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Locomotor Stimulant Effects of Cocaine and Novel Cocaine Analogs in DBA/2J and C57BL/6J Inbred Mice

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TOLLIVER, B. K. AND J. M. CARNEY. *Locomotor stimulant effects of cocaine and novel cocaine analogs in DBA/2J and C57BL/6J inbred mice.* PHARMACOL BIOCHEM BEHAV **50**(2) 163–169, 1995.—The current study compared the potencies of cocaine and a series of substituted phenyltropane analogs of cocaine in stimulating locomotor activity in two genetically distinct strains of mice previously shown to differ in their locomotor responsiveness to cocaine. In addition, these compounds were compared for their abilities to induce stereotyped behaviors in naive and cocaine-pretreated mice. All of the analogs tested were more potent locomotor stimulants than cocaine in both strains. Interstrain differences in the locomotor stimulant efficacy of RTI-31 and RTI-98 parallel those of cocaine, with DBA/2J mice being stimulated to a greater extent than C57BL/6J mice at maximally active doses. Significant differences exist in the onset and duration of action among cocaine and several analogs. Whereas the action of cocaine peaks in the first 10 min after injection and thereafter rapidly declines, the stimulant effects of RTI-31, RTI-98, and RTI-113 are maximal at 30–40 min and remain consistent through 60 min postinjection. The current results are discussed in the context of previously published reports of genotype-dependent differences in behavioral responsiveness to cocaine in the DBA/2J and C57BL/6J strains.

Cocaine WIN 35,428 RTI compounds Behavior genetics DBA/2J C57BL/6J Locomotor activity

INHERITED differences in responsiveness to a number of drugs of abuse have been demonstrated in genetically defined animals (13,18). Inbred and selectively bred mouse and rat strains have been used extensively to investigate the determinants of responses to drugs of abuse (9,11,20,24). Inbred strains are the result of at least 20 successive brother-sister matings and consist of genetically identical individuals for which the genomes are fixed and homozygous at all gene loci (12). Under constant environmental conditions, interstrain differences in the behavioral and physiological responses to a given drug are attributable to differences in the genotype between strains. Several investigators have reported large differences in cocaine's effects on heart rate (29), monoamine uptake inhibition (7), locomotor activity (15,21,33,38), stereotypy (36), and seizures and lethality (18) across a range of inbred mouse strains. Perhaps the best characterized of the inbred strains that differ in their responsiveness to cocaine are the DBA/2J and C57BL/6J strains, in which over 700 polymorphic loci have been mapped (34). Between these strains, interstrain differences in both acute and long-term locomotor responses to cocaine have been demonstrated (17,21,29,30,35). The absence of interstrain variation in brain cocaine levels after cocaine administration (29,35) suggests that the differences in behavioral responsiveness are the result of differential CNS sensitivities to cocaine in DBA/2J and C57BL/6J mice. The neurochemical substrates that may underlie differential sensitivities to cocaine remain unclear.

Cocaine is known to interact with several macromolecular sites in the brain (25,27,31,32), and any of these sites could potentially contribute to interstrain differences in behavioral responsiveness to cocaine. However, because cocaine's locomotor stimulant and reinforcing properties are thought to be mediated largely by its inhibition of neuronal dopamine uptake (2,28), the potential role of dopaminergic systems in interstrain differences in behavioral response to cocaine has recently received attention (15,19,37). Dopamine cell number in the ventral tegmental area has been shown to vary significantly across several inbred mouse strains (16), but the importance of

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this variation in the behavioral response to cocaine is unclear. Although differences in striatal dopamine receptor densities in the DBA/2J and C57BL/6J strains have been reported (3,15), the behavioral significance of these observations is complicated by the existence of selectively bred lines that differ in their response to cocaine but do not differ in their expression of dopamine receptors (19).

An alternative strategy for investigating potential neurochemical systems underlying interstrain behavioral variation is the use of drugs closely related to cocaine that have varying selectivities for the sites at which cocaine is known to bind. If these interstrain differences are due to cocaine's action at only one of these sites, then drugs acting selectively on that site should exhibit a response profile across strains that is very similar the profile of cocaine. Recently developed phenyltropane analogs of cocaine shown to differ widely in their in vitro binding and uptake inhibition at the dopamine, norepinephrine, and serotonin transporters (5,6,8) are ideal for such a study. The extent to which these drugs covary with cocaine in their potencies and efficacies as locomotor stimulants across strains can be evaluated in the context of their previously published monoamine binding and uptake inhibition profiles (6,8). The present study compares the potencies, efficacies, and onset and duration of action of the locomotor stimulant effects of cocaine and four substituted phenyltropane analogs in DBA/2J and C57BL/6J inbred mice. The effects of three additional cocaine analogs in DBA/2J mice are also reported.

METHOD

Animals and Drugs

Adult male DBA/2J and C57BL/6J mice (22–30 g) were purchased from the Jackson Laboratory (Bar Harbor, ME) and housed five per cage for at least 1 week on a 12L : 12D cycle with food and water available ad lib prior to testing.

Cocaine hydrochloride was obtained from Sigma (St. Louis, MO); WIN 35,428 tartrate, RTI-31 tartrate, and RTI-32 tartrate were obtained from the National Institute on Drug Abuse; RTI-98 (free base), RTI-113 HCl, RTI-120 HCl, and RTI-121 HCl were obtained from Dr. F. Ivy Carroll at the Research Triangle Institute (Research Triangle Park, NC). All drugs were dissolved in hot isotonic saline and were injected at room temperature (IP) in a volume of 10 μl/g of body weight.

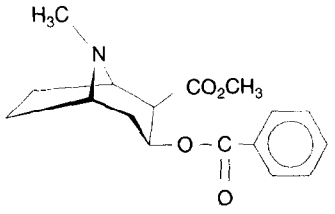
Locomotor Activity Testing

Locomotor activity was monitored in darkened 24-in. circular chambers equipped with orthogonally placed photocell detector systems. Interruptions of photocell beams were computer-registered as counts. Cumulative count totals were recorded for each of six 10-min intervals immediately following an injection of saline or drug. Naive mice (never exposed to drug or to the test chamber) of each strain were used for all locomotor experiments. Drug dosages used were as follows: cocaine—six doses from 2.9 to 290 μmol/kg (n = 5 each strain per dose); RTI-31—six doses from 0.072 to 7.22 μmol/kg (n = 3 each strain per dose); RTI-98—seven doses from 0.93 to 93 μmol/kg (n = 3 each strain per dose); RTI-113—five doses from 0.80 to 80 μmol/kg (n = 3 each strain per dose); WIN 35,428—five doses from 0.23 to 23 μmol/kg [n = 3 each strain per dose except 7.49 μmol/kg (n = 6)]. Three additional analogs were tested only in DBA/2J mice at the following doses: RTI-32—seven doses from 0.24 to 76 μmol/kg (n = 3 per dose); RTI-120—six doses from 0.27 to 270 μmol/kg (n = 3 per dose); RTI-121—five doses from 0.76 to 76 μmol/kg (n = 3 per dose).

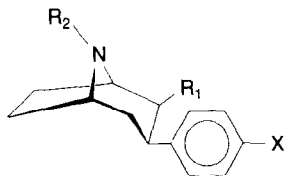
Data Analysis

Overall effects of cocaine and WIN 35,428, RTI-31, RTI-98, and RTI-113 were analyzed using two-way (strain × dose) analysis of variance (ANOVA) for each drug. Student-Newman-Keuls analysis was used for all post hoc multiple comparisons and interpretation of interactions. Overall effects of RTI-32, RTI-120, and RTI-121 in DBA/2J mice were analyzed using one-way ANOVA for each drug.

ED_{50} values were estimated as the dose required to produce 50% of the maximum locomotor stimulation using a nonlinear least-squares curve fit procedure described previously (14). Only data points from the ascending limb of the dose-response curves were analyzed. Using linear regression, ED_{50}



COCAINE



	R1	R2	X
WIN 35,428	CO_2CH_3	CH_3	F
RTI-31	CO_2CH_3	CH_3	Cl
RTI-32	CO_2CH_3	CH_3	CH_3
RTI-98	CO_2CH_3	H	I
RTI-113	CO_2Ph	CH_3	Cl
RTI-120	CO_2Ph	CH_3	CH_3
RTI-121	$CO_2CH(CH_3)_2$	CH_3	I

FIG. 1. Chemical structures of cocaine and selected cocaine analogs used in the present study.

and E_{max} values of cocaine and its analogs were compared with potencies for [^{3}H]monoamine uptake inhibition published previously (6). In cases in which a single outlying data point (cocaine data point) was sufficiently extreme to define a regression line, the analysis was conducted in the presence and absence of such points.

RESULTS

The effects of cocaine on locomotor activity in DBA/2J and C57BL/6J mice, as determined by two-way ANOVA, have been reported previously (37) and are included here for reference. All drugs (Fig. 1) elicited dose-dependent stimulation of locomotor activity, generating inverted U-shaped log dose-response curves characteristic of psychomotor stimulants (Fig. 2). All cocaine analogs were more potent locomotor stimulants than cocaine. The potency order for locomotor stimulation in DBA/2J mice, based on estimates of ED_{50} values, was RTI-31 > WIN 35,428 > RTI-32 ≥ RTI-121 = RTI-113 = RTI-98 > RTI-120 > cocaine (Table 1). In C57BL/6J mice, potencies of RTI-31 and WIN 35,428 were virtually identical to their respective potencies in DBA/2J mice, whereas RTI-98 and RTI-113 may be slightly more potent in C57BL/6J than in DBA/2J mice (Fig. 2).

Cocaine produced a dose-dependent elevation in locomotor activity in both strains [overall $F(13, 51) = 23.65$, $p < 0.0001$], with a strain × dose interaction present, $F(6, 51) = 8.55$, $p < 0.0001$. One-way ANOVA performed at each dose revealed significantly greater locomotor stimulation of DBA/2J mice relative to C57BL/6J mice at the 94 μmol/kg, $F(1, 7) = 20.86$, $p < 0.005$, and 164 μmol/kg, $F(1, 8) = 12.72$, $p < 0.01$, doses. Cocaine's maximal effect occurred in the first 10-min interval following injection of 94 μmol/kg in both strains (Fig. 3). No strain × interval interaction, $F(5, 41) = 1.99$, $p = 0.10$, was present.

RTI-31 stimulated locomotor activity in both strains [overall $F(12, 29) = 12.32$, $p < 0.0001$]. One-way ANOVA performed at each dose revealed significantly greater locomotor stimulation of DBA/2J mice than C57BL/6J mice at 0.45 μmol/kg, $F(1, 4) = 19.95$, $p < 0.02$, and 0.72 μmol/kg, $F(1, 4) = 13.46$, $p < 0.05$, doses. At the maximally active 0.72 μmol/kg dose, the maximal effect of RTI-31 was not reached until the third 10-min interval, in contrast to the rapid onset of action of cocaine (Fig. 3). No strain × interval interaction was present for RTI-31, $F(5, 24) = 2.07$, $p = 0.10$.

WIN 35,428 stimulated locomotor activity in both strains [overall $F(11, 30) = 7.98$, $p < 0.0001$] in a dose-dependent fashion, $F(5, 30) = 11.81$, $p < 0.0001$. A significant effect of strain, $F(1, 30) = 15.47$, $p < 0.0005$, and a strain × dose interaction, $F(5, 30) = 2.65$, $p < 0.05$, were also present. Analyzed by dose, significant interstrain differences in locomotor stimulation were found only at the 7.5 μmol/kg dose of

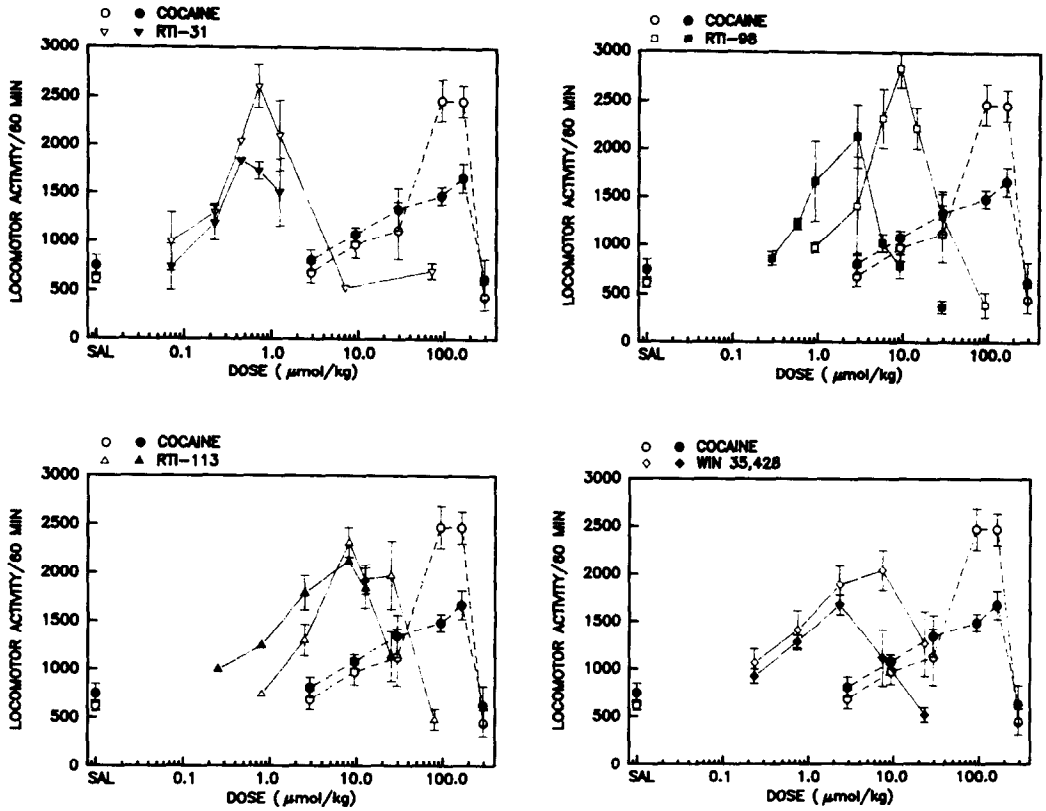


FIG. 2. Locomotor activity log dose-response curves for four analogs tested in both DBA/2J (open symbols) and C57BL/6J (closed symbols) strains. Cocaine curves (dashed lines) for each strain are included in each panel for reference. Data are presented as mean number of photocell interruptions in 60 min following IP injection ± SEM (n = 3–6 each strain per dose per drug).

TABLE 1

AVERAGE EFFECTIVE DOSES FOR LOCOMOTOR STIMULANT EFFECTS OF COCAINE AND ITS ANALOGS

	DBA/2J		C57BL/6J	
Compound	ED_{50} (μmol/kg)	E_{max} (counts/h)	ED_{50} (μmol/kg)	E_{max} (counts/h)
1. RTI-31	0.24 ± 0.11	2414 ± 473	0.23 ± 3.05	1692 ± 134
2. WIN 35,428	0.66 ± 0.22	2195 ± 181	0.28 ± 0.29	1376 ± 309
3. RTI-32	1.00 ± 0.82	2425 ± 113		
4. RTI-121	2.29 ± 0.07	2252 ± 23		
5. RTI-113	2.54 ± 5.11	2140 ± 193	0.81 ± 0.43	2059 ± 297
6. RTI-98	3.15 ± 0.88	2541 ± 371	0.71 ± 0.05	2222 ± 81
7. RTI-120	4.92 ± 0.52	1863 ± 48		
8. Cocaine	42.44 ± 18.13	2622 ± 192	17.15 ± 9.29	1776 ± 192

Average doses of cocaine and cocaine analogs required to produce half-maximal locomotor stimulation in DBA/2J and C57BL/6J mice. Data are presented as ED_{50} ± SD and E_{max} ± SD and were determined as described by DeLean et al. (14) using a minimum of 4–5 data points (n = 3–6 each point) on the ascending limb of the log dose-response curve for each compound.

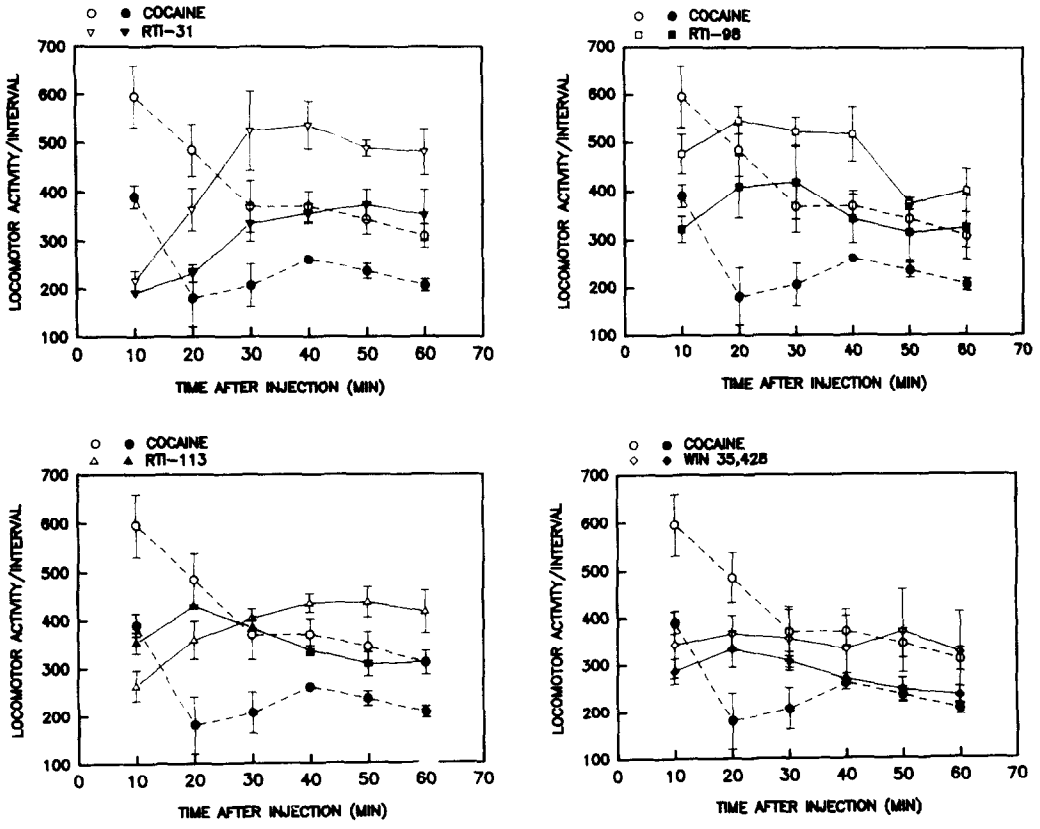


FIG. 3. Time course of locomotor stimulant effects of maximally active doses of cocaine and selected analogs tested in both DBA/2J (open symbols) and C57BL/6J (closed symbols) strains. Cocaine curves (dashed lines) are included in each panel for reference. Doses used are as follows: cocaine, 94 μmol/kg; RTI-31, 0.72 μmol/kg; RTI-98, 9.3 μmol/kg (DBA/2J) and 2.9 μmol/kg (C57BL/6J); RTI-113, 8.0 μmol/kg; WIN 35,428, 2.3 μmol/kg. Data are presented as mean number of photocell interruptions in each of six 10-min intervals following IP injection ± SEM (n = 3–6 each strain per drug).

WIN 35,428, $F(1, 7) = 6.47, p < 0.05$. Unlike cocaine, WIN 35,428 induced locomotor activity consistently over the six 10-min intervals (Fig. 3). No strain × interval interaction was present, $F(5, 24) = 1.00, p = 0.44$.

Significant interstrain differences in response to RTI-98 were found, with both a main effect of strain, $F(1, 33) = 22.95, p < 0.0001$, and a strain × dose interaction, $F(5, 33) = 12.92, p < 0.0001$, present. Although the data presented in Fig. 2 suggest that both the ascending and descending limbs of the log dose-response curves reflect a higher potency of RTI-98 in C57BL/6J mice than in DBA/2J mice, statistically significant strain differences were observed only at the 5.8 μmol/kg, $F(1, 4) = 16.28, p < 0.02$, and 9.3 μmol/kg, $F(1, 4) = 78.55, p < 0.001$, doses. Maximal locomotor stimulation (E_{max}) by RTI-98 did not differ between the two strains, $F(1, 7) = 1.30, p = 0.29$, but occurred at a threefold higher dose in DBA/2J. The onset and duration of action of maximally active doses of RTI-98 did not differ between strains, $F(5, 24) = 0.41, p = 0.84$.

No interstrain difference in the locomotor stimulant efficacy of RTI-113 was observed. One-way ANOVA performed at each dose revealed interstrain variability in response to only the 0.80 μmol/kg dose, which elevated locomotion to a greater extent in C57BL/6J mice than in DBA/2J mice, $F(1, 4) = 89.04, p < 0.001$. At the maximally active 8.0 μmol/kg dose, an interstrain difference in onset of action was present [strain × dose, $F(5, 24) = 7.11, p < 0.0005$], with RTI-113 producing its peak effect more quickly in C57BL/6J mice than in DBA/2J mice (Fig. 3). Three additional compounds were tested only in DBA/2J mice (Fig. 4). Dose-dependent locomotor stimulation was produced by RTI-32, $F(5, 12) = 11.03, p < 0.0005$, RTI-120, $F(5, 12) = 6.13, p < 0.005$, and RTI-121, $F(4, 10) = 11.22, p < 0.001$.

Results of linear regression of cocaine analog locomotor stimulant ED_{50} values against previously published K_i values for inhibition of monoamines in rat striatum in vitro were greatly affected by inclusion of cocaine itself in the analysis (Fig. 5). In DBA/2J mice, locomotor stimulant potencies were

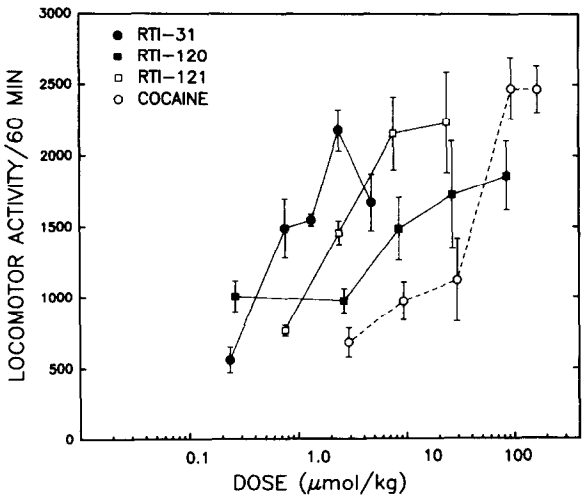


FIG. 4. Locomotor activity log dose-response curves for three analogs tested only in DBA/2J mice, with the curve for cocaine (dashed line) included for reference. Data are presented as mean number of photocell interruptions in 60 min following IP injection ± SEM (n = 3-6 per dose per drug).

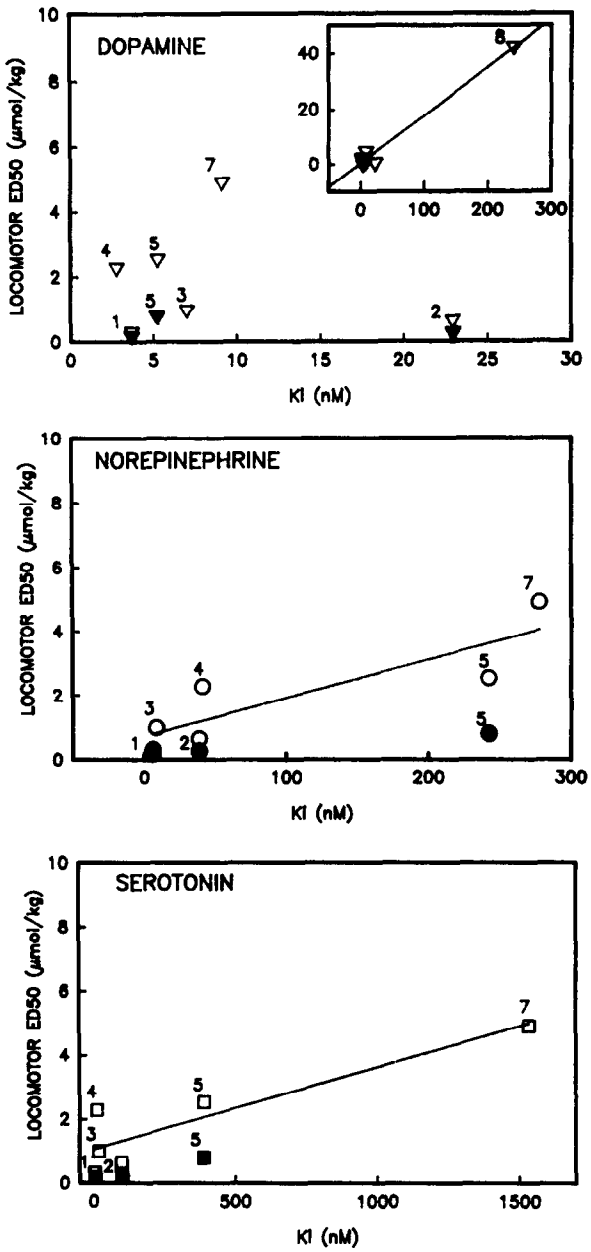


FIG. 5. Linear regression of locomotor stimulant ED_{50} values of cocaine analogs in DBA/2J (open symbols) and C57BL/6J (closed symbols) against previously published K_i values for inhibition of uptake of [^{3}H]dopamine, [^{3}H]norepinephrine, or [^{3}H]serotonin by rat brain homogenates in vitro. All K_i values are from Boja et al. (6). Numbered points correspond to those in Table 1. Because inclusion of cocaine (point 8) defined a regression line with essentially two points (top panel, inset), subsequent regression analyses were performed excluding cocaine from the data set. No uptake data have been published for RTI-98 (compound 6). See text for discussion of correlation coefficients and significance levels.

significantly correlated with dopamine uptake inhibition potencies ($r = 0.990, p < 0.0001$), but not the potencies for inhibition of norepinphrine uptake ($r = 0.277, p = 0.54$) or serotonin uptake ($r = -0.066, p = 0.89$) in rat brain when all analogs and cocaine were included in the analysis. How-

ever, the inclusion of cocaine defined a regression line with essentially two points (Fig. 5). When cocaine was excluded from the analysis, locomotor stimulant potencies in DBA/2J mice were significantly correlated with potencies for inhibition of norepinephrine uptake ($r = 0.754$, $p < 0.05$) and serotonin uptake ($r = 0.766$, $p < 0.05$), but not with potencies for inhibition of dopamine uptake ($r = -0.289$, $p = 0.53$). Results of the corresponding regression analyses including and excluding cocaine from the more restricted data set used in C57BL/6J mice were nearly identical to the DBA/2J results outlined above.

DISCUSSION

The present study extends previous observations of interstrain differences in behavioral responsiveness to cocaine in DBA/2J and C57BL/6J mice (15,17,21,29,35). Because cocaine's inhibition of the neuronal reuptake of dopamine is thought to play a central role in its locomotor stimulant effects (2), strain differences in locomotor response to cocaine may be hypothesized to reflect differences in dopaminergic systems between the two strains. In support of this hypothesis, interstrain differences in dopamine receptor densities have been consistently observed in the DBA/2J and C57BL/6J strains (3,4,15). However, recent studies in our laboratory have demonstrated that the highly selective dopamine uptake inhibitor GBR 12935 does not covary with cocaine in its behavioral effects across these strains (37), suggesting that cocaine's actions at neurochemical systems other than dopamine may contribute to interstrain variance in cocaine responsiveness in the DBA/2J and C57BL/6J strains. The use of multiple structural analogs of cocaine that vary widely in their selectivities at the monoamine reuptake sites (6) allows this question to be addressed in more detail.

All of the cocaine analogs used in the current study are more potent locomotor stimulants than cocaine itself in both strains (Fig. 2, Table 1). Similarly, all of these drugs are more potent ligands at the dopamine transporter, but not necessarily at the norepinephrine and/or serotonin transporters, than cocaine in rat brain in vitro (6). However, regression of locomotor ED_{50} and E_{max} in DBA/2J and C57BL/6J mice against previously published K_i for inhibition of dopamine, norepinephrine, or serotonin uptake by the analogs used in this study does not support a predominant role for dopamine uptake inhibition in the locomotor stimulant effects of cocaine analogs in either strain or in the interstrain differences in response to cocaine (Fig. 5). No correlation of locomotor stimulant potency to dopamine uptake inhibition potency was observed unless cocaine, an extreme outlying data point that was sufficient to redefine the regression line, was included in the regression analysis (Fig. 5). In fact, in the analogs tested in both strains, ED_{50} estimates from both DBA/2J and C57BL/6J mice were significantly correlated to inhibition of norepinephrine uptake. Likewise, ED_{50} estimates from DBA/2J mice were significantly correlated to inhibition of serotonin uptake at $p < 0.05$ whether the regression was performed using only those analogs tested in both strains or using the larger set tested only in DBA/2J mice (Fig. 5). However, these results must be viewed with caution due to the small number of compounds used and the limited number of subjects at each analog dose used to define ED_{50} estimates. Furthermore, the correlation analysis compared behavioral data from mice with in vitro binding data from rat brain, and the uptake inhibition profiles of the ligands used may not necessarily be identical across the two species. To conclude from these results that dopamine plays a minimal role in the locomotor stimulant effects of the selected cocaine analogs used in this study may be unsound, particularly because it has been recently reported that locomotor stimulation by several cocaine analogs in mice correlates well with their dopamine transporter binding in vivo (10).

Despite the lack of significant correlation of published dopamine uptake inhibition potencies with locomotor ED_{50}s, structural substitutions that alter dopamine transporter binding affinities (1,8,22,23,26) and dopamine uptake inhibition potencies (5,6) in some cases similarly alter behavioral potencies, as determined in the present study. Specifically, the higher behavioral potency of 4-chlorophenyl-substituted RTI-31 is consistent with its higher dopamine transporter binding and uptake inhibition potencies relative to the 4-flurophenyl (WIN 35,428) and 4-methylphenyl (RTI-32) analogs (5,6). In contrast, the replacement of the C2 methyl ester in RTI-31 and RTI-32 with a phenylester in RTI-113 and RTI-120, respectively, reduces locomotor stimulant potencies roughly 5–10-fold, whereas these substitutions alter dopamine uptake inhibition potencies very little (6).

An additional consideration in interpreting the regression results is the influence of pharmacokinetic factors on the log dose–response curves of cocaine and its analogs. Because locomotor response is determined over a 60-min period, behavioral potency differences among cocaine and its analogs may reflect differences in absorption and metabolism among the drugs as well as true pharmacodynamic potency differences. Indeed, in the present study, these compounds differed in their onset and duration of action (Fig. 3). Cocaine's peak locomotor stimulant effect occurs in the first 10 min following IP injection and thereafter declines rapidly in both strains. In contrast, RTI-31 did not exert its maximal effect until 30 min postinjection, but continued to stimulate locomotion consistently throughout the 60-min test period. Because much of the metabolic breakdown of cocaine is due to its cleavage by esterases, the prolonged duration of action of RTI-31 and other phenyltropane analogs relative to cocaine may be related to the absence of a C3 ester linkage in these compounds (10). Interestingly, a strain × time interaction present for RTI-113, which exerted its maximal locomotor stimulant effect much later in DBA/2J mice than in C57BL/6J mice (Fig. 3), suggests that interstrain differences in absorption and metabolism of this drug may exist that could contribute to its behavioral profile.

Of the analogs tested in both strains, RTI-113 is the most selective for inhibition of uptake of dopamine over norepinephrine (NE/DA potency ratio = 46) and serotonin (5-HT/DA potency ratio = 74) in vitro (6). Unlike the nonselective analog RTI-31 [NE/DA = 1.59, 5-HT/DA = 1.36 (6)] and cocaine itself [NE/DA = 0.69, 5-HT/DA = 0.46 (6)], RTI-113 has equal locomotor stimulant efficacy in both DBA/2J and C57BL/6J mice. This is not inconsistent with previous studies in our laboratory that demonstrating that GBR 12935, an even more selective dopamine uptake inhibitor, actually has higher locomotor stimulant efficacy in C57BL/6J mice than in DBA/2J mice (37). Together these results suggest that interstrain differences in responsiveness to cocaine may be mediated by neurochemical systems other than dopamine. In regard to this question, our laboratory has conducted quantitative trait loci (QTL) analysis of cocaine-related behavioral responses in BXD recombinant inbred mice derived from the DBA/2J and C57BL/6J progenitor strains (35). These studies did not implicate genetic polymorphisms in the gene loci for

such dopaminergic proteins as the D_1 or D_2 dopamine receptors or the dopamine transporter in interstrain differences in responses to cocaine. Such pharmacogenetic approaches may be valuable in the future in suggesting alternative candidate neurotransmitter sites that may influence behavioral responses to cocaine and other drugs of abuse.

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