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Antidepressant Drugs Appear to Enhance Cocaine-Induced Toxicity

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It has been shown that cocaine-induced convulsions and lethality appear to be mediated by serotonin and dopamine neurotransmission, respectively. However, many antidepressants considered for treatment of cocaine addiction target these monoamine systems and may thus amplify these toxic effects during relapse. In this study, the authors assessed whether pretreatment with antidepressants influences cocaine-induced toxicity in mice as well as the potency of these medications at cocaine-binding sites previously shown to be associated with cocaine toxicity. Overall, selective serotonin reuptake inhibitors (SSRIs) facilitated cocaine-induced convulsions but not lethality. Dopamine uptake inhibition facilitated cocaine-induced lethality, but not convulsion. The SSRI sertraline enhanced neither convulsions nor lethality and may be unique due to its high affinity for sigma reeptors. These results have important implications for safe and effective addiction treatments.

Antidepressant treatment approaches have been extensively studied as potential treatments for cocaine addiction. Although antidepressants appear to alleviate some symptoms of depression associated with cocaine withdrawal, efficacy studies have produced mixed results, and there is no general consensus regarding an effective treatment for cocaine addiction (see Kosten, 1989; Lacombe, Stanislav, & Marken, 1991; Meyer, 1992; Ziedonis & Kosten, 1991). The clinical reality is that most patients continue to abuse cocaine during maintenance treatment, and most addicts relapse to subsequent drug use following release from drug treatment programs (see Mendelson & Mello, 1996).

The issue of safety regarding the clinical application of antidepressant medications for patients who have histories of cocaine use is of clinical interest in light of the high relapse rate among cocaine addicts being treated with antidepressants. Convulsions and lethality have been reported in a clinical setting following ingestion of high doses of either antidepressants or cocaine (Dhuna, Pascual-Leone, Langendorf, & Anderson, 1991; Myers & Earnest, 1984; Peck, Stern, & Watkinson, 1983). To our knowledge, no one has examined whether an addict being treated with antidepressants is more susceptible to the toxic effects of cocaine following a relapse. However, it seems possible that the effects of cocaine may be enhanced by antidepressants because it is well established that both of these drugs inhibit reuptake of monoamines, such as dopamine, norepinephrine, and serotonin (5-HT).

Animal research from our laboratory suggests a potentially toxic interaction between cocaine and many common antidepressants. These results indicate that the toxic effects of cocaine are associated with dopamine and 5-HT neurotransmission. For example, using multiple receptor site analyses, we demonstrated that lethality produced by cocaine and related compounds is significantly associated with binding of these compounds to the dopamine transporter and that convulsions produced by these compounds are associated with binding to the 5-HT transporter (Ritz & George, 1993). Subsequent pharmacological studies supported the role of these neurotransmitters in mediating cocaine-induced toxicity because cocaine-induced lethality is facilitated by bupropion (Ritz & George, 1997b) and attenuated by the dopamine D_1 receptor antagonist SCH-23390 (Derlet, Albertson, & Rice, 1990; Ritz & George, 1997b). In addition, cocaine-induced convulsions are enhanced by the selective serotonin reuptake inhibitor (SSRI) fluoxetine (Ritz & George, 1997a) and attenuated by the 5-HT_2 receptor antagonists cinanserin and ketanserin (Ritz & George, 1997a; Schechter & Meehan, 1995). Collectively, these studies demonstrated that 5-HT and dopamine neurotransmission play an important role in mediating cocaine-induced convulsions and lethality, respectively.

We designed the present study to examine the effects of antidepressant administration on cocaine-induced convulsions and lethality in an animal model and thereby address potentially harmful interactions between antidepressants and cocaine toxicity. This study extends previous research with fluoxetine by assessing cocaine-induced toxicity following administration of the additional SSRI compounds citalopram, paroxetine, and sertraline, as well as the tricyclics imipramine and desipramine. In this study, we also used receptor binding methods to assess the potency and selectivity of antidepressant medications to inhibit binding

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to the dopamine and 5-HT transporter, as well as binding to sigma and muscarinic (M_1 and M_2) receptors. The affinity of the antidepressants for the dopamine and 5-HT transporter has important implications because these compounds are predicted to alter the toxic effects of cocaine via these neural sites. We also hypothesized that the affinity of the antidepressants for M_1 and M_2 and sigma sites would provide information about the influence of these sites on the toxic effects of cocaine. This hypothesis is based on previous research demonstrating that sigma and M_1 and M_2 receptors appear to attenuate or protect against cocaine-induced toxicity (Ritz & George, 1993, 1997a, 1997b).

The animals in our model received acute administration of cocaine and antidepressants. This allowed us to address the potential interaction of these compounds without interference from neurochemical changes that occur following chronic administration of these drugs. However, patients in drug treatment programs vary in their exposure to cocaine and antidepressants and in the amount of time that has elapsed since their last exposure to either compound. Therefore, it is difficult to develop an animal model that directly mimics a clinical population. Despite this, our results may have clinical relevance because they address whether a harmful neurochemical interaction exists between antidepressants and cocaine-induced toxicity.

Method

Animals

Experimentally naive male C57BL/6J mice (60–100 days old; n = at least 8 per group) obtained from the Jackson Laboratories (Bar Harbor, ME) were used. Animals were housed in groups of same-sex littermates with ad-lib access to laboratory chow (Teklad Rodent Diet 8604; Harlan, Madison, WI) and tap water. Mice were maintained in a temperature-controlled room (26 °C) with a 12-hr light–dark cycle (lights on at 0700). All studies were conducted in accordance with the *Guide for Care and Use of Laboratory Animals* (National Research Council, 1996) provided by the National Institutes of Health and approved by the local Institutional Animal Care and Use Committee.

Drugs

The following compounds were used: (-) cocaine HCl (National Institute on Drug Abuse, Washington, DC), bupropion HCl (Burroughs Wellcome, Research Triangle Park, NC), fluoxetine HCl (Eli Lilly, Indianapolis, IN), citalopram (Lundbeck, Copenhagen, Denmark), imipramine (Research Biomedicals, Natick, MA), paroxetine (Beecham Pharmaceuticals, Brentford, England), and sertraline (Pfizer, Groton, CT). Several antidepressants were used to compare the effects of these compounds on cocaine-induced toxicity with their varying affinities at the different cocaine-binding sites. All compounds were injected intraperitoneally with drug doses expressed as mg/kg base administered in a volume of 10 ml/kg. Each drug was solubilized in a normal saline or saline plus 1% polysorbate-80 vehicle.

Effects of Antidepressant Administration on Cocaine-Induced Convulsions and Lethality

The effects of antidepressant administration on convulsions and lethality produced by cocaine were determined. Animals were pretreated with vehicle or fluoxetine (3.00, 5.60, or 10.00 mg/kg), paroxetine (0.01 mg/kg), imipramine (10.00 mg/kg), citalopram (10.00 mg/kg), sertraline (0.30 mg/kg), bupropion (10.00 or 56.00 mg/kg), or desipramine (30.00 mg/kg) and were observed for 15 min before cocaine administration. Animals pretreated with the saline vehicle served as controls. The doses of antidepressants were based on initial pilot experiments in which we examined the dose-dependent effects of these antidepressants on convulsions and lethality produced by one dose of cocaine. In addition, the doses were based on the relative affinity of these compounds for the 5-HT transporter because previous research demonstrated that cocaine binding to these sites mediates cocaine-induced convulsions (Ritz & George, 1993). The antidepressant doses were not designed to directly reflect clinically relevant doses because the affinity of these compounds for 5-HT transporters does not appear to be directly related to clinically effective doses. Changes in the animals' behavior before cocaine administration were recorded as observations but were not quantified. This allowed for the observation of any changes in behavior produced by the antidepressant alone. Preliminary data indicated that 15 min is sufficient to allow for maximum or near-maximum drug absorption and activity for all compounds tested.

At 15 min after the first injection, mice were injected contralaterally with various doses of cocaine (42, 56, 65, 87, 100, or 133 mg/kg) and were then immediately placed into 30 × 30 cm^2 Plexiglas chambers. This dose range is based on research in our laboratory in which cocaine-induced toxicity in this strain of mice was examined (see O'Dell, Kreifeldt, George, & Ritz, 1999). In addition, other researchers used this dose range when studying cocaine-induced toxicity in mice (see Marley, Shimosato, Frieman, & Goldberg, 1993). Animals were scored for 15 min by a blind observer looking for the occurrence and latency of any of the following behavioral indicators of overt convulsant activity typically produced by cocaine: wild running, clonus, tonus, and clonic–tonic convulsion (Ritchie & Greene, 1985). The occurrence and latency of death was also recorded. In addition, although behavioral measures such as locomotor activity were not directly measured and quantified for these experiments, observations were made of the animals' posture and behavioral patterns during the 15 min period following the initial injection and following cocaine administration. Animals were observed for 15 min because initial studies indicated that the percentage of convulsions occurring within 15 or 60 min postinjection does not differ, and convulsions typically occurs within 2 to 4 min postinjection. CD_{50} (mg/kg) values for convulsions were determined by linear regression analyses of the resultant dose–response curves.

Determination of Antidepressant Drug Potencies at Specific Cocaine-Binding Sites

For receptor binding studies, drug-naive mice were killed by decapitation, and the brains were removed and immersed in cold saline. The brains were then dissected and stored at −70 °C until they were assayed. The day of the assay, tissues were homogenized in 20 volumes of assay buffer and centrifuged at 30,000 g for 10 min. The resulting pellet was washed, recentrifuged, and resuspended in buffer to yield the desired tissue concentration for addition to the assay.

Competition experiments were designed to measure drug inhibition of ligand binding at cocaine-binding sites that have been previously demonstrated to mediate cocaine-induced toxicity (i.e., dopamine and 5-HT transporters, as well as sigma and M_1 and M_2 receptors). Although cocaine has well-established effects on norepinephrine uptake, this site was not included in our binding analysis because much research has demonstrated that norepinephrine neurotransmission does not appear to mediate cocaine-induced toxicity (Jackson, Ball, & Nutt, 1990; Ritz & George 1993; 1997a). Although radiolabeled cocaine has been used as the binding ligand in several studies, we have used other ligands that bind with higher affinities and specificities to particular receptors and provide better specific-to-nonspecific binding ratios. ^{3}H-mazindol was used to identify dopamine uptake sites in striatal tissue (Javitch, Blaustein, & Snyder, 1984). Nonspecific binding was estimated for dopamine uptake sites in the presence of 10.0 μM nomifensine. Homogenized tissue (1.5 mg original weight per tube) was incubated for 1 hr at 0 °C in buffer (50.0 mM Tris, 120.0 mM NaCl, 5.0 mM KCl; pH = 7.8) containing a final ligand concentration of 4.0 nM in a final assay volume of 0.5 ml. ^{3}H-paroxetine was used to identify 5-HT uptake sites in the medulla (Habert, Graham, Tahraoui, Claustre, & Langer, 1985). Nonspecific binding was estimated for 5-HT uptake sites in the presence of 1 μM citalopram. Homogenized tissue (1.5 mg original weight per tube) was incubated at room temperature in 4.0 ml buffer (50.0 mM Tris, 120.0 mM NaCl, 5.0 mM KCl; pH = 7.8) for 90 min with a final ligand concentration of 0.2 nM. Sigma sites were labeled in buffer (50.0 mM Tris, 10.0 mM $MgSO_4$; pH = 7.8) containing a final concentration of 1.0 nM ^{3}H-haloperidol in the presence of 25.0 nM spiperone. Nonspecific binding was estimated in the presence of 100.0 μM (±) SKF-10047 (n-allylnormetazocine) in a final assay volume of 4.0 ml. Incubation at 25 °C for 90 min began with the addition of 8.0 mg homogenized cerebellum (original weight) to each assay tube. M_1 and M_2 receptors were labeled by 2.0 nM ^{3}H-pirenzepine and 1.0 nM ^{3}H-quinuclidinyl benzilate, respectively. Nonspecific binding was measured in the presence of 1.0 μM atropine in each case. For M_1 receptor sites, incubation in 10.0 mM sodium-phosphate buffer (pH = 7.8) at 25 °C for 60 min began with the addition of 1.0 mg homogenized hippocampus (original weight) to each assay tube. For M_2 receptor sites, homogenized medulla (1.0 mg original weight per tube) was incubated at 37 °C in 5.0 ml buffer (50.0 mM sodium-phosphate buffer; pH = 7.8) for 30 min.

At the end of the incubation period, all assay mixtures were filtered through Whatman GF/C filters (Brandel, Gaithersburg, MD), presoaked with 0.05% polyethylimine and washed with buffer. Filters were placed into plastic vials and scintillation fluid was added. Vials were shaken for 1 hr, and radioactivity was measured by liquid scintillation spectometry.

Statistical Analyses

All analyses were performed using SYSTAT for Macintosh (Wilkinson, 1987). Dose–response comparisons, including tests for parallelism, were performed using multiple regression analyses for binary dependent measures (PROBIT; Steinberg, 1988; Wilkinson, 1987). LD_{50} and CD_{50} (mg/kg) values were determined by linear regression analyses of the resultant dose–response curves for each compound. All values were computed from the linear data (i.e., nonlog values), and all data were plotted on linear scales. However, for graphic illustration, the scales of measurement have been normalized by transforming all values to their logarithms. For binding data, K_i values were determined from analyses of competition curves using the nonlinear least squares, curve-fitting program, LIGAND (Munson & Rodbard, 1980). The binding results served to compare the effects of these compounds of cocaine-induced toxicity and the affinity of the antidepressants at relevant cocaine-binding sites.

Results

Effects of Antidepressant Administration on Cocaine-Induced Convulsions and Lethality

Figure 1 illustrates the effects of fluoxetine administration on the dose-dependent effects of cocaine on convulsions (top panel) and lethality (bottom panel). Administration of fluoxetine facilitated cocaine-induced convulsions and lethality. Cocaine produced a dose-dependent increase in convulsions ($p < .0001$) that was significantly facilitated by fluoxetine pretreatment ($p < .02$; previously published in Ritz & George, 1997a). Cocaine also produced a dose-dependent increase in lethality ($p < .001$) that was facilitated by fluoxetine pretreatment ($p < .001$). However, this effect of fluoxetine on cocaine-induced lethality was likely related to the severity of cocaine-induced convulsions because fluoxetine facilitated cocaine-induced lethality only at high doses (5.6 and 10.0 mg/kg; $p < .005$), which also produced a

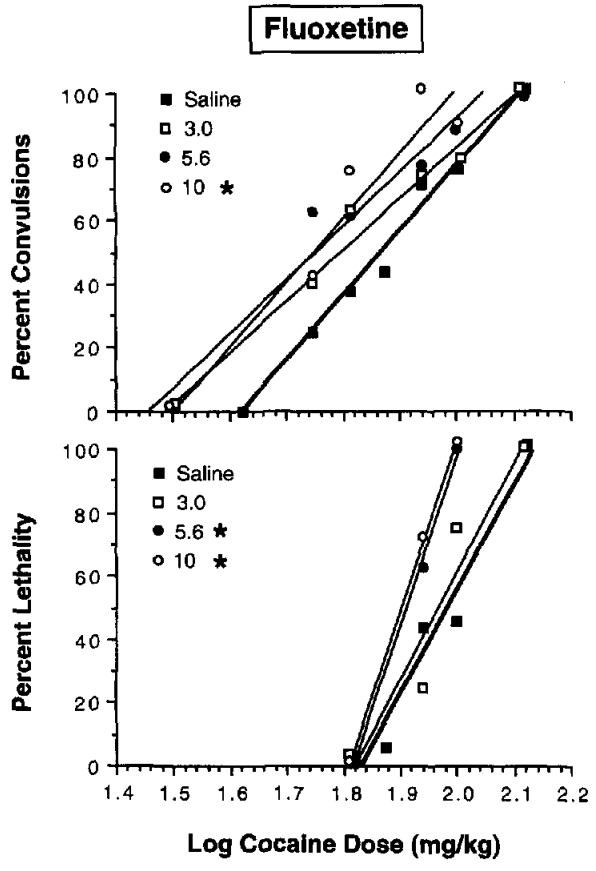

Figure 1. Effects of fluoxetine on the dose–response curve for cocaine-induced convulsions (top panel) and lethality (bottom panel). Drug doses are expressed as mg/kg base. Fluoxetine produced a dose-dependent increase in cocaine-induced convulsions ($p < .02$; previously reported in Ritz & George, 1997a, 1997b). Cocaine-induced lethality was only facilitated by high doses of fluoxetine ($p < .005$). *p at least <.05.

dramatic increase in the severity of cocaine-induced convulsions. In addition, although latency to convulsions was decreased, latency to death did not change.

Figure 2 illustrates the effects of paroxetine on the dose-dependent effects of cocaine on convulsions (top panel) and lethality (bottom panel). Paroxetine significantly facilitated cocaine-induced convulsions ($p < .05$). Similar to fluoxetine, paroxetine shifted the cocaine dose–response curve to the left in a parallel fashion. Paroxetine did not alter cocaine-induced lethality.

Figure 3 illustrates the effects of imipramine on the dose-dependent effects of cocaine on convulsions (top panel) and lethality (bottom panel). Administration of imipramine facilitated cocaine-induced convulsions and lethality. Imipramine significantly facilitated cocaine-induced convulsions ($p < .05$), shifting the cocaine dose–response curve to the left in a parallel fashion to fluoxetine and paroxetine. In contrast to the other drugs, however, imipramine facilitated cocaine-induced lethality ($p < .02$).

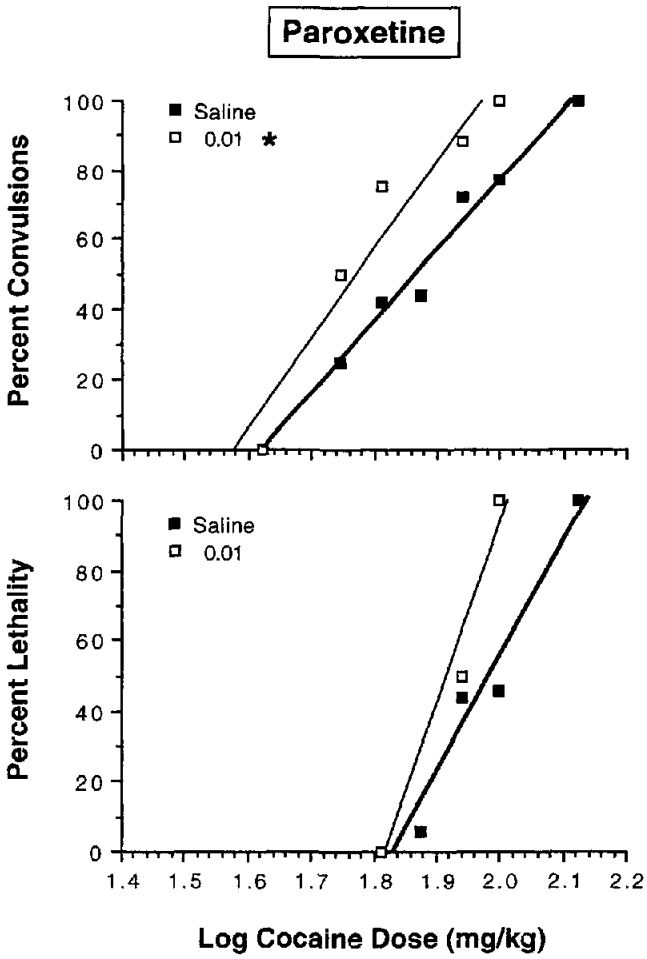

Figure 2. Effects of paroxetine on the dose–response curve for cocaine-induced convulsions (top panel) and lethality (bottom panel). Drug doses are expressed as mg/kg base. Paroxetine produced a dose-dependent increase in cocaine-induced convulsions ($p < .05$) but not lethality. Paroxetine shifted the dose–response curve for cocaine convulsions to the left in a parallel manner. *p at least <.05.

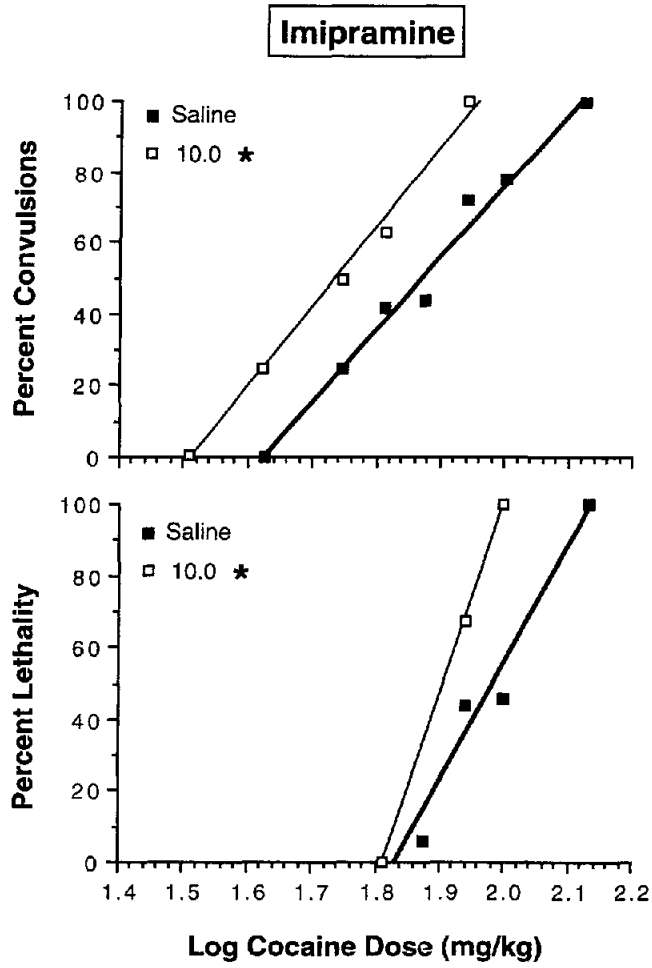

Figure 3. Effects of imipramine on the dose–response curve for cocaine-induced convulsions (top panel) and lethality (bottom panel). Drug doses are expressed as mg/kg base. Imipramine produced a dose-dependent increase in cocaine-induced convulsions ($p < .05$) and lethality ($p < .02$). Imipramine shifted the cocaine dose–response curve to the left in a parallel manner for both these toxic effects of cocaine. *p at least <.05.

Figure 4 illustrates the effects of citalopram on the dose-dependent effects of cocaine on convulsions (top panel) and lethality (bottom panel). Administration of citalopram significantly facilitated cocaine-induced convulsions ($p < .005$). However, unlike fluoxetine and paroxetine, citalopram shifted the cocaine dose–response curve to the left in a noncompetitive fashion ($p < .001$), suggesting that the effects of citalopram on cocaine-induced convulsions do not occur through a single neural mechanism. Citalopram did not significantly alter cocaine-induced lethality.

Figure 5 illustrates the effects of sertraline on the dose-dependent effects of cocaine on convulsions (top panel) and lethality (bottom panel). The most striking finding with sertraline was that administration of this potent SSRI did not potentiate cocaine-induced convulsions. In addition, this compound attenuated cocaine-induced lethality ($p < .05$) at low cocaine doses.

Figure 6 illustrates the effects of bupropion on the dose-dependent effects of cocaine on convulsions (top

panel) and lethality (bottom panel). Administration of bupropion facilitated cocaine-induced lethality but not convulsions. The finding that buproprion did not alter cocaine-induced convulsions is not surprising given the low potency of this compound to alter 5-HT uptake. However, a dose of bupropion (56 mg/kg) associated with significant dopamine uptake inhibition facilitated cocaine-induced lethality ($p < .005$; previously published in Ritz & George, 1997b). This finding is consistent with previous research demonstrating that cocaine-induced lethality is mediated by dopamine neurotransmission (Derlet et al., 1990; Ritz & George, 1993).

Figure 7 illustrates the effects of desipramine on the dose-dependent effects of cocaine on convulsions (top panel) and lethality (bottom panel). Administration of desipramine facilitated cocaine-induced convulsions ($p < .05$) and lethality ($p < .02$). However, desipramine shifted the cocaine convulsion dose–response curve to the left in a noncompetitive fashion ($p < .005$), suggesting that the effects of this compound on cocaine-induced convulsions do

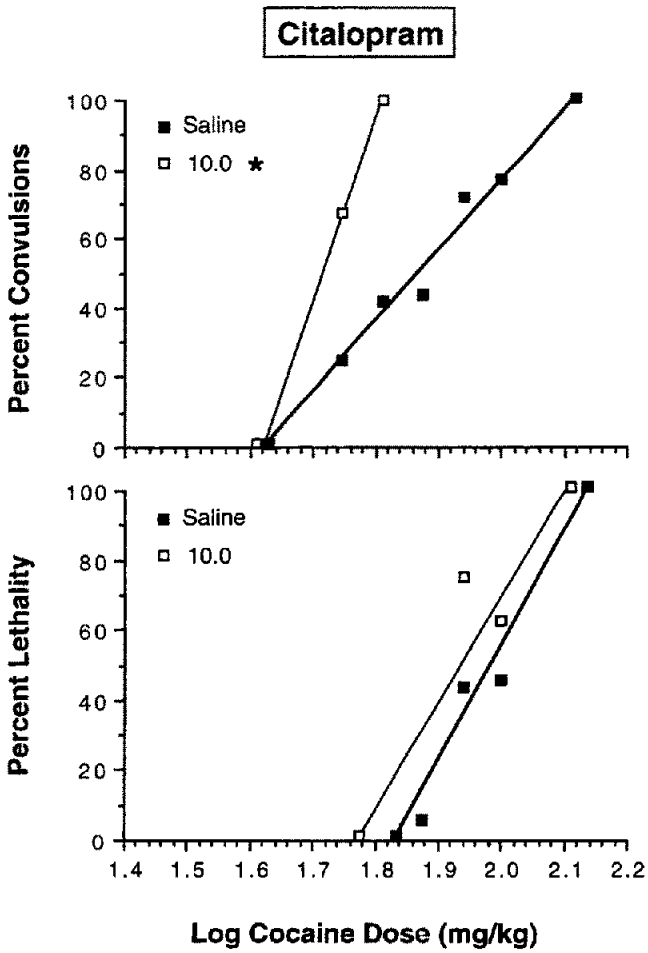

Figure 4. Effects of citalopram on the dose–response curve for cocaine-induced convulsions (top panel) and lethality (bottom panel). Drug doses are expressed as mg/kg base. Citalopram produced a dose-dependent increase in cocaine-induced convulsions ($p < .005$) but not lethality. Citalopram shifted the cocaine convulsion dose–response curve in a noncompetitive manner ($p < .001$). *p at least $<.05$.

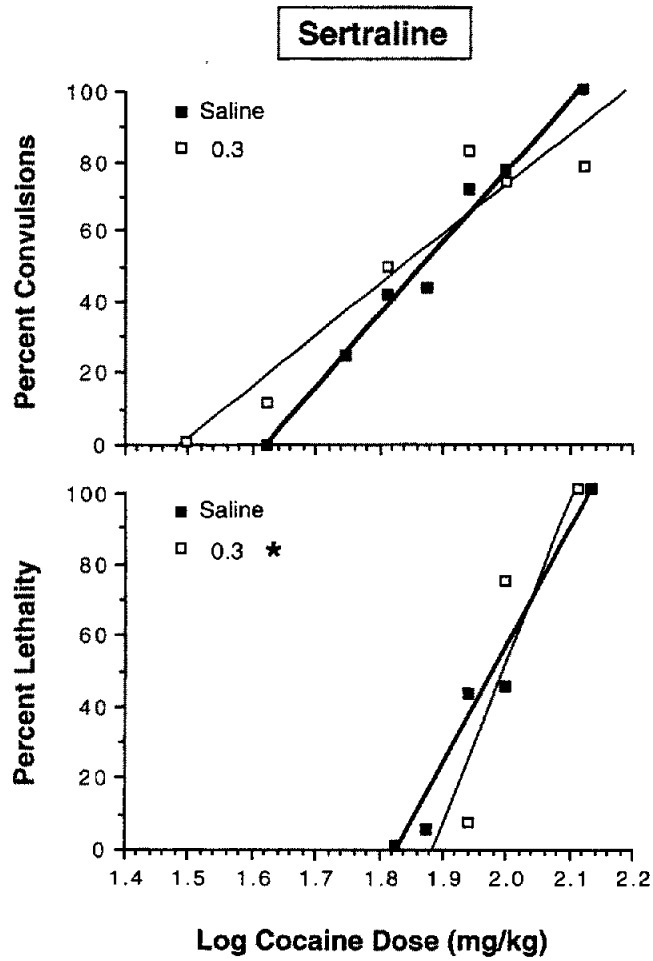

Figure 5. Effects of sertraline on the dose–response curve for cocaine-induced convulsions (top panel) and lethality (bottom panel). Drug doses are expressed as mg/kg base. Sertraline had no effect on cocaine-induced convulsions; however, this compound attenuated cocaine-induced lethality ($p < .05$) at low cocaine doses. *p at least $<.05$.

not occur through a single neural mechanism. Despite the high affinity of desipramine for norepinephrine uptake, noradrenergic mechanisms do not likely play a role in mediating cocaine-induced lethality given the previous research suggesting that norepinephrine does not appear to play a role in mediating this toxic effect of cocaine (Jackson et al., 1990; Ritz & George, 1993). The ability of desipramine to facilitate cocaine-induced lethality is more likely related to nonselective effects of this compound that alter several other neurotransmitter systems.

Affinity of Cocaine and Antidepressants for Selective Cocaine-Binding Sites

Table 1 illustrates the binding potencies for each compound tested in the present study at dopamine and 5-HT transporters as well as at sigma and M_1 and M_2 receptors, which we have previously shown to be associated with attenuation of cocaine-induced toxicity. The results revealed that cocaine displays a high affinity for dopamine and 5-HT transporters; however, the affinity of this compound for

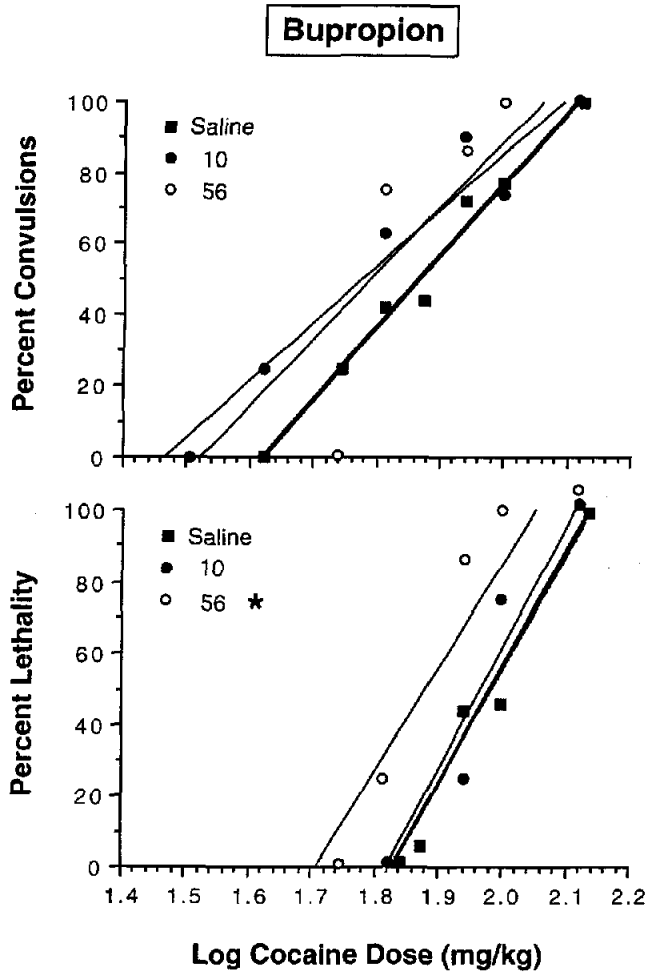

Figure 6. Effects of bupropion on the dose–response curve for cocaine-induced convulsions (top panel) and lethality (bottom panel). Drug doses are expressed as mg/kg base. Administration of bupropion did not alter cocaine-induced convulsions. However, administration of the highest dose of bupropion facilitated cocaine-induced lethality ($p < .005$; previously reported in Ritz & George, 1997a, 1997b). *p at least <.05.

5-HT transporters is higher relative to dopamine transporters. In addition, cocaine displayed a relatively low affinity for sigma and M_1, and M_2 receptors. As expected, fluoxetine, paroxetine, imipramine, citalopram, and sertraline displayed a high affinity for 5-HT transporters. Bupropion also displayed the expected high affinity for the dopamine transporter. Relative to other antidepressant compounds, desipramine and imipramine displayed a relatively high affinity for each of the M_1 and M_2 receptors. Imipramine also exhibited a relatively high affinity for sigma receptors. However, sertraline displayed at least a 100-fold greater affinity for sigma receptors than any of the other antidepressant compounds examined. This latter finding clearly distinguishes sertraline from the other antidepressants tested in this study.

Discussion

Administration of antidepressants having a high affinity and relative specificity for 5-HT transporters facilitated cocaine-induced convulsions. In contrast, these compounds did not significantly alter cocaine-induced lethality. However, the SSRI antidepressants did tend to enhance convulsant severity, thereby producing cocaine-induced convulsions, which were more frequently followed by lethality.

The finding that cocaine-induced convulsions were facilitated by antidepressants having a high affinity and relative specificity for 5-HT transporters is consistent with multiple receptor site analyses demonstrating that the potency of cocaine and related compounds to produce convulsions is correlated with the affinity of these compounds at the 5-HT transporter (Ritz & George, 1993). This study is also consistent with experiments demonstrating that cocaine-induced convulsions are facilitated by fluoxetine and attenuated by the 5-HT_2 antagonists ketanserin and cinanserin (Ritz & George, 1997a). In addition, administration of fenfluramine, which increases synaptic levels of 5-HT, facilitates cocaine-induced convulsions, whereas cinanserin attenuates this effect (Schechter & Meehan, 1995). These

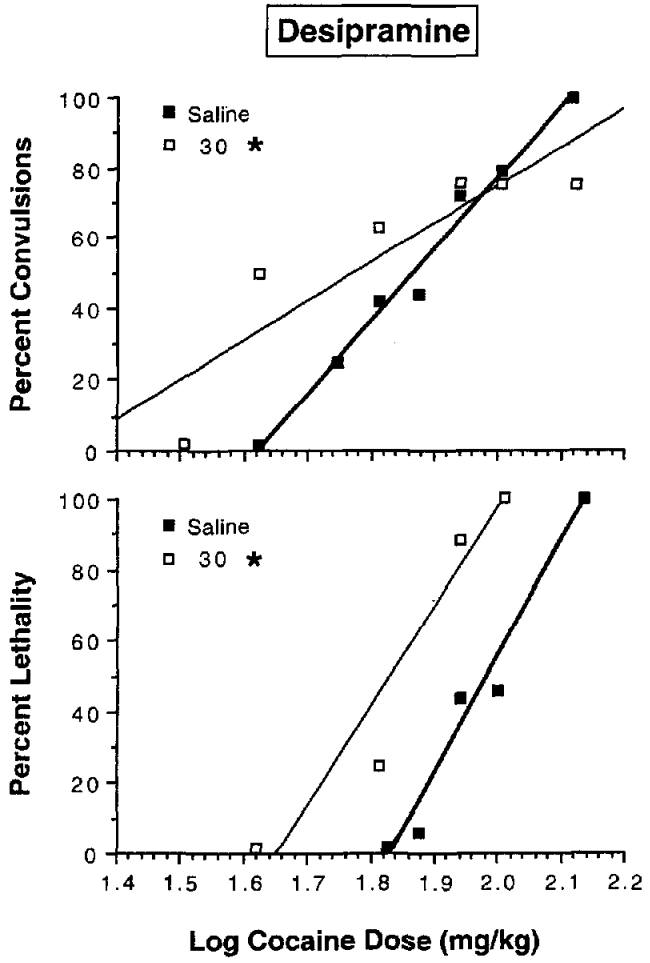

Figure 7. Effects of desipramine on the dose–response curve for cocaine-induced convulsions (top panel) and lethality (bottom panel). Drug doses are expressed as mg/kg base. Administration of desipramine facilitated cocaine-induced convulsions ($p < .05$) and lethality ($p < .02$). Desipramine shifted the cocaine dose–response curve to the left in a noncompetitive fashion for convulsions ($p < .005$) and in a parallel fashion for lethality. *p at least <.05.

Table 1
Affinities of Antidepressant Drugs for Selective Cocaine-Binding Sites

Drug	Transporter		Receptor		
	Dopamine	Serotonin	M_1	M_2	Sigma
Cocaine	0.64	0.120000	33.000	26.00	1.700
Fluoxetine	15.00	0.000540	0.450	1.49	0.150
Paroxetine	12.00	0.000007	0.058	0.22	0.140
Citalopram	81.00	0.000120	0.760	0.82	0.290
Imipramine	36.00	0.004100	0.020	0.04	0.080
Sertraline	2.00	0.000038	0.280	0.37	0.001
Bupropion	0.54	>100.000000	25.000	20.00	1.500
Desipramine	12.00	0.040000	0.050	0.06	0.920

Note. M_1 and M_2 = muscarinic receptors.

studies demonstrated that 5-HT neurotransmission plays an important role in mediating cocaine-induced convulsions.

A striking finding from this study is that sertraline, which exhibited the second highest affinity for 5-HT transporters, did not alter cocaine-induced convulsions and even modestly attenuated cocaine-induced lethality. In addition, we found that sertraline displays at least a 100-fold higher affinity for sigma receptors relative to the other antidepressants studied, a finding that is consistent with previous research (Narita, Hashimoto, Tomitaka, & Minabe, 1990). This high affinity of sertraline for sigma receptors may explain our current findings with this drug. This result is consistent with our previous findings that the ability of cocaine and related compounds to produce convulsions and lethality is inversely related to the affinity of these compounds to bind to sigma receptors (Ritz & George, 1993). In fact, these previous results demonstrated that binding of cocaine and related compounds to sigma sites accounts for 31% of the variance in the potency of these compounds for producing lethality and 11% of the variance in the potency of these drugs for producing convulsions. Moreover, the LD_{50} values produced by cocaine and cocaine-like compounds are more correlated with the ratio between drug affinity for dopamine transporters and affinity for sigma receptors than with the affinity of these drugs for dopamine transporters alone. Likewise, the CD_{50} values produced by cocaine or cocaine-like compounds are more correlated with the ratio between drug affinity for 5-HT transporters and affinity for sigma receptors than with the affinity of these drugs for 5-HT transporters alone. Pharmacological experiments support the role of sigma receptors in cocaine-induced toxicity because pharmacological agents acting at these sites attenuate cocaine-induced convulsions and lethality (McCracken, Bowen, de Costa, & Matsumoto, 1999; Ritz & George, 1997a, 1997b; Witkin et al., 1993). Thus, it may be that despite the fact that sertraline is a potent SSRI, it does not enhance cocaine-induced convulsions because it also binds potently to sigma sites, which appear to play a protective role in mediating cocaine-induced toxicity.

There may be other explanations for the finding that sertraline did not enhance cocaine-induced convulsions. First, it may be argued that the dose of sertraline was too low to alter cocaine-induced convulsions. However, this is not likely the case because a 30-fold lower concentration of paroxetine enhanced cocaine-induced convulsions, and these compounds have similar affinities at the 5-HT transporter. Moreover, the dose of sertraline used in the present study attenuates drug-reinforced behavior, and the magnitude of this effect does not differ following administration of a 3-fold higher concentration of sertraline (Gulley, McNamara, Barbera, Ritz, & George, 1995). Second, although several SSRI compounds possess the ability to inhibit cytochrome P4502D6, sertraline and citalopram do not (Brosen, 1993). Consequently, compounds such as sertraline, which lack the ability to inhibit this oxidative metabolic enzyme in the liver, may not stay in the system as long as other SSRI compounds. However, despite the fact that rapid elimination may partially explain the lack of effects of sertraline on cocaine-induced convulsions, this explanation is not consistent with the finding that sertraline attenuated cocaine-induced lethality. Furthermore, citalopram, which would also have a more rapid elimination, potently facilitated cocaine-induced convulsions. Third, a recent report found that fluoxetine and citalopram display a nanomolar affinity for $5\text{-}HT_{2C}$ receptors, whereas sertraline does not display significant binding (<1000 nM) to these sites (Palvimaki et al., 1996). Therefore, sertraline may not enhance cocaine-induced convulsions because of the low affinity of this antidepressant for $5\text{-}HT_{2C}$ receptors. This hypothesis is based on our finding that the relatively selective $5\text{-}HT_{2C}$ agonists mCPP and MK212 potentiate cocaine-induced convulsions (O'Dell et al., in press). Consequently, the lack of effects of sertraline on cocaine-induced convulsions may likely be related to a combination of high affinity for sigma receptors, which play a protective role in cocaine-induced convulsions, and a low affinity for $5\text{-}HT_{2C}$ receptors, which appear to play a role in the expression of this effect of cocaine.

Administration of bupropion, which primarily binds to dopamine transporters, facilitates cocaine-induced lethality but not convulsions, either at an effective antidepressant dose (10 mg/kg) or at a dose that effectively blocks dopamine uptake (56 mg/kg). These findings suggest that dopamine neurotransmission does not play a role in the expression of cocaine-induced convulsions. In addition, our findings are consistent with previous studies demonstrating that the ability of cocaine and related compounds to produce lethality is due to the ability of these compounds to alter dopamine neurotransmission (Derlet et al., 1990; Ritz & George, 1993, 1997b; Witkin et al., 1989). There is little clinical data that would enable us to examine the predictive validity of our hypothesis regarding the role of dopamine in

cocaine toxicity. However, one researcher demonstrated that neuroleptic administration heightens an agitated state associated with hyperthermia during a cocaine overdose, and this effect is believed to lead to death by heightening hypothermic effects (see Kosten, 1989). This finding suggests that dopamine systems may alter hypothermic effects, leading to cocaine-induced lethality.

The tricyclic compounds imipramine and desipramine facilitated cocaine-induced lethality. This finding appears to be inconsistent with our previous research because these antidepressants display a relatively high affinity for M_1 and M_2 receptors, which appear to play a protective role in mediating cocaine-induced lethality (Ritz & George, 1993, 1997b). However, tricyclics likely possess pharmacological effects that interact with dopamine systems, and this interaction may override any potential protective effects produced by binding to M_1 and M_2 sites. Although the nature of this interaction is beyond the scope of this study, our findings raise an important empirical question regarding the prevalence of cocaine-induced lethality among addicts being treated with tricyclic medications versus other antidepressant compounds.

In view of a prevailing assumption that cocaine-induced convulsions and lethality are causally linked, it is important to note that the antidepressants with the highest affinities for 5-HT uptake sites had striking effects on cocaine-induced convulsions, whereas these compounds had little effect on cocaine-induced lethality. This finding is consistent with previous research in our laboratory demonstrating that cocaine-induced convulsions and lethality are mediated by 5-HT and dopamine neurotransmission, respectively. Research from other laboratories also supports this hypothesis because 5-HT agonists facilitate and 5-HT antagonists attenuate cocaine-induced convulsions but not lethality (Schechter & Meehan, 1995). Also, the incidence of cocaine-induced convulsions and lethality is not correlated across different genetic stocks of mice (George, 1991). Collectively, these results from multiple regression analyses, pharmacological studies, and pharmacogenetic studies provide a preponderance of evidence that these toxic effects of cocaine are mediated by distinct biochemical mechanisms.

Patients in drug treatment programs vary in their exposure to cocaine and antidepressants and in the amount of time that has elapsed since their last exposure to either compound. Therefore, it is difficult to develop an animal model that precisely simulates a clinical population. Despite this, our results have important clinical relevance because there appears to be a neurochemical interaction between antidepressants and cocaine that facilitates toxic consequences. Specifically, our findings predict that cocaine addicts being treated with antidepressants may be at a greater risk for cocaine toxicity following relapse. To our knowledge, this possibility has not been examined. Research is needed to determine the predictive validity of our model, and in the future, researchers should compare the effects of antidepressants on convulsions produced by chronic cocaine to determine whether antidepressant medications reverse neurochemical changes that mediate sensitization of convulsions following chronic cocaine use.

References

Brosen, K. (1993). The pharmacogenetics of the selective serotonin reuptake inhibitors. *Clinical Investigations, 71*, 1002–1009.

Derlet, R. W., Albertson, T. E., & Rice, P. (1990). The effects of SCH 23390 against toxic doses of cocaine, *d*-amphetamine and methamphetamine. *Life Science, 47*, 821–827.

Dhuna, A., Pascual-Leone, A., Langendorf, F., & Anderson, D. C. (1991). Epileptogenic properties of cocaine in humans. *Neuro-Toxicology, 12*, 621–626.

George, F. R. (1991). Cocaine toxicity: Genetic evidence suggests different mechanisms for cocaine-induced seizures and lethality. *Psychopharmacology, 104*, 307–311.

Gulley, J. M., McNamara, C., Barbera, T. J., Ritz, M. C., & George, F. R. (1995). Selective serotonin inhibitors: Effects of chronic treatment on ethanol-reinforced behavior in mice. *Alcohol, 13*, 177–181.

Habert, E., Graham, D., Tahraoui, L., Claustre, Y., & Langer, S. Z. (1985). Characterization of [^{3}H] paroxetine binding to rat cortical membranes. *European Journal of Pharmacology, 118*, 107–114.

Jackson, H. C., Ball, D. M., & Nutt, D. J. (1990). Noradrenergic mechanisms appear not to be involved in cocaine-induced seizures and lethality. *Life Sciences, 47*, 353–359.

Javitch, J. A., Blaustein, R. O., & Snyder, S. H. (1984). [^{3}H] mazindol binding associated with neuronal dopamine and norepinephrine uptake sites. *Molecular Pharmacology, 26*, 35–44.

Kosten, T. R. (1989). Pharmacotherapeutic interventions for cocaine abuse: Matching patients to treatments. *Journal of Nervous and Mental Disease, 177*, 379–388.

Lacombe, S., Stanislav, S. W., & Marken, P. A. (1991). Pharmacologic treatment of cocaine abuse. *Drug Intelligence and Clinical Pharmacy, 25*, 818–823.

Marley, R. J., Shimosato, M., Frieman, M., & Goldberg, S. R. (1993). Genetic differences in the time course for the development and persistence of the anticonvulsant effects of carbamazepine against cocaine seizures. *Brain Research, 600*, 193–200.

McCracken, K. A., Bowen, W. D., de Costa, B. R., & Matsumoto, R. R. (1999). Two novel s receptor ligands, BD1047 and LR172, attenuate cocaine-induced toxicity and locomotor activity. *European Journal of Pharmacology, 370*, 225–232.

Mendelson, J. H., & Mello, N. K. (1996). Drug therapy: Management of cocaine abuse and dependence. *New England Journal of Medicine, 334*, 965–972.

Meyer, R. E. (1992). New pharmacotherapies for cocaine dependence . . . revisited. *Archives of General Psychiatry, 49*, 900–904.

Munson, P. J., & Rodbard, D. (1980). LIGAND: A versatile approach for the characterization of ligand binding systems. *Annals of Biochemistry, 107*, 220–239.

Myers, J. A., & Earnest, M. P. (1984). Generalized seizures and cocaine abuse. *Neurology, 34*, 675–676.

Narita, N., Hashimoto, K., Tomitaka, S., & Minabe, Y. (1990). Interactions of selective serotonin reuptake inhibitors with subtypes of sigma receptors in rat brain. *European Journal of Pharmacology, 307*, 117–119.

National Research Council. (1996). *Guide for care and use of laboratory animals*. Washington, DC: National Academy Press.

O'Dell, L. E., Kreifeldt, M. J., George, F. R., & Ritz, M. C. (1999). Serotonin$_{2C}$ receptors appear to mediate genetic sensitivity to cocaine-induced convulsions. *Psychopharmacology, 146*, 313–319.

Palvimaki, E. P., Roth, B. L., Majasuo, H., Laakso, A., Kuoppamaki, M., Syvalahti, E., & Hietala, J. (1996). Interactions of selective serotonin reuptake inhibitors with the serotonin 5-HT_{2C} receptor. *Psychopharmacology (Berlin), 126*, 234–240.

Peck, A. W., Stern, W. C., & Watkinson, C. (1983). Incidence of seizures during treatment with tricyclic antidepressant drugs and bupropion. *Journal of Clinical Psychiatry, 44*, 197–201.

Ritchie, J. M., & Greene, N. M. (1985). Local anesthetics. In A. G. Gilman, L. S. Goodman, & A. Gilman (Eds.), *The pharmacological basis of therapeutics* (6th ed., pp. 300–320). New York: Macmillan.

Ritz, M. C., & George, F. R. (1993). Cocaine-induced seizures and lethality appear to be associated with distinct central nervous system binding sites. *Journal of Pharmacology and Experimental Therapeutics, 264*, 1333–1343.

Ritz, M. C., & George, F. R. (1997a). Cocaine-induced convulsions: Pharmacological antagonism at serotonergic, muscarinic and sigma receptors. *Psychopharmacology, 129*, 299–310.

Ritz, M. C., & George, F. R. (1997b). Cocaine-induced toxicity: Concurrent influence of dopaminergic, muscarinic and sigma receptors in mediating cocaine-induced lethality. *Psychopharmacology, 129*, 311–321.

Schechter, M. D., & Meehan, S. M. (1995). Serotonergic mediation of cocaine seizures in mice. *Pharmacology, Biochemistry & Behavior, 51*, 313–316.

Steinberg, D. (1988). PROBIT: A supplementary module for SYSTAT and SYSGRAPH [Computer software]. Evanston, IL: SYSTAT.

Wilkinson, L. (1987). SYSTAT: The system for statistics. Macintosh version 3.2 [Computer software]. Evanston, IL: SYSTAT.

Witkin, J. M., Terry, P., Menkel, M., Hickey, P., Pontecorvo, M., Ferkany, J., & Katz, J. L. (1993). Effects of the selective sigma receptor ligand, 6-[6-(4-Hydroxypiperidinyl) hexyloxy]-3-Methylflavone (NPC 16377), on behavioral and toxic effects of cocaine. *Journal of Pharmacology and Experimental Therapeutics, 266*, 473–483.

Ziedonis, D. M., & Kosten, T. R. (1991). Pharmacotherapy improves treatment outcome in depressed cocaine addicts. *Journal of Psychoactive Drugs, 23*, 417–425.

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