COCAINE-INDUCED CONDITIONED TASTE AVERSIONS:

INVESTIGATIONS OF NEUROCHEMICAL MEDIATION

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This dissertation is dedicated to the late Dr. Milton A. Hammond, who sparked my interest in science and behavioral psychology, as a small token of my admiration and appreciation.

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ABSTRACT

Drugs of abuse have both rewarding and aversive effects, and it is the balance of these effects which impact abuse vulnerability. Although research has traditionally focused on the rewarding effects of drugs, their aversive effects have recently gained increasing attention. The present series of investigations sought to determine the neurochemical mediation underlying conditioned taste aversions (CTA) induced by cocaine. Given the role of dopamine (DA) in cocaine reward, this neurotransmitter system is of particular interest. The present experiments used direct pharmacological antagonism (with the DA antagonist haloperidol) as well as cross-drug preexposure (with DA transporter [DAT] inhibitor GBR 12909) to determine a role, if any, of DA in the induction of CTAs by cocaine. Following the determination of behaviorally active doses of haloperidol with no aversive effects on their own (Experiment 1), animals were given 1 mg/kg haloperidol prior to various doses of cocaine in a taste aversion procedure (Experiment 2). Under these conditions, haloperidol blocked cocaine-induced CTAs (at 18 and 32 mg/kg). In separate experiments, cocaine (18 mg/kg; Experiment 3) or GBR 12909 (32 mg/kg; Experiment 4 or 50 mg/kg; Experiment 5) was administered prior to aversion conditioning with cocaine (18 mg/kg) and GBR 12909 (32 mg/kg). Under these conditions, GBR 12909 (at 50 mg/kg only) blocked cocaine-induced CTAs but the reverse serial presentation did not result in significant cross-drug attenuation, indicating that the aversive properties of GBR 12909 and cocaine are similar, but not identical. Although these results indicate a role of DA in cocaine-induced CTAs, the extent to which each DA receptor subtype plays a role remains unknown. These results are

discussed in the context of previous work demonstrating roles for both norepinephrine (NE) and possibly serotonin (5-HT) in cocaine-induced CTAs. The neurochemical mediation of cocaine's aversive effects was discussed in the context of the neurochemical mediation of cocaine reward and the implications for drug abuse.

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CHAPTER 1

GENERAL INTRODUCTION

Conditioned taste aversion (CTA) learning was first discussed in 1955 after Garcia and his colleagues discovered that rats avoided novel tasting solutions that had been consumed during radiation (Garcia, Kimeldorf & Koelling, 1955). Garcia et al. argued that the rat associated the taste of the fluid with radiation sickness and subsequently avoided the taste as a result of this association. This avoidance was evident after a single saccharin-radiation pairing and lasted for over a month (with continuous access). Shortly after this initial demonstration, investigations using classical emetics (e.g., lithium chloride; LiCl) were conducted and extended Garcia's findings (see Freeman & Riley, 2009 for a history of CTAs). Interestingly, much debate stemmed from the notion that CTA was a unique form of learning, shaped by evolution to limit repeated consumption of poison-tainted foods (see Garcia, Buchwald, Hull & Koelling, 1964). That a CTA occurs after only one pairing of a taste with gastrointestinal malaise, occurs despite a long delay between ingestion and illness and appears selective to specific stimuli, e.g., taste, supported this position and suggested that taste aversion learning should be considered a unique form of learning, one impacted by the evolutionary history of the animal (Garcia & Ervin, 1968; Revusky & Garcia, 1970; Rozin & Kalat, 1971; see Freeman & Riley, 2009 for a review).

In the middle to late 1970's, the abovementioned focus on examining CTAs in the context of interpretations and implications for learning theory shifted to exploring the characterization of CTAs and the conditions under which they occurred. In addition to examining different taste stimuli, individuals began assessing other compounds for their ability to induce a CTA (Braveman, 1975; Brown, Amit, Smith & Rockman, 1978; H. Cappell & A. E. LeBlanc, 1977; Domjan, Foster & Gillan, 1979; Gamzu, 1977; Hunt & Amit, 1987; Nachman & Ashe,

1973; Riley & Tuck, 1985). Interestingly, these compounds included a wide range of drugs of abuse such as ethanol (Cunningham, 1979; Eckardt, 1975), morphine (Gaiardi et al., 1991; Gorman, de Obaldia, Scott & Reid, 1978) and amphetamine (Booth, Pilcher, D'Mello & Stolerman, 1977; Cappell & Le Blanc, 1975). The fact that compounds known to be rewarding in a variety of animal and human models also induced taste aversions was viewed as something of a paradox in that it was not clear if (or how) a single compound could have both affective properties (Gamzu, Vincent & Boff, 1985; Gamzu, 1977; Goudie, Dickins & Thornton, 1978; Hunt & Amit, 1987). Although initially argued that reward and aversion may be functions of the specific preparation in which they were reported (Gamzu, 1977; Goudie, 1979), the fact that one can see both behavioral effects, e.g., self-administration and taste aversion, in the same animals in response to the same drug injection (White, Sklar & Amit, 1977; Wise, Yokel & DeWit, 1976), suggested that the drug had both effects and that these effects occurred concurrently. That such drugs produced both rewarding and aversive effects is important in that it challenged the view that drug use and abuse reflect only the rewarding properties of a drug. Drugs of abuse also have aversive effects that shape or limit drug intake (for a discussion of this issue with alcohol , see Baker & Cannon, 1982). That is, the balance between these effects influences total drug intake such that at low doses, the subjective effects are primarily rewarding, leading to dose-dependent increases in drug intake or self-administration. At higher doses, the aversive effects begin to influence the amount of drug self-administered, leading to lower levels of intake. The degree to which the aversive effects are experienced during initial drug use impacts the probability of subsequent drug use, contributing to individual vulnerability. Changes in the aversive effects (resulting from experience with the drug or specific characteristics of the individual) impact a user's likelihood of continued drug use or abuse (see Figure 1). Thus, an

understanding of the use and abuse of drugs necessitates an understanding of the balance of these two affective states and how each is impacted by a host of experiential and subject variables (see Figure 1; Baker & Cannon, 1982; Gaiardi et al., 1991; Riley, Davis & Roma, 2009; Riley, 2011; Stolerman & D'Mello, 1981; Woods, 1991).

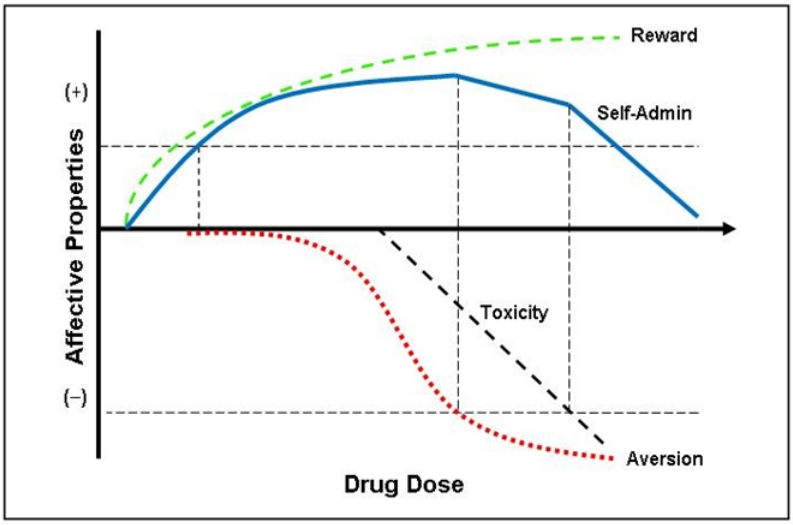

Figure 1. The balance between the rewarding and aversive affective properties of a drug influences total drug intake. When a drug of abuse is administered at low doses, the subjective effects are primarily rewarding (green-dashed line), leading to dose-dependent increases in drug intake or self-administration (blue-solid line). However, as the dose of the drug increases, aversive drug effects (red-dotted line) begin to influence the amount of drug self-administered (in their balance with the drug's rewarding effects), leading to lower levels of overall intake. The intensity of the aversive effects experienced during initial drug use impacts the probability of future drug taking. Changes in the aversive effects (resulting from experience with the drug or specific characteristics of the individual) impact a user's likelihood of subsequent use or abuse of the drug. Figure from Kohut & Riley (2010).

As noted, a variety of drugs of abuse induce taste aversions (see Freeman & Riley, 2009 for a review). One such compound that has received considerable attention in this regard is cocaine. As often reported, cocaine is readily self-administered by animals (Koob, Le & Creese, 1987; Ritz, Lamb, Goldberg & Kuhar, 1987; Goeders, Dworkin & Smith, 1986) and humans (Siegel, 1984; Washton, Gold & Pottash, 1984). It also readily induces conditioned place preferences (CPP) in animals at a range of doses (for a review see Bardo, Rowlett & Harris, 1995). Interestingly, initial attempts to induce CTAs with cocaine resulted in weak or no

aversions (H. Cappell & A. LeBlanc, 1977; Goudie et al., 1978). Even at high doses, cocaine induced only moderate CTAs relative to other compounds, e.g., LiCl (Smith, 1980), apomorphine (Stolerman & D'Mello, 1979), amphetamine (Carey & Goodall, 1974) and ethanol (Kulkosky, Sickel & Riley, 1980; see Booth et al., 1977; H. Cappell & A. LeBlanc, 1977; Goudie et al., 1978; Foltin & Schuster, 1982; though see also Foltin, Preston, Wagner & Schuster, 1981). From such findings, it was concluded that cocaine had little or no aversive effects (one study reported that an injection of cocaine after saccharin actually increased saccharin consumption upon subsequent presentations; H. Cappell & A. LeBlanc, 1977). Importantly, the abovementioned procedures used the intraperitoneal (IP) route of administration for cocaine. One report (Gale, 1984) described using subcutaneous (SC) cocaine in order to increase cocaine's duration of action (to maintain consistency in route/duration of action across several behavioral measures) and demonstrated robust CTAs. Subsequently, Ferrari and colleagues (Ferrari, O'Connor & Riley, 1991) compared cocaine-induced CTAs with different routes of administration. In their procedure, Ferrari et al. administered a novel saccharin solution followed by an injection of either cocaine (IP or SC) or vehicle (with control groups for both routes of administration). On the 3 days following this pairing, subjects were given access to water but no injections. This cycle of conditioning and 3 water-recovery days was repeated for a total of four cycles. Under these conditions, SC-administered cocaine resulted in significantly greater suppression of saccharin consumption across a range of doses relative to IP-administered cocaine (at the same doses; see Ferrari et al., 1991). When administered SC, cocaine-induced CTAs were, in fact, comparable to those induced by classical emetics as well as those induced by other drugs of abuse (Busse, Freeman & Riley, 2005; Riley, Jacobs & LoLordo, 1976; Escarabajal, De Witte & Quertemont, 2003). Similar to more traditional aversion-inducing

agents, aversions induced by cocaine have subsequently been shown to be dependent upon dose (Goudie et al., 1978), injection delay (Freeman & Riley, 2005), sex (Busse et al., 2005) and strain (Jones, Busse & Riley, 2006), as well as the number of conditioning trials (van Haaren & Hughes, 1990), concurrent drug administration (Grakalic & Riley, 2002b) and drug history (Riley & Diamond, 1998).

Although cocaine-induced CTAs are now well characterized (see www.ctalearning.com), there is little information regarding its underlying neurochemistry and neuroanatomy despite considerable work on the biology of taste aversion learning in general (Reilly, 2009; Barki-Harrington, Belelovsky, Doron & Rosenblum, 2009; Bernstein, Wilkins & Barot, 2009; Cunningham, Gremel & Groblewski, 2009). This latter work has conclusively demonstrated roles for a number of neurochemical systems and neuroanatomical pathways in the acquisition, expression, extinction and reinstatement of taste aversions. For example, the administration of various agonists and antagonists and the use of selective knockout (KO) preparations have implicated a number of neurotransmitters, e.g., dopamine (DA), gamma-aminobutyric acid (GABA) and glutamate (GLU; see Elkins et al., 2003a), as being critical to aversion learning (for examples with pharmacological agonists/antagonists see Hunt, Switzman & Amit, 1985; Schachtman et al., 2003; Sklar & Amit, 1977; for investigations using KO mice see Cannon, Scannell & Palmiter, 2005; Risinger, Freeman, Greengard & Fienberg, 2001; Blednov et al., 2003; Jacobson, Kelly, Bettler, Kaupmann & Cryan, 2006; Cai et al., 2006; Cui, Lindl, Mei, Zhang & Tsien, 2005; Masugi et al., 1999). Further, KO and lesion manipulations as well as c-Fos assays have shown mediation by specific nuclei and pathways, e.g., medial parabrachial nucleus (mPBN; Bielavska & Bures, 1994; Spector, Scalera, Grill & Norgren, 1995), the basolateral amygdala (BLA; Dunn & Everitt, 1988; Nachman & Ashe, 1974; Koh, Wilkins &

Bernstein, 2003; Koh & Bernstein, 2005; Reilly, 2009) and insular cortex (IC; Bernstein & Koh, 2007; Braun, Slick & Lorden, 1972; Roman, Nebieridze, Sastre & Reilly, 2006). Although such work has provided considerable insight into the neurobiology of taste aversion learning, it is important to note that the vast majority of this work has been with the traditional emetic LiCl. Little work exists with drugs of abuse (Blednov et al., 2003; Cai et al., 2006; Castañé, Soria, Ledent, Maldonado & Valverde, 2006; Elkins et al., 2003b, 2003a; Orr, Walters, Carl & Elkins, 1993; Risinger et al., 2001; Weinshenker, Rust, Miller & Palmiter, 2000; see Cunningham et al., 2009 for a review) and even less with cocaine (Grabus, Glowa & Riley, 2004; Geddes, Han, Baldwin, Norgren & Grigson, 2008 see below).

Further, the majority of the work assessing the mechanisms underlying aversion learning has focused primarily on taste processing and associative learning with little attention given to the specific neurochemical activity of the aversion-inducing agents (though see Barki-Harrington et al., 2009; Bernstein et al., 2009; Bermudez-Rattoni & McGaugh, 1991; Escobar & Bermúdez-Rattoni, 2000; Yamamoto, Shimura, Sako, Yasoshima & Sakai, 1994; Yamamoto & Fujimoto, 1991). Consequently, even for compounds that have been examined, relatively little is known about the biology of the drug's aversive effects and how such effects might be modulated.

The importance in understanding the biology of a drug's rewarding or aversive properties is in how such effects might be manipulated or controlled to impact the drug's overall perceived affect and, in turn, its vulnerability to use and abuse. It is in this context that an examination of cocaine's biological mediation is critical to addiction (see above). Cocaine is a nonspecific monoamine transporter inhibitor that increases extracellular levels of DA, norepinephrine (NE) and serotonin (5-HT; Reith, Li & Yan, 1997; Taylor & Ho, 1978). The role of monoamine transport inhibition has been implicated in a number of cocaine-induced effects, including

reward (Ritz et al., 1987). For example, 6-hydroxydopamine (6-OHDA) lesions of the nucleus accumbens (NA) decrease cocaine self-administration (see Roberts, Corcoran & Fibiger, 1977). Further, pretreatment with DA antagonists blocks cocaine self-administration (Fibiger, Phillips & Brown, 1992; Norman et al., 2011; Roberts & Vickers, 1987; Song et al., 2011; Woolverton, 1986). Several CPP investigations using selective DA agonists and antagonists have elucidated the role of specific receptor subtypes in cocaine reward. For example, D_1 receptor antagonists have been shown to block cocaine-induced CPP (Baker, Fuchs, Specio, Khroyan & Neisewander, 1998; Cervo & Samanin, 1995). In contrast, this effect is not seen with D_2 receptor antagonists (Baker, Khroyan, O'Dell, Fuchs & Neisewander, 1996; Nazarian, Russo, Festa, Kraish & Quinones-Jenab, 2004; except in preweanling rats, see Pruitt, Bolanos & McDougall, 1995). D_3 receptor antagonists have been shown to dose-dependently attenuate cocaine CPP (Cervo, Burbassi, Colovic & Caccia, 2005; Vorel et al., 2002; see Beninger & Banasikowski, 2008 for a review). Further, D_1 agonists have been shown to induce CPPs on their own (and reinstate cocaine-induced CPPs after extinction), while D_2/D_3 agonists do not (see Graham, Hoppenot, Hendryx & Self, 2007). While some D_3 agonists produce CPPs when administered alone, they have not been found to alter cocaine-induced CPP (Gyertyán & Gál, 2003). The abovementioned research clearly characterizes a role of DA in cocaine reward. Relative to this substantial amount of research, less has been done examining the biology of cocaine's aversive effects. Interestingly, despite this, the monoamines, more specifically DA, appear involved in this affective property as well.

Before discussing the role of DA in cocaine-induced CTAs specifically, it should be noted that DA has been implicated in taste aversion learning in general through the use of lesioning and transgenic KO experiments. That is, through the use of 6-OHDA, DA levels can be

depleted significantly, such that the role of DA in different behavioral preparations can be assessed. 6-OHDA administration has been shown to result in the attenuation of CTAs to LiCl (and amphetamine; see Roberts & Fibiger, 1975; Lorden, Callahan & Dawson, 1980). Although these results would implicate a dopaminergic role in aversion learning, 6-OHDA also results in depletion of NE levels. It is also important to consider that other experiments did not replicate this LiCl effect (see Wagner, Foltin, Seiden & Schuster, 1981), suggesting that catecholamine depletion may not be involved in aversion learning in general, but may be specific to aversions induced by the compounds used (i.e., amphetamine; see Fenu, Rivas & Di Chiara, 2005; Rabin & Hunt, 1989; Stricker & Zigmond, 1974; Wagner et al., 1981). Interestingly, D_1 receptor KO mice do not develop LiCl-induced CTAs (unless they are food deprived Cannon et al., 2005), further suggesting possible DA involvement in aversion learning. However, other reports do not support such a role of DA in this phenomenon. For example, when the medial prefrontal cortex (mPFC; a major DA projection) is lesioned, animals develop conditioned place aversions (CPA) as well as robust CTAs (Isaac, Nonneman, Neisewander, Landers & Bardo, 1989). If DA were responsible even in part for development of CTAs, the removal of such a large DA projection should attenuate aversions at least to some extent. Additionally, another report demonstrated that following development of LiCl-induced CTAs, subjects had decreased extracellular levels of DA (Mark, Blander & Hoebel, 1991). Such a result would indicate that low levels (rather than high) of DA is aversive. Although these reports do not indicate a definitive role of DA in aversion learning in general, the dopaminergic system has been implicated in the aversive effects of cocaine.

The evidence comes from a variety of sources. By virtue of its ability to block the reuptake of DA, cocaine results in an increase in synaptic DA levels. It is interesting in this

context that a variety of DA agonists (e.g., SKF38393, quinpirole) induce CTAs on their own (Asin & Montana, 1989). Further, compounds that increase extracellular levels of DA, such as amphetamine, have been shown to induce CTAs (Cappell, LeBlanc & Endrenyi, 1973) that are blocked by the DA antagonist pimozide (Grupp, 1977). Importantly, the selective DA transporter (DAT) inhibitor GBR 12909 also induces CTAs (Freeman, Rice & Riley, 2005; see Figure 3). Although both cocaine and GBR 12909 induce dose-dependent CTAs, the strength of these aversions is not equivalent across compounds. That is, cocaine induces more robust CTAs at all doses examined relative to GBR 12909 (Freeman et al., 2005). This could be a function of a number of differences between the two compounds. For example, although both act to inhibit DAT, their different molecular weights (cocaine > GBR 12909) would result in differential drug availability upon administration of comparable doses (see Freeman et al., 2005 for a discussion). While these assessments are all suggestive that DA action may be aversive (and, therefore, responsible to some extent for cocaine-induced CTAs), it should be noted that most of these compounds have effects other than dopaminergic action (Andersen, 1989; Ritz & Kuhar, 1989) and as such these are rather indirect ways of assessing a role of DA (through DAT inhibition) in cocaine-induced CTAs. The following experiments were designed to provide more direct evidence of the possible role of DA in cocaine-induced CTAs using two separate preparations designed to determine underlying mechanism. Specifically, Experiments 1 and 2 used pharmacological antagonism to reveal the role (if any) of DA receptors in cocaine-induced CTAs. Experiments 3, 4 and 5 used the cross-drug preexposure preparation with cocaine and a selective DAT inhibitor to further characterize a role of DAT inhibition in cocaine-induced CTAs.

CHAPTER 2

EXPERIMENT 1 INTRODUCTION

Although DA has been indirectly implicated in cocaine-induced CTAs (as mentioned above), the results from more direct assessments of the role of DA in cocaine's aversive effects have been somewhat equivocal (see Gale, 1984; Hunt, Switzman, et al., 1985). For example, Gale (1984) attempted to block cocaine-induced taste aversions with the DA antagonist pimozide. In this report, rats were given a novel saccharin solution to drink followed by an injection of cocaine. A subset of these subjects was injected with either pimozide (1 mg/kg; IP) or saline after saccharin but prior to cocaine. Animals injected with saline prior to cocaine acquired a robust aversion to the cocaine-associated solution. Interestingly, animals injected with pimozide prior to cocaine did not differ from those treated with saline, i.e., pimozide had no effect on the acquisition of the cocaine-induced aversions, although it has been reported to be behaviorally active for up to 24 hours and clearly overlapped the effects of cocaine (see Atalay & Wise, 1983). These results suggest that DA is not involved in cocaine's aversive effects; however, the dose of cocaine used during conditioning was very large (160 mg/kg; see Ferrari et al., 1991; Freeman et al., 2005) and delivered in a single bolus subcutaneously at a high concentration (400 mg/ml). The large dose coupled with the high concentration may have resulted in a prolonged drug effect that was responsible for the near complete suppression of consumption (a mean of 80% suppression) after only two conditioning trials (see Domjan, 1978; Goudie & Dickins, 1978 for a discussion on the relation of duration of drug effects and CTAs ; though see Goudie, 1980). Under such conditions, it is likely that some animals displayed complete suppression. Although cocaine may have been acting through DA, the antagonist

effects of pimozide may have been masked by such a large drug effect. Further, only a single dose of cocaine was administered in the Gale report, precluding identification of doses that produced intermediate suppression that may possibly be more subject to modulation by pimozide.

Hunt and colleagues (Hunt, Switzman, et al., 1985) also assessed the effects of pimozide on cocaine-induced taste aversions, but reported that such aversions were attenuated by the DA antagonist. In their design, animals were injected with 1 mg/kg pimozide (IP) prior to saccharin access which was subsequently followed by four spaced IP injections of cocaine (9 mg/kg; every 15 minutes) or saline, a procedure reported to extend the duration of action of cocaine (see Foltin et al., 1981). As noted, pimozide attenuated the cocaine-induced taste aversion. Although suggestive of a role for DA in cocaine's aversive effects, under this procedure pimozide unconditionally suppressed saccharin consumption prior to the pairing of saccharin with cocaine (compared to saline-pretreated subjects who drank at high levels at the outset of conditioning; see Braveman & Crane, 1977; Kalat, 1976 but see also ; Bond & Westbrook, 1982; see Pescatore, Glowa & Riley, 2005 for a discussion), introducing a potential confound of amount consumed as a factor in the differential acquisition of aversions. Further, pimozide may have affected sensory processes that could have impacted the acquisition of the aversion independent of any antagonism of cocaine's specific aversive effects (Sears & Steinmetz, 1997; K. Spivak & Z. Amit, 1986; K. J. Spivak & Z. Amit, 1986).

Experiments 1 and 2 were designed to address the role of DA in the aversive effects of cocaine directly by examining the effects of the DA antagonist haloperidol on cocaine-induced taste aversions using procedures that circumvented the abovementioned possible effect of near maximal suppression (Gale, 1984) and the intrusion of any possible confounds of the DA

antagonist (Hunt, Switzman, et al., 1985). Given that haloperidol, although typically referred to as a D_2 antagonist, is a nonspecific DA antagonist with binding affinity for several other DA receptor subtypes, including D_1, D_3, D_4 and D_5 (see LeBlanc & Cappell, 1975), this assessment should provide an initial investigation of DA's involvement (if any) in this phenomenon.

When using pharmacological antagonists to assess mechanism in the CTA design, it is important to consider the possibility that administration of the antagonist prior to saccharin and cocaine could impact behavioral, sensory and/or learning processes involved in CTA acquisition that might limit any conclusions regarding the ability of the antagonist to affect the drug's aversive effects (see above; Hunt, Switzman, et al., 1985). One way to control for this is to administer the antagonist after saccharin, rather than before. This method has been used in other assessments of the role of specific neurotransmitter systems in a variety of drug-induced taste aversions (see Bienkowski, Kuca, Piasecki & Kostowski, 1997; Fenu, Rivas & Di Chiara, 2009; Gommans, Stolerman & Shoaib, 2000; LeBlanc & Cappell, 1975), including those induced by cocaine (Freeman, Verendeev & Riley, 2008). One concern with this specific procedure is that if the antagonist itself induces aversions, any interpretation of the effects of the antagonist on cocaine would be confounded. For example, the display of an aversion in the antagonist-treated animals might be interpreted as the antagonist having no effect on cocaine when in fact aversions induced by the cocaine might have been blocked. As such, it is important to determine a behaviorally active dose of the antagonist that does not induce a CTA alone prior to assessing its effect on cocaine-induced aversions. Accordingly, in Experiment 1 the ability of the D_2 antagonist haloperidol to induce taste aversions was assessed. Specifically, different groups of subjects were given a novel saccharin solution to drink followed by varying doses of haloperidol (see also Asin & Montana, 1989). Given that other assessments of DA antagonists have not

found such compounds aversive (in the CTA design), it is also important to determine that the doses assessed are behaviorally active. As such, the doses of haloperidol examined in the CTA preparation were also examined for their ability to affect locomotor behavior.

CHAPTER 3

EXPERIMENT 1 METHOD

Subjects

The subjects were 34 experimentally naïve, male Sprague-Dawley rats (Harlan Sprague-Dawley, Indianapolis, Indiana) approximately 75 days old and between 250 and 350 g at the start of the experiment. Procedures recommended by the National Institutes of Health Guide for the Care and Use of Laboratory Animals (1985), the Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research (2003) and the Institutional Animal Care and Use Committee at American University were followed at all times. Animals were handled daily approximately 2 weeks prior to the initiation of the study to limit the effects of handling stress during conditioning and testing.

Apparatus

All subjects were individually housed in hanging wire-mesh cages on the front of which graduated Nalgene tubes could be placed for fluid presentation. Subjects were maintained on a 12:12 light-dark cycle (lights on at 0800h) and at an ambient temperature of 23 ^{o}C. Except where noted, food and water were available *ad libitum*. Locomotor assessments were conducted using a three chamber automated apparatus (San Diego Instruments Place Preference system, San Diego, CA) modified to assess locomotor activity. Specifically, all flooring and panels were identical such that the three-chamber apparatus was converted to an open field apparatus 70 cm wide x 21 cm deep x 34.5 cm high. White LED lights provided constant illumination throughout the apparatus. A total of eight identical apparatuses were used; each apparatus featured photobeam arrays for recording gross locomotor activity (consecutive beam breaks) and fine motor activity

(repeated breaks of the same beam). The room in which the locomotor assessments were made was illuminated by an 85-watt red light mounted to the ceiling in the center of the room, and background noise was masked by a white noise machine located in the front of the room.

Drugs and Solutions

Haloperidol (VWR) was prepared in acetic acid (0.4% of total volume) then added to distilled water and brought to a pH of approximately 5 at a concentration of 1.0 mg/ml. Saccharin (sodium saccharin, Sigma) was prepared as a 1 g/l (0.1%) solution in tap water.

Procedure

Habituation

Following 24 h water deprivation, subjects were given 20-min access to tap water daily. This daily access was repeated until consumption stabilized, i.e., subjects approached and drank from the tube within 2 s of its presentation and water consumption was within 2 ml of the previous day for a minimum of 4 consecutive days with no consistent increase or decrease. Throughout the study, fluid was presented in graduated 50-ml Nalgene tubes and measured to the nearest 0.5 ml by subtracting the difference between the pre- and post-consumption volumes.

Conditioning

Conditioning began the day after the final habituation session. On Day 1 of conditioning, all subjects were given 20-min access to the novel saccharin solution. Immediately following this presentation, animals were rank ordered based on saccharin consumption and assigned to treatment groups (n = 8/9 per group), such that overall consumption was comparable among groups. Specifically, 32 Subjects were assigned as described above into four groups and were injected IP with 0, 0.25, 0.50 and 1.0 mg/kg haloperidol, yielding Groups 0, 0.25, 0.50 and 1.0.

The vehicle group (Group 0) received injections that were matched in volume to the group receiving the high dose of haloperidol (Group 1.0). The 3 days following this initial saccharin presentation were water-recovery days during which animals were given 20-min access to tap water (no injections followed this access). This alternating procedure of conditioning and water recovery was repeated for a total of four complete cycles.

Final Aversion Test

Following the last water-recovery session after the fourth conditioning trial, animals were given 20-min access to saccharin in a final aversion test after which no injections followed.

Locomotor Assessment

Following this test, subjects were maintained on 20-min access to water for 2 weeks during which time no saccharin or injection was given. This period was introduced to limit any residual effects of haloperidol. After this period, subjects were administered a vehicle injection (IP; matched in volume to the dose of haloperidol with which they were initially conditioned) and placed into locomotor chambers for 60 min (baseline). The following day, subjects were administered an IP injection of haloperidol or vehicle (matched to the dose given during conditioning) and placed back into the locomotor chambers for 60 min (test).

Statistical Analysis

For the haloperidol dose-response assessment, the differences in mean saccharin consumption during conditioning were analyzed using a 4 x 4 mixed ANOVA with the between-subjects variable of Group (0, 0.25, 0.50 and 1.0 mg/kg) and the within-subjects variable of Trial (1-4). Where appropriate, individual differences were examined using Fisher's PLSD post-hoc analyses. Differences in mean saccharin consumption between groups on the Final Aversion Test

were analyzed using a one-way ANOVA. Fisher's PLSD post-hoc analyses were used to examine specific group differences in consumption on the Final Aversion Test. All significance levels were set at $p \leq 0.05$. For the locomotor assessment, fine and gross motor activity were combined into a single measure of total activity and collapsed across all four intervals. A 2 x 4 repeated measures ANOVA was then used to investigate differences in total activity with the between-subjects variable of Group (0, 0.25, 0.50 and 1.0 mg/kg) and the within-subjects variable of Day (baseline or test). One-way ANOVAs were used to investigate the differences between doses during the baseline and test day.

CHAPTER 4

EXPERIMENT 1 RESULTS

Conditioning

The 4 x 4 mixed ANOVA on consumption during conditioning revealed a significant effect of Trial [$F(3, 90) = 15.096$, $p < 0.001$] but no effect of Group [$F(3, 30) = 0.618$, $p = 0.609$] and no significant Trial x Group interaction [$F(9, 90) = 0.928$, $p = 0.505$]. In relation to the Trial effect, all groups increased consumption across conditioning, indicating that none of the doses of haloperidol induced a CTA (see Figure 2).

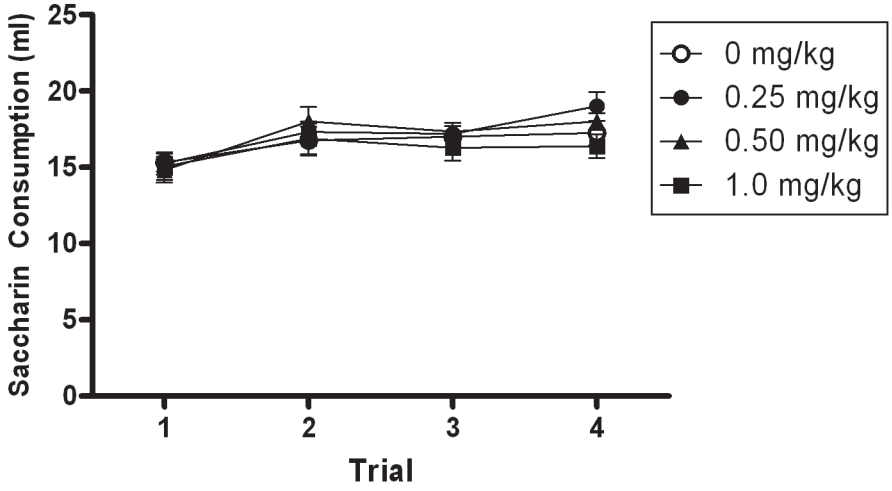

Figure 2. Mean (± SEM) saccharin consumption (ml) for all subjects in groups conditioned with haloperidol (0.25, 0.50, or 1.0 mg/kg) or vehicle (0 mg/kg). There was an effect of trial (all subjects increased consumption across trials), but there were no significant differences between groups.

Final Aversion Test

A one-way ANOVA on the Final Aversion Test revealed no significant differences in consumption [$F(3, 33) = 1.591$, $p = 0.212$], indicating that no CTA was induced by any of the doses of haloperidol (see Figure 3).

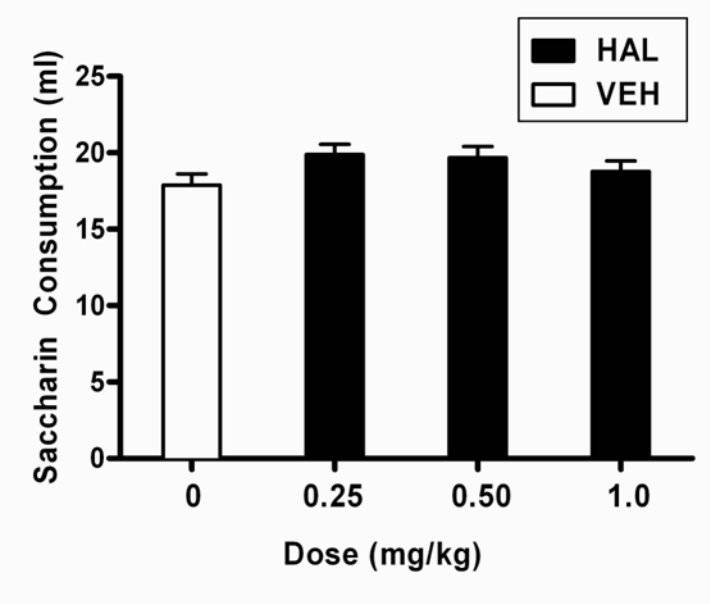

Figure 3. Mean (± SEM) saccharin consumption (ml) on the final aversion test for subjects conditioned with haloperidol (HAL; 0.25, 0.50, or 1.0 mg/kg) or vehicle (VEH; 0 mg/kg). No aversions were induced by haloperidol at any of the doses tested.

Locomotor Assessment

The 2 x 4 repeated measures ANOVA for total locomotor activity (collapsed across intervals) revealed a significant effect of Day [$F(1, 30) = 156.221$, $p < 0.001$] as well as a significant Day x Group interaction [$F(3, 30) = 14.741$, $p < 0.001$]. Given this interaction, one-way ANOVAs were run for each day (baseline and test). This analysis revealed that at baseline (Figure 4) subjects with a history of 0.25 mg/kg haloperidol displayed significantly more locomotor activity than subjects in the vehicle group ($p = 0.013$). One-way ANOVAs for the test day (Figure 4) revealed that all subjects injected with haloperidol (regardless of dose) significantly decreased locomotor activity relative to vehicle-injected controls (all p's < 0.05). Subjects injected with 0.50 mg/kg did not differ from subjects injected with 1.0 mg/kg haloperidol. All subjects decreased in activity on the test day within the first 30 min of the locomotor assessment (data not shown).

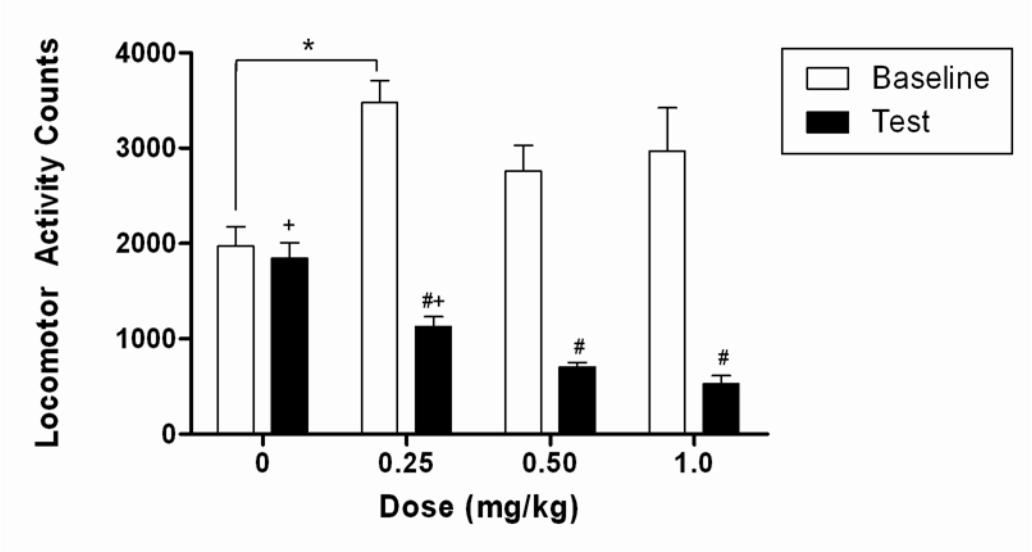

Figure 4. Mean (± SEM) total locomotor activity counts (averaged across all intervals) for all subjects in groups administered haloperidol or vehicle. Since there was a significant Day x Group interaction, individual group differences were examined for each day (see section 2.3.2). *Significantly different from saline treated rats on baseline day; $^{+}$significantly different from Groups 0.50 and 1.0 on test day; $^{\#}$significantly different from Group 0 on test day.

CHAPTER 5

EXPERIMENT 2 INTRODUCTION

Haloperidol (0.25, 0.50 and 1.0 mg/kg) was tested for its ability to induce CTAs. As noted, all doses tested failed to induce CTAs. Since these doses were not effective in the CTA design, locomotor activity was assessed in order to determine if these doses administered were behaviorally active. At baseline (when no drug was administered), subjects with a history of haloperidol (administered during taste aversion conditioning) displayed increased locomotor activity relative to controls. This is consistent with several reports demonstrating that animals with a history of antipsychotic administration (ranging in number of exposures) show enhanced stimulant-induced locomotor activity, indicating a change in DA receptor expression (see Eibergen & Carlson, 1976; LeDuc & Mittleman, 1993; Rebec, Peirson, McPherson & Brugge, 1982; Samaha et al., 2008; Seeger, Thal & Gardner, 1982). This increase in locomotor activity was only significant for subjects injected with the lowest dose of haloperidol (0.25 mg/kg; see Figure 4). When haloperidol was administered on the test day, animals injected with 0.50 and 1.0 mg/kg haloperidol displayed significant decreases in motor activity within 30 min of administration (and did not differ from each other). Since there was no difference between 0.50 and 1.0 mg/kg, the highest dose tested was used in the assessment of the effects of haloperidol on cocaine-induced CTAs (Experiment 2) to optimize the likelihood of detecting any effect of antagonism. In this assessment, the antagonist was administered following saccharin consumption (and prior to cocaine). Such a procedure has previously been used in an assessment of the role of DA in cocaine-induced aversions (see Gale, 1984); however, the dose of cocaine and its high concentration may have limited the ability to see antagonism. To circumvent this problem, in Experiment 2 animals were injected with cocaine at doses that produce graded

aversions that ranged from little to intermediate to near complete suppression (see Ferrari et al., 1991; Freeman et al., 2005). Such a dose range provides behavioral effects that are subject to modulation. Specifically, animals in Experiment 2 were given a novel saccharin solution to drink followed by an injection of 1.0 mg/kg haloperidol. Thirty min following this injection, animals were assigned to different groups and were injected with 10, 18 and 32 mg/kg cocaine. Previous studies in our laboratory have demonstrated necrosis following subcutaneous injections of cocaine at this dose range; however, such effects were not related to degree of aversions and no significant distress in these animals was observed.

CHAPTER 6

EXPERIMENT 2 METHOD

Subjects

The subjects were 60 experimentally naïve, male Sprague-Dawley rats (Harlan Sprague-Dawley, Indianapolis, Indiana) approximately 75 days old and between 250 and 350 g at the start of the experiment. Procedures recommended by the National Institutes of Health Guide for the Care and Use of Laboratory Animals (1985), the Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research (2003) and the Institutional Animal Care and Use Committee at American University were followed at all times. Animals were handled daily approximately 2 weeks prior to the initiation of the study to limit the effects of handling stress during conditioning and testing.

Apparatus

All subjects were individually housed in hanging wire-mesh cages on the front of which graduated Nalgene tubes could be placed for fluid presentation. Subjects were maintained on a 12:12 light-dark cycle (lights on at 0800h) and at an ambient temperature of 23 ^{o}C. Except where noted, food and water were available *ad libitum*.

Drugs and Solutions

Haloperidol (VWR) was prepared in acetic acid (0.4% of total volume) then added to distilled water and brought to a pH of approximately 5 at a concentration of 1.0 mg/ml. Cocaine hydrochloride (generously provided by the National Institute on Drug Abuse) was dissolved in distilled water at a concentration of 10 mg/ml and administered subcutaneously (SC). Cocaine

doses are expressed as the salt. Saccharin (sodium saccharin, Sigma) was prepared as a 1 g/l (0.1%) solution in tap water.

Procedure

Habituation

Following 24 h water deprivation, subjects were given 20-min access to tap water daily. This daily access was repeated until consumption stabilized, i.e., subjects approached and drank from the tube within 2 s of its presentation and water consumption was within 2 ml of the previous day for a minimum of 4 consecutive days with no consistent increase or decrease. Throughout the study, fluid was presented in graduated 50-ml Nalgene tubes and measured to the nearest 0.5 ml by subtracting the difference between the pre- and post-consumption volumes.

Conditioning

Conditioning began 4 days following the final habituation session. On Day 1 of conditioning, all subjects were given 20-min access to the novel saccharin solution. Immediately following this presentation, animals were rank ordered based on saccharin consumption and assigned to treatment groups (n = 7/8 per group), such that overall consumption was comparable among groups. Specifically, 60 subjects were ranked based on consumption and injected with 1.0 mg/kg haloperidol or vehicle (matched in volume to 1.0 mg/kg haloperidol). Approximately 30 min after haloperidol or vehicle injections, subjects were given a SC injection of cocaine (10, 18 or 32 mg/kg) or vehicle (matched in volume to 32 mg/kg cocaine), yielding eight experimental groups, specifically, vehicle-vehicle (V0; n = 7), vehicle-10 mg/kg cocaine (V10; n = 7), vehicle-18 mg/kg cocaine (V18; n = 7), vehicle-32 mg/kg cocaine (V32; n = 7), haloperidol-vehicle (H0 n = 8), haloperidol -10 mg/kg cocaine (H10; n = 8), haloperidol- 18 mg/kg cocaine (H18; n = 8) and haloperidol- 32 mg/kg cocaine (H32; n = 8). The 3 days following this initial saccharin

presentation were water-recovery days during which animals were given 20-min access to tap water (no injections followed this access). This alternating procedure of conditioning and water recovery was repeated for a total of four complete cycles.

Final Aversion Test

Following the last water-recovery session after the fourth conditioning trial, animals were given 20-min access to saccharin in a final aversion test after which no injections followed.

Statistical Analysis

Differences in mean saccharin consumption during conditioning for Experiment 2 were analyzed using a 2 x 4 x 4 mixed ANOVA with the between subjects variables of Pretreatment Drug (vehicle or 1.0 mg/kg haloperidol) and Conditioning Drug (0, 10, 18, or 32 mg/kg cocaine) and the within-subjects variable of Trial (1-4). Where appropriate individual differences were examined using Fisher's PLSD post-hoc analyses. Differences in mean saccharin consumption between groups on the Final Aversion Test were analyzed using a one-way ANOVA. Significant interactions were investigated using Fisher's PLSD post hoc analysis to determine specific group differences where appropriate. All significance levels were set at $p \leq 0.05$.

CHAPTER 7

EXPERIMENT 2 RESULTS

Conditioning

The 2 x 4 x 4 mixed ANOVA revealed significant effects of Trial [$F(3, 156) = 7.468$, $p < 0.001$], Pretreatment Drug [$F(1, 52) = 6.809$, $p = 0.012$] and Conditioning Drug [$F(3, 52) = 40.390$, $p < 0.001$] as well as significant Trial x Pretreatment Drug [$F(3, 156) = 10.985$, $p < 0.001$], Trial x Conditioning Drug [$F(9, 156) = 35.941$, $p < 0.001$] and Trial x Pretreatment Drug x Conditioning Drug [$F(9, 156) = 3.657$, $p < 0.001$] interactions. In relation to the significant three-way interaction, subsequent Fisher's PLSD post-hoc analyses revealed the following significant differences among groups for each trial. On Trial 1, there were no significant differences among groups. On Trial 2, subjects injected with the high dose of cocaine (Groups V32 and H32) drank significantly less than subjects injected with vehicle (Groups V0 and H0; all p's < 0.05), indicating a significant cocaine CTA at 32 mg/kg for both cocaine-injected groups. Subjects in Group V32 drank significantly less than subjects in all other groups (all p's < 0.05) except Group H32. Group H32 drank significantly less than all other groups (all p's < 0.05) except Group V18. On Trial 3, these differences were maintained. Additionally, subjects in Group V18 drank significantly less than all other groups (except Group H32) and significantly more than subjects in V32 (all p's < 0.05). Additionally, Group V32 drank significantly less than subjects in Group H32. That Group H18 drank more than Group V18, and that Group H32 drank more than Group V32 indicates a significant attenuation of CTAs by haloperidol. All of these differences were maintained on Trial 4, (all p's < 0.05; see Figure 5).

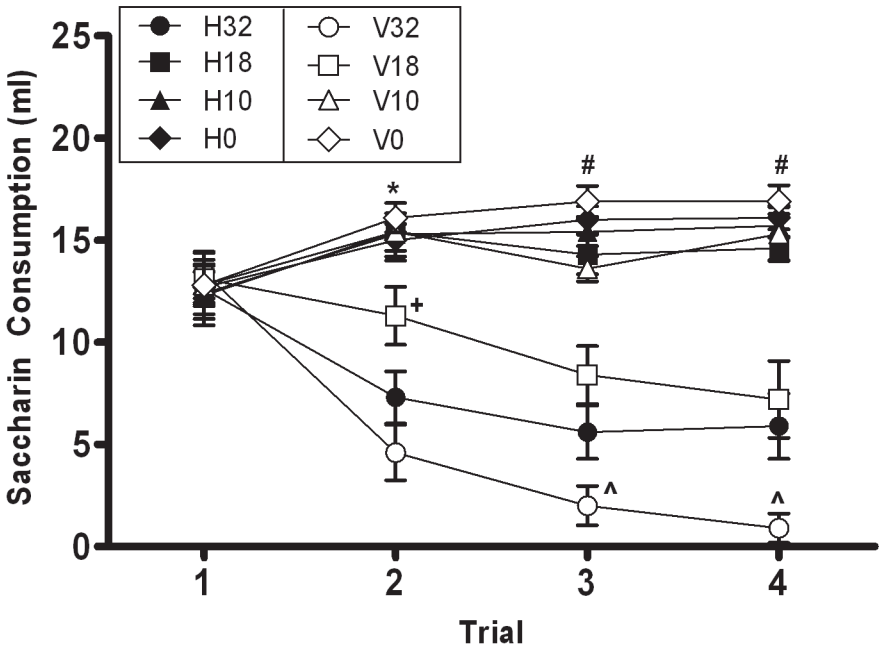

Figure 5. Mean (± SEM) saccharin consumption (ml) for all subjects in groups pretreated with haloperidol (H; 1.0 mg/kg) or vehicle (V) and conditioned with cocaine (10, 18, 32 mg/kg) or vehicle (0). Since there was a significant Trial x Pretreatment Drug x Conditioning Drug interaction, individual group differences were examined (see section 3.3.1). *Significantly different from Groups H32 and V32; #significantly different from Group V18, H32 and V32; ^significantly different from all other groups; +significantly different from all groups except H32.

Final Aversion Test

A one-way ANOVA on the Final Aversion Test revealed significant differences in consumption between groups [$F(7, 59) = 29.541$, $p < 0.001$]. Fisher's PLSD post-hoc analysis revealed that subjects injected with the high dose of cocaine (Groups V32 and H32) drank significantly less than subjects injected with vehicle (Groups V0 and H0; all p's < 0.05), indicating a significant cocaine CTA at 32 mg/kg for both cocaine-injected groups. Subjects in Group V32 drank significantly less than subjects in all other groups (all p's < 0.05). Group H32 drank significantly less than all other groups (all p's < 0.05) except Group V18. Additionally, subjects in Group V18 drank significantly less than all other groups (except Group H32) and significantly more than subjects in V32 (all p's < 0.05). That Groups H18 and H32 drank more

than Group V18 and Group V32 (respectively) indicates a significant attenuation of CTAs by haloperidol (see Figure 6).

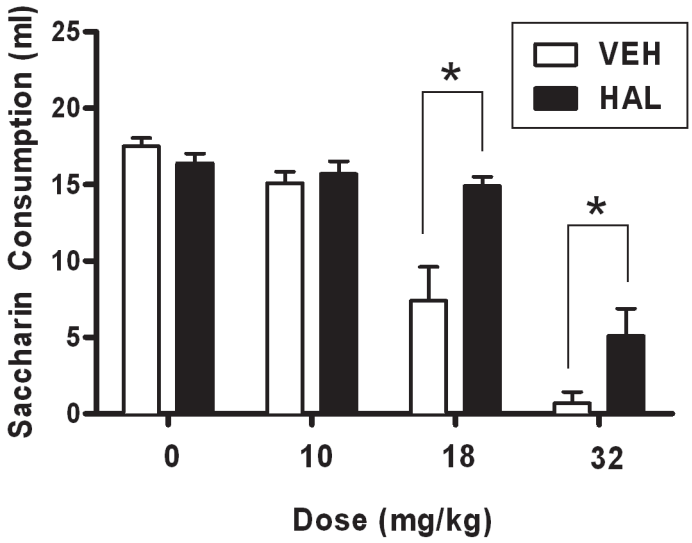

Figure 6. Mean (± SEM) saccharin consumption (ml) on the final aversion test for subjects pretreated with haloperidol (HAL; 1.0 mg/kg) or vehicle and conditioned with cocaine (10, 18, 32 mg/kg) or vehicle (0). Haloperidol pretreatment attenuated cocaine-induced CTAs at 18 mg/kg; *Significantly different from vehicle controls.

CHAPTER 8

EXPERIMENT 3 INTRODUCTION

To examine a role for DA receptor activation in the induction of cocaine's aversive effects, haloperidol was administered following saccharin access (but prior to a range of cocaine doses) in a CTA procedure. As described, the effects of cocaine were dose-dependent with aversions induced by 18 and 32 mg/kg (see Ferrari et al., 1991; Freeman et al., 2005). Further, aversions at these two doses were attenuated by haloperidol (1.0 mg/kg). These results are consistent with those of Hunt and colleagues (1985) using a design that allows for an assessment of the ability of a D_2 antagonist to block cocaine-induced aversions without the possible confounds of an effect of haloperidol on fluid consumption or sensory processes. The present data also suggest that the failure of pimozide to block cocaine-induced CTAs as demonstrated by Gale (1984) may have been a function of the dose and concentration of cocaine used in that assessment (see above). Together with these initial assessments of D_2 antagonism on cocaine-induced aversions, the present data indicate that DA activity induced by cocaine, as a DAT inhibitor, may mediate its aversive effects at least as measured in the CTA preparation.

If DA is involved in cocaine's aversive effects, it should be possible to demonstrate this in other preparations used to assess such mechanisms. One such procedure, the cross-drug preexposure preparation, has been used by our lab previously to investigate NE and 5-HT in the context of cocaine-induced CTAs (see General Discussion; Serafine & Riley, 2009; Serafine & Riley, 2010; see also Riley & Simpson, 2001 for a review of US preexposure). In this design, animals are given exposure to one compound before taste conditioning with another. If attenuation is seen after this drug history, it is interpreted to be a function of cross-tolerance between some common aversion inducing mechanism shared between compounds (De Beun,

Rijk & Broekkamp, 1993; Olivier et al., 1999; Serafine & Riley, 2009; for a review see Riley & Simpson, 2001). For example, in one of the first demonstrations of the use of this procedure for investigations of common stimulus properties, De Beun and colleagues (1993) reported that CTAs induced by the selective 5-HT agonist 8-OHDPAT were blocked by preexposure to compounds that also had 5-HT agonist activity (for the same receptor subtype, e.g., 5-HT1A; see De Beun et al., 1993). Given that these compounds (ipsapirone, buspirone, RU-24969, sertraline, d-amphetamine, LSD, metergoline and idazoxane) were effective in blocking 8-OHDPAT-induced CTAs, De Beun and colleagues concluded that cross-drug preexposure could be used to assess the commonalities in aversion-inducing mechanism between different compounds (De Beun et al., 1993). Since this demonstration, several other investigations have also utilized this procedure to examine common mechanisms in the aversive effects of various compounds (see De Beun, Lohmann, Schneider & De Vry, 1996; Gommans et al., 1998; Jones, Hall, Uhl, Rice & Riley, 2009; Kayir et al., 2008; Olivier et al., 1999; Van Hest, Hijzen, Slangen & Olivier, 1992; Serafine & Riley, 2009, 2010). According to this same logic, if DA is involved in cocaine-induced aversions, it might be expected that a history with cocaine would impact subsequent aversion learning induced by other compounds that increase DA levels (and vice versa), as a function of this cross tolerance (or adaptation) to the shared aversion-inducing effects of the two drugs (Berman & Cannon, 1974; Jones et al., 2009; LeBlanc & Cappell, 1974; Simpson & Riley, 2005; Serafine & Riley, 2009, 2010; for reviews and alternative interpretations, see H. Cappell & A. E. LeBlanc, 1977; Randich & LoLordo, 1979; Riley & Simpson, 2001). To assess the possible role of DA in aversions induced by cocaine, in the present experiment animals were preexposed to cocaine (18 mg/kg) prior to aversion conditioning with the selective DAT inhibitor GBR 12909 (32 mg/kg). This dose of cocaine has been found to attenuate cocaine-

induced CTAs (Serafine & Riley, 2009) when administered during preexposure and to induce intermediate aversions when administered during conditioning (see Freeman et al., 2005). GBR 12909 (at 32 mg/kg) has also been reported to produce intermediate aversions (Freeman et al., 2005). Given that preexposure can result in the attenuation or potentiation of aversions, it was necessary to choose conditioning doses that would not cause complete suppression (or that would reliably induce a CTA; see Riley & Simpson for a review).

CHAPTER 9

EXPERIMENT 3 METHODS

Subjects

The subjects were 51 experimentally naïve, male Sprague-Dawley rats (Harlan Sprague-Dawley, Indianapolis, Indiana), approximately 75 days old and between 250 and 350 g at the start of the experiments. Procedures recommended by the National Institutes of Health Guide for the Care and Use of Laboratory Animals (1985), the Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research (2003) and the Institutional Animal Care and Use Committee at American University were followed at all times. Animals were handled daily approximately 2 weeks prior to the initiation of the study to limit the effects of handling stress during conditioning and testing.

Apparatus

All subjects were individually housed in hanging wire-mesh cages on the front of which graduated Nalgene tubes could be placed for fluid presentation. Subjects were maintained on a 12:12 light-dark cycle (lights on at 0800h) and at an ambient temperature of 23 ^{o}C. Except where noted, food and water were available *ad libitum*.

Drugs and Solutions

Cocaine hydrochloride (generously provided by the National Institute on Drug Abuse) and GBR 12909 bismethanesulfonate monohydrate (synthesized at the Chemical Biology Research Branch of the National Institute on Drug Abuse) were each dissolved in distilled water at a concentration of 10 mg/ml. All injections were administered SC. All drug doses are

expressed as the salt. Saccharin (sodium saccharin, Sigma) was prepared as a 1 g/l (0.1%) solution in tap water.

Procedure

Habituation

Following 24 h water deprivation, subjects were given 20-min access to tap water daily. This daily access was repeated until consumption stabilized, i.e., subjects approached and drank from the tube within 2 s of its presentation and water consumption was within 2 ml of the previous day for a minimum of 4 consecutive days with no consistent increase or decrease. Throughout the study, fluid was presented in graduated 50-ml Nalgene tubes and measured to the nearest 0.5 ml by subtracting the difference between the pre- and post-consumption volumes.

Preexposure

Water consumption for all subjects was recorded and averaged over the last 3 days of habituation. Animals were then ranked on average water consumption and assigned to a preexposure condition (cocaine or vehicle). Five hours following their regular 20-min water access, animals were injected with cocaine (18 mg/kg) or vehicle (matched in volume) every 4th day for a total of 5 days (five total drug or vehicle injections). No injections were given during intervening days. Water consumption was monitored throughout this phase.

Conditioning

Four days following the last preexposure injection, subjects were given 20-min access to the novel saccharin solution. Following saccharin consumption, rats were ranked based on consumption (such that overall consumption was comparable between groups) and injected with either 18 mg/kg cocaine, 32 mg/kg GBR 12909 or vehicle (matched in volume to GBR 12909),

yielding six experimental groups, specifically, cocaine-cocaine (COC-COC; n = 9), cocaine-GBR 12909 (COC-GBR; n = 8), cocaine-vehicle (COC-VEH; n = 8), vehicle-vehicle (VEH-VEH; n = 8), vehicle-GBR 12909 (VEH-GBR; n = 9), and vehicle-cocaine (VEH-COC; n = 9). The first series of letters in each group designation refer to the drug given during preexposure; the second series of letters refer to the drug given during conditioning. The 3 days following this initial saccharin presentation were water-recovery days during which animals were given 20-min access to tap water (no injections followed this access). This alternating procedure of conditioning and water recovery was repeated for a total of four complete cycles.

Final Aversion Test

Following the last water-recovery session after the fourth conditioning trial, animals were given 20-min access to saccharin in a final aversion test after which no injections followed.

Statistical Analysis

During drug preexposure, the differences in mean water consumption were analyzed using a 2 x 20 repeated measures ANOVA with a between-subjects variable of Preexposure Drug (cocaine or vehicle) and a within-subjects variable of Preexposure Day (1-20). Where appropriate, Fisher's PLSD post-hoc analyses were run to examine group differences on individual days. During conditioning, the differences in mean saccharin consumption were analyzed for each experiment using a 2 x 3 x 4 mixed-model ANOVA with the between-subjects variables of Preexposure Drug (cocaine or vehicle) and Conditioning Drug (cocaine, vehicle or GBR 12909) and a within-subjects variable of Trial (1-4). Where appropriate, Fisher's PLSD post-hoc analyses were used to examine mean saccharin consumption differences between groups on each individual trial. Differences in mean saccharin consumption between groups on the Final Aversion Test were analyzed using a one-way ANOVA. Fisher's PLSD post-hoc

analyses were used to examine specific group differences in consumption on the Final Aversion Test. All significance levels were set at $p \leq 0.05$.

CHAPTER 10

EXPERIMENT 3 RESULTS

Preexposure

The 2 x 20 repeated measures ANOVA revealed a significant effect of Preexposure Day [F (19, 931) = 10.125, $p < 0.001$] and Preexposure Drug [F (1, 49) = 4.603, $p = 0.037$], but no significant Preexposure Drug x Preexposure Day interaction [F (19, 931) = 1.307, $p = 0.170$]. Regarding the effect of Preexposure Day, all subjects (regardless of preexposure drug) increased consumption over the preexposure phase. Regarding the main effect of Preexposure Drug, all subjects preexposed to cocaine drank significantly more than subjects preexposed to vehicle (see Figure 7).

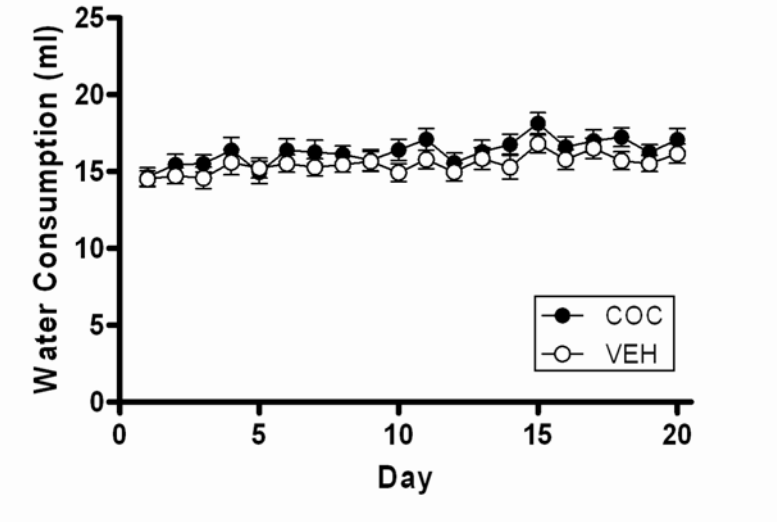

Figure 7. Mean (± SEM) water consumption (ml) for all subjects in groups preexposed to cocaine (COC) or vehicle (VEH). There was a significant main effect of Preexposure Day and a significant main effect of Preexposure Drug, but no significant Preexposure Day x Preexposure Drug interaction. Regarding the effect of Preexposure Day, all subjects (regardless of preexposure drug) increased consumption over the preexposure phase. Regarding the main effect of Preexposure Drug, all subjects preexposed to cocaine drank significantly more than subjects preexposed to vehicle.

Conditioning

The 2 x 3 x 4 mixed-model ANOVA revealed significant effects of Trial [$F(3, 132) = 14.063$, $p < 0.001$], Preexposure Drug [$F(1, 44) = 13.921$, $p = 0.001$] and Conditioning Drug [$F(2, 44) = 18.307$, $p < 0.001$] and significant Trial x Conditioning Drug [$F(6, 132) = 11.459$, $p < 0.001$] and Trial x Preexposure Drug [$F(3, 132) = 3.647$, $p = 0.014$] interactions. In relation to the significant Trial x Preexposure Drug interaction, subjects preexposed to cocaine drank significantly more saccharin than those preexposed to vehicle. That is, regardless of conditioning drug, there were differences between subjects preexposed to cocaine and those preexposed to vehicle across trials. In order to examine these specific differences, one-way ANOVAs examining preexposure drug (cocaine or vehicle) on individual trials revealed the following significant differences. Although on Trial 1 there were no significant group differences, on Trial 2 groups preexposed to cocaine (COC-VEH, COC-GBR and COC-COC) drank significantly more saccharin than those preexposed to vehicle (VEH-VEH, VEH-GBR and VEH-COC). This was maintained on Trial 3 (all p's > 0.05); however, on Trial 4 these differences were no longer significant.

In relation to the significant Trial x Conditioning Drug interaction, subjects conditioned with GBR 12909 or cocaine drank significantly less than those conditioned with vehicle (indicating CTAs induced by both compounds). That is, regardless of preexposure condition, there were differences between subjects that were conditioned with cocaine, GBR 12909 and vehicle across trials. In order to examine these specific differences, one-way ANOVAs examining conditioning drug (cocaine, GBR 12909 or vehicle) on individual trials revealed the following significant differences. Although on Trial 1 there were no differences between any groups, on Trial 2 groups conditioned with GBR 12909 (VEH-GBR and COC-GBR) and with cocaine (VEH-COC and COC-COC) drank significantly less than those conditioned with vehicle

(VEH-VEH and COC-VEH; all p's < 0.047). On Trials 3, and 4, these differences were maintained (all p's < 0.05). Since there was no significant interaction of Trial x Preexposure Drug x Conditioning Drug, Fisher's PLSD post-hoc analyses were not run on individual groups for individual trials (see Figure 8).

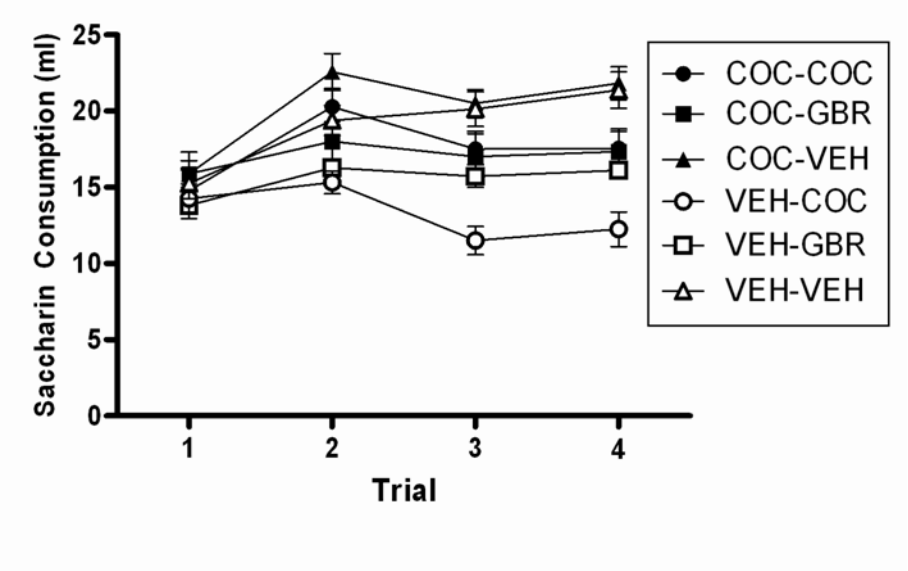

Figure 8. Mean (± SEM) saccharin consumption (ml) for all subjects in groups preexposed to cocaine (COC) or vehicle (VEH) and conditioned with cocaine (18 mg/kg), GBR 12909 (GBR; 32 mg/kg) or vehicle. All COC preexposed subjects (regardless of conditioning drug) drank significantly more than VEH preexposed subjects (regardless of conditioning drug) on Trials 2 and 3. All drug conditioned subjects (collapsed across preexposure condition) drank significantly less than all vehicle conditioned subjects (collapsed across preexposure condition) on Trials 2, 3 and 4. Since no significant three-way interaction was observed, no post-hoc analyses were run individual groups.

Final Aversion Test

A one-way ANOVA on the Final Aversion Test revealed significant group differences [$F(5, 50) = 10.267$, $p < 0.001$]. Fisher's PLSD post-hoc analyses revealed the following. Subjects injected with vehicle during conditioning (Groups VEH-VEH and COC-VEH) drank significantly more than subjects injected with drug, i.e., Groups VEH-COC and VEH-GBR (all p's < 0.046; demonstrating CTAs induced by both compounds). Vehicle-injected (Group VEH-VEH) controls also drank significantly more than subjects preexposed to cocaine and conditioned with cocaine, i.e., COC-COC ($p = 0.024$). Additionally, subjects in Group COC-

VEH drank significantly more than subjects in Group COC-COC and Group COC-GBR (all p's < 0.004). Subjects in Group VEH-GBR drank more than subjects in Group VEH-COC (p = 0.002), indicating that cocaine induced a stronger aversion than GBR 12909. Finally, subjects preexposed and conditioned with cocaine (Group COC-COC) drank significantly more than subjects in Group VEH-COC (p = 0.004), indicating a US preexposure effect. Subjects in Group COC-GBR, however, did not differ significantly in consumption compared to subjects in Group VEH-GBR (p = 0.637), indicating no significant effect of cross-drug preexposure (see Figure 9).

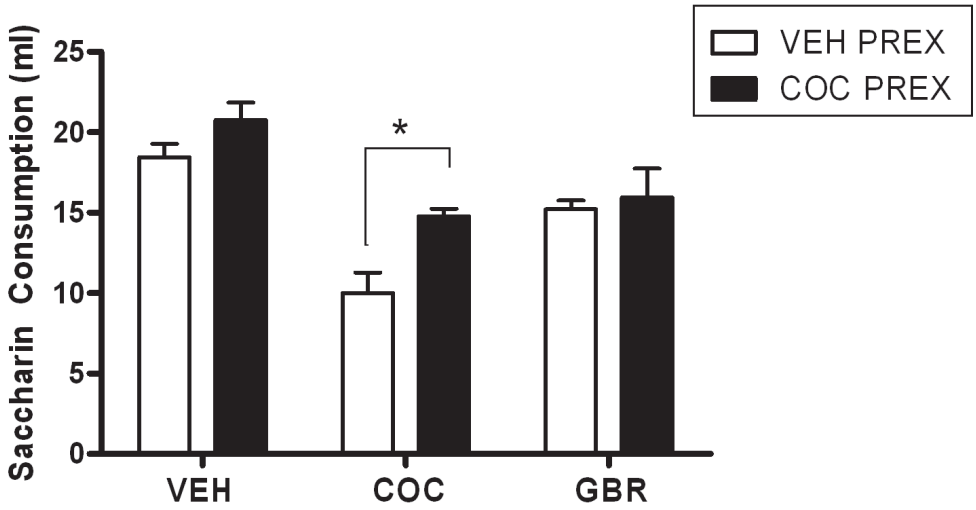

Figure 9. Mean (± SEM) saccharin consumption (ml) on the Final Aversion Test for subjects preexposed to cocaine (COC; 18 mg/kg) or vehicle (VEH) and conditioned with cocaine (COC; 18 mg/kg), GBR 12909 (GBR; 32 mg/kg) or vehicle (0). COC preexposure attenuated cocaine-, but not GBR-, induced CTAs. All GBR conditioned subjects drank significantly less than vehicle controls. VEH preexposed, cocaine conditioned subjects also drank less than VEH preexposed, vehicle conditioned controls. *Significantly attenuated relative to VEH preexposed controls.

CHAPTER 11

EXPERIMENT 4 INTRODUCTION

As described, preexposure to cocaine had no effect on the aversion induced by GBR 12909. Although the basis for this effect is not known, there are several possibilities. First, the failure of cocaine exposure to attenuate GBR 12909-induced aversions could reflect the fact that there is no overlap in the aversive effects of the two drugs. If there is no overlap, such a history would not be expected to impact subsequent aversions. The failure to see any attenuating effects in Experiment 3, however, may be a function of the relative degree of overlap of the stimulus properties of cocaine and GBR 12909. According to this explanation, the two drugs may have similar, but non-identical, stimulus properties and it is the degree of the overlap that impacts any attenuating effects. That is, a compound like cocaine has multiple actions (general monoamine transport inhibition) and aversions may be induced by any one (or some combination) of all of these actions. On the other hand, GBR 12909 has one selective action (i.e., DAT inhibition) and it is this action which likely mediates its aversive effects. Preexposure to cocaine with its multifaceted action may induce tolerance to monoamine transport inhibition sufficiently enough to attenuate cocaine-induced CTAs, but may not induce tolerance to DAT inhibition alone significantly enough to attenuate aversions to GBR 12909 (whose aversive effects are completely DAT mediated). Although cocaine preexposure may not affect aversions induced by GBR 12909, it is possible that the reverse serial presentation (GBR 12909 preexposure before cocaine conditioning) may result in an attenuation (if DAT inhibition is playing some role in their aversive effects). In this case, when animals are preexposed to GBR 12909, tolerance to the effects of DAT inhibition will occur (given that there is no other effect of GBR 12909). If cocaine-induced CTAs are mediated to any degree by this same mechanism, preexposure (and

the accompanying tolerance) should result in an attenuation of cocaine-induced CTAs. It is interesting in this context that such asymmetrical cross-drug preexposure effects have been reported for other combinations of drugs (De Beun et al., 1996; Gommans et al., 1998; Goudie & Thornton, 1975; see also Riley & Simpson, 2001; see Grakalic & Riley, 2002a; Serafine & Riley, 2009; 2010 for examples with cocaine) and are generally interpreted as evidence of similar, but non-identical, mechanisms responsible for the induction of CTAs by the two compounds. Given these reports of asymmetry with cocaine in the cross-drug preexposure design, the following experiment examined the effects of preexposure to the highly selective DAT inhibitor GBR 12909 on aversions induced by itself and the relatively nonselective monoamine transport inhibitor cocaine. The same dose of cocaine used in Experiment 3 was used in Experiment 4, given that it induces intermediate aversions during conditioning (Freeman et al., 2005). Since GBR 12909 has not been reported using the cross-drug preexposure design, the intermediate dose used in Experiment 3 for conditioning was used in Experiment 4 for preexposure and conditioning.

CHAPTER 12

EXPERIMENT 4 METHODS

Subjects

The subjects were 50 experimentally naïve, male Sprague-Dawley rats (Harlan Sprague-Dawley, Indianapolis, Indiana), approximately 75 days old and between 250 and 350 g at the start of the experiments. Procedures recommended by the National Institutes of Health Guide for the Care and Use of Laboratory Animals (1985), the Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research (2003) and the Institutional Animal Care and Use Committee at American University were followed at all times. Animals were handled daily approximately 2 weeks prior to the initiation of the study to limit the effects of handling stress during conditioning and testing.

Apparatus

All subjects were individually housed in hanging wire-mesh cages on the front of which graduated Nalgene tubes could be placed for fluid presentation. Subjects were maintained on a 12:12 light-dark cycle (lights on at 0800h) and at an ambient temperature of 23 ^{o}C. Except where noted, food and water were available *ad libitum*.

Drugs and Solutions

Cocaine hydrochloride (generously provided by the National Institute on Drug Abuse) and GBR 12909 bismethanesulfonate monohydrate (synthesized at the Chemical Biology Research Branch of the National Institute on Drug Abuse) were each dissolved in distilled water at a concentration of 10 mg/ml. All injections were administered SC. All drug doses are

expressed as the salt. Saccharin (sodium saccharin, Sigma) was prepared as a 1 g/l (0.1%) solution in tap water.

Procedure

Habituation

Following 24 h water deprivation, subjects were given 20-min access to tap water daily. This daily access was repeated until consumption stabilized, i.e., subjects approached and drank from the tube within 2 s of its presentation and water consumption was within 2 ml of the previous day for a minimum of 4 consecutive days with no consistent increase or decrease. Throughout the study, fluid was presented in graduated 50-ml Nalgene tubes and measured to the nearest 0.5 ml by subtracting the difference between the pre- and post-consumption volumes.

Preexposure

Water consumption for all subjects was recorded and averaged over the last 3 days of habituation. Animals were then ranked on average water consumption and assigned to a preexposure condition (GBR 12909 or vehicle). Five hours following their regular 20-min water access, animals were injected with GBR 12909 (32 mg/kg) or vehicle (matched in volume) every 4th day for a total of 5 days (five total drug or vehicle injections). No injections were given during intervening days. Water consumption was monitored throughout this phase.

Conditioning

The conditioning procedure is described in Experiment 3 was also used for Experiment 4 (see above). In Experiment 4, subjects were assigned to a treatment group and injected with either 18 mg/kg cocaine, 32 mg/kg GBR 12909 or vehicle (matched in volume to GBR 12909), yielding six experimental groups, specifically, GBR 12909-vehicle (GBR-VEH; n = 8), GBR

12909-GBR 12909 (GBR-GBR; n = 9), GBR 12909-cocaine (GBR-COC; n = 9), vehicle-vehicle (VEH-VEH; n = 8), vehicle-GBR 12909 (VEH-GBR; n = 8) and vehicle-cocaine (VEH-COC; n = 8). The first series of letters in each group designation refer to the drug given during preexposure; the second series of letters refer to the drug given during conditioning. The 3 days following this initial saccharin presentation were water-recovery days during which animals were given 20-min access to tap water (no injections followed this access). This alternating procedure of conditioning and water recovery was repeated for a total of four complete cycles.

Final Aversion Test

Following the last water-recovery session after the fourth conditioning trial, animals were given 20-min access to saccharin in a final aversion test after which no injections followed.

Statistical Analysis

During drug preexposure, the differences in mean water consumption were analyzed using a 2 x 20 repeated measures ANOVA with a between-subjects variable of Preexposure Drug (GBR 12909 or vehicle) and a within-subjects variable of Preexposure Day (1-20). Where appropriate, Fisher's LSD post-hoc analyses were run to examine group differences on individual days. During conditioning, the differences in mean saccharin consumption were analyzed for each experiment using a 2 x 3 x 4 mixed-model ANOVA with the between-subjects variables of Preexposure Drug (GBR 12909 or vehicle) and Conditioning Drug (cocaine, GBR 12909 or vehicle) and a within-subjects variable of Trial (1-4). Where appropriate, Fisher's PLSD post-hoc analyses were used to examine mean saccharin consumption differences between groups on each individual trial. Differences in mean saccharin consumption between groups on the Final Aversion Test were analyzed using a one-way ANOVA. Fisher's PLSD post-hoc

analyses were used to examine specific group differences in consumption on the Final Aversion Test. All significance levels were set at $p \leq 0.05$.

CHAPTER 13

EXPERIMENT 4 RESULTS

Preexposure

The 2 x 20 repeated measures ANOVA revealed a significant effect of Preexposure Day [F (19, 912) = 3.276, $p < 0.001$] and Preexposure Drug [F (1, 48) = 7.005, $p = 0.011$] as well as a significant Preexposure Drug x Preexposure Day interaction [F (19, 912) = 4.131, $p < 0.001$]. Subsequent one-way ANOVAs comparing specific differences between Preexposure Drug on each Preexposure Day revealed that subjects preexposed with GBR 12909 drank significantly more than subjects preexposed with vehicle on Days 4, 6, 8 - 10, 12 - 14, 16, 18 and 20 (all p's < 0.032). These days do not correspond to preexposure injections, since those only occurred on Days 1, 5, 9, 13, and 17. Overall, all subjects increased consumption over the preexposure phase (see Figure 10).

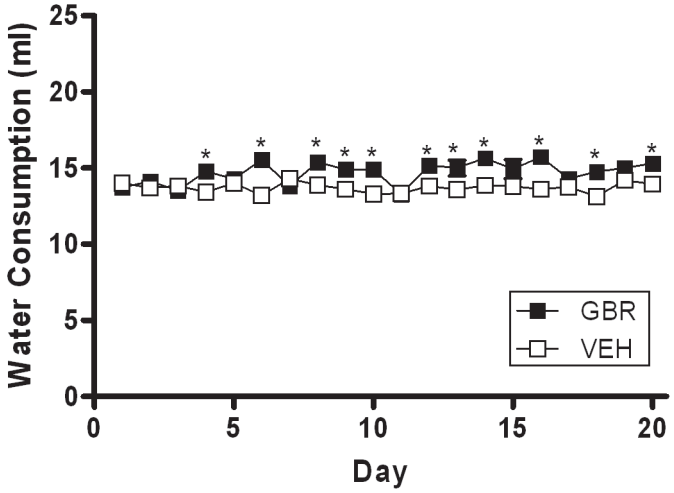

Figure 10. Mean (± SEM) water consumption (ml) for all subjects in groups preexposed to GBR 12909 (GBR) or vehicle (VEH). There was a significant main effect of Preexposure Day and a significant main effect of Preexposure Drug, and a significant Preexposure Day x Preexposure Drug interaction. Although there were differences between groups on certain days, these days did not correspond to preexposure injections. Overall, all subjects increased consumption over the preexposure phase. *Significantly different than vehicle preexposed subjects.

Conditioning

The 2 x 3 x 4 mixed-model ANOVA revealed significant effects of Trial [$F(3,132) = 14.063$, $p < 0.001$], Preexposure Drug [$F(1,44) = 13.921$, $p = 0.001$] and Conditioning Drug [$F(2,44) = 18.307$, $p < 0.001$] and significant Trial x Conditioning Drug [$F(6, 132) = 11.459$, $p < 0.001$] and Trial x Preexposure Drug [$F(3,132) = 3.647$, $p = 0.014$] interactions. In relation to the significant Trial x Preexposure Drug interaction, subjects preexposed to GBR 12909 drank significantly more saccharin than those preexposed to vehicle. That is, regardless of conditioning drug, there were differences between subjects preexposed to GBR 12909 and those preexposed to vehicle across trials. In order to examine these specific differences, one-way ANOVAs examining preexposure drug (GBR 12909 or vehicle) on individual trials revealed the following significant differences. Although on Trial 1 there were no significant group differences, on Trial 2 groups preexposed to GBR 12909 (GBR-VEH, GBR-GBR and GBR-COC) drank significantly more saccharin than those preexposed to vehicle (VEH-VEH, VEH-GBR and VEH-COC). This difference was no longer significant on Trial 3; however, on Trial 4 the GBR 12909-preexposed groups again consumed more saccharin than those preexposed with vehicle (all p's < 0.05).
In relation to the significant Trial x Conditioning Drug interaction, subjects conditioned with GBR 12909 or cocaine drank significantly less than those conditioned with vehicle (indicating CTAs induced by both compounds). That is, regardless of preexposure condition, there were differences between subjects that were conditioned with cocaine, GBR 12909 and vehicle across trials. In order to examine these specific differences, one-way ANOVAs examining conditioning drug (cocaine, GBR 12909 or vehicle) on individual trials revealed the following significant differences. Although on Trial 1 there were no differences between any groups, on Trial 2 groups conditioned with GBR 12909 (VEH-GBR and GBR-GBR) and with cocaine (VEH-COC and GBR-COC) drank significantly less than those conditioned with vehicle (VEH-VEH and GBR-

VEH; all p's < 0.047). On Trials 3 and 4, these differences remained with the additional difference that groups conditioned with cocaine (VEH-COC and GBR-COC) drank less saccharin on average than those conditioned with GBR 12909 (VEH-GBR and GBR-GBR; all p's < 0.009). Since there was no significant interaction of Trial x Preexposure Drug x Conditioning Drug, Fisher's PLSD post-hoc analyses were not run on individual groups for individual trials (see Figure 11).

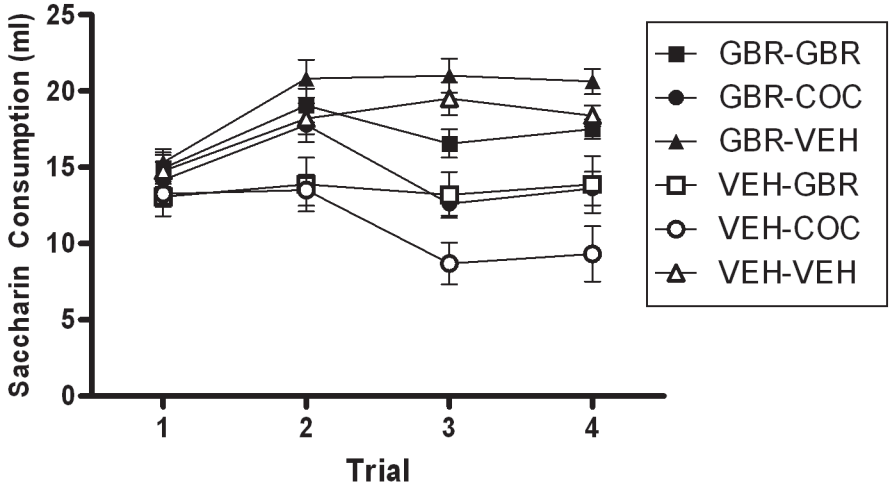

Figure. 11. Mean (±SEM) saccharin consumption (ml) for all subjects in groups preexposed to GBR 12909 (GBR) or vehicle (VEH) and conditioned with cocaine (COC; 18 mg/kg), GBR (32 mg/kg) or vehicle. There was no significant interaction of Trial x Preexposure Drug x Conditioning Drug, therefore no post-hoc analyses were run for individual groups for individual trials.

Final Aversion Test

A one-way ANOVA on the Final Aversion Test revealed significant group differences [$F(5, 49) = 19.347$, $p < 0.001$]. Fisher's PLSD post-hoc analyses revealed the following. Subjects injected with vehicle during conditioning (Groups VEH-VEH and GBR-VEH) drank significantly more than subjects injected with drug, i.e., Groups VEH-COC and VEH-GBR (demonstrating CTA's induced by both compounds). Vehicle-injected controls also drank significantly more than subjects preexposed to GBR 12909 and conditioned with cocaine, i.e.,

GBR-COC (all p's < 0.001). Additionally, subjects in Group GBR-VEH drank significantly more than GBR-GBR (p = 0.016). Subjects in Group VEH-GBR drank more than subjects in Group VEH-COC (p = 0.005), indicating that cocaine induced a stronger aversion than GBR 12909. Finally, subjects preexposed and conditioned with GBR 12909 (Group GBR-GBR) drank significantly more than subjects in Group VEH-GBR (p = 0.009), indicating a US preexposure effect. Subjects in Group GBR-COC, however, did not differ significantly in consumption compared to subjects in Group VEH-COC (p = 0.056), indicating no significant effect of cross-drug preexposure (see Figure 12).

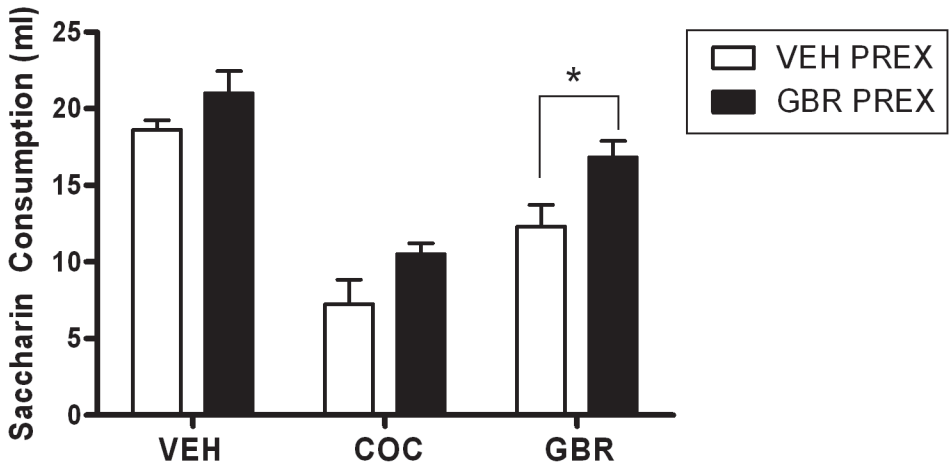

Figure 12. Mean (± SEM) saccharin consumption (ml) on the final aversion test for subjects preexposed with GBR 12909 (GBR; 32 mg/kg) or vehicle (VEH) and conditioned with cocaine (COC; 18 mg/kg), GBR (32 mg/kg) or vehicle (0). GBR preexposure attenuated GBR-induced CTAs. *Significantly attenuated relative to VEH preexposed controls; all COC conditioned subjects drank significantly less than VEH conditioned controls. VEH preexposed, GBR conditioned subjects also drank less than VEH conditioned controls.

CHAPTER 14

EXPERIMENT 5 INTRODUCTION

Preexposure to a dose of 32 mg/kg of GBR 12909 failed to attenuate cocaine-induced CTAs, an effect similar to that observed in Experiment 3 in which cocaine preexposure failed to attenuate aversions induced by GBR 12909. Although suggestive that the two drugs do not share a common aversion-inducing effect, it should be noted that aversions induced by GBR 12909 were weaker than those induced by cocaine in both Experiment 3 and 4. Given that a more robust attenuating effect is generally seen when higher doses are used during preexposure (see Riley & Simpson, 2001 for an overview), it is possible that the effects of GBR 12909 in Experiment 4 were too weak to impact cocaine's aversive effects. That is, the effects of drug preexposure are dose-dependent (see De Beun et al., 1993; Gommans et al., 1998 for examples of dose-dependent effects with cross-drug preexposure ; see Hunt, Spivak & Amit, 1985; Berman & Cannon, 1974 for examples with the same drug used during preexposure and conditioning; see Riley & Simpson, 2001 for a review) and it is possible that higher doses of GBR 12909 would affect aversions induced by cocaine. In order to further assess GBR 12909 in the cross-drug preexposure preparation with cocaine, 50 mg/kg was administered during preexposure in Experiment 5.

CHAPTER 15

EXPERIMENT 5 METHODS

Subjects

The subjects were 48 experimentally naïve, male Sprague-Dawley rats (Harlan Sprague-Dawley, Indianapolis, Indiana), approximately 75 days old and between 250 and 350 g at the start of the experiments. Procedures recommended by the National Institutes of Health Guide for the Care and Use of Laboratory Animals (1985), the Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research (2003) and the Institutional Animal Care and Use Committee at American University were followed at all times. Animals were handled daily approximately 2 weeks prior to the initiation of the study to limit the effects of handling stress during conditioning and testing.

Apparatus

All subjects were individually housed in hanging wire-mesh cages on the front of which graduated Nalgene tubes could be placed for fluid presentation. Subjects were maintained on a 12:12 light-dark cycle (lights on at 0800h) and at an ambient temperature of 23 ^{o}C. Except where noted, food and water were available *ad libitum*.

Drugs and Solutions

Cocaine hydrochloride (generously provided by the National Institute on Drug Abuse) and GBR 12909 bismethanesulfonate monohydrate (synthesized at the Chemical Biology Research Branch of the National Institute on Drug Abuse) were each dissolved in distilled water at a concentration of 10 mg/ml. All injections were administered SC. All drug doses are

expressed as the salt. Saccharin (sodium saccharin, Sigma) was prepared as a 1 g/l (0.1%) solution in tap water.

Procedure

Habituation

Following 24 h water deprivation, subjects were given 20-min access to tap water daily. This daily access was repeated until consumption stabilized, i.e., subjects approached and drank from the tube within 2 s of its presentation and water consumption was within 2 ml of the previous day for a minimum of 4 consecutive days with no consistent increase or decrease. Throughout the study, fluid was presented in graduated 50-ml Nalgene tubes and measured to the nearest 0.5 ml by subtracting the difference between the pre- and post-consumption volumes.

Preexposure

Water consumption for all subjects was recorded and averaged over the last 3 days of habituation. Animals were then ranked on average water consumption and assigned to a preexposure condition (GBR 12909 or vehicle). Five hours following their regular 20-min water access, animals were injected with GBR 12909 (50 mg/kg) or vehicle (matched in volume) every 4th day for a total of 5 days (five total drug or vehicle injections). No injections were given during intervening days. Water consumption was monitored throughout this phase.

Conditioning

The conditioning procedure that was described in Experiments 3 and 4 was also used for Experiment 5. In Experiment 5, 48 subjects were assigned to a treatment group and injected with either 18 mg/kg cocaine, 32 mg/kg GBR 12909 or vehicle (matched in volume to GBR 12909), yielding six experimental groups, specifically, GBR 12909-vehicle (GBR-VEH; n = 8), GBR

12909-GBR 12909 (GBR-GBR; n = 8), GBR 12909-cocaine (GBR-COC; n= 8), vehicle-vehicle (VEH-VEH; n = 8), vehicle-GBR 12909 (VEH-GBR; n = 8) and vehicle-cocaine (VEH-COC; n = 8). The first series of letters in each group designation refer to the drug given during preexposure; the second series of letters refer to the drug given during conditioning. The 3 days following this initial saccharin presentation were water-recovery days during which animals were given 20-min access to tap water (no injections followed this access). This alternating procedure of conditioning and water recovery was repeated for a total of four complete cycles.

Final Aversion Test

Following the last water-recovery session after the fourth conditioning trial, animals were given 20-min access to saccharin in a final aversion test after which no injections followed.

Statistical Analysis

During drug preexposure, the differences in mean water consumption were analyzed using a 2 x 20 repeated measures ANOVA with a between-subjects variable of Preexposure Drug (GBR 12909 or vehicle) and a within-subjects variable of Preexposure Day (1-20). Where appropriate, Fisher's LSD post-hoc analyses were run to examine group differences on individual days. During conditioning, the differences in mean saccharin consumption were analyzed for each experiment using a 2 x 3 x 4 mixed-model ANOVA with the between-subjects variables of Preexposure Drug (GBR 12909 or vehicle) and Conditioning Drug (cocaine, GBR 12909 or vehicle) and a within-subjects variable of Trial (1-4). Where appropriate, Fisher's PLSD post-hoc analyses were used to examine mean saccharin consumption differences between groups on each individual trial. Differences in mean saccharin consumption between groups on the Final Aversion Test were analyzed using a one-way ANOVA. Fisher's PLSD post-hoc

analyses were used to examine specific group differences in consumption on the Final Aversion Test. All significance levels were set at $p \leq 0.05$.

CHAPTER 16

EXPERIMENT 5 RESULTS

Preexposure

The 2 x 20 repeated measures ANOVA revealed a significant effect of Preexposure Day [F (19,874) = 11.450, $p < 0.001$] and Preexposure Drug [F (1, 46) = 11.296, $p = 0.002$] as well as a significant Preexposure Drug x Preexposure Day interaction [F (19, 874) = 6.499, $p < 0.001$]. Subsequent one-way ANOVAs and Fisher's LSD post-hoc analyses comparing Preexposure Drug on each Preexposure Day revealed that subjects preexposed to GBR 12909 drank significantly more than subjects preexposed to vehicle on Days 6, 8, 10, 12-14, and 16-20 (all p's < 0.012). These days do not all correspond to preexposure injections which took place on Days 1, 5, 9, 13 and 17. Overall, all subjects increased consumption over the preexposure phase (see Figure 13).

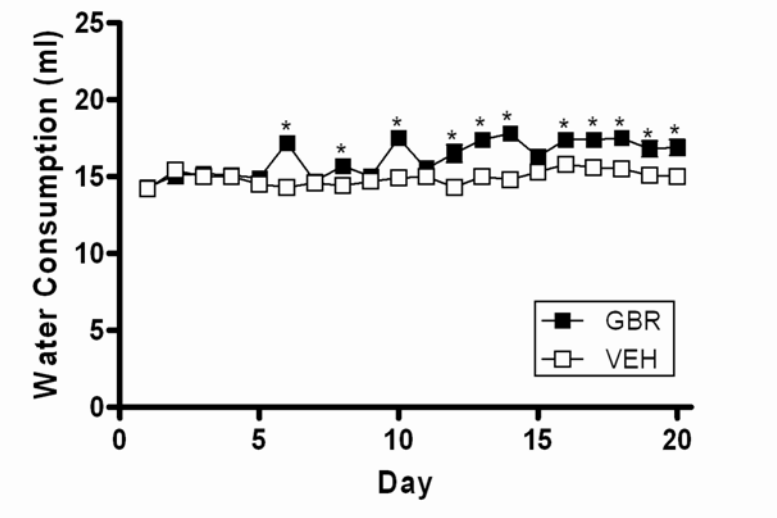

Figure 13. Mean (± SEM) water consumption (ml) for all subjects in groups preexposed to GBR 12909 (GBR) or vehicle (VEH). There was a significant effect of Preexposure Day, Preexposure Drug and a significant Preexposure Day x Preexposure Drug interaction. There were differences between groups on certain days; however, these did not always correspond to preexposure injections. Overall, all subjects increased consumption over the preexposure phase. *Significantly different than VEH preexposed subjects.

Conditioning

The 2 x 3 x 4 mixed-model ANOVA revealed significant effects of Trial [$F(3,126) = 17.168$, $p < 0.001$], Preexposure Drug [$F(1,42) = 33.788$, $p = 0.001$] and Conditioning Drug [$F(2,42) = 12.976$, $p < 0.001$] and significant Trial x Conditioning Drug [$F(6, 126) = 8.783$, $p < 0.001$], Trial x Preexposure Drug [$F(3,126) = 9.763$, $p < 0.001$] and Trial x Preexposure Drug x Conditioning Drug [$F(6,126) = 3.313$, $p < 0.005$] interactions. Since there was a significant Trial x Preexposure Drug x Conditioning Drug interaction, Fisher's PLSD post-hoc analyses were run on individual groups for individual trials. There were no significant differences on Trial 1. On Trial 2, subjects in Group VEH-COC drank significantly less than subjects in Group VEH-VEH ($p = 0.001$), indicating a significant cocaine-induced CTA. Subjects in Group VEH-GBR did not differ from subjects in Group VEH-VEH, indicating that GBR 12909 was not effective in inducing aversions after only a single conditioning trial. On this trial, subjects preexposed and conditioned with GBR 12909 (Group GBR-GBR) drank significantly more than subjects in Group VEH-GBR, demonstrating a US preexposure effect (despite the lack of significant GBR 12909 induced aversions; $p < 0.009$). Interestingly, subjects in Group GBR-COC also drank significantly more than subjects in Group VEH-COC, indicating a significant cross-drug preexposure effect on this trial. These differences were all maintained on Trial 3, with additional differences between subjects in Group VEH-VEH and Group VEH-GBR (indicating that on this trial, there was a significant GBR 12909-induced CTA) and between Group GBR-GBR and Group GBR-COC (indicating that the US preexposure group drank more than the cross-drug preexposure group; p's < 0.032). These differences all were maintained on Trial 4, with the additional difference between subjects in Group GBR-VEH and Group GBR-COC (indicating a weakening over trials of the cross-drug preexposure effect demonstrated; $p = < 0.033$; see Figure

14). That is, by Trial 4, the cross-drug preexposure effect began to weaken, such that the subjects in this group drank less than their vehicle conditioned controls.

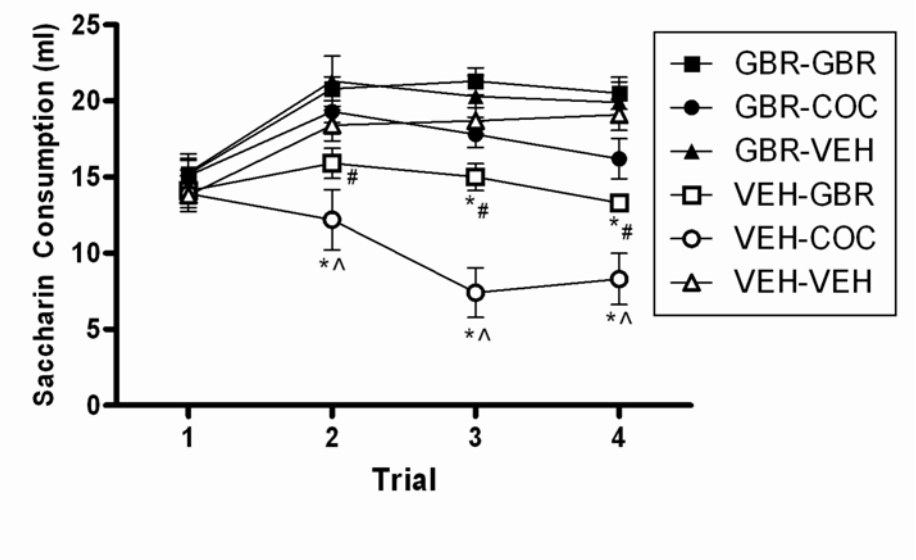

Figure 14. Mean (±SEM) saccharin consumption (ml) for all subjects in groups preexposed to GBR 12909 (GBR) or vehicle (VEH) and conditioned with cocaine (COC; 18 mg/kg), GBR 12909 (32 mg/kg) or vehicle. *Significantly different from Group VEH-VEH; #significantly different from Group GBR-GBR; ^significantly different from Group GBR-COC.

Final Aversion Test

A one-way ANOVA on the Final Aversion Test revealed significant group differences [$F(5, 47) = 15.502$, $p < 0.001$. Fisher's PLSD post-hoc analyses revealed the following. Subjects injected with vehicle during conditioning (Groups VEH-VEH and GBR-VEH) drank significantly more than subjects injected with drug, i.e., Groups VEH-COC and VEH-GBR (demonstrating CTA's induced by both compounds; all p's < 0.003). Subjects in Group VEH-GBR drank more than subjects in Group VEH-COC ($p = 0.0025$), indicating that cocaine again induced a stronger aversion than GBR 12909. Finally, subjects preexposed and conditioned with GBR (Group GBR-GBR) drank significantly more than subjects in Group VEH-GBR ($p < 0.001$), indicating a US preexposure effect. Subjects in Group GBR-GBR also drank significantly more than those in Group GBR-COC (p's < 0.009), indicating that the effects of

same-drug preexposure was greater than that of cross-drug preexposure. Subjects preexposed to GBR 12909 and conditioned with cocaine (Group GBR-COC) drank significantly more than subjects in Group VEH-COC, indicating a significant effect of cross-drug preexposure ($p < 0.001$; see Figure 15).

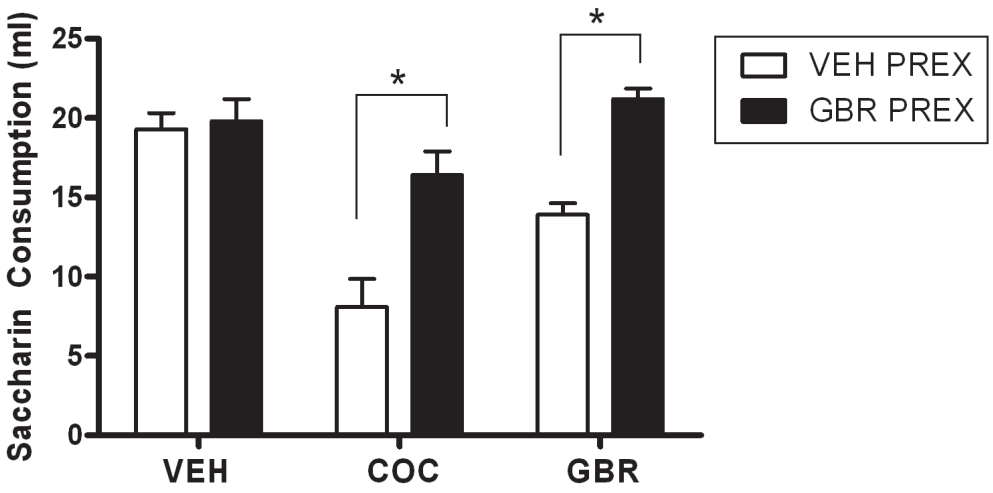

Figure 15. Mean (± SEM) saccharin consumption (ml) on the Final Aversion Test for subjects preexposed to GBR 12909 (GBR; 50 mg/kg) or vehicle (VEH) and conditioned with cocaine (COC; 18 mg/kg); GBR (32 mg/kg) or vehicle (0). GBR preexposure attenuated GBR-induced and cocaine-induced CTAs; *Significantly attenuated relative to VEH preexposed controls; VEH preexposed, COC conditioned and GBR conditioned subjects drank significantly less than VEH conditioned controls.

CHAPTER 17

GENERAL DISCUSSION

In the present experiments two separate assessments were used in order to characterize the role of DA in cocaine's aversive effects. Specifically, Experiment 1 and 2 demonstrated that a behaviorally active dose of haloperidol, which was non-aversive when administered alone, significantly attenuated cocaine-induced CTAs at two doses on three trials. Although implicating DA in cocaine's aversive effects, these results do not provide direct evidence for which DA receptors are involved in this phenomenon (or if actions at other sites play a role at all). That is, although haloperidol is a D_2 receptor antagonist, its selectivity for D_2 over other DA receptor subtypes is relatively low (see Missale, Nash, Robinson, Jaber & Caron, 1998; Vangveravong et al., 2010). Specifically, in addition to binding to the D_2 receptor, haloperidol has relatively high affinity for D_5 and also binds to D_1, D_3, and D_4 (Missale et al., 1998). Therefore, it is possible that the dose chosen (1.0 mg/kg) antagonized not only D_2 but other subtypes as well. Given the different roles of DA receptor subtypes in mediating cocaine reward (Beninger & Miller, 1998; Caine et al., 2002; Volkow et al., 1993; Vorel et al., 2002), antagonists that are more selective for DA receptor subtypes should be investigated in the CTA procedure with cocaine in order to determine if D_2 action alone mediates the aversive effects of cocaine.

Interestingly, haloperidol also has affinity for receptors other than dopamine. Specifically, haloperidol has affinity for the α_1 (Stahl, 2008) and σ_1 (and to a lesser extent σ_2) receptors (Vangveravong et al., 2010). Its ability to attenuate cocaine-induced CTAs could be a product of its antagonist effects at these sites, either alone or in some combination with its actions at DA receptors. Recently our laboratory has investigated the effects of α_1 receptor antagonism on cocaine-induced CTAs. Specifically, when prazosin was administered prior to

cocaine in a similar preparation as used in the present experiment, cocaine-induced CTAs were potentiated (Freeman et al., 2008). The fact that haloperidol attenuated (rather than potentiated) cocaine-induced CTAs suggests that the dose of haloperidol used in the present study did not cause strong α_1 receptor antagonism (or at least not strong enough to negate the attenuation produced by some other action of haloperidol administration). Haloperidol is also a high affinity σ_1 antagonist (Cobos, del Pozo & Baeyens, 2007; Matsumoto & Pouw, 2000; Stone et al., 2006). In fact, haloperidol's affinity for σ_1 is almost as strong as its affinity for D_2 (Vangveravong et al., 2010). Although the effects of selective σ_1 antagonists have not been examined in the context of cocaine-induced taste aversions, such antagonists have been shown to affect a number of other cocaine-induced behaviors including locomotor sensitization, convulsions and CPPs (see Ujike, Kuroda & Otsuki, 1996; Ritz & George, 1997; Romieu, Phan, Martin-Fardon & Maurice, 2002, respectively).

Experiments 3, 4 and 5 demonstrated that GBR 12909 preexposure (at the high dose only) resulted in a significant attenuation of cocaine-induced CTAs suggesting that DA may be mediating the aversions induced by both compounds. It should be noted, however, that cocaine preexposure had no effect on GBR 12909-induced aversions. In this context, it is important to again note the asymmetrical feature of cross-drug preexposure, i.e., that reversal of the serial presentation of compounds does not always result in symmetrical attenuation of CTAs (see Riley & Simpson, 2001 and Experiment 4 Introduction for an overview). The general explanation for such asymmetrical effects is that although the compounds do share stimulus properties, these properties are not identical and the effects of such preexposure may be dependent upon the order of presentation. For example, preexposure to a compound with one selective action may result in the attenuation of aversions induced by a compound with multiple actions due to some

adaptation of the stimulus effects of the shared action. However, exposure to a compound with multiple actions may produce adaptation to only a subset of these actions, and possibly not the one shared with the second compound. Consequently, there may be no weakening of the aversion induced by that compound (see Grakalic & Riley, 2002a; though see also Kunin, Smith & Amit, 1999). In relation to the present series of studies, preexposure to GBR 12909 may result in adaptation to the effects of DAT inhibition that impacts this component of the mechanism underlying cocaine-induced aversions. Conversely, exposure to cocaine results in adaptation to the effects of monoamine transporter inhibition (some of a select subset) that can affect cocaine-induced aversions. However, adaptation to the DAT mediated effects may not occur or may be sufficiently small to have little effects on GBR 12909 whose aversion should be completely mediated by its effect on DAT. That GBR 12909 preexposure attenuates cocaine-induced CTAs (as demonstrated in Experiment 5) however, does suggest that DA mediates aversions induced by both compounds.

Such a conclusion regarding the role of DA in cocaine's aversive effects is consistent with other work supporting such a role. As mentioned, transgenic models using DAT KO mice in the CTA preparation also support a role of DA in cocaine-induced CTAs (Jones, Hall, Uhl & Riley, 2010). Specifically, mice with deletions of DAT display weaker cocaine-induced CTAs relative to wild type controls (Jones et al., 2010). Importantly, this effect is relatively weak in that the KO and the wild type differ at only the highest dose of cocaine used (50 mg/kg) and for this dose only on one trial (see Jones et al., 2010). Although supportive of a role for DA in cocaine-induced aversions, work with KO mice does have some interpretational concerns. For example, despite the often reported role for DA in cocaine reward, DAT KO mice display cocaine-induced conditioned place preferences (Sora et al., 1998; see also Beninger & Miller,

1998; Caine et al., 2002) and cocaine self-administration (Ritz et al., 1987; Rocha et al., 1998), suggesting that DA may play a limited role in cocaine's rewarding and reinforcing effects. However it is important to consider that transgenic KO mice lack the target gene throughout development, which can give rise to compensatory mechanisms. Specifically, other mechanisms can develop in response to the inability to reuptake DA. For example, NET or 5-HT transporters (SERT) can work as alternate reuptake sites for DA in DAT KO mice (Sora et al., 2001). Evidence of this is demonstrated by the fact that NET and SERT inhibitors condition place preferences in DAT KO (but not wild type) mice (Hall et al., 2002). One way to circumvent this developmental compensation is to use a knock-in procedure. When knock-in (KI) mice are used that have cocaine-insensitive DAT, cocaine CPP is blocked (Chen et al., 2006). That is, when compensatory mechanisms are limited by selective KI procedures, a role for DA in cocaine reward is clearly demonstrated. The inability for DAT gene deletions to eliminate cocaine-induced CPP or CTA (on more trials and across different doses), therefore, may be a function of such compensatory mechanisms.

Although the present data support a role of DA in cocaine-induced taste aversions, such an effect does not preclude the involvement of other neurotransmitter systems in cocaine's aversive effects. Given that cocaine inhibits reuptake of all three monoamines, it is important to consider the role of DA in context of these other systems. NE does not appear to be involved in cocaine's rewarding effects (Roberts et al., 1977; Schmidt & Pierce, 2006; Woolverton, 1987; for a review see Weinshenker & Schroeder, 2006) except in circumstances involving stress-induced reinstatement (Erb et al., 2000; Leri, Flores, Rodaros & Stewart, 2002; Mantsch et al., 2010; Shalev, Grimm & Shaham, 2002). Its role in cocaine-induced taste aversions remains unknown, despite the fact that NE has been extensively investigated in aversion learning in

general, primarily through the use of lesioning studies examining NE projections. In these reports, NE appears to mediate several components of aversion learning, such as extinction and sensory preconditioning (Archer, Cotic & Järbe, 1986; Järbe, Callenholm, Mohammed & Archer, 1986; Mason & Fibiger, 1979; Mohammed et al., 1986; but see also Borsini & Rolls, 1984; Jarbe, Falk, Mohammed & Archer, 1988). Although such assessments with classical emetics demonstrate some involvement of NE in CTA learning in general, only a few studies have addressed its role in cocaine-induced aversions and these reveal somewhat equivocal results.

If cocaine's ability to induce taste aversions is a function of its NE activity, it might be expected that compounds that act to increase extracellular NE (e.g., amphetamine) would induce aversions as well. In this context, amphetamine has been shown to induce CTAs at a range of doses (Cappell & Le Blanc, 1973; Carey & Goodall, 1974). It would also be expected that other NET inhibitors would induce aversions, although their potency relative to cocaine would be a function of binding affinity and general efficacy. In such an examination, Freeman and colleagues (Freeman et al., 2005) have reported that the NET inhibitor desipramine induced aversions, and did so in a manner comparable to cocaine (see Serafine & Riley, 2009; see Jones et al., 2009 for a similar demonstration with nisoxetine). Importantly, although desipramine is a NET inhibitor, it also has affinity for several other binding sites (Stahl, 2008), which makes determining the mechanism by which this compound is aversive difficult to identify. That is, desipramine's action on another site might be responsible (alone or in combination with NET inhibition) for aversions induced by this compound. Similarly, amphetamine has actions other than its effects on NE (e.g., reverse transport of DAT; Ritz & Kuhar, 1989). Given the rather indirect nature of the abovementioned evidence implicating NE involvement, other procedures

are necessary to more directly characterize the relative contribution (if any) of NE (through NET inhibition in cocaine-induced CTAs).

In a more direct test of the role of NE in cocaine's aversive effects, Freeman and colleagues (Freeman et al., 2008) assessed the ability of the NE antagonists prazosin (α_1) and propranolol (β) to antagonize aversions induced by a range of doses of cocaine. Specifically, they gave rats access to a novel saccharin solution, followed immediately by an injection of propranolol or prazosin (as doses ineffective in inducing aversions on their own) or vehicle and 30 min later an injection of either cocaine or vehicle. Under these conditions, NE antagonists did *not* block cocaine-induced CTAs. As mentioned above, administration of prazosin actually significantly *enhanced* cocaine-induced CTAs at all doses tested, and propranolol administration significantly potentiated low dose cocaine-induced CTAs (Freeman et al., 2008). The fact that NE antagonists do not attenuate cocaine-induced CTAs appears to indicate that NE is not involved in cocaine's aversive effects. However, as noted, these compounds strengthened cocaine-induced aversions, suggesting the possibility that NE activity actually weakens cocaine's aversive effects. That is, given that both receptor antagonists resulted in the significant potentiation of cocaine-induced CTAs, perhaps some cascade of NE-mediated effects is responsible for limiting the strength of cocaine-induced CTAs, an effect that would be interesting in light of the fact that antagonism of α and β NE receptors often has opposing effects on cocaine-induced behaviors (Harris, Hedaya, Pan & Kalivas, 1996; Kleven & Koek, 1998; Spealman, 1995; Wellman, Ho, Cepeda-Benito, Bellinger & Nation, 2002; see Freeman et al., 2008 for an overview). Independent of the mechanism for a noradrenergic modulation of cocaine-induced aversions, it is clear that a simple explanation assuming that NE mediates cocaine's aversive effects is not supported.

Using a procedure similar to that described in Experiments 3, 4 and 5, with GBR 12909 (Serafine, Briscione, Rice & Riley, submitted), Serafine and Riley examined the possible attenuating effects of exposure to desipramine (a relatively selective NET inhibitor) on cocaine-induced aversions (Serafine & Riley, 2009). Specifically, Serafine and Riley exposed rats every 4^{th} day to desipramine (18 mg/kg) for a total of five injections prior to taste aversion conditioning with cocaine (18 mg/kg). Every 4^{th} day during conditioning, subjects were given a pairing of saccharin and cocaine or vehicle (for a total of four pairings) followed by a final aversion test (see above for a similar methods description using GBR 12909). Under these conditions, desipramine blocked cocaine-induced CTAs (Serafine & Riley, 2009), suggesting that NET inhibition (and thus NE activity) is involved in cocaine's ability to induce a CTA. Further evidence of this role is seen from a similar assessment in which the NET inhibitor nisoxetine also attenuated cocaine-induced CTAs in mice (Jones et al., 2009). In order to examine a role of NET inhibition in cocaine-induced CTAs using cross-drug preexposure, however, the compound used should, in fact, be selective for NET. While desipramine certainly has a higher affinity for NET over other sites, it is not selective (Tatsumi, Groshan, Blakely & Richelson, 1997; but see also Owens, Morgan, Plott & Nemeroff, 1997). Desipramine, like most tricyclic antidepressants (Stahl, 2008), also has affinity for SERT and antagonizes H_1 histaminergic, α_1 adrenergic and muscarinic cholinergic receptors (Owens et al., 1997). Attenuation of cocaine-induced CTAs by desipramine does not prove NET involvement, but indicates instead that the two compounds share some common aversion-inducing mechanism without identifying what that mechanism is. In the case of GBR 12909 and cocaine's asymmetrical cross-drug effects, GBR 12909's selectivity for DAT suggests that DAT inhibition is the common mechanism shared between compounds. Given desipramine's wide spectrum of

actions, it is difficult to determine what that overlapping mechanism might be, especially in light of the fact that cocaine also inhibits SERT. Further, it is important to consider that this common mechanism could be some downstream effect that is a product of each compound's multiple (and non-shared) pharmacological effects. For example, both compounds may cause some action (e.g., stress), but they may do so via a different neurochemical action. If this action (stress) is the underlying basis of aversions induced by both, it would seem that the initiating neurochemical effect is irrelevant for cross-tolerance, as long as the end result (stress) is the same.

As with the present assessments using GBR 12909, the reverse serial presentation was also examined. Specifically, subjects were exposed to cocaine prior to aversion conditioning with desipramine. Under these conditions, there was no evidence of attenuated aversions, again revealing an asymmetrical preexposure effect (Serafine & Riley, 2009). As noted above, such asymmetrical effects may be indicative of shared, but non-identical, aversive stimulus properties of the two compounds. The asymmetry itself, however, is not nearly as concerning as the fact that cocaine preexposure actually *potentiated* desipramine-induced aversions (relative to vehicle-preexposed, desipramine-conditioned controls, see Serafine & Riley, 2009), an effect which cannot be explained by differences in stimulus properties of cocaine and desipramine alone. Interestingly, this potentiation is similar to the results of the antagonism experiments, in that a preparation designed to reduce NE effects resulted in a stronger aversion (induced by cocaine in the antagonism studies or by desipramine in the cross drug studies). It is possible that NE's role in the aversive effects of both compounds is not inducing a CTA, but rather limiting their overall aversiveness. If NE is playing an aversion-limiting role, it is likely that receptor antagonism would strengthen cocaine-induced aversions. Similarly, this would explain why, when administered alone, the NE antagonist prazosin induced aversions (Freeman et al., 2008). That is,

receptor antagonism will result in blocking endogenous neurotransmitter action at these sites, which if NE is an aversion-limiting factor, would be aversive in and of itself. Along these lines, NE has been shown to modulate DA levels in several areas, including the mPFC and to some extent the NA (Herve et al., 1989; Tassin, 1992; Yamamoto & Novotney, 1998) such that DA reuptake is regulated by NET in these sites. Although DA reuptake by NET would not account for the potentiation effects seen in the abovementioned studies, it is interesting that these NT systems have been shown to interact. The nature of how these systems interact to produce the potentiation noted above remains unknown.

When considering these data, which demonstrate weak (dose-response comparisons; Freeman et al., 2005), equivocal (cross-drug preexposure; Serafine & Riley, 2009) or no (antagonism; Freeman et al., 2008) support for NE in cocaine-induced CTAs, it is interesting to note that work with transgenic mice does support a role for NE in this effect. Specifically, Jones et al. (2010) gave NET KO mice and their wild type controls access to a novel saccharin solution followed by an injection of cocaine (18, 32 or 50 mg/kg) or vehicle (matched in volume to cocaine). Under these conditions, wild type controls acquired the cocaine-induced taste aversions and to a degree greater than those acquired by the NET KO mice, implicating a noradrenergic role in cocaine's aversive effects (Jones et al., 2010). Although suggestive of such a role, it should be noted that the difference between wild type and NET KO mice was evident only at two doses and again only on a single trial (18 mg/kg, Trial 2; 50 mg/kg, Trial 3). Further, potential compensatory mechanisms in KO mice that may emerge due to development without the specific targeted gene may limit general conclusions of the importance of such gene and their product in behavioral outcomes. KI assessments provide more conclusive evidence for specific gene involvement without these compensatory mechanisms. Although such cocaine-insensitive NET

KI models exist (see Wei, Hill & Gu, 2009), they have not been used in assessments of the role of NET in cocaine aversion.

Taken together, the abovementioned assessments do not provide substantial support for NE in mediating cocaine-induced CTAs. That is, while NE acting compounds (e.g., desipramine, amphetamine) have been demonstrated to induce CTAs, none of the compounds investigated are limited in their actions to just NE. The fact that NE antagonists induce CTAs on their own and potentiate cocaine-induced aversions indicates that NE action on its own receptors may serve as an aversion-limiting factor (see Freeman et al., 2008). Cross-drug preexposure data using desipramine support this notion, since cocaine preexposure increases the strength of aversions induced by desipramine. Transgenic models using NET KO mice provide the only direct evidence for a possible NE role in cocaine-induced CTAs, and that particular evidence is relatively weak and subject to other interpretations. It appears that DA action is necessary for cocaine-induced CTAs and NE action may serve to limit that overall aversive effect.

Interestingly, considerable work has been conducted investigating serotonergic involvement in cocaine's behavioral effects. Several 5-HT receptor subtypes have been implicated in cocaine's rewarding effects, primarily based on work from selective agonists and antagonists, as well as transgenic models (discussed below). Initial studies demonstrated that serotonergic compounds did not alter cocaine SA or CPP. Specifically, the selective 5-HT reuptake inhibitor (SSRI) fluoxetine did not significantly alter cocaine SA (Tella, 1995). A related compound, fluvoxamine, (investigated as a pretreatment compound administered prenatally) also had no effect on cocaine CPP (Hsiao, Cherng, Yang, Yeh & Yu, 2005). These results are somewhat perplexing given that cocaine-dependent individuals demonstrate lower use of cocaine following SSRI treatment (in combination with behavioral therapy; see Moeller et al.,

2007). Importantly, 5-HT has seven families of receptors with at least 14 known subtypes (see Muller & Huston, 2006 for an overview). SSRIs result in increased levels of 5-HT; however, the binding of 5-HT to its receptors may be important regarding modulation of cocaine-induced behaviors. For example, some receptor subtypes are decreased following extended access to cocaine (e.g., 5-HT_{1B}; O'Dell, Manzardo, Polis, Stouffer & Parsons, 2006). Stimulation of this same subtype results in attenuated cocaine SA (Przegalinski, Golda, Frankowska, Zaniewska & Filip, 2007), and subjects overexpressing this receptor subtype display altered CPP and CPA to cocaine (Barot, Ferguson & Neumaier, 2007), suggesting a facilitative role in cocaine's rewarding effects. However, stimulation of other receptor subtypes (e.g., 5-HT_{1A}) has been found to increase cocaine SA (Czoty, McCabe & Nader, 2005), as well as affect cocaine-induced reinstatement (Schenk, 2000; Burmeister, Lungren, Kirschner & Neisewander, 2004), but it does not alter cocaine-induced CPP (Ali & Kelly, 1997), suggesting a more inhibitory role of 5-HT (at least at this receptor subtype) in cocaine's rewarding effects. Other receptor subtypes also have been found to have an inhibitory role, such that action at these sites may limit cocaine's rewarding effects (i.e., 5-HT_{2C}; Burbassi & Cervo, 2008; Cunningham et al., 2011; 5-HT_3; Allan, Galindo, Chynoweth, Engel & Savage, 2001; 5-HT_6; Fijal, Pachuta & McCreary, 2010). These apparent opposing results seem to indicate that different receptor subtypes play different roles in the modulation of cocaine reward.

In addition to this work assessing the role of 5-HT in drug reward, there is substantial evidence (although similarly contradictory; see below) indicating its importance in the aversive effects of drugs in general. For example, lesioning the raphe nuclei (which in turn causes depletion of 5-HT levels) results in potentiation of LiCl-induced CTAs (Lorden & Margules, 1977; Lorden & Oltmans, 1978), indicating that decreased 5-HT levels may contribute to the

induction of CTAs. Interestingly, and somewhat contradictory, in the PBN of Long Evans rats, 5-HT has been shown to increase after initial saccharin exposure as well as after LiCl injections (alone); yet no significant change in 5-HT levels were observed in subjects exposed to saccharin plus LiCl injections (Petr, Jiri & Karel, 2006). However, the authors conclude that the 5-HT level increase following LiCl is indicative that 5-HT may be involved in its aversive effects. Other evidence, reported by Elkins and colleagues using selective rat lines, also suggests that increased 5-HT may be responsible for aversion learning. Specifically, the brains of taste aversion prone (TAP) and taste aversion resistant (TAR) rats have been shown to differ regarding 5-HT levels. TAP rats tend to have higher levels of 5-HT than TAR rats (Orr et al., 1993). Interestingly, TAR rats have been shown to have less efficient 5-HT reuptake than TAP rats (Elkins et al., 2000). Given the large number of 5-HT receptor families, these contradictory results could in part be explained by differential involvement of specific receptor subtypes in different aspects of aversion learning.

Although it seems 5-HT may be involved in aversion learning in general, determining the specific nature of this role requires the use of compounds selective for 5-HT receptors. 5-HT_{1A} antagonists have been shown to weaken or eliminate LiCl-induced CTAs in rats (Wegener, Smith & Rosenberg, 1997), and 5-HT_3 antagonists attenuate the acquisition of LiCl-induced conditioned avoidance in shrews (Kwiatkowska & Parker, 2005). These results suggest that 5-HT_{1A} and 5-HT_3 receptors may be important for CTA learning in general. In addition to the work using LiCl, several investigations have been conducted examining 5-HT's role in ethanol-induced CTAs. Lesioning of 5-HT pathways does not disrupt ethanol-induced CTAs (Bienkowski, Iwinska, Piasecki & Kostowski, 1997; Piasecki, Bienkowski, Dudek, Koros & Kostowski, 2001). Counter to the work with LiCl, 5-HT_{1A} and 5-HT_3 antagonists do not

significantly alter CTAs induced by ethanol (Bienkowski, Kuca, et al., 1997; Risinger & Boyce, 2002), suggesting that at least in the case of ethanol, action on these receptors might not contribute to aversion learning. What is clear from these reports is that while 5-HT is involved in aversion learning, different 5-HT receptor subtypes appear to play different roles (similar to their differential roles in reward).

The role of 5-HT in cocaine's aversive effects has also been examined. As with DA and NE, these investigations have focused on the ability of compounds with similar action to induce aversions, cross-drug attenuation with drug history and changes in aversions in transgenic KO mice. In relation to compounds with similar actions, if cocaine's ability to induce aversions is via its effects on 5-HT, it might be expected that compounds with similar actions would also be aversive (in the CTA design). In this context, a variety of 5-HT receptor agonists, e.g., those selective for $5\text{-HT}_{1A, 1B, 2A, 2B}$ and $_{2C}$, dose-dependently induce CTAs (see De Vry, Eckel, Kuhl & Schreiber, 2000; Mosher, Smith & Greenshaw, 2006), whereas those selective for 5-HT_3 agonists do not (see Rudd, Ngan & Wai, 1998). Agonists at other receptor subtypes have yet to be investigated. Interestingly, 5-HT_3 antagonists block or attenuate aversions induced by amino acid deficient diets (Terry-Nathan, Gietzen & Rogers, 1995; but not ethanol, Bienkowski, Kuca, et al., 1997) and do not appear to induce CTAs on their own (although see Mele, McDonough, McLean & O'Halloran, 1992). 5-HT_{1A} receptor antagonists also do not induce CTAs when administered alone (see Berendsen & Broekkamp, 1999).

Beyond these assessments with agonists and antagonists, several other compounds that result in increases to extracellular levels of 5-HT have also been examined. Fenfluramine, which works to increase extracellular levels of 5-HT by vesicular transport inhibition has been shown to induce CTAs (Barnfield & Clifton, 1989; Ervin et al., 1995; see also Barnfield, Parker, Davies

& Miles, 1994 for examples with taste reactivity). Additionally, fluoxetine (a SERT inhibitor and 5-HT $_{2C}$ antagonist) induces CTAs at a range of doses (Berendsen & Broekkamp, 1994; Ervin et al., 1995; Prendergast, Hendricks, Yells & Balogh, 1996; Serafine & Riley, 2010), as do fluvoxamine (Gommans et al., 1998; Olivier et al., 1999) and clomipramine (Freeman et al., 2005). These reports indicate that serotonergic action may be aversive, although to what extent action at individual receptor subtypes mediates this effect remains undetermined.

Although the abovementioned experiments suggest that 5-HT action may be involved in cocaine-induced CTAs, a more direct assessment would be to examine selective 5-HT antagonists in the CTA design with cocaine. To date, no such assessment using selective 5-HT antagonists have been examined in this context. However, a few experiments have been conducted using other preparations. Using a procedure similar to that described above with cocaine, GBR 12909 and desipramine, our laboratory has recently investigated the selective 5-HT transport inhibitor fluoxetine in the cross-drug preexposure design with cocaine. Specifically, after conducting a dose response assessment to determine a non-aversive dose of fluoxetine in rats Serafine and Riley exposed rats every 4th day to fluoxetine (10 mg/kg) for a total of five injections prior to taste aversion conditioning with cocaine (18 mg/kg, Serafine & Riley, 2010). During conditioning, subjects were given pairings of saccharin and cocaine or vehicle (every 4th day for a total of four pairings) followed by a final aversion test (see above for a similar methods using GBR 12909 and desipramine). Under these conditions, fluoxetine did not attenuate cocaine-induced CTAs (Serafine & Riley, 2010), suggesting that inhibition of SERT does not play a role in cocaine's aversive effects. However, this is not a function of fluoxetine's inability to induce a preexposure effect in general, as CTAs induced by fluoxetine were significantly attenuated by fluoxetine preexposure (on a separate analysis of the final aversion test only; data

reanalyzed from Serafine & Riley, 2010). Importantly, subjects preexposed to fluoxetine and conditioned with cocaine appear to show some increase in consumption that, although not statistically significant, may necessitate the use of higher doses of fluoxetine during preexposure (see Experiment 5 Introduction for a description with GBR 12909 preexposure). Interestingly, this same procedure did result in cross-drug attenuation in mice (Jones et al., 2010). That this effect was seen with mice, but not rats, may have been due to the use of an insufficient dose in the assessment with rats (10 mg/kg vs. 50 mg/kg used in the mouse assessment; see Jones et al., 2010).

As with previous investigations, the reverse serial presentation of these compounds was also examined. Interestingly, fluoxetine-induced CTAs were significantly attenuated by preexposure to cocaine (Serafine & Riley, 2010). Once more, an asymmetrical cross-drug effect is evident between compounds, although importantly in the case of fluoxetine the direction of the asymmetry is reversed relative to GBR 12909 and desipramine. That is, this is the first case in which cocaine preexposure not only attenuated aversions induced by itself, but also those induced by the selective monoamine transporter inhibiter. That cross-tolerance to fluoxetine developed following cocaine history is also evidence of a serotonergic role in cocaine's aversive effects since the primary action of fluoxetine is SERT inhibition. This attenuation (along with the aforementioned results using mice) makes the examination of a higher dose of fluoxetine during preexposure especially warranted, given the clear mechanistic overlap between the two compounds and prior work with higher doses reported with other neurotransmitter systems (see DA and NE above).

However, given that no such assessment with higher doses has been conducted, the use of other procedures to investigate mechanism can provide further evidence of a 5-HT role in

cocaine's aversive effects. In addition to examining DAT and NET KO mice, Jones and colleagues also assessed SERT KO mice in their ability to display cocaine-induced CTAs (Jones et al., 2010). Interestingly, while SERT KO mice conditioned with cocaine drank significantly more than wild-type controls conditioned with cocaine (only at the highest dose tested), they did not differ from SERT KO mice conditioned with saline except on the last trial, indicating a delayed acquisition of cocaine-induced CTAs relative to wild-type controls and DAT KO mice (that developed a significant CTA relative to saline conditioned controls a full trial before SERT KO mice; Jones et al., 2010). The authors conclude that based on this delayed acquisition (and the cross-drug asymmetry described above), SERT inhibition may play a role (relative to DAT inhibition) in cocaine's aversive effects. This conclusion is somewhat at odds with other evidence of SERT involvement in cocaine's rewarding effects. Specifically, DAT KO alone does not eliminate cocaine CPP, but DAT/SERT KO does (Sora et al., 2001; Uhl, Hall & Sora, 2002). If 5-HT is involved in cocaine aversion (as DA is), then removal of SERT should result in an enhancement (rather than the elimination) of cocaine reward. Indeed, SERT KO mice demonstrate enhanced cocaine-induced CPP (Sora et al., 1998). It is possible, however, that 5-HT regulates both effects. Following this logic, elimination of DAT or SERT alone would not eliminate CPP or CTA induced by cocaine, since DAT and SERT probably work together to mediate both reward and aversion in the intact animal (see Uhl et al., 2002 for an overview). To date, no such combined DAT/SERT KO mice have been investigated in the CTA procedure.

Collectively these data support a primary role for DA in cocaine's aversive effects, with modulatory functions of NE (and possibly 5-HT although more data are required to describe this role). These conclusions are based on work primarily from four experimental investigations, i.e., comparison of dose-response acquisition curves, pharmacological antagonism, cross-drug

preexposure and transgenic KO mice. Although none of these preparations is without interpretational concerns, the strongest evidence is that from investigations of direct pharmacological antagonism. Under such conditions, one can assess the role of a specific receptor subtype (and its removal) on the behavior in question (in this case cocaine-induced taste aversion). Although it is possible that acute administration of antagonists can causes sensitization which would impact behavioral expression (see White-Gbadebo & Holtzman, 1994 for examples with opioids), this procedure has the fewest interpretational concerns. The cross-drug preexposure procedure, although useful for investigating shared mechanism between compounds, does not allow for the actual identification of the specific mechanism in question. For example, when no cross attenuation is observed between compounds, it is concluded that there is no shared mechanism between the two. Yet when attenuation is observed, little about the specific mechanism involved is revealed. The only clear conclusion that can be drawn is that there is a commonality between compounds. Work with genetic KO mice is a bit more specific, in that the removal of a transporter can demonstrate its role in a behavior. However, because this model causes the lifelong absence of the transporters, compensatory mechanisms develop that may affect conclusions that could be inferred from the results. As such, only the direct pharmacological antagonism work can stand alone to provide evidence of mechanism. The other preparations, although still useful, should be considered in the context of this more direct data (rather than in isolation). Under these conditions, it is clear that cocaine's aversive effects are primarily mediated by DA, and limited by NE, while 5-HT's role is not yet clear, i.e., if it plays a primary role or one secondary to DA.

The fact that DA mediates cocaine-induced aversions is interesting in light of its role in cocaine's rewarding effects. Such a conclusion brings this discussion full circle, given that it

began with the position that drugs have both aversive and rewarding properties and the balance between these effects determines overall abuse liability (see Figure 1). Stating that a drug has both effects is one thing; suggesting that the same system mediates each may seem counterintuitive. It is likely that DA at different neuroanatomical substrates mediates the two effects and does so independently (see Carr & White, 1986; Grabus et al., 2004; but see also Carlezon Jr & Thomas, 2009). In this context, it is interesting to note that the rewarding and aversive effects of a number of drugs can be dissociated, demonstrating their independence. For example, preexposure to morphine has been shown to increase its rewarding (Harris & Aston-Jones, 2003; He, Bao, Li & Sui, 2010; Manzanedo, Aguilar, Rodríguez-Arias & Miñarro, 2005) but decrease its aversive (Dacanay & Riley, 1982; Domjan & Siegel, 1983; Cappell, LeBlanc & Herling, 1975; for an overview see Verendeev & Riley, in preparation) effects. Further, Shram et al., (2006) found that adolescent rats acquired place preferences (but not taste aversions) to nicotine, while adult rats acquired taste aversions (but not place preferences), suggesting differential sensitivity to reward and aversion across age ranges. The strongest evidence that reward and aversion operate independently is from work using a combined CPP/CTA procedure in which subjects are given a single injection that induces both aversions and preferences in the same animal (see Verendeev & Riley, 2011; see also Sherman, Pickman, Rice, Liebeskind & Holman, 1980; Simpson & Riley, 2005; White et al., 1977; Wise et al., 1976). In this design, the animal is given access to saccharin, injected with a drug, e.g., morphine, and then placed in a place preference chamber. Under these conditions, both taste aversions and place preferences are acquired, but there is no relationship between the strength of CTA and CPP. That is, the extent that a drug is aversive is not dependent on the strength of its rewarding effects. These results indicate that although the two effects may interact to alter SA, they are independent of each

other, such that individual animals display varying degrees of each (Gaiardi et al., 1991; Martin, Bechara & van der Kooy, 1988; Simpson & Riley, 2005; Verendeev & Riley, 2011). What remains to be demonstrated is what specific neuroanatomical substrates or pathways mediate these effects. As noted above, although the pathways for reward (for cocaine and other drugs of abuse) are well characterized, little work exists on the neurobiology of cocaine's aversive effects (see Grabus et al., 2004).

The fact that DA mediates cocaine reward and aversion may have interesting implications for treatment of drug abuse. That is, one could imagine administering a compound that increased DA which in turn would increase cocaine's aversive effects. Such a treatment would in principle limit its abuse potential. However, treatments involving compounds which increase DA are likely themselves to be addictive substances (given that directly or indirectly increasing DA is a common feature of drugs of abuse; see Koob & Le Moal, 2006). The fact that cocaine's aversive effects can be strengthened by NE receptor antagonism is especially of interest when considering treatment options for cocaine abuse. That is, if the drug's aversive effects act to limit overall abuse liability of a compound like cocaine, it is possible that using compounds which potentiate this effect could be used in treatment. It is interesting in this context that individuals treated with tricyclic antidepressants (which increase extracellular levels of NE) do not show efficacy of treatment (measured by urine-confirmed cocaine abstinence Nunes et al., 1995) unless they have underlying major depressive symptoms (McDowell et al., 2005). That is, only when subjects are clinically depressed, do these compounds show efficacy in reducing cocaine use. It is possible that due to an increase of NE action following antidepressant administration, these individuals experience decreases in the aversive effects of cocaine, such that abuse liability increases. It would be interesting to see if NE antagonists affect cocaine use in dependent subjects. Based on

the antagonism work in rodents, it would seem that such a treatment could result in enhancement of cocaine's aversive effects if taken concurrently. Administration of β blockers (e.g., propranolol) in cocaine-dependent individuals with hypertension has been shown to decrease the incidence of death or myocardial infarction (Dattilo, Hailpern, Fearon, Sohal & Nordin, 2008; Freeman & Feldman, 2007) in spite of historical concern that their use would cause increasing α receptor stimulation (see Ramoska & Sacchetti, 1985). However, the use of propranolol for treatment of cocaine SA (i.e., promotion of cocaine abstinence) has had mixed results (Sofuoglu & Kosten, 2006; Kampman et al., 2006). Further investigations assessing the use of NE acting compounds as possible treatments for cocaine dependence should be conducted given the results discussed here. Pending further investigations examining the role of 5-HT in cocaine-induced CTA, it is difficult to speculate on the possible treatment implications of 5-HT acting compounds for cocaine abuse. However, it is interesting that fluoxetine (a commonly prescribed SSRI) does not reduce the aversive effects of later cocaine administration (except under certain conditions, i.e., high doses in mice), while tricyclic antidepressant history (with desipramine) does, suggesting that antidepressant compounds affect later cocaine use differently.

The present data indicate that cocaine's actions on the monoamines contribute to its rewarding and aversive effects. While DA appears to facilitate both cocaine reward and aversion, NE limits cocaine's aversive effects (with minimal effects on cocaine reward). Although 5-HT is reported to impact cocaine reward, it is also argued to have an inhibitory role. Its role in cocaine aversion remains undetermined. In future research investigating the neurochemical mediation of cocaine's affective properties, the extent of involvement of the monoamines (and their interactions) should be explored, along with the possible neurobiological substrates of these effects. Furthermore, characterization of each monoamine's involvement in each of cocaine's

multifaceted effects should be explored through continued investigation using selective agonists and antagonists, as well as cross-drug preexposure and transgenic models.

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