that systemic injections of PYY3-36 decrease not only food-priming-induced reinstatement but also discrete-cue-induced reinstatement of high-fat food seeking (Ghitza *et al.*, 2007). Interestingly, arcuate nucleus injections of PYY3-36 decreased food-priming-induced reinstatement but had no effect on discrete-cue-induced reinstatement. At present, the brain sites that mediate the effect of PYY3-36 on discrete-cue-induced reinstatement are unknown.

Sigma 1 receptors—Sigma 1 receptors play a role in the rewarding effects of cocaine as assessed in the CPP procedure (Hayashi and Su, 2005; Maurice and Romieu, 2004). Romieu et al. (2004) also found that systemic injections of the sigma 1 antagonist BD 1047 decrease cocaine-priming-induced reinstatement of cocaine CPP. Recently, Martin-Fardon et al. (2007) examined the effect of BD 1047 (1 to 30 mg/kg) on discriminative-cue-induced reinstatement of cocaine seeking and food (sweetened condensed milk) seeking. BD 1047 dose-dependently decreased reinstatement of cocaine seeking, but decreased reinstatement of food seeking only at the highest dose tested (30 mg/kg). Interpretation of the data is complicated by a potential floor effect: the response rate in the food-trained rats in the vehicle condition (~12-responses/1-h) was probably too low for reliable detection of the effect of a pharmacological agent. Thus, the role of sigma 1 receptors in cue-induced reinstatement of food seeking is a subject for future research.

D. Brain sites involved in cue induced-reinstatement

Two published studies provide data on the brain sites involved in discrete-cue-induced reinstatement of food seeking. McLaughlin et al. (2007) found that this reinstatement is potentiated by reversible inactivation of the caudal portion of the basolateral amygdala with the local anesthetic bupivacaine, but not affected by inactivation of the rostral basolateral amygdala. An issue to consider in interpretation of these data is that the behavioral effects of bupivacaine may be due to inactivation of fibers that pass through the target area rather than inactivation of cell bodies in the target area.

Floresco et al. (2008) found that discrete-cue-induced reinstatement of food seeking is attenuated by reversible inactivation of the accumbens core by injections of muscimol +baclofen (GABA_A and GABA_B agonists), but increased by inactivation of the accumbens shell. However, because the accumbens shell cannulae potentially passed through the ventricles, it is likely that the GABA agonists diffuse to the ventricles (Johnson and Epstein, 1975) and consequently to other brain areas. Thus, more research is needed to clarify the exact site of action for the surprising potentiation of discrete-cue-induced reinstatement by muscimol +baclofen injections aimed at accumbens shell.

Hamlin et al. (2006) investigated brain sites involved in context-induced reinstatement of sucrose seeking. Their methodology was to stain for c-Fos, the protein product of the immediate early gene c-fos that has been used in many studies as a neuronal activity marker (Curran and

Morgan, 1995; Morgan and Curran, 1991). Their main finding was that context-induced reinstatement was associated with c-Fos induction in the accumbens shell, lateral hypothalamus, basolateral amygdala, and rostral agranular insular cortex.

Hamlin et al. (2006) also examined the role of D1 receptors in context-induced reinstatement of sucrose seeking. They found that systemic SCH 23390 injections, which decreased context-induced reinstatement of sucrose seeking, also decreased context-induced induction of c-Fos in the accumbens shell, lateral hypothalamus, and rostral agranular insular cortex. These data suggest that context-induced reinstatement of food seeking involves D1 receptor activation in those brain sites. This idea needs to be confirmed by experiments in which SCH 23390 is injected into these brain sites prior to the context-induced reinstatement tests. In this regard, Marchant et al. (2009) recently reported that inactivation of the lateral hypothalamus attenuates context-induced reinstatement of sucrose seeking.

VI. Yohimbine-induced reinstatement

Systemic injections of yohimbine, an alpha-2 adrenoceptor antagonist that induces stress-like responses in humans and non-humans (see Introduction), reliably reinstate cocaine seeking in monkeys (Lee *et al.*, 2004), and cocaine (Feltenstein and See, 2006), methamphetamine (Shepard *et al.*, 2004), and alcohol (Le *et al.*, 2005) seeking in rats. Based on these studies, we and others have used yohimbine as a pharmacological stressor in feeding studies and have shown that it also reliably reinstates food seeking (Ghitza *et al.*, 2006; Nair *et al.*, 2008; Nair *et al.*, 2006). Below we describe initial studies on the neuropharmacology of yohimbine-induced reinstatement of food seeking.

A. Corticotrophin-releasing factor (CRF)

Footshock-stress-induced reinstatement of drug seeking involves activation of extrahypothalamic but not hypothalamic CRF receptors (the latter are a component of the hypothalamic-pituitary-adrenal [HPA] axis); this has been found for seeking of heroin (Shaham *et al.*, 1997b), cocaine (Erb *et al.*, 1998; Wang *et al.*, 2005), alcohol (Le *et al.*, 2002; Le *et al.*, 2000), and nicotine (Zislis *et al.*, 2007). The same has also been found for reinstatement of heroin or cocaine seeking induced by acute 24-h food deprivation stress (Shalev *et al.*, 2006; Shalev *et al.*, 2003).

Based on these findings, we examined the effect of the CRF1 receptor antagonist antalarmin on yohimbine-induced reinstatement of food seeking (Ghitza *et al.*, 2006). We showed that antalarmin selectively attenuates yohimbine-induced reinstatement at doses that have no effect on food-priming-induced reinstatement or ongoing food-reinforced responding. These findings parallel those of Marinelli et al. (2007) who reported that antalarmin attenuates yohimbine-induced reinstatement of alcohol seeking. These investigators also found that antalarmin has no effect on yohimbine-induced increases in plasma corticosterone levels. Plasma corticosterone levels can be considered an index of HPA axis activation (Dallman *et al.*, 1995; Selye, 1956); therefore, the findings by Marinelli et al. suggest that yohimbine's effect on reinstatement is independent of its effect on the HPA axis.

The brain sites involved in antalarmin's attenuation of yohimbine-induced reinstatement are currently unknown. One site that deserves future investigation is the bed nucleus of the stria terminalis (BNST) where footshock-stress-induced reinstatement of drug seeking is attenuated by microinjection of CRF1 receptor antagonists (Erb and Stewart, 1999; Wang *et al.*, 2006) or reversible inactivation with tetrodotoxin (Shaham *et al.*, 2000a). Yohimbine injections increase CRF mRNA expression in the BNST, a finding that supports a potential role for the BNST in the effect of antalarmin on yohimbine-induced reinstatement (Funk *et al.*, 2006).

B. Noradrenaline

Yohimbine is widely used as a prototypical alpha-2 adrenoceptor antagonist in neuropharmacological studies (Bremner *et al.*, 1996a, b), but it also acts on other receptor subtypes, including D2 receptors (Scatton *et al.*, 1980), alpha-1 adrenoceptors (Doxey *et al.*, 1984) benzodiazepine binding sites (Matsunaga *et al.*, 2001), and 5-HT1A receptors (Winter and Rabin, 1992). Despite yohimbine's lack of pharmacological selectivity, our initial hypothesis regarding its mechanism of action on reinstatement of food seeking was that it involves activation of central noradrenergic systems that mediate stress responses (Redmond and Huang, 1979; Stanford, 1995; Stone, 1983; Tanaka *et al.*, 1990). Several lines of evidence seemed to support this hypothesis. First, as mentioned in the Introduction, yohimbine increases brain noradrenergic cell firing (Aghajanian and VanderMaelen, 1982) and norepinephrine release (Abercrombie *et al.*, 1988). Second, alpha-2 adrenoceptor agonists such as clonidine and lofexidine decrease footshock-stress-induced reinstatement of heroin seeking (Shaham *et al.*, 2000b), cocaine seeking (Erb *et al.*, 2000), heroin-cocaine combination seeking (Highfield *et al.*, 2001), and nicotine seeking (Zislis *et al.*, 2007). Third, Lee *et al.* (2004) reported that yohimbine-induced reinstatement of cocaine seeking in monkeys is attenuated by clonidine and is mimicked by the selective alpha-2 adrenoceptor antagonist RS 79948 (Milligan *et al.*, 1997).

However, a different picture has emerged from recent studies in which we tried to confirm that the effect of yohimbine on reinstatement is mediated by alpha-2 adrenoceptors (Fig. 3). Because the results from these studies were negative, we did not publish them in an empirical paper and instead present them in this review. The experimental procedures were similar to those we described above (Section IV A) and in Nair *et al.* (2008). We determined the effect of systemic injections of the alpha-2 adrenoceptor agonist clonidine (0.04 or 0.08 mg/kg, i.p.) on reinstatement of lever responding induced by yohimbine (2 mg/kg, i.p.). In other groups of rats, we tested whether the effect of yohimbine on reinstatement is mimicked by the selective alpha-2 adrenoceptor antagonist RS 79948 (Hume *et al.*, 1996; Milligan *et al.*, 1997) (0.5, 1.0, and 1.5 mg/kg, i.p.). The doses of RS 79948 were chosen on the basis of previous reports (Packard and Wingard, 2004; White and Birkle, 2001).

As seen in Fig. 3, yohimbine-induced reinstatement of food seeking was not blocked by clonidine, even at doses 4–8 times higher than those required to block both footshock-stress-induced reinstatement of drug seeking (Erb *et al.*, 2000; Shaham *et al.*, 2000b) and yohimbine's effects in other behavioral procedures (Soderpalm *et al.*, 1995). Additionally, yohimbine's effect on reinstatement of food seeking was not mimicked by RS 79948. These results are in agreement with those of Brown *et al.* (Brown *et al.*, 2009) who reported that systemic injections of clonidine (40 mg/kg) do not attenuate yohimbine-induced reinstatement of cocaine seeking. Together, these results do not support our initial hypothesis that yohimbine's effect on reinstatement is mediated by alpha-2 adrenoceptor activation.

An issue to consider in our studies with yohimbine is that the effective yohimbine doses in our studies (1–2 mg/kg) are somewhat lower than those typically used in studies on the anxiogenic effects of yohimbine. Thus, yohimbine's effect on reinstatement may be unrelated to its ability to induce a stress-like state in the rat under our experimental conditions. This possibility, however, is unlikely since we found that at the doses used to reinstate food and drug seeking in our studies, yohimbine induces a stress-like state in a social-interaction test, and that this effect is blocked by the CRF1 receptor antagonist, antalarmin (Ghitza *et al.*, 2006).

Still unknown are the reasons for the discrepant results in the mechanisms underlying yohimbine-induced reinstatement between the studies in rats trained to self-administer food or cocaine and the study by Lee *et al.* (2004) with monkeys trained to self-administer cocaine. Also relatively unknown is the receptor subtype/s involved in the effect of yohimbine on

reinstatement of food seeking. One candidate is the dopamine D1 family receptor (see Section VI C). Another potential candidate is the 5-HT1A autoreceptor on serotonergic cell bodies in the raphe nuclei (Chaput and de Montigny, 1988; Sharp *et al.*, 1989). As mentioned above, yohimbine binds to 5-HT1A receptors (Millan *et al.*, 2000; Winter and Rabin, 1992) and also substitutes for the prototypical 5-HT1A agonist 8-OH-DPAT in a DRUG DISCRIMINATION procedure, suggesting agonist or partial agonist actions at this receptor. Indeed, there is evidence from biochemical assays that yohimbine is a partial agonist at 5-HT1A receptors (Arthur *et al.*, 1993). Additionally, like 8-OH-DPAT, systemic injections of yohimbine decrease dorsal raphe cell firing and serotonin release in the frontal cortex; these effects are reversed by pretreatment with the 5-HT1A antagonist WAY100,635 (Millan *et al.*, 2000), but see Cheng *et al.* (1993) for different results.

C. Dopamine

We recently studied the role of D1-family receptors in yohimbine-induced reinstatement of food seeking (Fig. 2A), using procedures similar to those in our previous work (Nair *et al.*, 2009; Nair *et al.*, 2008). After training and extinction of food-reinforced lever responding, systemic injections of SCH 23390 (5 or 10 µg/kg, s.c.) decreased reinstatement of lever responding induced by yohimbine. These doses of SCH 23390 had no effect on food-reinforced operant responding (Fig. 2C). These results suggest that D1-family receptors play an important role in yohimbine-induced reinstatement of food seeking. The brain sites involved are currently unknown.

D. Hypocretin

The studies described below on the role of hypocretin in yohimbine-induced reinstatement of food seeking were inspired by a paper by Boutrel *et al.* (2005). They found that ventricular injections of hypocretin 1 reinstate cocaine seeking, an effect attenuated by the alpha-2 adrenoceptor antagonist clonidine and the nonselective CRF receptor antagonist d-Phe-CRF. As mentioned above, CRF receptor antagonists and alpha-2 adrenoceptors agonists attenuate footshock-stress-induced reinstatement of drug seeking (Shaham *et al.*, 2000a). Boutrel *et al.* found that the hypocretin 1 receptor antagonist SB 334867 also attenuates footshock-stress-induced reinstatement of cocaine seeking. Together, these results suggest that stress-induced activation of brain hypocretin systems (Boutrel and de Lecea, 2008; Winsky-Sommerer *et al.*, 2005) is involved in stress-induced reinstatement of cocaine seeking.

However, in a recent study with food-restricted rats trained to self-administer high-fat food pellets, we found that systemic injections of SB 334867, at doses that led to significant attenuation of ongoing pellet self-administration, have no effect on yohimbine-induced reinstatement (Nair *et al.*, 2008). Additionally, as mentioned in Section II, SB 334867 had no effect on hypocretin 1-induced reinstatement of food seeking. These results contrast with those of Richards *et al.* (2008), who reported that in food-sated rats trained to lever press for an oral sucrose solution, SB 334867 attenuated yohimbine-induced reinstatement of sucrose (and alcohol) seeking but had no effect on ongoing sucrose self-administration.

As discussed in Section II, one possible explanation for these discrepant results is a difference in non-operant feeding conditions: free access to regular nutritionally-balanced food in the study by Richards *et al.* versus restricted feeding to about 65–70% of daily free-feeding ration in our study. Alternatively, the discrepancy may be due to the use of different reinforcers: 5% oral sucrose solution in the Richards *et al.* study versus 35% fat pellets in our study.

VII. Discussion

In this section we first provide our main conclusions regarding the neuropharmacology of reinstatement of food seeking. Subsequently, we discuss similarities and differences between reinstatement of food seeking and reinstatement of drug seeking. We then discuss the degree to which the reinstatement procedure provides a suitable animal model for understanding neuronal mechanisms of relapse to old unhealthy eating habits during dietary treatments in humans. We conclude by briefly discussing future research directions.

A. General summary: neuronal mechanisms of relapse to food seeking

The study of the neuropharmacological mechanisms of reinstatement of food seeking is in its infancy, but based on the data reviewed, we offer several tentative conclusions.

Food-priming-induced reinstatement of food seeking—Activation of **D1 and D2** but not **D3** dopamine receptors is critical for food-priming-induced reinstatement. A critical brain site for the **D2**-receptor-mediated effect is the dorsal mPFC. Glutamate transmission is also critical, especially in the nucleus accumbens. Two other brain sites implicated in food-priming-induced reinstatement are the ventral pallidum and the arcuate nucleus. Food-priming-induced reinstatement is inhibited by **PYY3-36** via its action on **Y2** receptors, suggesting an inverse relationship between circulating levels of endogenous **PYY3-36** and this type of reinstatement.

Cue-induced reinstatement of food seeking—Glutamate transmission is critical, regardless of whether the cues are discrete, discriminative, or contextual. Central amygdala glutamate transmission plays an important role in the time-dependent increases in cue-induced sucrose seeking (incubation of sucrose craving). There is also evidence for an important role of **D1** receptors (potentially in accumbens shell, basolateral amygdala, and/or rostral agranular insular cortex) in context-induced food seeking. Endocannabinoid actions at **CB1** receptors can play an important role in discrete-cue-induced reinstatement, but this effect is dependent on the food type used during training. As in the case with food-priming-induced reinstatement, there appears to be an inverse relationship between vulnerability to cue-induced reinstatement and circulating levels of endogenous **PYY3-36**. Manipulations of serotonin transmission modulate cue-induced reinstatement, but in a complex way. Finally, reversible-inactivation studies suggest a role of accumbens core in discrete-cue-induced reinstatement.

Yohimbine-induced reinstatement of food seeking—The effect of yohimbine likely involves activation of **CRF1** receptors at extrahypothalamic sites, **D1-family receptors**, and, surprisingly, appears to be independent of its action at **alpha-2** adrenoceptors. Brain hypocretin systems may also be involved, but this involvement appears to depend on the type of food reward used **and/or home-cage feeding conditions**.

Very few studies have directly compared the effect of a given neuropharmacological manipulation on more than one reinstating stimulus. Additionally, very few studies have compared the effect of a given manipulation on both food-reinforced responding and reinstatement. However, results from our recent studies in which these comparisons were made lead to two tentative conclusions: (1) the neuronal mechanisms of food-priming- and cue-induced reinstatement are largely dissociable from those of reinstatement induced by the pharmacological stressor yohimbine, and (2) the neuronal mechanisms of reinstatement of food seeking are likely different from those underlying ongoing food-reinforced responding (Table 5).

Supporting the first conclusion of pharmacological dissociation across reinstating stimuli, is the finding that the **CRF1** receptor antagonist antalarmin attenuates yohimbine-induced reinstatement but not food-priming-induced reinstatement, while **PYY3-36** attenuates food-

priming- and cue-induced reinstatement but not yohimbine-induced reinstatement (Ghitza *et al.*, 2006; Ghitza *et al.*, 2007). Supporting the second conclusion of pharmacological dissociation between self-administration and reinstatement, are the findings that the hypocretin 1 receptor antagonist SB 334867 and the **MCH1 receptor antagonist SNAP 94847** attenuate food-reinforced responding but have no effect on food-priming and cue-induced reinstatement, while PYY3-36 attenuates food-priming- and cue-induced reinstatement but has no effect on food-reinforced responding (Ghitza *et al.*, 2007; Nair *et al.*, 2008). Additionally, while accumbens injections of D2-family receptor antagonists attenuate food-reinforced responding (Nowend *et al.*, 2001; Salamone *et al.*, 1991), these injections have no effect on food-priming-induced reinstatement (Anderson *et al.*, 2006; Chausmer and Ettenberg, 1999).

Interestingly, we reached similar conclusions about reinstatement of cocaine and heroin seeking after reviewing a much larger number of studies: “Taken together, it appears that multiple and dissociable brain systems are involved in relapse to heroin and cocaine seeking induced by drug priming, conditioned cues and stress. Somewhat surprisingly, it also appears that the neuronal events that mediate heroin- or cocaine-induced reinstatement are to some degree different from those involved in their reinforcing effects” (Shalev *et al.*, 2002).

Finally, an unexpected conclusion based on the studies reviewed is that the neuropharmacological mechanisms of a given reinstating stimulus might differ depending on the food type used and/or the non-operant baseline feeding conditions (restricted feeding versus freely available food). As mentioned above, the CB1 receptor antagonist rimonabant, attenuates cue-induced reinstatement after a history of sucrose or Ensure but not corn-oil self-administration (De Vries *et al.*, 2005; Ward *et al.*, 2007). Additionally, the hypocretin 1 receptor antagonist SB 334867 attenuates yohimbine-induced reinstatement in food-sated rats trained to self-administer sucrose, but not in food-restricted rats trained to self-administer high-fat food pellets (Nair *et al.*, 2008; Richards *et al.*, 2008).

B. Similarities and differences between reinstatement of food and drug seeking

The rewarding effects of palatable foods and abused drugs appear to overlap substantially in their neurobiological mechanisms (Kelley and Berridge, 2002; Volkow and Wise, 2005). Results from studies by Hoebel and colleagues demonstrate that rats given long-term access to palatable food (sugar solution) develop a constellation of behavioral and neurochemical symptoms resembling those that occur after repeated exposure to addictive drugs, thus supporting the notion of “food addiction” (Avena *et al.*, 2008; Colantuoni *et al.*, 2002; Colantuoni *et al.*, 2001). Based on those studies, and on the fact that most studies of reinstatement of food seeking were performed by addiction researchers interested in the selectivity of their experimental manipulations for drug versus food reward (Fig. 1B), we discuss below the degree of overlap in the mechanisms underlying reinstatement of food versus drug seeking. Table 6—and Table 7 show the effects of different pharmacological agents on the two types of reinstatement induced by priming (Table 6) and cues (Table 7).

Reinstatement of food and drug seeking by pharmacological agents—Similarity between reinstatement of food seeking and drug seeking is suggested by instances of pharmacological overlap. For example, ventricular injections of hypocretin 1 reinstate both food and cocaine seeking (Boutrel *et al.*, 2005; Nair *et al.*, 2008). Systemic delta-9-THC injections reinstate both food and alcohol seeking (McGregor *et al.*, 2005). Systemic nicotine injections reinstate nicotine, alcohol, and food seeking (after prior exposure to nicotine) (Le *et al.*, 2006; Le *et al.*, 2003; Shaham *et al.*, 1997a). Systemic injections of D2-family receptor agonists reinstate heroin, cocaine, and food seeking (De Vries *et al.*, 2002; Self *et al.*, 1996; Shaham *et al.*, 1997a; Wise *et al.*, 1990). On the other hand, indirect dopamine agonists like cocaine and amphetamine reliably reinstate opiate and psychostimulant seeking (De Vries *et*

al., 1998; de Wit, 1996; Self, 2004) but not food seeking (de Wit and Stewart, 1981; Odum and Shahan, 2004; Weerts and Griffiths, 2003). Caffeine and the A2A/A1 receptor antagonist CGS 15943 reinstate cocaine but not food seeking (Schenk and Partridge, 1999; Weerts and Griffiths, 2003). Together, the data suggest some overlap in the neurotransmitter systems involved in food and drug seeking. The data discussed below further support this view.

Priming-induced reinstatement—Non-contingent delivery of a small number of food pellets likely induces reinstatement because of the pellet's taste/smell cue properties, whereas drug priming reinstatement is primarily due to direct pharmacological effects on identified receptors or transporters in the brain (Stewart, 1984). Despite this important difference, as depicted in Table 6 there seems to be some overlap between the mechanisms underlying priming-induced reinstatement of food and drug seeking.

It is difficult to integrate these data in the context of the neuronal circuitry underlying food-priming-versus drug-priming-induced reinstatement, especially in light of recent findings of Rogers *et al.* (2008) suggesting that even the circuitry of heroin-priming- and cocaine-priming-induced reinstatement only partially overlap. Another interpretation issue to consider is that for a given brain area, central injections of selective dopaminergic and glutamatergic drugs often lead to behavioral effects that are different from those obtained after reversible inactivation with GABAergic agonists or local anesthetics (Bossert *et al.*, 2005b). For example, food-priming-induced reinstatement is not decreased by muscimol+baclofen inactivation of the dorsal mPFC or accumbens core (McFarland and Kalivas, 2001), but is decreased by dorsal mPFC eticlopride or SCH 23390 injections or by accumbens core LY 379268 injections (Peters and Kalivas, 2006; Sun and Rebec, 2005).

Even with these considerations, it appears that dorsal mPFC dopamine transmission and accumbens core glutamate transmission, which mediate drug-priming-induced reinstatement (Capriles *et al.*, 2003; Cornish and Kalivas, 2000; McFarland and Kalivas, 2001; Park *et al.*, 2002), are also critical for food-priming-induced reinstatement (Peters and Kalivas, 2006; Sun *et al.*, 2005). Additionally, neuronal activity in the ventral pallidum is important for heroin-priming-, cocaine-priming-, and food-priming-induced reinstatement (McFarland and Kalivas, 2001; Rogers *et al.*, 2008). A question for future research is whether VTA neuronal activity, which is critical for drug-priming-induced reinstatement (Kalivas and McFarland, 2003; Stewart, 1984), also mediates food-priming-induced reinstatement. As mentioned above, Sun *et al.* (2005) reported that VTA injections of kynurenate (an antagonist at ionotropic glutamate receptors) attenuate cocaine-priming- but not food-priming-induced reinstatement. However, there are methodological issues related to the food-priming manipulation in this study (see Section II) that limit interpretation of their negative findings.

Together, the results depicted in Table 6 suggest that the mechanisms of food- and drug-priming-induced reinstatement partially overlap. The overlap appears to include dorsal mPFC dopamine, nucleus accumbens glutamate, and yet to be identified neurotransmitter(s) in the ventral pallidum.

Cue-induced reinstatement—Unlike priming-induced reinstatement, cue-induced reinstatement is procedurally similar regardless of whether the reinforcer being studied is food or a drug. As mentioned above, the cues may be discrete, discriminative, or contextual, and cue-induced food seeking has also been assessed in a single extinction test. Like priming-induced reinstatement, cue-induced reinstatement shows partial but not complete mechanistic overlap for drug seeking versus food seeking (Table 7).

Integration of these data is complicated for several reasons. One issue is that the neuronal mechanisms of reinstatement induced by discrete versus contextual drug cues only partially

overlap (Bossert *et al.*, 2007; Feltenstein and See, 2008). Another issue is that even within a given cue type (i.e., discrete, discriminative, contextual), it is not clear to what extent the brain circuits mediating reinstatement are similar across drug classes (Crombag *et al.*, 2008a). For example, context-induced reinstatement of alcohol seeking but not cocaine seeking is associated with activation of lateral hypothalamic hypocretin neurons (Hamlin *et al.*, 2008; Hamlin *et al.*, 2007). Additionally, excitotoxic lesions of the basolateral amygdala attenuate cue-induced cocaine but not heroin seeking, as assessed in a SECOND-ORDER REINFORCEMENT SCHEDULE (Alderson *et al.*, 2000; Everitt and Robbins, 2000; Whitelaw *et al.*, 1996).

Another issue relevant for interpreting results is the response rate during testing. When the response rates are high, pharmacological manipulations are more likely to produce a detectable decrease. Investigators have argued that dopaminergic agents, the glutamatergic agent LY 379268, and the sigma 1 antagonist BD 1047 have selective or preferential effects on cue-induced drug seeking, because the drugs either did not significantly decrease responding in food-trained rats (Gal and Gyertyan, 2006), or decreased responding at doses higher than those required to decrease responding in cocaine-trained rats (Baptista *et al.*, 2004; Martin-Fardon *et al.*, 2007). In these studies, however, responding for food cues was substantially lower (2–3 times) than that for cocaine cues. Thus, an alternative interpretation is that the differential response to the pharmacological agents reflects differences in response rates rather than biological differences in mechanisms underlying cue-induced drug versus food seeking.

Together, the data suggest an overlap in the mechanisms underlying cue-induced reinstatement of food and drug seeking. These mechanisms include activation of group II metabotropic receptors (mGluR2 and mGluR3), D1 dopamine receptors, CB1 receptors, and mu opioid receptors, all of which contribute to reinstatement of heroin, cocaine, alcohol, and food seeking induced by several types of cues. There is also evidence for a role of mGluR1 and 5-HT1A and/or 5-HT1B receptors in discretecue-induced reinstatement of both food and cocaine seeking. Additionally, there is evidence that activity in the accumbens core mediates discretecue-induced cocaine, heroin, and food seeking and that activity in the lateral hypothalamus mediates context-induced reinstatement of both alcohol and food seeking. Nonetheless, the degree of overlap in the neuronal circuitry mediating cue-induced drug versus food seeking remains an open question. Involvement of different circuits is supported by findings of opposite effects of reversible inactivation of the basolateral amygdala on discretecue-induced reinstatement of food versus drug seeking (McLaughlin and See, 2003; McLaughlin and Floresco, 2007). However, these two studies differed from each other in the method of inactivation (bupivacaine or tetrodotoxin, both of which also inactivate fibers of passage) and in the training procedure used. Thus, the results of McLaughlin *et al.* (2003; 2007) need to be confirmed with more selective pharmacological agents and more precisely matched experimental procedures.

Stress-induced reinstatement—Our studies on yohimbine-induced reinstatement of food seeking were inspired by our previous work on stress-induced reinstatement of drug seeking (Shaham *et al.*, 2000a). This line of investigation was initiated with the demonstration that intermittent uncontrollable footshock reinstates heroin seeking (Shaham and Stewart, 1995), cocaine seeking (Erb *et al.*, 1996), and alcohol seeking (Le *et al.*, 1998) in rats. In subsequent studies using the operant and the CPP reinstatement procedures, we and others have shown that the effect of intermittent footshock generalizes to some stressors but not others (Lu *et al.*, 2003). In the operant reinstatement procedure, effective stressors are acute food deprivation (Shalev *et al.*, 2000), a conditioned fear cue previously paired with shock (Liu and Weiss, 2003) (but see (Shaham *et al.*, 2000a)), and several pharmacological stressors, such as CRF (Le *et al.*, 2002; Shaham *et al.*, 1997b), the kappa agonists spiradoline and enadoline (Valdez *et al.*, 2007), and yohimbine (Lee *et al.*, 2004; Shepard *et al.*, 2004). Ineffective stressors

include restraint, a fox odor that induces stress responses in rats, intermittent loud noise, and the pharmacological stressors FG 7142 and PTZ (benzodiazepine inverse agonist and antagonist, respectively) (unpublished data and Shaham *et al.*, 2000a; Shalev *et al.*, 2000). In the CPP reinstatement procedure, effective stressors are intermittent footshock (Wang *et al.*, 2006), restraint (Sanchez *et al.*, 2003), conditioned fear (Sanchez and Sorg, 2001), swim stress (Kreibich and Blendy, 2004), tail pinch (Ribeiro Do Couto *et al.*, 2006), social defeat (Ribeiro Do Couto *et al.*, 2006), and the pharmacological stressor U 50488 (a kappa receptor antagonist) (Carey *et al.*, 2007).

Together, the findings show that the phenomenon of footshock stress-induced reinstatement in the operant model generalizes to the CPP reinstatement procedure and to several other stressors. In contrast, the only stressor currently known to reliably reinstate food seeking is yohimbine. In early studies, we and others found that the effect of intermittent footshock on reinstatement does not generalize to food-restricted rats trained to self-administer regular (nutritionally balanced) food pellets (Ahmed and Koob, 1997; Mantsch and Goeders, 1999) or to food-sated rats trained to self-administer sucrose pellets or solutions (Buczek *et al.*, 1999; Le *et al.*, 1998).

The reasons for the differential effects of yohimbine and intermittent footshock on reinstatement of food seeking are unknown. One issue to consider is that while stressors activate systems involved in general appetitive motivation states and approach behaviors toward different rewards (e.g., the mesocorticolimbic dopamine system (Deutch and Roth, 1990; Kalivas and Stewart, 1991; Stewart *et al.*, 1984)), they also activate fight-or-flight stress preparatory systems (e.g., the sympathetic nervous system (Cannon, 1935; Mason, 1975)) that inhibit feeding-related behaviors. Thus, we speculate that at the doses used to induce reinstatement, yohimbine's effect on appetitive motivational systems is stronger than its effect on the stress preparatory systems that would inhibit food-taking behavior. In contrast, intermittent footshock, at parameters that effectively reinstate drug seeking, more strongly activates stress systems that inhibit food-taking behavior than systems involved in appetitive motivational states, resulting in little reinstatement of food seeking.

However, it would be premature to conclude that the only effective stressor for reinstatement of food seeking is yohimbine, or even that intermittent footshock is categorically ineffective: systematic parametric studies with different shock intensities, different food types, and different food-restriction conditions are yet to be performed. Additionally, there are no published data on the effects of other stressors, such as tail pinch, restraint, and pharmacological stressors other than yohimbine. Thus, the generality of the phenomenon of yohimbine-induced reinstatement of food seeking to other stressors is a subject that deserves future research.

C. The reinstatement procedure, dietary lapses, and health outcomes: a clinical perspective

Taking a broader view, we note that the public-health importance of the preclinical work discussed here is partly predicated on a causal chain whose links can be challenged. The link between triggers (e.g., food cues, stress) and overeating is inferred mostly from laboratory experiments (Grilo *et al.*, 1989; Herman and Polivy, 1975) or from retrospective reports (Oliver and Wardle, 1999), and the link between overeating and obesity has been questioned by proponents of the idea of a metabolically defended "set point" for weight (Major *et al.*, 2007). We will briefly address each of these issues in turn.

The ability of stressors or food-associated cues to trigger overeating requires confirmation in prospective naturalistic studies. Pencil-and-paper-based diary studies support such a relationship showing, for example, that dietary lapses are specifically associated with sadness and stress (Carels *et al.*, 2004; Carels *et al.*, 2001). One weakness of these studies is that paper diaries permit high levels of faked compliance with daily assessment (Stone *et al.*, 2003). In

collaboration with other investigators, we have recently completed an electronic-diary study of weight-loss maintenance in dieters, and our preliminary analyses show that dietary lapses were associated with, among other things, negative moods that are often associated with life stress (Mitola *et al.*, in preparation). Thus, evidence is emerging to support the clinical relevance of the sorts of triggers of dietary lapse that are tested in the reinstatement procedure.

The link between overeating and obesity, and the link between medically safe caloric restriction and weight loss, are each more open to question than they might appear. The question arises due to this seeming paradox: over the past few decades, the prevalence of overweight and obesity have increased at a rate suggestive of behavioral causes, yet 80% of overweight individuals are unable to maintain weight loss successfully through behavioral change (Wing and Phelan, 2005). There is experimental evidence that humans defend “set points” for weight, adjusting metabolic energy expenditure to compensate for behavioral changes that would otherwise induce weight loss (Macias, 2004).

An individual’s set point might be established prenatally or perinatally (Levin, 2005; Vickers *et al.*, 2007), perhaps through mechanisms that formerly would have been considered impossible, such as inheritance of epigenetic changes (Hunter, 2008; Morgan *et al.*, 1999; Waterland and Jirtle, 2003). These possibilities would help resolve the paradox of the rapid rise in overweight and obesity versus the difficulty of maintaining weight loss through behavioral change. However, there is vigorous debate about whether the metabolic defense of set points can overwhelm the effects of compliance to a reasonable regimen of calorie restriction and exercise (Flatt, 2007; Major *et al.*, 2007). Even if the defense of a set point can overwhelm a behavioral strategy, rodent studies suggest the possibility that an individual may defend two different set points—one that dominates when the diet consists mostly of highly palatable food, and another that dominates when the diet consists mostly of ordinary food (Levin, 2005). If this is the case, then reduction of intake of the most rewarding caloric-rich food (such as fast food), which is often provoked by food cues (e.g., the sight of a fast-food restaurant) or stress might help maintain long-term weight loss. Thus, the impact of behavioral and pharmacological interventions aimed at decreasing the impact of food cues and stress on the seeking and craving of high-calories palatable food can be tested in the reinstatement procedure.

To sum up, we caution against facile assumptions linking stress- and cue-induced overeating to obesity. Nonetheless, we think that the evidence supports a place in public-health policy for prevention of trigger-induced overeating; interventions aimed at such prevention are best viewed as one component of a more comprehensive strategy. These interventions, especially pharmacological ones, are good candidates for testing in reinstatement studies. Reinstatement studies are thus not intended to address the whole of the clinical problem of obesity, but only the components that are amenable to behavioral and pharmacological interventions to prevent relapse to old eating habits during dieting.

D. Implications for medication development, future directions, and concluding remarks

Implications for medication development—Medications for dietary treatment have typically been developed based on their effects on physiological mechanisms that regulate ongoing food intake or food metabolism (Bray and Greenway, 2007). Yet it has been known for many years that physiological states of hunger and satiety are often dissociable from human feeding behaviors. Instead, feeding behaviors are to a significant extent under the control of external stimuli such as food cues and stressors (Carels *et al.*, 2004; Carels *et al.*, 2001; Kozlowski and Schachter, 1975; Schachter, 1968, 1974). Thus, the use of the reinstatement procedure should allow for the identification of pharmacological agents that prevent the effects of such stimuli. To the degree that the reinstatement procedure specifically mimics relapse to unhealthy food seeking in humans, these potential medications are unlikely to reach clinical

development if the targeted outcome in rodents (or humans) is reduction in ongoing food-reinforced responding (see Table 5) or, as is typically targeted in rodents, home-cage feeding. Additionally, while we acknowledge that few studies directly address mechanisms underlying food reinstatement, the available results suggest that medications effective against food-priming-induced or cue-induced reinstatement may not be effective against stress-induced reinstatement (Table 5). Thus, clinical pharmacological regimens intended to prevent dietary lapses may require a combination of drugs.

Future directions—We have two specific recommendations for future studies on the neuronal mechanisms of relapse to palatable food seeking. The first is the adaptation of the drug conditioned place preference (CPP) reinstatement procedure to study mechanisms underlying relapse to food seeking. In this variation of the reinstatement procedure, laboratory animals are trained to associate a distinct environment with drug injections and are then subjected to extinction training, during which they are exposed to the same environment in the absence of drug. Resumption of preference for that environment is then determined after non-contingent priming injections of the drug (Mueller and Stewart, 2000; Parker and McDonald, 2000) or exposure to different stressors (Kreibich and Blendy, 2004; Sanchez and Sorg, 2001; Wang *et al.*, 2006). The adaptation of the CPP reinstatement procedure for studying food-priming and stress-induced relapse to palatable food seeking would be worthwhile for two main reasons. First, the equipment cost and expertise required for experiments using the CPP procedure are less than that required for the operant self-administration procedure. Second, the choice of the food type to be used in the CPP is not restricted by technical issues related to the making of 45 mg or 20 mg food pellets for use in operant pellet dispensers. As mentioned above, the type of food used during training may determine the effects of pharmacological agents on cue- and yohimbine-induced reinstatement. Thus, the CPP reinstatement procedure is ideally suited to study the important question of whether different neurobiological mechanisms mediate cue- or stress-induced reinstatement for foods of different fat and carbohydrate compositions.

Our second recommendation is that efforts be made to identify the molecular mechanisms and genes that influence reinstatement of food seeking. Over the last several years, there has been considerable attention given to the molecular mechanisms of food intake (Abizaid *et al.*, 2006; Hommel *et al.*, 2006; Trinko *et al.*, 2007) and drug addiction (Nestler, 2001; Thomas *et al.*, 2008), including relapse to drug seeking (Conrad *et al.*, 2008; Kalivas and Hu, 2006; Self *et al.*, 1998). In contrast, we know of no systematic, hypothesis-driven studies on the molecular mechanisms of relapse to food seeking. Additionally, molecular genetic techniques in mice that allow for the selective induction or suppression of genes have led to new discoveries on genes regulating feeding and body weight (Friedman and Halaas, 1998; Horvath, 2005). In contrast, we know of no systematic studies on the role of genes in relapse to food seeking. The application of genetic techniques to the study of reinstatement of food seeking may lead to new understanding of the genes involved in relapse to unhealthy eating patterns during dietary treatment. The mouse is a suitable species for studying food-induced reinstatement, because, like rats, hungry mice can be trained to self-administer palatable food pellets and sweet solutions. Mice are also highly responsive to food cues in several learning tasks (Crombag *et al.*, 2008b; Mead and Stephens, 2003) and demonstrate reliable cue-induced reinstatement of food seeking (Mead *et al.*, 2007; Yan *et al.*, 2007).

Concluding remarks—Our goal was to provide an overview of research on the neuropharmacological mechanisms of relapse to food seeking as assessed in the reinstatement procedure. This has been a challenging task, because most of the studies reviewed were not part of systematic, hypothesis-driven research programs focused on food seeking. Instead, most of the studies were focused on drug seeking; the food component was introduced primarily to assess possible performance deficits. It is not always straightforward to interpret of results of

such studies in terms of reinstatement of drug versus food seeking, because investigators often do not attempt to equate the experimental conditions (e.g., response rates, number of rewards delivered during training, food restriction conditions, etc.) across reinforcer type. Finally, inasmuch as relapse to old, unhealthy eating habits during dieting is as important a public-health problem as relapse to drug seeking during abstinence, we hope that this review will encourage future systematic studies aimed at elucidating the mechanisms mediating relapse to food seeking, as assessed in the reinstatement procedure.

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Figure 1. Cumulative number of studies that used the reinstatement model in laboratory animals from 1988 to 2008

(A) Cumulative number of reinstatement studies in which only food-trained rats were used.

(B) Cumulative number of drug reinstatement studies in which food-trained rats were also used.

(C) Cumulative number of reinstatement studies with drugs (cocaine, heroin, alcohol, amphetamine, methamphetamine, nicotine).

Figure 2. Effect of systemic injections of SCH 23390 on yohimbine- and food-priming-induced reinstatement of food seeking and food-reinforced responding

(A) Mean±SEM number of active-lever presses after injections of the D1-family receptor antagonist SCH 23390 (5, 10 μg/kg, i.p.) or its vehicle immediately prior to injections of yohimbine (2 mg/kg, i.p.) or its vehicle during reinstatement tests (n=10). Yohimbine or its vehicle was injected 20–25 min prior to the test sessions. (B) Mean±SEM number of active-lever presses after injections of SCH 23390 (5, 10 μg/kg, i.p.) or its vehicle 20–25 minutes prior to exposure to food priming (exposure to 3 pellets delivered non-contingently) or no priming during a 3-hour session (n=10). (C) Mean±SEM number of 35% fat pellets self-administered 20–25 minutes after i.p. injections of SCH 23390 (5, 10 μg/kg) or its vehicle

(saline) during a 3-hour session (n=10). Prior to the reinstatement tests, the rats were trained to lever press for high-fat (35%) food pellets for 10–12 sessions (3 h/session every other day). Subsequently, the food pellets were removed and the rats were given 9 daily 3-hour extinction sessions.

Figure 3. Effect of systemic injections of clonidine on yohimbine-induced reinstatement of food-seeking and effect of RS 79948 on reinstatement of food seeking

(A) Mean±SEM number of active-lever presses after injections of the prototypical alpha-2 adrenoceptor agonist clonidine (0.04, 0.08 mg/kg, i.p.) or its vehicle 15 min prior to injections of yohimbine (2 mg/kg, i.p.) or its vehicle during reinstatement tests (n=9 per dose). Yohimbine or its vehicle was injected 45 min prior to the test sessions. (B) Mean±SEM number of active-lever presses after injections of the highly selective alpha-2 adrenoceptor antagonist RS 79948 (0.5, 1.0, and 1.5 mg/kg, i.p.) or its vehicle 30 min prior to the reinstatement tests (n=10).

Table 1
Glossary of terminology

ACTIVE LEVER: Responses on this lever are reinforced by a reward (food or drug) during self-administration training. During extinction training and tests for reinstatement, responses on this lever are not reinforced. In reinstatement studies, non-reinforced responding on the active lever during testing is the operational measure of reinstatement of reward-taking behavior (often referred to as reinstatement of reward seeking) (Shaham *et al.*, 2003).

CONDITIONED PLACE PREFERENCE (CPP): A classical conditioning (Pavlovian) procedure used to study the reinforcing effects of unconditioned stimuli (e.g., food, drugs). During training, one portion of a test chamber is associated with a stimulus and another portion is not. During testing, in the absence of the stimulus, the subject is allowed to choose between the two portions. An increase in preference for the stimulus-paired portion or environment serves as a measure of its Pavlovian reinforcing effects (Tzschentke, 1998).

CONTEXT-INDUCED REINSTATEMENT: In this procedure, laboratory animals are first trained to self-administer a drug or non-drug reinforcer in an environment (typically termed context A) associated with a specific set of “background” stimuli (e.g., operant chamber fan, time of day). During training, these stimuli become associated with the availability and effects of the reinforcer. Lever pressing is then extinguished in a different environment (typically termed context B) with a different set of “background” stimuli. During reinstatement testing under extinction conditions, exposure to the context previously paired with the reinforcer (context A) reliably reinstates operant responding (Crombag *et al.*, 2008a). **The procedure for context-induced reinstatement is based on a “renewal” procedure used in the learning field to assess the role of contexts in resumption of conditioned responses to aversive and appetitive cues after extinction (Bouton and Bolles, 1979; Nakajima *et al.*, 2000; Welker and McAuley, 1978).**

DISCRETE-CUE-INDUCED REINSTATEMENT: In this procedure, laboratory animals are first trained to self-administer a drug or non-drug reinforcer; each reinforcer delivery is temporally paired with a discrete cue (e.g., tone, light). Lever pressing is then extinguished in the absence of the reinforcer and the cue. During reinstatement testing, exposure to the cue, which is earned contingently during testing, reliably reinstates responding (See, 2005).

DISCRIMINATIVE-CUE-INDUCED REINSTATEMENT: In this procedure, rats are trained to self-administer a reinforcer in the presence of distinct discriminative stimuli; one set of stimuli signals reinforcer availability (S+) and the other signals unavailability (S-). Lever pressing is then extinguished in the absence of the discriminative stimuli. During the reinstatement test, re-exposure to the S+ reinstates lever responding (McFarland and Ettenberg, 1997; Weiss *et al.*, 2000).

DISCRIMINATIVE STIMULUS: An environmental stimulus that after discrimination training signals whether instrumental performance is reinforced. During training, this stimulus, termed the S+ (or SD) is presented just before the reinforcer becomes available or throughout the period of self-administration; a different stimulus, termed the S- (or SA), is presented when the reinforcer is not available, typically on alternate days or sessions (Catania, 1992).

DRUG DISCRIMINATION: In this procedure, subjects are trained to discriminate between drug and non-drug interoceptive cues. In a typical experiment, an animal is trained to lever-press for food in a two-lever operant chamber. Responding on one lever is reinforced with food after a drug injection, while responding on the other lever is reinforced with food after a vehicle injection. After subjects meet a predefined criterion of correct responding during training, dose-response curves are typically determined by injecting subjects with various doses of the training drug or other drugs from the same or different drug classes (a test for stimulus generalization) (Stolerman, 1992).

EXTINCTION: The decrease in the frequency or intensity of learned responses after the removal of the unconditioned stimulus (e.g., food, drug) that has reinforced the learning (Pavlov, 1927; Skinner, 1953).

FOOD-PRIMING-INDUCED REINSTATEMENT: In this procedure, laboratory animals are first trained to self-administer food (e.g., high-fat food pellets, sucrose solutions). Operant responding (e.g. lever pressing or nose-poking) is then extinguished in the absence of food. During reinstatement testing, non-contingent exposure to the previously self-administered food reinstates operant responding.

FOOD SEEKING: A behavioral state inferred from the post-extinction reinstatement of food-taking behavior that occurs in the absence of contingent delivery of food. This behavioral state is also inferred from initial non-reinforced responding in an extinction session in the presence of food-associated cues after a period of unavailability of the self-administered food.

INACTIVE LEVER: Responses on this lever do not lead to the delivery of a reinforcer during self-administration training. In reinstatement studies, responses on this lever during testing are often used to measure non-specific activity and/or response generalization (Shalev *et al.*, 2002). However, there is a lack of empirical evidence that inactive lever responding truly reflects these behaviors.

INCUBATION OF SUCROSE CRAVING: A hypothetical process inferred from the findings of time-dependent increases in cue-induced sucrose seeking after cessation of sucrose self-administration training. Incubation of sucrose craving has been assessed in either discrete-cue-induced reinstatement tests (Grimm *et al.*, 2005) or in extinction tests in the presence of the sucrose-associated cues (Lu *et al.*, 2004; Uejima *et al.*, 2007).

INCENTIVE MOTIVATION: Refers to a motivational state induced by exposure to unconditioned aversive or appetitive stimuli or cues that become associated with these stimuli (Bindra, 1974). In the case of appetitive stimuli (rewards) like food or drugs, this motivational state typically leads to increased activity and reward seeking. An incentive stimulus or an incentive motivational stimulus is a stimulus that motivates or entices an animal to action. Palatable food has unconditioned incentive motivational properties, leading to approach and eating responses. Stimuli associated with palatable food or rewarding drugs acquire similar properties, i.e., conditioned incentive motivational properties. These reward-associated stimuli are conditioned incentive motivational stimuli or, more simply, conditioned incentive stimuli (Beninger, 1983; Beninger *et al.*, 1989; Stewart *et al.*, 1984).

OPERANT SELF-ADMINISTRATION: In this procedure, laboratory animals perform an operant response (e.g., lever press, nose-poke) for appetitive unconditioned stimuli such as palatable food or drugs of abuse. The premise of this procedure is that drugs or non-drug rewards control behavior by functioning as positive reinforcers. A stimulus is defined as a positive reinforcer in operant conditioning if its presentation following a response increases or maintains the likelihood of the response (Catania, 1992).

PALATABLE FOODS: A subjective term that refers here to readily self-administered foods with a presumably pleasant taste that contain high levels of carbohydrates (e.g., sugar) and/or fat.

REINSTATEMENT: In studies of reinstatement of drug or food seeking, reinstatement typically refers to the resumption of reward seeking after extinction following exposure to food or drug priming, cues, or stressors (Shaham *et al.*, 2003). In the learning literature, reinstatement refers to the recovery of a learned response (e.g., lever-pressing behavior) that occurs when a subject is exposed non-contingently to the unconditioned stimulus (e.g., food) after extinction (Bouton and Swartzentruber, 1991).

RUNWAY REINSTATEMENT PROCEDURE: In this procedure, the dependent measure is the run time from a start box to a goal box associated with a reward (e.g. food or drug). During daily training sessions, food-restricted rats are given food pellets when they reach the goal box, and over sessions they decrease their run time. During the subsequent extinction sessions, food is not available in the goal box, and over daily sessions the rats' run time progressively increases (reflecting extinction). A single exposure to food pellets during extinction leads to a faster run time on the subsequent daily session; this decrease in run time is the operational measure of food-priming-induced reinstatement (Horvitz and Ettenberg, 1988). A unique feature of the runway reinstatement procedure is that the effects of pharmacological manipulations are assessed on a subsequent, drug-free day. This helps rule out the possibility that any observed effects of pharmacological manipulations are due to locomotor activation or sedation during testing.

RELAPSE: A term used here to refer to the human condition of resumption of old unhealthy eating habits during dieting. In the addiction literature, this term is used to refer resumption of drug-taking behavior during periods of abstinence in humans (Wikler, 1973).

SECOND-ORDER REINFORCEMENT SCHEDULE: A complex schedule of reinforcement in which completion of the response requirements of one schedule (often referred to as the unit schedule) is treated as a unitary response that is reinforced according to another schedule. Often a stimulus is briefly presented at the completion of the unit schedule requirements, and this stimulus can acquire conditioned reinforcing effects (Goldberg, 1976).

STRESS: A complex psychological construct that, despite many years of research (Cannon, 1935; Selye, 1956), has yet to be adequately operationally defined (Chrousos and Gold, 1992; Cohen *et al.*, 1982). In the context of animal models of psychiatric disorders, stress can be defined broadly as forced exposure to events or conditions that are normally avoided (Piazza and Le Moal, 1998). In humans, the definition is extended to incorporate cognitive and emotional responses—for example, “stress is a condition in which the environmental demands exceed the coping abilities of the individual” (Cohen *et al.*, 1986). In laboratory animals, the precipitating events or conditions can be divided into two categories (Lu *et al.*, 2003). The first category includes environmental events such as restraint, footshock, tail pinch, and defeat, as well as pharmacological events such as administration of a normally avoided drug (e.g., yohimbine). The second category includes food deprivation, social isolation, and maternal deprivation; each of these entails the removal of an environmental condition that is important for maintaining the animal's normal physiological and psychological steady-state conditions, a state that the subject will attempt to ameliorate by seeking food, conspecific partners, or the dam.

Table 2

Effect of pharmacological agents on reinstatement of food seeking.

Pharmacological agent	Food type; Food restriction in testing; Reinforcement schedule; Species	Re-instatement	Reference
<u>Adenosine antagonists</u>			
CGS 15943 (0.01–0.32 mg/kg, i.v.)	1g food pellets; monkey free-food ration; FR-10; Baboon	No	(Weerts and Griffiths, 2003)
Caffeine (0.1–3.2 mg/kg, i.v.)	Same as above	No	(Weerts and Griffiths, 2003)
<u>Cannabinoid agonist</u>			
Δ 9THC (0.3–3 mg/kg, i.p.)	Sucrose solution; ad lib food; FR-3, VR-6, VR-10; W rat	Yes	(McGregor <i>et al.</i> , 2005)
<u>Cholinergic agonist</u>			
Nicotine (0.075–0.3 mg/kg, s.c.)	45 mg food pellets; 20 g/day; FR-1; Long-Evans rat	<u>No</u> nicotine-naive	(Shaham <i>et al.</i> , 1997a)
		<u>Yes</u> nicotine-experienced	
<u>Dopamine indirect agonists</u>			
Amphetamine (3.0 mg/kg, i.p.)	45 mg food pellets; Restricted diet to 85% BW; VR2, VR5, RI; LE rat	No	(Odum and Shahan, 2004)
Amphetamine (1.0 mg/kg, i.v.)	Food pellets; ad lib food; SD rats	No	(de Wit and Stewart, 1981)
Cocaine (15 mg/kg, i.p.)	45 mg food pellets; Restricted diet to 85% BW; FR-1; Wistar rat	?	(Dias <i>et al.</i> , 2004)
Cocaine (0.1–3.2 mg/kg, i.v.)	1g food pellets; daily monkey free-food ration; FR-10; Baboon	No	(Weerts and Griffiths, 2003)
Cocaine (1–2 mg/kg, i.v.)	Food pellets; ad lib food; SD rats	No	(de Wit and Stewart, 1981)
Cocaine (0.03–1.0 mg/kg, i.v.)	1 g banana flavored food pellets; Restricted diet to maintain 95% BW; FR-50; Cynomolgus monkeys	No	(Banks <i>et al.</i> , 2007)
Cocaine (10 mg/kg, i.p.)	45 mg food pellets; Restricted diet to 90% BW; FR-1, FR-5; Wistar rat	No	(Keiflin <i>et al.</i> , 2008)
<u>D1-family agonist</u>			
SKF 82958 (0.25 mg/kg, i.p.)	45 mg food pellets; Restricted diet to 85% BW; FR-1; Wistar rat	?	(Dias <i>et al.</i> , 2004)
<u>D2-family agonists</u>			
Quinelorane (0.25 mg/kg, i.p.)	45 mg food pellets; Restricted diet to 85% BW;FR-1; Wistar rat	No	(Dias <i>et al.</i> , 2004)
Quinelorane (0.004– 2 mg/kg, i.p.)	45 mg food pellets; 13 g/d chow; FR-1; Wistar rat	No	(Duarte <i>et al.</i> , 2003a)
Bromocriptine (4, 8 mg/kg, i.p.)	45 mg food pellets; 20 g/day; FR-1; LE rat	Yes	(Shaham <i>et al.</i> , 1997a)

Pharmacological agent	Food type; Food restriction in testing; Reinforcement schedule; Species	Re-instatement	Reference
<u>D3-family agonist</u>			
7-OH-DPAT (0.25 mg /kg, i.p.)	45 mg food pellets; Restricted diet to 85% BW; FR-1; Wistar rat	No	(Dias <i>et al.</i> , 2004)
7-OH-DPAT (2–4 mg /kg, s.c.)	45 mg food pellets; 13 g/d chow; FR-1; Wistar rat	Yes	(Duarte <i>et al.</i> , 2003a)
<u>D2/D3-family agonist</u>			
Apomorphine (0.125–0.25 mg/kg, s.c.)	45 mg food pellets; 13 g/d chow; FR-1; Wistar rat	Yes	(Duarte <i>et al.</i> , 2003a)
<u>GABA-A agonist</u>			
Midazolam (0.15–1.5 mg/kg, i.p.)	Sucrose solution; ad lib food; FR-3, VR-6, VR-10; Wistar rats	No	(McGregor <i>et al.</i> , 2005)
<u>Hypocretin (orexin)</u>			
Hypocretin-1 (1, 2.5, 5 µg, i.c.v)	45 mg food pellets; ad lib food; FR-1; Wistar rat	Yes	(Boutrel <i>et al.</i> 2005)
Hypocretin-1 (3, 6 µg, i.c.v)	45 mg 35% fat pellets, 16 g rat chow/d; FR-1; LE rat	Yes	(Nair <i>et al.</i> 2008)
<u>Melanin concentrating hormone (MCH)</u>			
MCH (2.5–20 µg, i.c.v)	45 mg 35% fat pellets, 16 g rat chow/d; FR-1; LE rat	Yes	(Nair <i>et al.</i> 2009)

Abbreviations: W, Wistar; LE, Long-Evans; SD, Sprague-Dawley; AMPH, Amphetamine; FR, fixed ratio reinforcement schedule; VR, variable ratio reinforcement schedule; BW, body weight; ?, results that are difficult to interpret.

Table 3

Effect of systemic drug injections of pharmacological agents on reinstatement of food seeking induced by food priming or cues.

Pharmacological agent	Food type; Food restriction in testing; Reinforcement schedule; Species	Food priming	Cue	Reference
<u>CB1 antagonist</u>				
SR 141716A (1–3 mg/kg)	45 mg sucrose pellets; ad lib food; FR-1; Wistar rat		↓ (DC)	(De Vries <i>et al.</i> , 2005)
SR 141716A (1–10 mg/kg)	Ensure or corn oil; ad lib food; FR-1; C57Bl/6 mice		↓ (Ensure) - (Corn oil) (DC)	(Ward <i>et al.</i> , 2007)
<u>CRF1 antagonist</u>				
Antalarmin (20–40 mg/kg)	45 mg 25% fat pellets; 20 g rat chow/d; FR-1; LE rat	—		(Ghitza <i>et al.</i> , 2006)
<u>Partial D2 agonist</u>				
Aripiprazole (0.25, 1 mg/kg)	45 mg food pellets; Restricted diet to 85–90% BW; FR-1- FR-5; SD rat	—		(Feltenstein <i>et al.</i> , 2007)
<u>Partial D3 agonist</u>				
BP- 897 (0.5, 1 mg/kg)	10% sucrose; ad lib food; FR-1; LE rat		— (E)	(Gal and Gyertyan, 2006)
<u>D1-family antagonist</u>				
SCH 39166 (0.1–1 mg/kg)	45 mg food pellets, Restricted diet to 85% BW; SD rat (runway procedure)	—		(Chausmer and Ettenberg, 1997)
SCH 23390 (0.01 mg/kg)	10% sucrose, ad lib food for 1 h daily, FR-1 schedule, LE rat		↓ (C)	(Hamlin <i>et al.</i> , 2006)
<u>D2-family antagonist</u>				
Haloperidol (0.15 – 0.3 mg/kg)	45 mg food pellets; Restricted diet to 85% BW; SD rat (runway procedure)	↓		(Horvitz and Ettenberg, 1988)
Haloperidol (0.2 mg/kg)	10% sucrose; ad lib food; FR-1; LE rat		— (E)	(Gal and Gyertyan, 2006)
Raclopride (0.25 – 1 mg/kg)	45 mg food pellets, Restricted diet to 85% BW; SD rat (runway procedure)	↓		(Chausmer and Ettenberg, 1997)
<u>D3 antagonist</u>				
SB 277011-A (5, 20 mg/kg)	10% sucrose; ad lib food; FR-1; LE rat		— (E)	(Gal and Gyertyan, 2006)
SB 277011-A (10 mg/kg)	45 mg sucrose pellets; ad lib food; FR-1; SD rat		— (DS)	(Cervo <i>et al.</i> , 2007)
NGB 2904 (1, 5 mg/kg)	5% sucrose; ad lib food; FR-1, FR-2, PR; LE rat	—		(Xi <i>et al.</i> , 2006)
<u>mGluR2/3 agonists</u>				
LY379268 (0.3 – 3.0 mg/kg)	Sweetened condensed milk, ad lib food; FR-1; Wistar rat		↓ (DS)	(Baptista <i>et al.</i> , 2004)

Pharmacological agent	Food type; Food restriction in testing; Reinforcement schedule; Species	Food priming	Cue	Reference
LY379268 (0.3 – 3.0 mg/kg)	45 mg food pellets; Restricted diet to 85–90% BW; FR-1 to FR-5; SD rat	↓		(Peters and Kalivas, 2006)
LY379268 (0.3 – 3.0 mg/kg)	45 mg food pellets; Restricted diet to 20 g/d; FR-5; Wistar rat		↓ (DC)	(Liechti <i>et al.</i> , 2007)
LY379268 (1, 3 mg/kg)	5% sucrose; Restricted diet 20 g/d; FR-1; LE rat		↓ (C, DC)	(Bossert <i>et al.</i> , 2006)
<u>mGlu1 antagonist</u>				
EMQMCM (2.5 – 10 mg/kg)	45 mg Noyes food pellets; FR-1 to FR-5; Wistar rat		↓ (DS)	(Dravolina <i>et al.</i> , 2007)
<u>mGlu5 antagonist</u>				
MPEP (1–10 mg/kg)	45 mg food pellets; Restricted diet to 16 g/d; FR-1 to FR-5; Wistar rat		— (DS)	(Bespalov <i>et al.</i> , 2005)
MTEP (0.3–3 mg/kg)	45 mg food pellets; Restricted diet to 20 g/d; FR-1; Sprague-Dawley rat		— (DC)	(Gass <i>et al.</i> , 2009)
MTEP (0.3–10 mg/kg)	Sweetened condensed milk, ad lib food; FR-1; Wistar rat		↓ (DS)	(Martin-Fardon <i>et al.</i> , 2009)
<u>Hypocretin 1 antagonist</u>				
SB 334867 (20 mg/kg)	45 mg 35% fat pellets, 16 g rat chow/d; FR-1; LE rat	—	— (DC)	(DC) (Nair <i>et al.</i> , 2008); unpublished data
<u>Mixed mu opiod agonist-kappa-antagonist</u>				
Buprenorphine (3.0 mg/kg/day)	Sucrose pellets; ad lib food; FR-1, FR-5 and PR; LE rat	↓ (DC)		(Hood <i>et al.</i> , 2007)
<u>Preferential mu opiod antagonist</u>				
Naltrexone (0.25–2.5 mg/kg)	45 mg sucrose pellets; ad lib food; FR-1, TO 20-s; SD rat		— (DS)	(Burattini <i>et al.</i> , 2008)
Naloxone (0.001–10 mg/kg)	10% sucrose solution, ad lib food; FR-1, TO 40-s; LE rat		↓ (DC)	(Grimm <i>et al.</i> , 2007)
<u>Nicotinic antagonist</u>				
Mecamylamine (0.5–2 mg/kg)	45 mg food pellets; 20 g/d chow; FR-1- FR-5; SD rat		— (DC)	(Liu <i>et al.</i> , 2007)
<u>5-HT/1B agonist</u>				
RU 24969 (0.3–3.0 mg/kg)	45 mg sucrose pellet; ad lib food; FR-1, VR-3, VR-5; SD rat		↓ (DC)	(Acosta <i>et al.</i> , 2005)
<u>5-HT2B/2C agonist</u>				
Ro 60-0175 (1 mg/kg)	45 mg sucrose pellets; ad lib food; FR-1, TO 20-s; SD rat		— (DS)	(Burbassi and Cervo, 2008)

Pharmacological agent	Food type; Food restriction in testing; Reinforcement schedule; Species	Food priming	Cue	Reference
<u>Sigma 1 antagonist</u>				
BD1047 (1–30 mg/kg)	Sweet condensed milk; ad lib food; FR-1m TO 20-s; W rat		↓ (DS)	(Martin-Fardon <i>et al.</i> , 2007)
<u>Y2 agonist</u>				
Peptide YY3-36 (0.1–0.2 mg/kg)	45 mg 35% fat pellets, 16 g rat chow/d; FR-1; LE rat	↓	↓ (DC)	(Ghitza <i>et al.</i> , 2007)

Abbreviations/symbols: W, Wistar; LE, Long-Evans; SD, Sprague-Dawley; FR, fixed ratio schedule; VR, variable ratio schedule; PR, progressive ratio schedule; BW, body weight; ↓, decrease; ↑, increase; -, no effect, blank space, not tested. For cue column: DC, discrete cue; DS, discriminative stimulus cue; C, contextual cue; E, cue responding in a single extinction test.

Table 4

Effect of intracranial drug injections of pharmacological agents on reinstatement of food seeking induced by food priming or cues.

Pharmacological agent	Food type; Food restriction in testing; Reinforcement schedule; Species	Food priming	Cue	Reference
<u>D1-family antagonist</u>				
SCH 23390 (dorsal mPFC)	45 mg sucrose pellets; Restricted diet to 85–90% BW; FR-5; SD rat	↓		(Sun and Rebec, 2005)
<u>D2-family antagonist</u>				
Eticlopride (dorsal mPFC)	45 mg sucrose pellets; Restricted diet to 85–90% BW; FR-5; SD rat	↓		(Sun and Rebec, 2005)
Raclopride (accumbens)	45 mg food pellets, Restricted diet to 85% BW; SD rat (runway procedure)	—		(Chausmer and Ettenberg, 1999)
<u>D2/D3 antagonist</u>				
Sulpiride (accumbens shell)	Sucrose pellets; Restricted diet; FR-1, FR-5; SD rat	—		(Anderson et al., 2006)
<u>GABA_A+GABA_B agonists</u>				
Muscimol+baclofen				
Ventral pallidum	45 mg food pellets; Restricted diet to 90% BW; FR-1-FR-5; SD rat	↓		(McFarland and Kalivas, 2001)
Dorsal mPFC		—		
Accumbens core		—		
Accumbens core	45 mg food pellets, Restricted diet to 85% BW, FR-1-FR-2-VR-5, LE rat		↓ (DC)	(Floresco et al., 2008)
Accumbens shell	10% sucrose solution, ad lib food, FR-1, LE rat		↑ (DC)	
Lateral hypothalamus			↓ (C)	(Marchant et al., 2009)
<u>Local anesthetic</u>				
Bupivacaine				
Caudal BLA	45 mg food pellets, Restricted diet to 85% BW, FR-1-FR-2-VR-5, LE rat		↑ (DC)	(McLaughlin and Floresco, 2007)
Rostral BLA			— (DC)	
<u>mGluR2/3 agonists</u>				
LY379268 (accumbens)	45 mg food pellets; Restricted diet to 85–90% BW; FR-1- FR-5; SD rat	↓		(Peters and Kalivas, 2006)
<u>Glutamate blocker</u>				
Kynurenate (VTA)	45 mg sucrose pellets; Restricted diet to 85–90% BW; FR-5; SD rat	—		(Sun et al., 2005)
<u>μ opioid antagonist</u>				

Pharmacological agent	Food type; Food restriction in testing; Reinforcement schedule; Species	Food priming	Cue	Reference
CTAP (ventral pallidum)	45 mg food pellets; Restricted diet 20 g/d; FR-1-FR-5; SD rat	—		(Tang et al., 2005)
<u>Y2 agonist</u>				
Peptide YY3-36 (Arcuate nucleus)	45 mg 35% fat pellets; 16 g rat chow/d; FR-1; LE rat	↓	— (DC)	(Ghitza et al., 2007)

Abbreviations/symbols: W, Wistar; LE, Long-Evans; SD, Sprague-Dawley; FR, fixed ratio schedule; VR, variable ratio schedule; PR, progressive ratio schedule; mPFC, medial prefrontal cortex; BW, body weight; ↓, decrease; ↑, increase; -, no effect, blank space, not tested; BLA, Basolateral amygdala. For cue column: DC, discrete cue; DS, discriminative stimulus cue; C, contextual cue; E, cue responding in a single extinction test.

Table 5
Effect of pharmacological agents ongoing food-reinforced responding (food self-administration) and reinstatement.

Peptide receptor agonist/antagonist	Food-reinforced responding	Reinstatement of food seeking			Reference
		Priming	Cue	Yohimbine	
<u>Hypocretin 1 receptor antagonist</u> SB 334867 (10, 20 mg/kg)	↓	—	—	—	(Nair <i>et al.</i> , 2008) and unpublished observation
<u>MCH 1 receptor antagonist</u> SNAP 94847 (10–30 mg/kg)	↓	—	—	—	(Nair <i>et al.</i> , 2009)
<u>Y2 receptor agonist</u> Peptide YY 3-36 (0.1, 0.2 mg/kg)	—	↓	↓	—	(Ghitza <i>et al.</i> , 2007)
<u>D1 receptor antagonist</u> SCH 23390 (5, 10 µg/kg)	—	↓		↓	Fig. 2A, 2B, 2C
<u>CRF1 receptor antagonist</u> Antalarmin (20, 40 mg/kg)	—	—		↓	(Ghitza <i>et al.</i> , 2006)

Abbreviations/symbols: ↓, decrease; ↑, increase; —, no effect, blank space, not tested

Table 6

Effect of pharmacological agents on priming-induced reinstatement of food- versus drug-seeking.

Pharmacological manipulation	Food priming	Drug priming	Reference
<u>Systemic injections</u>			
<u>5-HT1B antagonist</u>			
SB 216641	—	↓ (cocaine)	(Przegalinski <i>et al.</i> , 2008)
GR127935	—	↓ (cocaine)	
<u>5-HT1B agonist</u>			
CP 94253	↓	↑ (cocaine)	(Przegalinski <i>et al.</i> , 2008)
<u>Cysteine prodrug</u>			
N-acetylcysteine	—	↓ (cocaine)	(Baker <i>et al.</i> , 2003)
<u>D1-family antagonist</u>			
SCH 23390	—	↓ (heroin)	(Chausmer and Ettenberg, 1997; Shaham and Stewart, 1996)
<u>Partial D2 agonist</u>			
Aripiprazole	—	↓ (cocaine)	(Feltenstein <i>et al.</i> , 2007)
<u>D2-like agonists</u>			
Quinpirole	↑		(Duarte <i>et al.</i> , 2004)
7-OH-DPAT		↑	(Self <i>et al.</i> , 1996)
<u>D2 - like antagonists</u>			
Haloperidol	↓	↓ (heroin)	(Chausmer and Ettenberg, 1997; Ettenberg <i>et al.</i> , 1996; Schenk and Gittings, 2003; Shaham and Stewart, 1996)
Raclopride	↓	↓ (heroin)	
Eticlopride		↓ (cocaine)	
<u>D3 antagonist</u>			
NGB 2904	—	↓ (cocaine)	(Xi <i>et al.</i> , 2006)
<u>L-type calcium channel antagonist</u>			
Diltiazem	—	↓ (cocaine)	(Anderson <i>et al.</i> , 2008)
<u>mGluR2/3 agonists</u>			
LY379268	↓	↓ (cocaine)	(Peters and Kalivas, 2006)
<u>Y2 agonist</u>			
Peptide YY3-36	↓	— (heroin)	(Ghitza <i>et al.</i> , 2007)
<u>Intracranial injections</u>			
<u>Calcium-calmodulin kinase II inhibitor</u>			
KN-93 (accumbens shell)	—	↓ (cocaine)	(Anderson <i>et al.</i> , 2008)
<u>D1-family antagonist</u>			
SCH 23390 (Dorsal PFC)	↓	↓ (cocaine)	(Sun <i>et al.</i> , 2005)
<u>D2-family antagonist</u>			

Pharmacological manipulation	Food priming	Drug priming	Reference
Eticlopride (Dorsal PFC)	↓	↓ (cocaine)	(Sun <i>et al.</i> , 2005)
Raclopride (accumbens)	—		(Chausmer and Ettenberg, 1999)
Sulpiride (accumbens shell)	—	↓ (cocaine)	(Anderson <i>et al.</i> , 2006)
<u>GABAa+GABAb agonists</u>			
Muscimol+baclofen			
Ventral pallidum	↓	↓ (cocaine)	(McFarland and Kalivas, 2001)
Dorsal mPFC	—	↓ (cocaine)	
Accumbens core	—	↓ (cocaine)	
<u>GluR2-trafficking inhibitor</u>			
Pep2-EVKI (accumbens shell)	—	↓ (cocaine)	(Famous <i>et al.</i> , 2008)
<u>L-type calcium channel antagonist</u>			
Diltiazem (accumbens shell)	—	↓ (cocaine)	(Anderson <i>et al.</i> , 2008)

Abbreviations/symbols: ↓, decrease; ↑, increase; —, no effect, blank space, not tested

Table 7

Effect of pharmacological agents on cue-induced reinstatement of food versus drug seeking.

Pharmacological manipulation	Food cue	Drug cue	Reference
Systemic injections			
<u>Nicotinic cholinergic antagonist</u>			
Mecamylamine	— (DC)	↓ (nicotine) (DC)	(Liu <i>et al.</i> , 2007)
<u>D1-family antagonist</u>			
SCH 23390 or SCH 39166	— (DS, runway) ↓ (C)	↓ (cocaine [DS,DC,C], heroin [C], alcohol (C)	(Alleweireldt <i>et al.</i> , 2002; Bossert <i>et al.</i> , 2007; Hamlin <i>et al.</i> , 2006; Hamlin <i>et al.</i> , 2008; Hamlin <i>et al.</i> , 2007; Weiss <i>et al.</i> , 2001)
<u>D2-family antagonist</u>			
Haloperidol	— (E)	↓ (cocaine) (E)	(Gal and Gyertyan, 2006)
<u>D3 antagonist</u>			
SB 277011-A	— (E)	↓ (cocaine) (E)	(Gal and Gyertyan, 2006)
SB 277011-A	— (DS)	↓ (cocaine) (DS)	(Cervo <i>et al.</i> , 2007)
<u>D3 partial agonist/D2 antagonist</u>			
BP-897	— (E)	↓ (cocaine) (E)	(Gal and Gyertyan, 2006)
<u>mGluR2/3 agonists</u>			
LY379268	↓ (DC, DS, C)	↓ (cocaine [DS], nicotine [C,DC], heroin [DC,C])	(Baptista <i>et al.</i> , 2004; Bossert <i>et al.</i> , 2005a; Bossert <i>et al.</i> , 2004; Bossert <i>et al.</i> , 2006; Liechti <i>et al.</i> , 2007)
<u>mGluR5 antagonist</u>			
MPEP	— (DS)	↓ (nicotine) (DS)	(Bespalov <i>et al.</i> , 2005) (Gass <i>et al.</i> , 2009)
MTEP	— (DC) ↓ (DS)	↓ (methamphetamine) (DC) ↓ (cocaine) (DS)	(Martin-Fardon <i>et al.</i> , 2009)
<u>mGluR1 antagonist</u>			
EMQMCM	↓ (DS)	↓ (nicotine) (DS)	(Dravolina <i>et al.</i> , 2007)
<u>CB1 antagonist</u>			
SR 141716 ^a	↓ (DC)	↓ (cocaine, heroin, methamphetamine [DC], nicotine [DC and DS], ethanol [DS])	(Anggadiredja <i>et al.</i> , 2004; De Vries <i>et al.</i> , 2005; Diergaarde <i>et al.</i> , 2008; Economidou <i>et al.</i> , 2006; Ward <i>et al.</i> , 2007)
<u>Preferential mu opioid antagonist</u>			
Naltrexone	— (DS) ↓ (DC)	↓ (cocaine, alcohol) (DC, DS, C)	(Burattini <i>et al.</i> , 2008; Burattini <i>et al.</i> , 2006; Grimm <i>et al.</i> , 2007)
<u>Y2 agonist</u>			
Peptide YY3-36	↓ (DC)	— (DC)	(Ghitza <i>et al.</i> , 2007)
<u>5-HT/1B agonist</u>			
RU 24969	↓ (DC)	↓ (cocaine) (DC)	(Acosta <i>et al.</i> , 2005)
<u>5-HT2B/2C agonist</u>			
Ro 60-0175	— (DS)	↓ (cocaine) (DS, C)	(Burbassi and Cervo, 2008)
<u>Sigma 1 antagonist</u>			

Pharmacological manipulation	Food cue	Drug cue	Reference
BD1047	↓ (DS)	↓ (DS)	(Martin-Fardon <i>et al.</i> , 2007)
Intracranial injections			
<u>GABAA+GABAb agonists</u>			
Muscimol+baclofen			
Accumbens core	↓ (DC)	↓ (cocaine, heroin) (DC)	(Floresco <i>et al.</i> , 2008; Fuchs <i>et al.</i> , 2004)
Accumbens shell	↑ (DC)	— (cocaine, heroin) (DC)	(Rogers <i>et al.</i> , 2008)
Lateral hypothalamus	↓ (C)	↓ (alcohol) (C)	(Marchant <i>et al.</i> , 2009)
<u>Non-selective inactivation</u>			
Bupivacaine or tetrodotoxin			
Basolateral amygdala	↑ (DC)	↓ (DC)	(Fuchs and See, 2002; Grimm and See, 2000; McLaughlin and Floresco, 2007)

Abbreviations/symbols: -, not tested. DC, discrete cue; DS, discriminative stimulus cue; C, contextual cue; E, cue responding in a single extinction test; ↓, decrease; ↑, increase; -, no effect, blank space, not tested