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Mediation of the Discriminative Stimulus Properties of Cocaine by Mesocorticolimbic Dopamine Systems

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CALLAHAN, P. M., R. DE LA GARZA II AND K. A. CUNNINGHAM. *Mediation of the discriminative stimulus properties of cocaine by mesocorticolimbic dopamine systems.* PHARMACOL BIOCHEM BEHAV **57**(3) 601–607, 1997.— This paper provides a brief review of the scientific evidence implicating the mesocorticolimbic dopamine (DA) system in modulating the discriminative stimulus properties of cocaine in rats. Briefly, systemic administration of DA releasers, reuptake inhibitors, and DA D_1, D_2, and putative D_3 receptor agonists engendered partial to full substitution for the discriminative stimulus effects of cocaine. Dopamine D_1 and D_2 receptor antagonists attenuate this behavioral property of cocaine. Intracranial microinjection studies have indicated certain key limbic nuclei as loci of action for DA in mediating the discriminative stimulus effects of cocaine. Microinjections of cocaine into either DA cell body (i.e., ventral tegmental area, substantia nigra) or DA terminal regions (i.e., prefrontal cortex, central amygdala, caudate putamen) have failed to reproduce the systemic cocaine discriminative stimulus. Only infusion of cocaine into the nucleus accumbens has been demonstrated to substitute fully for the systemic effects of this psychostimulant. Interestingly, microinjections of the DA D_1 receptor antagonist SCH 23390 into either the prefrontal cortex, nucleus accumbens, or central or basolateral amygdala have been demonstrated to block the discriminative stimulus properties of cocaine. Although a determination of the antagonism of the cocaine discriminative stimulus following intra-accumbens microinjection of DA D_2 receptor antagonists has not been made, intra-accumbens administration of the DA D_2 receptor antagonist sulpiride blocked the discriminative stimulus effects of another psychostimulant, amphetamine. 6-Hydroxydopamine lesions of DA terminals in the nucleus accumbens also attenuated the dose–effect curve for systemic administration of cocaine. Taken together, this intracranial evidence suggests that DA D_1 and D_2 receptors in the mesocorticolimbic system are involved in modulating the discriminative stimulus properties of psychostimulants and that the nigrostriatal DA system is not primarily involved. © 1997 Elsevier Science Inc.

Amphetamine Cocaine Drug discrimination Mesocorticolimbic terminal fields Microinjection Nucleus accumbens Ventral tegmental area Rat

THE physiological and psychological consequences of cocaine abuse and dependence present a profile of complexity, and attempts to treat abusers with conventional pharmacotherapy have met with mixed results (25,27,35). Therefore, gaining a better understanding of the neuropharmacological actions and neuroanatomical pathways underlying the in vivo effects of cocaine may ultimately lead to the development of pharmacotherapeutic compounds that are successful in combating the effects of this highly abused drug.

The central effects of cocaine can be attributed to its local anesthetic properties (41) and to the blockade of dopamine (DA), norepinephrine (NE), and serotonin (5-HT) reuptake that results in an increased availability of these monoamines in the synaptic cleft (42). In addition, cocaine also possesses affinity for 5-HT_3 receptors (33), M_1 and M_2 muscarinic receptors (46), and σ-receptors (45). Whereas all of these neurotransmitter systems may contribute to the pharmacological actions associated with cocaine, increased DA neurotransmission via blockade of the DA transporter appears to be the primary mechanism mediating many of the behavioral effects of cocaine, including its subjective and rewarding aspects (29,50).

An environmental event that signals the availability of reinforcement contingent upon a particular behavioral response

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is called a discriminative stimulus. Drugs can serve as discriminative stimuli, and drug discrimination assays have been used to classify chemically induced changes in an organism's internal environment associated with administration of psychoactive compounds ("cues") and as a means of elucidating the mechanism(s) of action underlying this unique property of psychoactive agents (3). There is significant overlap in the classification of drugs based upon similarities in "subjective" effects in humans and the discriminative stimulus properties of these same drugs in animals (31,39). In the typical drug vs. saline discrimination task, a subject is trained to emit an operant response following administration of the drug (such as a left-lever press to obtain a food or water reinforcer) and a different response (a right-lever press to receive a reinforcer) following administration of the vehicle (3,39). After acquisition of such a discrimination, several test manipulations [e.g., generalization (substitution) and combination (antagonism or potentiation) tests] can be performed in an effort to discern the mechanism(s) of action of the training drug. In generalization (substitution) tests, the degree of similarity to the training drug cue is assessed by administering various doses of the training drug or novel pharmacological agents. In combination (antagonism or potentiation) tests, either a fixed dose or various doses of novel test compounds are coadministered with various doses of the training drug to assess alterations in the discriminability of the training drug. Generalization and combination tests can also be performed when drugs are microinjected through indwelling catheters implanted into specific brain regions to map the brain circuitry that mediates the discriminative stimulus properties of psychoactive compounds. Similiarly, reassessment of the dose–response relationship for the training drug following localized lesions of specific neurotransmitter systems can also provide insight into the relevant neural circuitry (3,39).

Drug discrimination procedures have been particularly useful in characterizing the neuronal mechanism(s) underlying the in vivo effects of cocaine. Results from these studies have demonstrated the relative importance of DA D_1 and D_2 receptors in mediating the discriminative stimulus properties of cocaine (5,8–10,12,19,28,36,48,51–53) and the role of 5-HT and NE systems as modulatory influences (11,15,28,47,49). The purpose of the present paper is to provide a brief review of the scientific evidence that supports this contention in rats and to identify areas of research that would further elucidate these processes.

EFFECTS OF DA RECEPTOR COMPOUNDS ON COCAINE DISCRIMINATION

Substitution tests have shown that selective DA reuptake inhibitors such as bupropion, GBR 12909, and mazindol substitute completely for the discriminative stimulus properties of cocaine, whereas selective reuptake inhibitors for 5-HT and NE do not mimic the cocaine cue (Table 1) (4,7,16,47,49). Agonists for the DA D_1 (e.g., SKF 38393), D_2 (e.g., quinpirole), and D_3 receptors [e.g., (±)-7-OH-DPAT] engender partial to full substitutions for the discriminative stimulus properties of cocaine (Table 1) (1,5,8,10,32,49,51,52). On the whole, these positive findings with indirect and direct DA agonists are not replicated when agonists for 5-HT and NE are substituted for cocaine (11,15,54).

In studies of DA receptor antagonists, both DA D_1 (e.g., SCH 23390) and D_2 (e.g., haloperidol and bromuride) receptor antagonists attenuate the discriminative stimulus effects of cocaine (Table 2) (4,5,8,10,51,52). Interestingly, the DA release inhibitor CGS 10746B [(43), but see (22)] and DA D_2 receptor partial agonists (e.g., preclamol and terguride) have also been observed to antagonize the cocaine discriminative

TABLE 1

SUMMARY OF SUBSTITUTION TESTS WITH DA REUPTAKE INHIBITORS AND DA D_1, D_2, AND D_3 RECEPTOR AGONISTS ASSESSED IN RATS TRAINED TO DISCRIMINATE COCAINE FROM SALINE

Action	Drug	Complete Substitution (⩾80%)	Partial Substitution (60–79%)	No Substitution (⩽59%)
Reuptake inhibition	buproprion	(4,7)		
	GBR 12909	(7,16,32[a],49[b],51)	(4)	
	mazindol	(4,51)		
	nomifensine	(4,7)		
D_1 full agonist	SKF 77434	(32[a],49[b])	(49[b])	
	SKF 75670	(49[b])	(51)	
D_1 partial agonist	SKF 38393	(49[b])	(8,51,52)	(5)
D_2 full agonist	bromocriptine	(10)	(10)	(7)
	quinpirole	(5,8,10,49[b])		(51)
D_2 partial agonist	preclamol			(10)
	SDZ 208912			(49[b])
	terguride			(10)
D_3 full agonist	(±)-7-OH-DPAT	(1)		
	(+)-PD 128907	(1)		

A test compound was said to have substituted fully for cocaine if at least 80% cocaine-lever responding was observed following at least one dose of that compound. Failure of a test compound to substitute was said to have occurred at values ⩽59% cocaine-lever responding, whereas values between these levels (60–79%) were defined as partial substitutions. The cocaine training dose for most studies was 10 mg/kg, with the exception of two studies which used a training dose of 2-mg/kg[a] or 3-mg/kg[b].

TABLE 2

SUMMARY OF ANTAGONISM TESTS WITH DA D_1, D_2, AND D_3 RECEPTOR ANTAGONISTS ASSESSED IN RATS TRAINED TO DISCRIMINATE COCAINE FROM SALINE

Action	Compound	Complete Antagonism (≤30%)	Partial Antagonism (31–60%)	No Antagonism (≥61%)
Release inhibitor	CGS 10746B	(43)		(22)
D_1 antagonist	SCH 23390	(4,12)	(5,8,51)	(5)
	SCH 39166	C&C		
	SKF 83566	C&C		
D_2 antagonist	bromuride	(10)		
	haloperidol	(10)	(4,8,10,52)	(5,10,51)
	sulpiride	(4)	(52)	
D_2 partial agonist	preclamol		(10)	
	terguride	(10)		
D_3 antagonist	(+)-AJ 76			(13)
	(+)-UH 232			(13)

Complete antagonism was said to have occurred when ≤30% cocaine-lever responding occurred after pretreatment with at least one dose of a test drug given in combination with cocaine. Failure of a drug to antagonize cocaine was said to have occurred at values ≥61% cocaine-lever responding, whereas values between these levels (31–60%) were defined as partial antagonisms. C&C, P. M. Callahan and K. A. Cunningham, unpublished data.

stimulus (10), whereas the putative DA D_3 receptor antagonists (e.g., AJ-76 and UH 232) do not substitute for or block the cocaine cue (13).

Despite the overall finding that DA agonists substitute and DA antagonists block, disparate results exist with regard to the magnitude of these effects. Such disparities are typically viewed as "methodological distinctions" between and among the various laboratories. However, failure to consider sound pharmacological principles may often account for the observed inconsistencies. In particular, the training dose of cocaine and the pharmacokinetic and pharmacodynamic properties of the test compounds appear to be the principal variables that determine the level of substitution for or antagonism of the discriminative stimulus properties of cocaine (10,32,47,49). For example, we demonstrated that for the DA D_2 receptor agonist bromocriptine to substitute fully for the discriminative stimulus properties of cocaine, a postinjection interval that corresponded to maximum occupation of DA D_2 postsynaptic receptors (90 min) was required; a shorter injection interval (30 min) resulted in only partial substitution (10). Similarly, the magnitude of antagonism observed following administration of the DA D_2 receptor antagonist haloperidol was dependent on the duration of the pretreatment interval (10). By increasing the interval between injection of haloperidol (0.5 mg/kg) and testing for recognition of the cocaine cue from 30 min to 120 min, the percentage of cocaine antagonism increased from 20% to 85%. Thus, this antagonism of the discriminative stimulus effects of cocaine appeared to reflect a requirement for optimal DA D_2 postsynaptic receptor occupancy by haloperidol.

ROLE OF MESOCORTICOLIMBIC DA REGIONS IN MODULATION OF COCAINE DISCRIMINATION

Perikarya in the ventral tegmental area (VTA) give rise to DA pathways that innervate numerous limbic (e.g., nucleus accumbens, amygdala) and cortical structures (e.g., prefrontal cortex). Playing a predominant role in motivational and reward processes, the mesocorticolimbic DA system is functionally distinct from the nigrostriatal DA system, which originates in the substantia nigra (SN) and preferentially terminates in the dorsal striatum (6,21). However, despite the functional separation of these two DA pathways, anatomical evidence demonstrates a significant overlap such that both VTA and SN contribute to pathways that innervate limbic forebrain regions (6,21). Additionally, the nucleus accumbens can be divided into two subnuclei termed the "shell" and "core," which appear to be preferentially interconnected with limbic and nigrostriatal systems, respectively (18,26). Thus, intracranial microinjection and neurotoxin lesion techniques are required to probe the roles of specific mesencephalic and forebrain nuclei in the discriminative stimulus effects of cocaine. Only a handful of studies have been conducted to date, and their results support a critical role for the nucleus accumbens in the cocaine cue, as intra-accumbens cocaine has been demonstrated to substitute fully for systemically administered cocaine (Fig. 1) (12,53). Additionally, following destruction of DA terminals within the nucleus accumbens by localized infusion of 6-hydroxydopamine (6-OHDA), the dose–response function for systemically administered cocaine was abolished (Fig. 2) (19). In comparison, intracranial microinjections of cocaine into either the central amygdala (9), prefrontal cortex (53), or caudate putamen (53) failed to reproduce the discriminative effects of systemically administered cocaine (Fig. 1). These results are in overall agreement with studies of amphetamine as a discriminative stimulus in which microinjection of amphetamine into the nucleus accumbens, but not into the dorso- or ventrolateral striatum, mimicked the systemic amphetamine effect (38). Taken together, these observations suggest that the actions of cocaine (and amphetamine) on DA terminals within the nucleus accumbens are critical to the generation of its discriminative stimulus properties.

Dopamine cell bodies serve as a site of action for cocaine due to the extensive localization of DA transporters on these

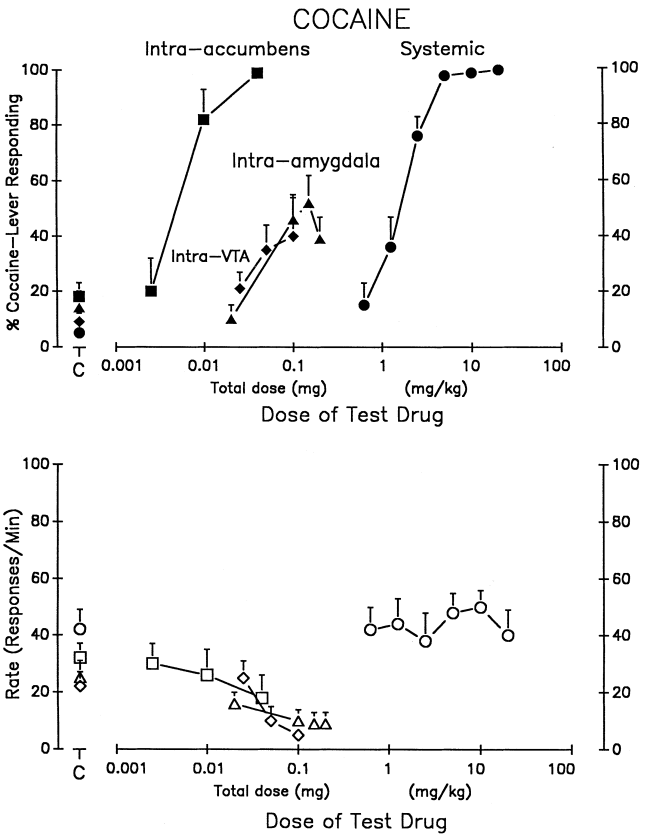

FIG. 1. Summary of intracranial microinjection studies with cocaine. Rats were trained to discriminate cocaine (10 mg/kg, IP) from saline in a two-lever, water-reinforced FR 20 procedure. Dose–effect curves for cocaine were established before and after the implantation of bilateral cannulae into the nucleus accumbens ($n = 8$), amygdala ($n = 8$), or VTA ($n = 12$); the systemic dose–effect curve for the amygdala-implanted rats is shown for comparison (circles). Symbols represent data collected from rats with bilateral cannulae implanted into the nucleus accumbens (squares), amygdala (triangles), or VTA (diamonds). Top: Closed symbols denote the mean percentage of cocaine-appropriate responses (±SEM). Bottom: Open symbols denote the mean number of responses/min (±SEM). The percentages of cocaine-lever responding and response rates observed following intracerebral infusion of artificial cerebrospinal fluid into each brain area are also illustrated by the corresponding symbols along the left ordinate (C). [Redrawn from Callahan et al. (12), Callahan et al. (9), and De La Garza et al. (17).]

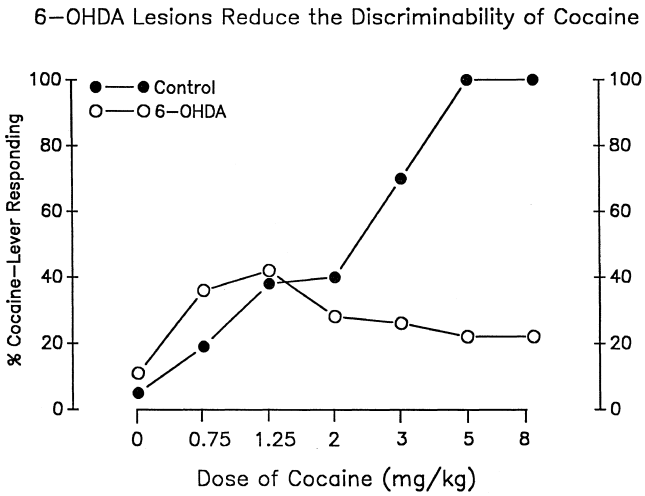

FIG. 2. Effects of 6-hydroxytryptamine (6-OHDA) lesions of the nucleus accumbens on the discriminability of cocaine. Rats were trained to discriminate cocaine (10 mg/kg, IP) from saline in a two-lever, food-reinforced FR 10 procedure. A cumulative dose–effect curve for cocaine was reestablished following lesion 3 days prior with either 6-OHDA (6 μg/0.4 ml over 7.5 min) or its vehicle microinfused into the nucleus accumbens. Symbols represent the percentage of cocaine-appropriate responses in rats following either vehicle (open symbols) or 6-OHDA microinfused into the nucleus accumbens (closed symbols). [Redrawn from Dworkin and Smith (19).]

cells (37). Both systemic and local iontophoretic application of cocaine result in an autoreceptor-mediated (albeit partial) inhibition of DA cell firing within the VTA (20), and intra-VTA infusion of cocaine has also been shown to reduce extracellular DA in the nucleus accumbens (14). Thus, intra-VTA injection of cocaine might not be expected to engender similar discriminative stimulus effects with systemically administered cocaine due to a relative suppression of DA transmission in the VTA–accumbens circuitry. Moreover, considering the relative functional distinctions between mesolimbic and nigrostriatal pathways, manipulation of DA neurotransmission in the SN would not be expected to mimic the discriminative stimulus effects of cocaine. We have recently investigated these hypotheses and found that microinjections of cocaine into the VTA (Fig. 1) failed to engender cocaine-like responding (17), upholding our expectation. Additionally, microinjections of the putative DA D_3 receptor agonist (±)-7-OH-DPAT failed to substitute for the systemic cocaine cue (data not shown) (17). Likewise, intra-SN microinjections of either cocaine or (±)-7-OH-DPAT were also ineffective (data not shown). These findings are preliminary and set the stage for a more thorough analysis to firmly establish that reduction of accumbens DA transmission consequent to focal activation of VTA autoreceptors would result in an attenuation of the discriminative stimulus effects of cocaine.

Of note, despite the fact that a systemic injection of cocaine engenders an internal state associated with numerous physiological and behavioral components, an infusion of a small quantity of cocaine into one specific brain region (i.e., nucleus accumbens) is capable of replicating the interoceptive state associated with the discriminative stimulus effects of systemically administered cocaine. Interestingly, there are data to suggest that the nucleus accumbens may actually be a prominent neural substrate responsible for the production of the discriminative stimulus properties of other classes of psychoactive compounds and not only those of psychostimulants (38). For example, in rats trained to discriminate the hallucinogen *d*-lysergic acid diethylamide (LSD) from saline, Nielsen and Scheel-Kruger (38) demonstrated that microinjections of LSD into the nucleus accumbens engendered a complete substitution for the systemic LSD cue.

A limited number of experiments have addressed the question of site-specific antagonism of the discriminative stimulus effects of cocaine. In contrast to the regional results with regard to microinjection of cocaine, microinfusion of the DA D_1 receptor antagonist SCH 23390 into either the nucleus accumbens or the central amygdala (Fig. 3) has been demonstrated

to produce a dose-dependent blockade of the discriminative stimulus effects of cocaine (9,12). Additionally, microinjection of a fixed dose of SCH 23390 (1 μg/side) into either the medial prefrontal cortex, nucleus accumbens (D. C. S. Roberts, pers. comm.), or central (9) or basolateral amygdala (36) resulted in significant rightward shifts in the dose–response function of systemically administered cocaine. Although studies to assess the efficacy of site-specific microinjection of DA D_2 receptor antagonists in attenuating the discriminative stimulus effects of cocaine have not yet been conducted, intra-accumbens administration of the DA D_2 receptor antagonist sulpiride has been shown to completely antagonize the substitution of intra-accumbens amphetamine in amphetamine-trained rats (38).

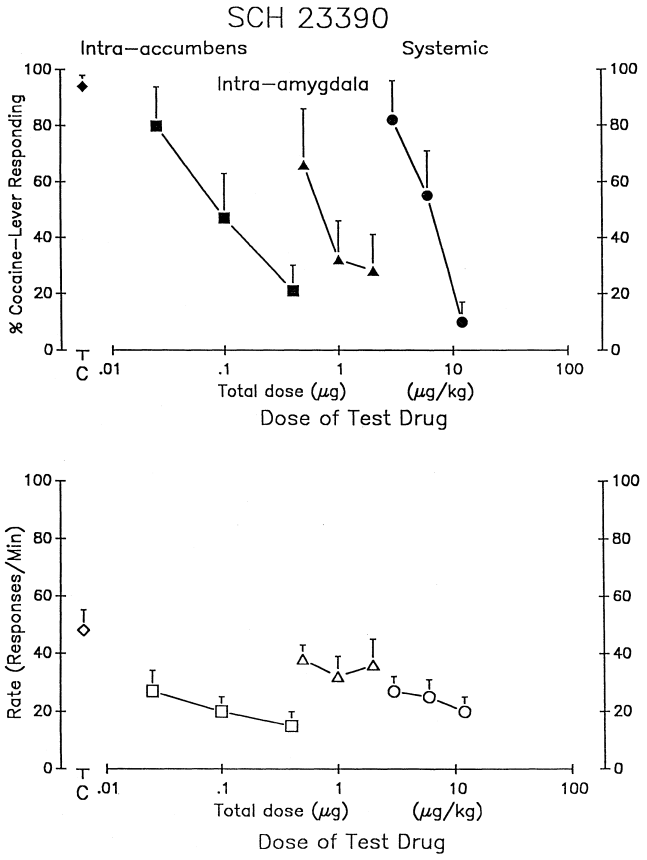

FIG. 3. Summary of intracranial microinjection studies with SCH 23390. Rats were trained to discriminate cocaine (10 mg/kg, IP) from saline in a two-lever, water-reinforced FR 20 procedure, and bilateral cannulae were implanted into the nucleus accumbens (n = 8) or amygdala (n = 8) through which SCH 23390 was microinfused prior to an injection of 5 mg/kg of cocaine. The dose–effect curve for the antagonism of cocaine by systemic SCH 23390 is shown for comparison (circles). Symbols represent data collected in rats with bilateral cannulae implanted into the nucleus accumbens (squares) or amygdala (triangles). Top: Closed symbols denote the mean percentage of cocaine-appropriate responses (±SEM). Bottom: Open symbols denote the mean number of responses/min (±SEM). The percentage of cocaine-lever responding and response rate observed following systemic administration of 5 mg/kg of cocaine alone (diamonds) are also illustrated along the left ordinate (C). [Redrawn from Callahan et al. (12) and Callahan et al. (9).]

The efficacy of intra-amygdala and intra-prefrontal cortex microinjection of the DA D_1 receptor antagonist SCH 23390 in blocking the discriminative stimulus effects of cocaine is somewhat surprising in light of the failure of intracranial injections of cocaine into these same nuclei to mimic the systemic cocaine cue. Recent findings suggest that DA neural transmission appears to be regionally specific among forebrain-projecting DA neurons and dependent upon a delicate balance between release, reuptake, diffusion, and degradation of DA (23,24,30,34). Some of the unique characteristics of the mesocorticolimbic DA system appear to be related to the absence (or insensitivity) of impulse-regulating somatodendritic as well as synthesis-modulating nerve terminal autoreceptors (24,34). Furthermore, transporter kinetics appear to differ significantly among forebrain regions. For example, a significantly higher K_m and a lower V_{max} for DA reuptake were recently observed in the basolateral amygdala as compared with the nucleus accumbens and caudate putamen (30). In this same study, cocaine had no observable effect on the apparent K_m in the basolateral amygdala, whereas this psychostimulant increased the apparent K_m in the accumbens and caudate by over 25-fold (30). Regional differences also exist with regard to the distribution of DA D_1 and D_2 receptor populations in limbic and cortical areas (2,40,44). Thus, it may be possible to manipulate the behavioral effects of systemically administered cocaine via blockade of postsynaptic DA D_1 receptors within the amygdala or prefrontal cortex, yet cocaine itself may be relatively inactive due to its diminished ability to focally affect DA neurotransmission in these brain areas. Because intra-amygdala and intra-prefrontal cortex microinjection of the D_1 antagonist SCH 23390, but not cocaine, is effective, it will be important in the future to test DA D_1 receptor agonists microinjected into these regions to determine if direct stimulation of these receptors can mimic the discriminative stimulus properties of cocaine.

SUMMARY

Dopamine D_1 and D_2 receptors within the mesocorticolimbic system play a significant role in modulating the discriminative stimulus properties of cocaine. Of the forebrain terminal regions tested to date, only intra-accumbens cocaine injections reproduce the systemic effects associated with the cocaine cue. Conversely, nigrostriatal DA pathways do not appear to be critically involved in mediating this behavioral property of cocaine. Further systematic experimentation is required to fully map the underlying circuitry involved in the psychostimulant discrimination and compare it with that which mediates the reinforcing effects associated with psychostimulants. Such studies should incorporate efforts to stimulate the mesocorticolimbic pathway through chemical activation of the VTA and should involve microinjections with specific agonists and antagonists into the nucleus accumbens (core vs. shell), amygdala, and frontal cortex nuclei. These studies, coupled with destruction of DA terminals within these forebrain regions prior to assessment of the discriminability of cocaine, should provide information important to our overall understanding of the neuropharmacological effects of cocaine.

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