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Comparison of Cocaine and GBR 12935: Effects on Locomotor Activity and Stereotypy in Two Inbred Mouse Strains

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TOLLIVER, B. K. AND J. M. CARNEY. *Comparison of cocaine and GBR 12935: Effects on locomotor activity and stereotypy in two inbred mouse strains.* PHARMACOL BIOCHEM BEHAV 48(3) 733–739, 1994.—The current study compares the acute and long-term effects of GBR 12935 and cocaine on locomotor activity and stereotypy in two genetically distinct strains of mice. Although cocaine stimulated locomotor activity maximally in both strains at 32 mg/kg, a single injection of cocaine stimulated locomotion to a greater degree in DBA/2J mice than in C57BL/6J mice. In contrast, GBR 12935 elevated locomotion to a greater extent in C57BL/6J mice at the maximally active dose of 10 mg/kg. The stimulant effects of cocaine diminished to near control levels in DBA/2J mice upon repeated injections, whereas cocaine-induced locomotion remained relatively consistent in C57BL/6J mice. Locomotor stimulation by GBR 12935 remained consistent in both strains with repeated injections. DBA/2J mice became sensitized to cocaine-induced stereotypy with repeated injections. Cocaine induced no stereotypy in C57BL/6J mice on any test day. No stereotypies were induced by GBR 12935 in either strain on any test day. Moreover, no cross-sensitization between cocaine and GBR 12935 was observed. These results demonstrate differences in the behavioral effects of two dopamine uptake inhibitors, and suggest that genetically controlled factors other than dopamine uptake inhibition contribute to the acute and adaptive behavioral responses to cocaine.

Cocaine GBR 12935 Behavior genetics DBA/2J C57BL/6J

COCAINE is a widely abused psychomotor stimulant that is known to interact with a number of macromolecular sites in the brain, including the transporters responsible for the neuronal reuptake of dopamine, norepinephrine, and serotonin (35). Cocaine's inhibition of dopamine uptake is thought to play a central role in its locomotor stimulant and reinforcing properties (4,24,30,34). A number of other ligands, some with higher affinity and/or selectivity for the dopamine transporter, have been identified that inhibit dopamine uptake (19). Many of these drugs, such as the closely related cocaine analogs WIN 35,428 and WIN 35,065-2, share cocaine's locomotor stimulant and reinforcing properties in a manner that parallels their relative binding potencies at the dopamine transporter (7,12,30). Other high-affinity dopamine uptake inhibitors such as GBR 12935 {(1-[2-diphenylmethoxy]-ethyl)-4-(3-phenylpropyl)piperazine}, GBR 12909, mazindol, and nomifensine are less potent as reinforcers and/or as locomotor stimulants in animals (and as euphoriants in humans) than cocaine despite their higher potency in inhibiting dopamine uptake (7,11,20,46). For example, in the rat GBR 12909 is 700 times more potent than cocaine in inhibiting dopamine uptake in vitro (2) but is threefold less potent than cocaine in increasing rates of responding under a fixed-interval schedule of stimulus termination and under a second-order schedule of self-administration in the squirrel monkey (20). It has also been reported that GBR 12909 must occupy a significantly higher proportion of dopamine transporters than cocaine to produce an equivalent increase in locomotor activity (38). These behavioral data, together with many reports of differences in the binding characteristics of these drugs compared with cocaine (discussed below), have prompted the suggestion that as an inhibitor of dopamine uptake cocaine may have unique properties that could contribute to its abuse potential.

Several analogs in the GBR series of drugs have been well characterized as potent and highly selective inhibitors of dopamine uptake (19). Of these compounds, the closely related

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analogs [^{3}H]GBR 12935 and [^{3}H]GBR 12909 have been used extensively to label the dopamine transporter in vitro and in vivo (1,2,5,47). Because cocaine and other dopamine uptake inhibitors such as methylphenidate, benztropine, nomifensine, and mazindol have been reported to displace [^{3}H]GBR 12935 with potencies similar to their potencies in inhibiting dopamine uptake (1), it has been suggested that [^{3}H]GBR 12935 and cocaine competitively inhibit dopamine uptake by binding to the dopamine recognition site on the transporter (33). However, several lines of evidence contradict this hypothesis. First, [^{3}H]cocaine and the cocaine analogs [^{3}H]WIN 35,428 and [^{3}H]RTI-55 have been shown to label two binding sites associated with the dopamine transporter [see (10) for review), whereas [^{3}H]GBR 12935 labels only one site. Second, cocaine, but not mazindol, has been shown to decrease the B_{max} of [^{3}H]GBR 12935 binding without changing K_d in rat striatal membranes, which suggests an allosteric interaction (6). Furthermore, GBR 12909 maximally displaces only 90% of the binding of [^{3}H]WIN 35,428 in monkey striatum whereas cocaine fully displaces [^{3}H]WIN 35,428 (26). In addition, peripherally administered GBR 12909 results in a much smaller increase in striatal extracellular dopamine as measured by in vivo microdialysis than does cocaine, and the increase in extracellular dopamine following the administration of both GBR 12909 and cocaine is not additive (37). In fact, GBR 12909 reportedly antagonizes the ability of cocaine to elevate extracellular dopamine. Because the ability to elevate mesolimbic extracellular dopamine levels may be central to cocaine's abuse potential (14), these properties of GBR 12909 have led some investigators to consider GBR series drugs as potential therapeutically useful cocaine antagonists (37).

One potential strategy for investigating whether cocaine is a unique inhibitor of dopamine uptake focuses on the differences in behavioral profiles between cocaine and other dopamine uptake inhibitors. Behavioral genetic methods may be useful in identifying mechanistic differences in response to acute and long-term administration of these drugs. Several previous studies have reported significant variation in responsiveness to cocaine across inbred strains of rats and mice (9,15,16,39,43). The use of inbred strains of animals offers the advantage of genotypically distinct populations consisting of genetically identical individuals that are homozygous at all gene loci (13). Two drugs working through the same mechanism at identical sites may be expected to covary across genetically defined strains that differ in their responsiveness to the drugs. This approach has successfully demonstrated differences in the sites of action for cocaine and amphetamine locomotor stimulant effects using inbred rat strains (17). Recent studies from our laboratory have demonstrated robust differences in the behavioral responsiveness to both acute and repeated cocaine in the DBA/2J and C57BL/6J inbred strains of mice (44,45). The present study is designed to determine whether GBR 12935 covaries with cocaine in its acute and long-term effects on locomotor activity and stereotypy across the two strains.

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 for at least 1 week on a 12 L : 12 D cycle with food and water available ad lib prior to testing. Mice tested for locomotor activity were housed five per cage throughout the testing period. Mice tested for stereotypy were housed three per cage.

Cocaine hydrochloride (Sigma, St. Louis, MO) and GBR 12935 (Research Biochemicals Incorporated, Natick, MA) were dissolved in hot isotonic saline and injected IP in a volume of 10 μl per gram of body weight.

Locomotor Activity Testing

Spontaneous 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, cocaine, or GBR 12935. Two locomotor activity experiments were conducted as follows. In Experiment 1, naive mice never exposed to either drug or to the test chamber received an initial injection of saline, cocaine (1.0, 3.2, 10.0, 32.0 56.0, 100.0 mg/kg; n = 5 each strain per dose), or GBR 12935 (1.0, 3.2, 10.0, 32.0 mg/kg; n = 5 each strain per dose) and tested for locomotor activity. On subsequent days for 1 week, mice received repeated injectons of the drug and dose administered previously and

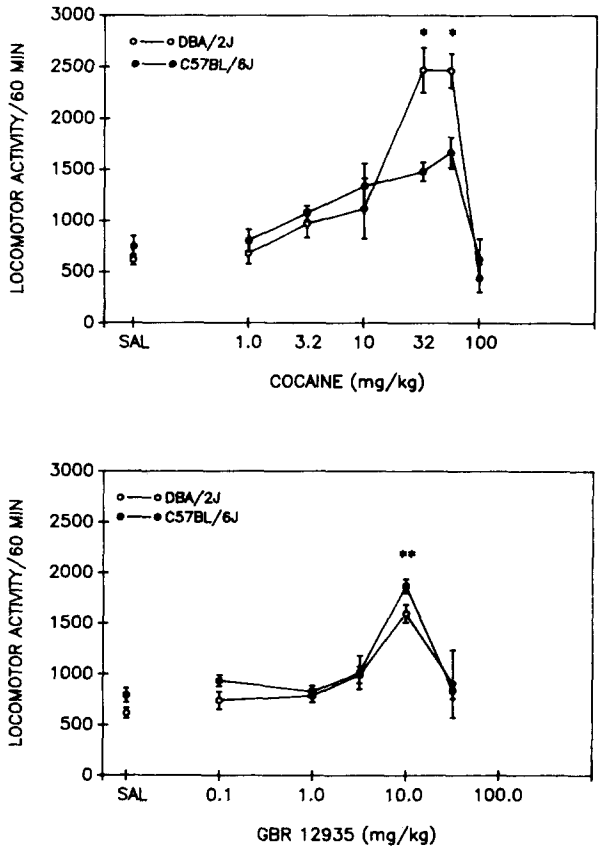

FIG. 1. Effects of six doses of acute cocaine (top panel) and five doses of acute GBR 12935 (bottom panel) on locomotor activity in DBA/2J and C57BL/6J mice. Data are presented as mean ± SEM, n = 5 each strain per dose. *Significant interstrain differences at 32 mg/kg, $F(1, 7) = 20.86$, $p < 0.005$, and 56 mg/kg, $F(1, 8) = 12.72$, $p < 0.01$. **Significant interstrain difference at 10 mg/kg GBR 12935, $F(1, 8) = 5.84$, $p < 0.05$.

were tested for locomotor activity following each injection. In Experiment 2, mice received repeated injections of saline, 10 mg/kg GBR 12935, or 32 mg/kg cocaine. All injections were paired with test chamber exposures. On the final day, saline-treated mice received a challenge dose of 10 mg/kg GBR 12935 or 32 mg/kg cocaine (n = 5 each strain per drug challenge) and were tested for locomotor activity. Accordingly, cocaine-treated mice were challenged with saline or 10 mg/kg GBR 12935, and GBR-treated mice were challenged with saline or 32 mg/kg cocaine. In both experiments, mice were returned to home cages after each test session.

Stereotypy Scoring

Mice received seven daily injections of saline, 32 mg/kg cocaine, or 10 mg/kg GBR-12935 (n = 6 each strain per drug). These doses were chosen for long-term stereotypy experiments because initial observations indicated that 32 mg/kg cocaine and 10 mg/kg GBR 12935 induced running but were subthreshold doses for inducing stereotypy with a single exposure. Stereotypy scoring was conducted following the first, fourth, and seventh daily injections in lighted circular locomotor chambers. On the eighth day, each group was divided into two groups of three mice. Saline-pretreated mice were challenged with an injection of 32 mg/kg cocaine (n = 3 each strain) or 10 mg/kg GBR-12935 (n = 3 each strain). Cocaine-pretreated mice received a challenge injection of saline (n = 3 each strain) or 10 mg/kg GBR-12935 (n = 3 each strain). Correspondingly, GBR-pretreated mice received a challenge injection of saline or 32 mg/kg cocaine (n = 3 each strain per drug).

The scoring procedure used is a modification of that described previously (28). Each animal was rated by an observer for 30-s periods every 5 min beginning 10 min before and continuing until 50 min after an injection of saline, cocaine, or GBR-12935. Initial scoring was conducted by an observer not blind to the treatment conditions; subsequent scoring by a second observer blind to the treatment conditions was highly consistent with initial scores. The following rating scale was used: 0—normal quiet behavior, no locomotion, with or without grooming; 1—normal exploratory behavior, slow ambulation, sniffing; 2—rapid locomotion, running, no grooming; 3—stereotyped behavior, repetitive rearing and locomotion within a more restricted area of cage; 4—intense stereotypy, disrupted locomotion with repetitive gnawing and head bobbing in a restricted area of cage. Mice were exposed to the test chambers only on test days and were returned to the home cages after injections on all other days.

Data Analysis

Locomotor activity and stereotypy data were analyzed using two-way and three-way analyses of variance (ANOVAs) for between-subject and mixed-factorial experiments as appropriate. Student-Newman-Keuls analysis was used for all post hoc multiple comparisons and interpretation of interactions.

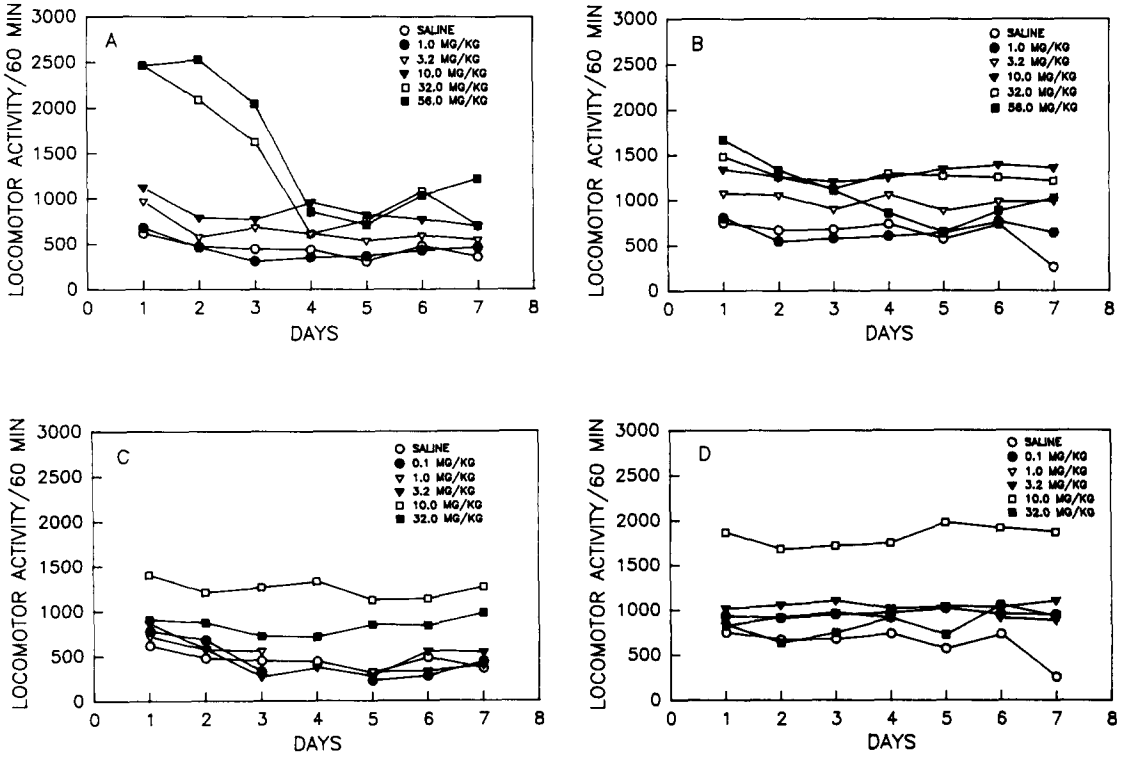

FIG. 2. Top panels: locomotor effects of seven daily cocaine injections in DBA/2J (A) and C57BL/6J (B) mice. Significant effect of day, $F(6, 42) = 14.98$, $p < 0.0001$, and drug × day interaction, $F(6, 42) = 9.83$, $p < 0.0001$, present in DBA/2J but not C57BL/6J mice. Bottom panels: locomotor effects of seven daily injections of GBR 12935 in DBA/2J (C) and C57BL/6J (D) mice. C57BL/6J mice are stimulated to a greater extent by 10 mg/kg GBR 12935 throughout the 7-day test period, $F(1, 49) = 64.44$, $p < 0.0001$. No effects or interactions of treatment day were present in either strain.

TABLE 1

CROSS-TOLERANCE/CROSS-SENSITIZATION TO LOCOMOTOR STIMULATION BY COCAINE AND GBR 12935 WITH REPEATED INJECTIONS

		Locomotor Activity/60 min	
Pretreatment	Challenge	DBA/2J	C57BL/6J
Saline × 6	Cocaine	1628.0 ± 339.7	1737.5 ± 267.2
Cocaine × 6	Cocaine	697.5 ± 55.0*	1206.0 ± 77.4*
GBR 12935 × 7	Cocaine	1994.4 ± 372.4	2016.2 ± 115.5
Saline × 6	GBR 12935	997.0 ± 106.6	1394.0 ± 123.1
Cocaine × 6	GBR 12935	1408.2 ± 175.3	1488.8 ± 88.6
GBR 12935 × 6	GBR 12935	1265.0 ± 114.3	1868.2 ± 101.4†

Effects of repeated injections of cocaine or GBR 12935 on locomotor stimulation produced by a challenge dose of the drugs. Doses used for all pretreatment injections and challenges were 32 mg/kg cocaine and 10 mg/kg GBR 12935. Values represent mean activity counts/60 min ± SEM; $n = 5$ each strain per treatment group.

*Significant at $p < 0.005$.

†Significant at $p < 0.05$.

RESULTS

Locomotor Activity

Acute administration of cocaine elicited a dose-dependent increase in locomotion in both strains [overall $F(13, 51) = 23.65$, $p < 0.0001$]. Both DBA/2J and C57BL/6J mice were stimulated maximally by the 32-mg/kg and 56-mg/kg doses of cocaine, but a significant strain × dose interaction, $F(6, 51) = 8.55$, $p < 0.0001$, was found. One-way ANOVA performed at each dose revealed significantly greater locomotor stimulation of DBA/2J mice relative to C57BL/6J mice at the 32-mg/kg, $F(1, 7) = 20.86$, $p < 0.005$, and 56-mg/kg, $F(1, 8) = 12.72$, $p < 0.01$, doses. In contrast, acute GBR 12935 stimulated C57BL/6J mice to a greater extent than DBA/2J mice (Fig. 1). Although GBR 12935 elicited a dose-dependent increase in locomotion in both strains [overall $F(11, 47) = 8.20$, $p < 0.0001$], post hoc analysis indicated that locomotor stimulation was greater in C57BL/6J mice at the maximally active dose of 10 mg/kg ($p < 0.05$).

As was true of the acute response to the two drugs, the adaptive responses to repeated cocaine and GBR 12935 did not covary across strains (Fig. 2). Whereas the locomotor stimulation produced by 32 mg/kg cocaine remained relatively consistent in C57BL/6J mice with repeated daily injections, locomotor activity in DBA/2J mice decreased to near saline levels by the fourth day of repeated injections [significant strain × day interaction at 32 mg/kg: $F(6, 42) = 10.41$, $p < 0.0001$]. Two-way ANOVA of each strain indicated a significant effect of day, $F(6, 42) = 14.98$, $p < 0.0001$, and a drug × day interaction, $F(6, 42) = 9.83$, $p < 0.0001$, in DBA/2J mice. No such effects or interactions were present in C57BL/6J mice. In contrast, the maximally active dose of 10 mg/kg GBR 12935 stimulated locomotion consistently in both strains throughout the 7-day testing period, $F(27, 98) = 16.38$, $p < 0.0001$. At 10 mg/kg, C57BL/6J mice were stimulated to a significantly greater extent than DBA/2J mice across the 7-day period, $F(1, 49) = 64.44$, $p < 0.0001$. There were no effects or interactions of treatment day in either strain. Finally, whereas repeated daily cocaine injections diminish the ability of 32 mg/kg cocaine to stimulate locomotor activity in DBA/2J mice, repeated GBR 12935 injections do not significantly alter the locomotor response to 32 mg/kg cocaine in either strain (Table 1).

Stereotypy

Repeated injections of 32 mg/kg cocaine resulted in the emergence of stereotyped behavior in DBA/2J but not C57BL/6J mice (Fig. 3). Three-way mixed factorial ANOVA revealed significant strain differences across the 7-day testing period, $F(1, 90) = 27.47$, $p < 0.0001$, and a strain × drug × day interaction, $F(4, 90) = 4.23$, $p < 0.005$. Secondary analysis by two-way ANOVA for each drug indicated significantly higher cocaine-induced stereotypy in DBA/2J mice than in C57BL/6J mice, $F(1, 30) = 29.40$, $p < 0.0001$, and a strain × day interaction, $F(2, 30) = 5.46$, $p < 0.001$. Six daily cocaine injections significantly sensitized DBA/2J mice to cocaine-induced stereotypy, $F(1, 10) = 14.28$, $p < 0.005$. No such sensitization was observed in C57BL/6J mice. In contrast to cocaine, repeated injections of 10 mg/kg GBR 12935 do not induce stereotypy in either strain on any day of the testing period ($p = 0.736$).

No cross-sensitization between cocaine and GBR 12935 developed in either strain with repeated injections (Table 2). No stereotypy was induced by an eighth day challenge of 10 mg/kg GBR 12935 in mice pretreated with seven daily injections of either 32 mg/kg cocaine or saline ($p < 0.759$). Similarly, seven daily injections of 10 mg/kg GBR 12935 did not increase the ability of a 32 mg/kg eighth day cocaine challenge to induce stereotypy relative to repeated saline ($p < 0.437$).

DISCUSSION

The present study demonstrates significant differences in the acute and long-term behavioral effects of two dopamine uptake inhibitors in genetically distinct strains of mice. Upon an initial exposure, both cocaine and GBR 12935 produce increases in locomotion at moderate doses and disrupted locomotion at high doses, presumably due to the induction of stereotypy (22). However, cocaine is a much more efficacious locomotor stimulant in DBA/2J mice than in C57BL/6J mice, whereas GBR 12935 exerts greater stimulant effects in C57BL/

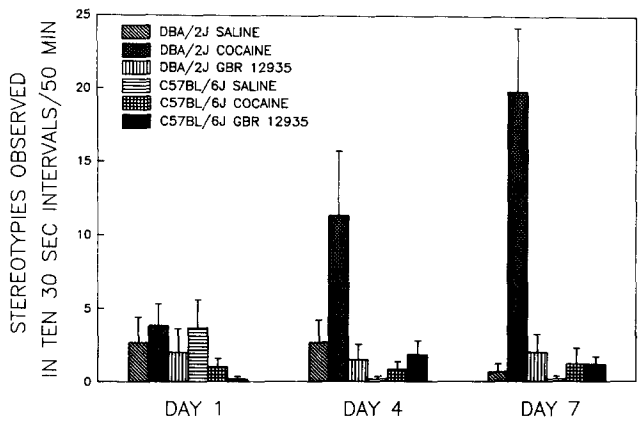

FIG. 3. Frequency of stereotyped behaviors in DBA/2J and C57BL/6J mice following repeated injections of saline, 32 mg/kg cocaine, or 10 mg/kg GBR 12935. Data are presented as mean ± SEM, $n = 6$ each strain per treatment. Significantly greater cocaine-induced stereotypy in DBA/2J mice than in C57BL/6J mice, $F(1, 30) = 29.40$, $p < 0.0001$, and significant sensitization to stereotypy in DBA/2J, $F(1, 10) = 14.28$, $p < 0.005$, but not C57BL/6J mice. No GBR 12935-induced stereotypy was observed in either strain.

6J mice. Several possible explanations may be offered to account for these differences. First, the two drugs differ greatly in their selectivity of binding at the dopamine transporter relative to other sites. GBR 12935 has been shown to bind with low nanamolar affinity only to the dopamine transporter (1) and cytochrome P450IID1, the "piperazine acceptor" site (27). In contrast, cocaine binds with equal or higher affinity to the serotonin and norepinephrine transporters than to the dopamine transporter (34), and has also been shown to bind to voltage-gated sodium channels (29), sigma sites (40), and muscarinic cholinergic receptors (41). Although cocaine's actions at one or more of these sites may augment or diminish its locomotor stimulant effect, the actions of cocaine on noradrenergic and serotonergic systems may be particularly important. Serotonergic 5-HT_3 receptors are known to control mesolimbic dopamine release (21), and 5-HT_3 antagonists have been shown to attenuate cocaine-induced locomotor stimulation (31), as has the α_1-adrenoceptor antagonist prazosin (42). Furthermore, synaptosomes from DBA mice have been shown to be much more sensitive to inhibition of [^{3}H]5-HT accumulation, but not [^{3}H]dopamine accumulation, by cocaine than those from C57 mice (9). Such interstrain differences in sites other than the dopamine transporter may therefore contribute to the differences in responses to the two drugs and their failure to covary across strains.

Pharmacokinetic factors may also play a role in the interstrain differences in response to cocaine and GBR 12935. Due to the structural unrelatedness to cocaine, as well as the greater lipophilicity and longer half-life of GBR 12935 (3), the pharmacokinetic properties of the two drugs may not necessarily be expected to covary across strains. Whereas brain cocaine levels 15 min after a single injection or after the last of seven daily injections do not differ between DBA/2J and C57BL/6J mice (45), we have not determined brain GBR 12935 levels after acute or repeated administration. It is conceivable that a strain × drug interaction could exist for differences in GBR 12935 absorption into, or distribution within, the brain across the two strains. Therefore, the possibility that a 10 mg/kg dose of GBR 12935 may result in a higher brain concentration in C57BL/6J mice that may correlate with its higher locomotor stimulation cannot be ruled out. However, if DBA/2J mice metabolize GBR 12935 more rapidly than do C57BL/6J mice, the locomotor activation produced by the drug may be expected to diminish more rapidly in DBA/2J mice over the 60-min test procedure. Instead, GBR-induced locomotor stimulation of the two strains diminished in parallel across each of the six 10-min test intervals (data not shown).

Although less likely, another possible explanation for the

TABLE 2

CROSS-TOLERANCE/CROSS-SENSITIZATION TO INDUCTION OF STEREOTYPY BY COCAINE AND GBR 12935 WITH REPEATED INJECTIONS

		Stereotypies Observed	
Pretreatment	Challenge	DBA/2J	C57BL/6J
Saline × 6	Saline	0.67 ± 0.54	0.17 ± 0.18
Cocaine × 7	Saline	0.00 ± 0.00	0.00 ± 0.00
GBR 12935 × 7	Saline		
Saline × 7	Cocaine	5.67 ± 4.02	1.00 ± 1.22
Cocaine × 6	Cocaine	19.83 ± 4.39*	1.20 ± 1.08
GBR 12935 × 7	Cocaine	1.33 ± 1.08	3.33 ± 2.94
Saline × 7	GBR 12935	2.33 ± 2.86	0.66 ± 0.82
Cocaine × 7	GBR 12935	1.00 ± 0.71	0.66 ± 0.41
GBR 12935 × 6	GBR 12935	2.00 ± 1.23	1.17 ± 0.52

Effects of repeated cocaine or GBR 12935 injections on the induction of stereotyped behaviors induced by challenge doses of the two drugs. Doses used for all pretreatment and challenge injections were 32 mg/kg cocaine and 10 mg/kg GBR 12935. Values represent mean number of stereotypies observed in 50 min following the challenge injection ± SEM; $n = 3$ each strain per challenge.

*Significant at $p < 0.001$.

present results is that the dopamine transporter itself differs between the two strains and that this alteration affects the binding of cocaine and GBR 12935 differently. Whether the two drugs are competitive inhibitors at the same site (presumably the dopamine recognition site) on the transporter protein remains controversial. Although some investigators maintain that both GBR 12935 and cocaine and its analogs bind to a single, mutually exclusive site (32,33), many groups have reported that [^{3}H]cocaine and its analogs [^{3}H]WIN 35,428, [^{3}H]WIN 35,065-2, and [^{3}H]RTI-55 label two sites associated with the dopamine transporter (10,25,26). That both sites are associated with the dopamine transporter is confirmed by the demonstration of two-site binding of [^{3}H]WIN 35,428 in COS cells transfected with a single dopamine transporter cDNA (8). Reportedly GBR 12909 can maximally displace only 90% of the binding of [^{3}H]WIN 35,428 in monkey striatum, whereas cocaine is fully effective (26). It has been shown that GBR 12909 is less effective than cocaine in elevating extracellular dopamine (37) and must occupy a greater number of dopamine transporters than cocaine to produce equivalent locomotor stimulation (38). Whether these properties of GBR are related to its inability to fully displace cocaine analogs is unknown. It is conceivable that a subset of cocaine binding sites on (or affinity states of) the dopamine transporter exists that is not bound by GBR series drugs. That interstrain differences in such a site could exist that contribute to differences in behavioral responses to the two drugs remains an intriguing possibility.

Significant differences also exist in the adaptive responses to repeated administration of cocaine and GBR 12935 across the two strains. Although cocaine-induced locomotor stimulation in DBA/2J mice is diminished in parallel with the emergence of sensitization to stereotypy upon repeated daily injections, no sensitization or tolerance to repeated GBR 12935 is observed in either strain. This is in contrast to previous reports of sensitization to the locomotor stimulant effect of the closely related analog GBR 12909 with repeated injections (18,23). Because only a single dose of GBR 12935 was used in the stereotypy experiments, it is possible that sensitization may have developed with repeated administration of other doses. However, because stereotypy is accompanied by disrupted locomotion, the emergence of sensitization to stereotypy should be paralleled by decreased locomotor stimulation with repeated injections, as is the case for cocaine (44). Unlike those for cocaine, locomotor experiments employing repeated injections of a range of doses of GBR 12935 reveal no such decreases in either strain (Fig. 2).

Further evidence that the long-term responses to repeated cocaine and GBR 12935 are regulated differently is the lack of cross-tolerance or cross-sensitization between the two drugs. Whereas the ability of 32 mg/kg cocaine to stimulate locomotion is greatly reduced in cocaine-pretreated mice relative to saline-pretreated mice, a challenge dose of 10 mg/kg GBR 12935 is more effective in cocaine-treated DBA/2J mice than saline controls (Table 1). Additionally, the locomotor stimulant effect of 32 mg/kg cocaine is, if anything, somewhat enhanced by repeated injections of 10 mg/kg GBR 12935. Furthermore, no cross-sensitization to stereotypy between cocaine and GBR 12935 was observed in either strain. Whereas cocaine-pretreated DBA/2J mice exhibited stereotypy to a previously subthreshold dose of cocaine, the response of cocaine-sensitized mice to 10 mg/kg GBR 12935 did not differ from saline-treated mice (Table 2). Moreover, 32 mg/kg cocaine did not induce stereotypy in mice of either strain pretreated with seven daily injections of GBR 12935. It should be noted, however, that only a single pretreatment dose and a single challenge dose for each drug were used in these experiments. Because one previous study has demonstrated that the occurrence of cross-sensitization is dependent on the challenge dose used (3), full dose–response approaches to cross-sensitization/cross-tolerance studies are clearly warranted.

The current results demonstrate significant differences in the acute and adaptive behavioral profiles of two dopamine uptake inhibitors in homogeneous, genetically distinct mouse strains. These data are particularly interesting in the context of the previous suggestions that dopamine uptake inhibitors may be grouped into two classes based upon their tendency to be abused by humans, and that compounds such as the GBR series drugs may offer therapeutic potential as cocaine antagonists or substitutes (36,37). In addition, these results imply that properties of cocaine other than its inhibition of dopamine uptake may contribute to the development of sensitization and tolerance, and suggest that genetically defined animals may be useful in elucidating the mechanisms underlying these phenomena.

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