weight DNA in a homogeneous electric field. Because the electric field is homogeneous, relative mobilities between adjacent lanes in a gel are not subject to artifactual variation. It is therefore possible to carry out analysis of the variation in molecular weight between germline and rearranged DNA.

We used the FIGE technique to characterize the Sal I fragments that encode the γ-chain locus in germline and rearranged configurations; that is, a single 425-kb Sal I fragment derived from Ly65, a B cell lymphoma (nonrearranged) DNA, hybridized to both variable and constant region probes (Fig. 2A). A smaller Sal I restriction fragment was found in digests of DNA from the T cell lines CCRF–HSB-2 and HPB-MLT; at the resolution afforded in this analysis the broad band in HSB-2 and the upper band in MLT appear to comigrate. HPB-MLT contains two rearrangements, one to Vγ1.2 and the other to another Vγ1 family member. The resolved doublet in MLT would then represent rearrangements to these family members. The HSB-2, and MLT Sal I fragments do not encode the Jγ1.2 and Vγ4 segments because they do not hybridize to these probes (Fig. 2). The germline size of the Sal I fragment is 425 kb whereas the Sal I fragment (or fragments) in HSB-2 is approximately 340 kb. The linkage between Vγ2 and Vγ3 is less than 10 kb. HSB-2 contains one chromosome with a germline Vγ2 and a rearranged Vγ3; the other chromosome contains only a rearranged Vγ2. Hence the HSB-2 Sal I fragment is an unresolved doublet, one band contributed by each chromosome. The difference in molecular weight between the Sal I fragments in HSB-2 and Ly65 is 85 kb. This segment of 85 kb represents the distance between Vγ3 and Jγ2.3. The distance between Vγ3 and Vγ4 is known, as is the complete physical map of the joining–constant-region locus. Thus, after adjustment for the 9 kb between Vγ3 and Vγ4 and the 25 kb between Jγ2.3 and Jγ1.1, the Jγ-to-Vγ4 distance is about 50 kb. Figure 2B shows the physical map of the human T cell γ locus with relevant distances.

We determined the complete molecular map of the human TCRγ locus (Fig. 2B). Rearrangement of γ-chain segments occurs by deletion of the sequences separating variable and joining segments. By measuring the sizes of the fragments bearing rearranged γ-chain genes, we can calculate the sizes of the deletions. The basis of our physical map relies on two independent lines of data: direct linkage of TCRγ genes on restriction fragments resolved by conventional agarose gel electrophoresis, and direct linkage of TCRγ genes resolved by the FIGE method. It is apparent that there are intrinsic differences between resolving restriction fragments of high molecular weight and those of conventional size. Few restriction enzymes yield large fragments. Those that have a rare distribution in mammalian DNA are sensitive to methylation. The distribution of rare cutting enzymes is also problematic. Several reports have shown that rare cutting enzymes are distributed nonrandomly in the mammalian genome (*7, 8*). It is important that our two physical approaches agree and furthermore that they confirm the deletion data. The loss of the well-characterized markers Vγ4 or Jγ1.2 with the retention of Vγ1 or Jγ2.3 is due to gene rearrangement. The most striking feature of the map is the proximity of the most 5′ Jγ to the most 3′ Vγ; this distance is about 50 kb. The overall size of the locus therefore is approximately 160 kb.

There are six human loci that encode immunoglobulin-like genes. Yancopolous and Alt (*9*) speculated that all of these loci are substrates for the same enzyme or enzymes. However, little is known about the substrate preferences of these enzymes. As this is the first complete characterization of a mammalian immunoglobulin-like locus, there is little opportunity to compare the organization to other loci. As more loci are completely described, canonical features may emerge in the organization of the germline substrates for the mammalian site-specific recombination system. Iwamoto *et al.* (*10*) linked a murine Vγ sequence to a Jγ on a single λ phage, the full organization remains to be elucidated. Most immunoglobulin-like gene loci have the arrangement V_1-V_2-V_3 . . . V_n–J-C. An exception is the TCRβ chain locus, which has one Vβ chain segment on the 3′ side of the constant-region locus (*11*), whereas most of the Vβ segments sit in tandem array, presumably on the 5′ side of the joining-region locus (*12*). However, the physical distance between the other variable and joining segments in other loci remain to be determined. Knowledge of these distances will provide further information about the complex mechanism by which two segments located at great distance in germline DNA can be joined together to form a functional gene.

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Cocaine Receptors on Dopamine Transporters Are Related to Self-Administration of Cocaine

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Although cocaine binds to several sites in the brain, the biochemical receptor mechanism or mechanisms associated with its dependence producing properties are unknown. It is shown here that the potencies of cocaine-like drugs in self-administration studies correlate with their potencies in inhibiting [^{3}H]mazindol binding to the dopamine transporters in the rat striatum, but not with their potencies in binding to a large number of other presynaptic and postsynaptic binding sites. Thus, the cocaine receptor related to substance abuse is proposed to be the one associated with dopamine uptake inhibition.

COCAINE IS A POWERFUL REINFORCER that has become a popular drug of abuse. It has a variety of pharmacological effects on the central nervous system (CNS), the cardiovascular system, body temperature, the sympathetic nervous system, and nerve conduction. In man, CNS effects that are related to the abuse of cocaine include feelings of well-being and eu-

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phoria (*1*). Brain dopamine systems are thought to mediate reinforcement (*2*), and it is often assumed that cocaine's inhibition of dopamine uptake is the mechanism underlying its reinforcing effects. However, there are no receptor binding data that support this notion. Indeed, several cocaine binding sites have been found (*3*), but the receptor or receptors related to its reinforcing effects and abuse have not been identified as such. Some of these binding sites are related to nerve terminal transport mechanisms for monoamine neurotransmitters (*3–5*).

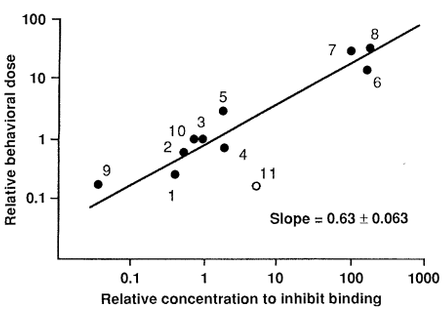

Fig. 1. Relation between the relative behavioral doses of cocaine and related compounds in self-administration studies and their relative inhibitory concentrations for [^{3}H]mazindol binding at the dopamine transporter. Linear regression of logarithms of relative behavioral doses on logarithms of relative inhibitory concentrations for compounds 1 through 10 from Table 1 were calculated with BMDP (*21*). Value shown is slope ± SD. Compound 11 (open circle) was not included in the regression analysis (see text for discussion). A two-tailed test of significance was applied ($P < 0.00001$).

A fundamental requirement for the identification of a pharmacologically relevant receptor is the demonstration of a significant relation between the potency of drugs in producing a response and the potency of drugs at the binding site. Thus, the identification of a receptor that mediates the reinforcing effects of cocaine, the goal of this study, requires that a relation exist between the potency of a variety of cocaine-related drugs in relevant models of substance abuse and their potency at a binding site in the brain.

Drug self-administration by primates, rodents, and other species, as is used in operant conditioning studies, is considered to be a useful model of human drug taking and has been used in the preclinical assessment of abuse liability and the reinforcing effects of drugs. In such experiments, animals perform a learned behavioral response to obtain access to the test drug. Most drugs that humans abuse can function as reinforcers of drug self-administration behavior in animals (*6*). Therefore, we used concentration-response data from our own (*7*) and published studies (*8–15*) of drug self-administration to determine the relative potencies of cocaine-related drugs with respect to reinforcing effects. Because various classes of drugs may share some stimulant properties with cocaine, but may have different pharmacokinetics and mechanisms of action, we mainly considered drugs similar to cocaine. These included cocaine, cocaine analogs, ester- and amide-containing local anesthetics structurally related to cocaine, and some other psychostimulant compounds (Table 1). Of these drugs, compounds 1 through 11 are positive reinforcers, while compounds 12 through 16 are not (*8–15*). Compound 17 has not been tested in drug self-administration studies.

Other types of studies also provide information relevant to abuse liability. Drug discrimination studies, in particular, can determine if a drug is cocaine-like, that is, produces similar subjective effects in humans or similar discriminative effects in animals. Drugs 3, 5, 6, and 17 have been studied with this method (*16, 17*). The behavioral potencies of these drugs were similar in both drug discrimination and drug self-administration studies in which they were tested.

Cocaine has well-known inhibitory effects at nerve terminal transporters for monoamine neurotransmitters including serotonin, dopamine, and norepinephrine, and there are cocaine binding sites at these transporters (*3–5*). Thus, the potencies of the various cocaine-related drugs were examined at these sites by in vitro binding techniques. Choline uptake sites and a variety of neurotransmitter receptor sites were also examined. Although radiolabeled cocaine has been used as the binding ligand for

Table 1. Potencies of cocaine and related compounds in self-administration and biochemical studies. The relative behavioral potencies in self-administration studies were determined by averaging values obtained from studies of cocaine reinforcement (*7–15*). These could not be determined (ND) for compounds 12 to 16 due to their low potencies or toxic side effects. Compound 17 was tested only in discrimination studies. Except in two cases, the animals utilized were monkeys. [^{3}H]Mazindol was used to label dopamine (10^{-5} *M* nomifensine blank) and norepinephrine transport sites (5×10^{-6} *M* desmethylimipramine blank) in striatum and frontal cortex, respectively (*18*). Tissues were homogenized, then incubated for 1 hour in buffer (50 m*M* tris, 120 m*M* NaCl, 5 m*M* KCl; *p*H 7.8; 4°C) containing a final [^{3}H]mazindol concentration of 4 n*M*. Serotonin transport sites were labeled in brain stem with [^{3}H]paroxetine (*19*). Nonspecific binding was defined by the addition of 10^{-6} *M* citalopram. Homogenized tissue was incubated at room temperature in the same buffer as above for 90 minutes with a final ligand concentration of 0.2 n*M*. Tissues for all experiments were dissected from the brains of male Sprague-Dawley rats (Harlan Sprague-Dawley, Indianapolis, Indiana), 60 to 120 days old. K_i values were determined from analyses of competition curves. Standard errors for K_i values (mean of three to five assays) were less than 10% of the values. DEAE, diethylaminoethanol.

Compound	Relative behavioral potency	Dopamine uptake		Serotonin uptake		Norepinephrine uptake	
		K_i (μ*M*)	Relative potency	K_i (μ*M*)	Relative potency	K_i (μ*M*)	Relative potency
1. WIN 35,065-2	0.26	0.26	0.41	0.23	1.64	0.26	0.1625
2. WIN 35,981	0.58	0.36	0.56	0.025	0.18	0.008	0.005
3. (−)Cocaine	1	0.64	1	0.14	1	1.60	1
4. Dimethocaine	0.67	1.29	2.02	65	464	62	39.0
5. (+/−)Norcocaine	2.82	1.21	1.89	0.022	0.158	1.27	0.79
6. Procaine	14.1	104	164	276	1971	217	136
7. Chloroprocaine	29	65	102	50	358	60	37.5
8. (+)Pseudococaine	33	116	183	4.3	32	61	38.1
9. Mazindol	0.17	0.023	0.036	0.025	0.18	0.004	0.0025
10. Methylphenidate	1	0.39	0.61	15	107	1.86	1.16
11. (+)Amphetamine	0.20	3.6	5.63	8	57	0.88	0.55
12. Lidocaine	ND	3298	5153	377	2693	241	151
13. Procainamide	ND	1943	3036	362	2586	1586	991
14. DEAE	ND	18197	28433	6353	45379	23158	14474
15. WIN 35,065-3	ND	385	602	107	767	85	53
16. (+)Cocaine	ND	136	213	67	479	235	147
17. WIN 35,428	—	0.17	0.27	0.026	0.19	1.09	0.68
18. (+/−)Cocaine	—	1.51	2.36	0.17	1.21	2.93	1.83

uptake sites in several studies (*3*), we have utilized other ligands that bind with higher affinities and specificities and provide better specific-to-nonspecific binding ratios. We used [^{3}H]mazindol binding to identify dopamine transport sites in rat striatal tissue and norepinephrine transport sites in rat frontal cortex (*18*) and [^{3}H]paroxetine binding to identify serotonin transport sites in rat brain stem (*19*). Other binding sites were studied by standard assays (*20*).

Drugs that were potent in self-administration studies were also potent inhibitors of binding at the transport sites for dopamine, serotonin, and norepinephrine, but they showed little inhibition at a large number of other presynaptic and postsynaptic sites (Tables 1 and 2). Mazindol and the cocaine analogs, compounds 1 and 2, were more potent inhibitors than (+/−)cocaine and (−)cocaine. In addition, the cocaine-related drugs that have not been shown to function as positive reinforcers (compounds 12 through 16) bound to these uptake sites with very low potencies. (−)Cocaine was most potent at the serotonin uptake site under these experimental conditions. There was a marked stereospecificity at all three sites; the behaviorally active stereoisomers (−)cocaine and WIN 35,065-2 showed much greater potency than (+)cocaine and WIN 35,065-3, respectively. Binding inhibition by cocaine-related drugs was not found for the choline uptake system, however. Inhibitory constant (K_i) values for (−)cocaine and (+)cocaine at the [^{3}H]hemicholinium binding site are 248 μM and 40 μM, respectively. These potencies indicate a marked reverse stereospecificity at choline uptake sites and show that cocaine is not a potent inhibitor of all uptake sites.

Our findings suggest that dopamine transport inhibition is the primary mechanism associated with the reinforcing effects of cocaine, although we cannot rule out some involvement of other sites. A multiple regression (*21*) analysis, relating the logarithms of the relative concentrations to inhibit binding and the logarithms of the relative behavioral doses for compounds 1 through 10, indicates that dopamine transporter inhibition is indeed significantly and positively associated with the reinforcing effects of cocaine (slope = 0.72 ± 0.13, $P < 0.001$). These statistics also indicate that there is little relation between cocaine-reinforced behavior and either serotonin transport inhibition (slope = -0.08 ± 0.10, $P < 0.45$) or norepinephrine transport inhibition (slope = -0.01 ± 0.13, $P < 0.93$). Correlation analysis leads to similar conclusions (*22*). Thus, it can be seen from the multiple regression analysis that cocaine binding to the dopamine uptake site, after adjustment for the norepinephrine and serotonin uptake sites, is the only significant contributor to the regression. In other words, the cocaine inhibition of dopamine transporter alone is sufficient to explain most of the variability (multiple $R^2 = 0.94$) in cocaine self-administration. Further, confirmation of this conclusion is shown in Table 3, which examines the order in which the sites are added to the regression model. If dopamine data are added to either norepinephrine or to serotonin data, or if dopamine data are added to the model containing both norepinephrine and serotonin data, the improvement in the goodness of fit is substantial. Conversely, if either norepinephrine or serotonin data, separately or together, are added to the model containing dopamine, no significant increases in goodness of fit are seen.

Because amphetamines generalize to cocaine in drug discrimination studies (*23*) and brain dopamine may be involved in mediating their reinforcing effects (*24, 25*), it seemed likely that the mechanism of action associated with amphetamine reinforcement may also involve dopamine uptake inhibition. However, *d*-amphetamine inhibited striatal [^{3}H]mazindol binding with a K_i of 3.6 μM (Table 1) and is self-administered in monkeys with a potency relative to cocaine of approximately 0.20 (*8, 26*). Thus, considering the regression analysis for compounds 1 through 10, *d*-amphetamine is more potent in self-administration studies than would be expected on the basis of its binding potency at the dopamine uptake site, and its data point is somewhat removed from the regression line (Fig. 1). This relatively weak binding potency has been observed in other studies (*27*). This is consistent with many reports indicating that *d*-amphetamine and (−)cocaine have different molecular mechanisms of action at the dopamine nerve terminal (*27*). CNS stimulants can be divided into two classes on the basis of their biochemical effects on catecholamine-containing neurons in brain: the amphetamines and the nonamphetamines (cocaine and methylphenidate). Drugs in the former class inhibit reuptake and are potent releasers, while drugs in the latter class inhibit reuptake but are more restricted in their releasing properties. Also, the effects of drugs in the nonamphetamine class are blocked by reserpine pretreatment, suggesting that different pools of dopamine are involved in mediating the effects of drugs from these two different classes (*27*). Perhaps the dopamine transporter is a relevant receptor for amphetamine, but a different overall mechanism is utilized. For these reasons, *d*-amphetamine was not included in our regression analysis (Table 1 and Fig. 1).

Table 2. Receptors not bound by cocaine or norcocaine. Dopamine receptors were assessed in rat striatal tissue. Benzodiazepine and γ-aminobutyric acid (GABA) receptors were assayed in bovine cerebral cortex and cerebellum, respectively. Glutamate and arginine vasopressin sites were assayed in rat cerebellum and rat liver, respectively. All other receptors were studied in rat frontal cortex. Neither (+/−) cocaine nor (+/−)norcocaine, in maximum concentrations of 0.1 mM, competed with the radiolabeled ligands used for binding to any of these receptors. VIP, vasoactive intestinal peptide; PCP, phencyclidine; TCP, *N*-(1[2-thienyl]cyclohexyl)-3,4-piperidine.

Receptor	Ligand
D_1 Dopamine	[^{3}H]SCH 23390
D_2 Dopamine	[^{3}H]Spiperone
S_1 Serotonin	[^{3}H]LSD (in the presence of ketanserin)
S_2 Serotonin	[^{3}H]Ketanserin
β-Adrenergic	[^{3}H]Dihydropropranolol
α_1-Adrenergic	[^{3}H]Prazosin
α_2-Adrenergic	[^{3}H]Para-aminoclonidine
Benzodiazepine	[^{3}H]Flunitrazepam
Substance P	[^{3}H]Substance P
Adenosine	[^{3}H]*N*-ethylcarboxyamino-adenosine
Neurotensin	[^{3}H]Neurotensin
VIP	[^{125}I]VIP
$GABA_A$	[^{3}H]GABA
Glutamate	[^{3}H]Glutamate (in presence of Cl^-)
Arginine vasopressin	[^{3}H]Arginine vasopressin
PCP	[^{3}H]TCP

Tricyclic antidepressants also inhibit striatal [^{3}H]mazindol binding. Imipramine, which is not self-administered at tested doses (*6, 28*), is about 30-fold weaker than cocaine (*18*) in inhibiting [^{3}H]mazindol binding. If imipramine was administered such that its blood levels were 30-fold higher than behaviorally efficacious blood levels of cocaine (*1, 29*), then the blood levels of imipramine would be in the range for human lethality (*30*). Therefore, at least some tricyclic antidepressants and other compounds that inhibit dopamine uptake may not be self-administered because of the toxic side effects that occur at blood levels required for uptake inhibition and self-administration.

These results relating binding to dopamine transporters and the reinforcing properties of cocaine are consistent with reports related to the mechanisms of cocaine self-administration. Blood levels of cocaine in humans that are associated with subjective feelings of "high" are in the micromolar range (*1, 29*), similar to the K_i for (−)cocaine at the dopamine uptake site. In the clinical setting, compounds potentiating dopaminergic transmission, including methylphenidate and bromocriptine, decrease the craving for cocaine (*31*). In animal studies, dopamine-containing neuronal systems, particularly in the limbic region leading to the

Table 3. Multiple regression test results for order of incorporation of the three binding sites, N, norepinephrine; S, serotonin; D, dopamine.

Site variables tested	*P* value
N adding S	0.497
D adding S	0.23
S adding N	0.0520
D adding N	0.37
S adding D	0.000062
N adding D	0.00054
N and D adding S	0.45
D and S adding N	0.93
N and S adding D	0.0013

frontal cortex, have been strongly implicated in self-administration of cocaine (*2, 32*). Intravenous substitution of dopaminergic agonists can maintain cocaine-reinforced behavior (*33*). Self-administration of cocaine via intracranial injections has been inhibited by lesions of limbic dopaminergic tracts and by concurrent administration of D_2 dopamine receptor blockers; but D_1 dopamine, muscarinic cholinergic, β-adrenergic, and α-adrenergic receptor blockers do not modulate cocaine intake at micromolar levels. Injections of dopamine, but not serotonin, into the medial prefrontal cortex after 6-hydroxydopamine lesions reinstated this cocaine-related behavior (*2, 32*). The local anesthetic effects of cocaine-related drugs do not correlate with reinforcing effects, but may correlate to binding at sodium channels (*34, 35*) or to effects at cholinergic presynaptic or postsynaptic receptors (*36*). The discriminative stimulus effects of cocaine are also primarily mediated by dopamine pathways and are not influenced by various hallucinogenic, opiate, barbiturate, or cannabinoid compounds (*37*). Dopamine uptake inhibition has also been related to locomotor activity, rotational behavior, stereotypy, heart rate, and other physiological effects of cocaine in rats and mice (*5, 35, 38*).

Other neurotransmitters, in contrast to dopamine, are apparently not involved in the mediation of the positively reinforcing effects of cocaine. Serotonin agonists, in contrast to dopamine agonists, decrease cocaine-reinforced behavior (*39*). Other serotonin-related drugs such as fenfluramine, imipramine, *d*-lysergic acid diethylamide (LSD), and DOM (2,5-dimethoxy-4-methylphenyl-2-aminopropane) are not reinforcing in animals (*6*). In addition, lesions of cerebral serotonin neurons with the neurotoxin 5,7-dihydroxytryptamine increase intravenous self-administration of *d*-amphetamine; pretreatments with serotonin uptake blockers or postsynaptic receptor agonists, however, decrease this self-administration (*40*). Thus, serotonin uptake inhibition may attenuate psychostimulant self-administration under some conditions. Norepinephrine also appears to have little influence on the self-administration of cocaine. Noradrenergic blockers do not affect the reinforcing effects of cocaine in animals, whereas, dopamine blockers do (*2*). Also, lesions of dorsal and ventral noradrenergic bundles do not affect responding for cocaine, while 6-hydroxydopamine lesions of dopamine-containing nerve terminals in the nucleus accumbens and medial prefrontal cortex reduce responding (*24, 41*). Thus, although cocaine affects norepinephrine transport and serotonin transport as well as dopamine transport, the above studies are consistent with our conclusions that dopamine uptake inhibition mediates cocaine reinforcement.

Because [^{3}H]mazindol is the ligand used to label dopamine transport sites in our study, its binding site is the one associated with cocaine's reinforcing properties. Indeed, mazindol is self-administered in animals (*15*). It is unknown if mazindol binds to the dopamine recognition site on the transporter, to the ionic site, or to some other site associated with the dopamine transport mechanism. Some evidence has been presented that suggests that the site recognized by [^{3}H]mazindol is not the same site as that which recognizes and binds the catecholamines (*18, 27*). Cocaine is also a competitive inhibitor of [^{3}H]mazindol binding, and [^{3}H]cocaine binds to the dopamine transporter (*3*). Thus, the cocaine binding site may be the same as or at least is closely related to the mazindol site. Other ligands may bind to this site as well (*42*). In summary, the cocaine binding site related to dopamine uptake inhibition is proposed to be the receptor mediating the reinforcing properties of cocaine and at least some other psychostimulants.

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7. We used operant self-administration procedures similar to those described by S. R. Goldberg [*J. Pharmacol. Exp. Ther.* **186**, 18 (1973)]. Squirrel monkeys responded under a 30-response fixed-ratio schedule (FR 30) of intravenous injection for a baseline dose of 56 μg of cocaine hydrochloride per kilogram of body weight per injection; 30 lever-press responses were required to produce each injection; each injection was followed by a 5-minute time out, and sessions were 1 hour in length. At least 2 days of baseline cocaine responding separated substitution of each test dose. The potencies of (+)cocaine, (+)pseudococaine, and (−)norcocaine were compared to that of (−)cocaine in squirrel monkeys. Our results are consistent with previous findings that norcocaine was slightly less potent than cocaine and (+)cocaine did not serve as a reinforcer. The potency of (+)pseudococaine in self-administration studies has not been previously reported.
8. The relative behavioral potencies of drugs in Table 1 were determined by averaging values obtained from operant studies of drug reinforcement. The published reports used to supply relevant behavioral information about the drugs studied in these experiments are listed below. We used only those studies that utilized an operant model of drug self-administration and in which behavioral potencies could be determined relative to (−)cocaine directly. The experimental procedures in these studies are quite similar. Drugs were administered to the animals via an intravenous catheter. Squirrel or rhesus monkeys were used as subjects with only one exception; Risner and Jones (*14*) compared the effects of norcocaine in beagle dogs, and the results were consistent with the other studies of norcocaine self-administration in monkeys. Most of the studies used an experimental protocol involving a substitution procedure in which various concentrations of the test drugs were compared to a standard concentration of cocaine that had been established as a reinforcer in the subjects. The standard concentrations of cocaine administered to the animals were similar in all of the studies and were in the range that elicits near maximal response levels. One study (see Spealman and Kelleher) compared entire concentration-response curves of cocaine with similar curves generated for other test drugs. Data were always reported for individual animals separately. Thus, we determined the concentrations of test drugs that resulted in levels and patterns of responding that were most similar to those associated with the standard cocaine concentration for individual animals. These values were averaged for each paper. If drugs were tested in more than one study, the behavioral values were also averaged across studies to give final average reinforcing potency of the drug. Drugs 1, 2, 5, and 11: R. D. Spealman and R. T. Kelleher, *J. Pharmacol. Exp. Ther.* **216**, 532 (1981).
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22. Although correlative statistics are not appropriate analyses for this data set, correlation coefficients were also calculated for descriptive purposes and for comparison with previous studies of this type. Pearson product-moment correlation coefficients, relating the logarithms of the relative binding potencies to logarithms of the relative behavioral potencies for compounds 1 through 10, were 0.96, 0.57, and 0.77 for dopamine, serotonin, and norepinephrine sites, respectively. Similarly to the multiple regression analysis, partial correlations indicate that dopamine uptake inhibition is positively related to the reinforcing effects of cocaine ($r = 0.92$) and that the action of cocaine at the dopamine uptake site accounts for a large proportion of the variance in cocaine-reinforced behavior. These statistics also indicate that the relation between cocaine-reinforced behavior and serotonin uptake inhibition tends to be negative ($r = -0.31$). Norepinephrine uptake inhibition appears to have little influence on behavior ($r = -0.04$).
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43. We thank R. Balster, G. Battaglia, E. Cone, M. Fischman, F. George, R. Griffiths, J. Jaffe, J. Katz, K. Kumor, K. Lloyd, J. Sharkey, and R. Spealman for helpful discussions; R. Balster, E. Cone, R. Heikkila, E. Johnson, and R. Spealman for supplying drugs for these experiments; F. Snyder and G. Chase for help with statistical analyses and particularly A. Kimball for preparing Table 3; T. Kopajtic, M. Milberger, and Nova Pharmaceuticals for technical assistance; and T. Pierce and M. Flutka for clerical assistance. An abstract describing these data has appeared [M. C. Ritz and M. J. Kuhar, *Fed. Proc.* **46**, 404 (1987)].

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