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Pharmacological Characterization of the Enhancement of Apomorphine-Induced Gnawing in Mice by Cocaine

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TIRELLI, E. AND J. M. WITKIN. *Pharmacological characterization of the enhancement of apomorphine-induced gnawing in mice by cocaine.* PHARMACOL BIOCHEM BEHAV **55**(1) 135–140, 1996.—The present study was designed to provide additional information on the behavioral and pharmacological mechanisms associated with the augmentation of apomorphine-induced gnawing in C57BL/6J mice. (−)-Cocaine enhanced apomorphine-induced gnawing at doses devoid of effects on gnawing when given alone. The effect was stereoselective, with (+)-cocaine devoid of activity in this test. Peripheral synapses may also not be critical to the cocaine enhancement, as cocaine methiodide, a charged species, was also without effect. The local anesthetic actions of cocaine were evaluated with lidocaine, a local anesthetic without prominent dopaminergic actions. Like (−)-cocaine, lidocaine augmented the gnawing response to apomorphine without increasing climbing or gnawing when given alone. (+)-Amphetamine enhanced apomorphine-induced gnawing but only at a high dose that increased gnawing by itself. The selective dopamine uptake blocker, GBR 12909, augmented apomorphine-induced gnawing without increasing gnawing when given alone; however, unlike cocaine or lidocaine, GBR 12909 increased climbing at doses that augmented the gnawing response. These data indicate that the cocaine-augmented gnawing response to apomorphine does not appear to be the result of psychomotor stimulation per se. Rather, this effect may be due to blockade of dopamine uptake and/or the local anesthetic actions of cocaine.

Apomorphine (+)-Amphetamine (−)-Cocaine (+)-Cocaine Cocaine methiodide Lidocaine GBR 12909 Gnawing Climbing C57BL/6J mice

GNAWING and climbing are typically induced in laboratory rodents by drugs increasing dopaminergic neurotransmission, rendering these behaviors useful for the rapid in vivo assessment of intensive dopaminergic mobilization [cf. (29,30,33,54)]. Such methods have been used to study effects of abused drugs such as cocaine and amphetamines. For example, gnawing in mice has been used to distinguish between direct- and indirect-acting dopamine agonists (49) and as a means of detecting a dopaminergic hypersensitivity induced by prior, high dose cocaine administration (47).

Apomorphine-induced gnawing in mice can be further increased by cocaine (9,10,47,48). Given that intact D_1 and D_2 dopaminergic receptors are required for both climbing and gnawing to be induced by apomorphine and apomorphine-like compounds (4,24,53), it is probable that cocaine, whose many effects depend upon dopaminergic sites [cf. (21,55,59)], acts via these receptors to potentiate apomorphine-induced climbing and gnawing. However, the pharmacological basis for this effect has not been specifically investigated. The use of dopamine antagonists to characterize the potentiating effects of cocaine is not possible because these compounds also attenuate apomorphine-induced gnawing, in the absence of cocaine (4,5,52,53).

The present study was designed to further characterize cocaine potentiation of apomorphine-induced gnawing. Stereoselectivity was examined with (+)-cocaine, which has no appreciable affinity for the dopamine transporter (23,36,40). To isolate cocaine potentiation of apomorphine-induced gnawing to the central nervous system, effects of a stable, charged cocaine analog, (−)-cocaine methiodide (41,45), were explored. The role of dopamine uptake blockade was studied by comparing effects of cocaine, which nonselectively blocks

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monoamine and indolamine uptake [cf. (16,18,37–38)] with that of GBR 12909, a relatively selective blocker of dopamine uptake (18,50) and (+)-amphetamine, which increases synaptic dopamine availability primarily through the release of dopamine (2,3). Cocaine also has marked local anesthetic actions. This effect of cocaine on the potentiation of apomorphine-induced gnawing was studied with lidocaine. As a local anesthetic, lidocaine, unlike many local anesthetics, such as procaine, has low affinity for the dopamine transporter (35).

The present observations were carried out in an environment in which climbing can occur simultaneously with gnawing [cf. (46,48)], because under conditions in which climbing cannot occur, apomorphine does not induce gnawing in the C57BL/6J mouse strain studied here (49). The lowest dose of apomorphine that produces gnawing (8 mg/kg) was used so as to be able to both enhance and decrease this behavioral effect of apomorphine by treatment with the test compounds. Although this dose of apomorphine produces maximal levels of climbing when given alone, simultaneous measurement of both gnawing and climbing was useful for examining the specificity with which drugs alter the effects of apomorphine on gnawing. That is, do the drugs enhance apomorphine-induced gnawing at doses that do not alter gnawing or climbing when given alone?

METHOD

Animals

Male C57BL/6J mice (Jackson Laboratories, Bar Arbor, ME), 9–13 weeks old, 21–31 g, were housed in groups of six in clear, polypropylene cages (19 × 27 × 15 cm) with sawdust, ad lib food, and tap water. Animals were kept in a large colony room, under a 12 L:12 D cycle beginning at 0700 h, and an ambient temperature maintained at 22–25°C throughout the course of the investigations.

Behavioral Methods

Behavioral observations were conducted with individual mice in enclosed wire mesh cages (1 cm mesh × 15 × 15 cm size × 26 cm high) resting on a smooth, clean lab bench. Mutually exclusive categories of behaviors were established a priori on the basis of previous observations of C57BL/6J mice under apomorphine (47,48). Gnawing (biting) was defined as the incisors over the wire, often involving typical repetitive jaw movements. Under apomorphine, mice gnaw mostly while climbing. Climbing was scored when all four paws were gripping the wire mesh. Stationary gripping with all four paws was not distinguished from gripping while moving. Behaviors were quantified using a modified multisubject time-sampling technique (47,48).

Each mouse was scored during four samples of 2 min separated by 14 min, for a total session duration of 64 min. A session involved eight mice observed singly in turn, and there were four turns (each involving one 2-min sample) within each session. Every 2-min sample was divided into 24-point samples for momentary scoring. On the moment of each point-sample (first second of the 5-s interval), the observer recorded whether or not one of the targeted behaviors was occurring. A score of 1 was assigned if the behavior was present, and a score of 0 was attributed if the behavior was absent. The possible, final, maximal score for a given behavior was 24 (point samples) × 4 (turns) = 96.

Mice were tail marked with a felt-tipped pen and weighed in the test room approximately 30 min before experimentation. They were first injected with one of the pretreatment drugs (either saline or a dose of a test drug) 16 min prior to the administration of 8 mg/kg apomorphine. Between the two pharmacological treatments, mice remained in their home cage placed in the testing room. Drugs were given to successive mice every 2 min, which was the duration of a time sample, to keep a constant interval between the injections and the start of the behavioral scoring. Therefore, given that eight mice were tested in a session, scoring began 8 × 2 = 16 min after the last injection.

Drugs

Apomorphine HCl, (+)-amphetamine sulfate (Sigma Chemical Co., St. Louis, MO), lidocaine HCl, GBR-12909 HCl, and (−)-cocaine HCl (Mallinkrodt/Nuclear, Orlando, FL) were all dissolved in 0.9% NaCl solution. Optically pure (+)-cocaine base, synthesized by Research Triangle Institute (Research Triangle Park, NC) according to the methods of Lewin et al. (22), was dissolved in distilled water with the pH adjusted to 6.5 by acid/base titration. Cocaine methiodide (National Institute on Drug Abuse, Rockville, MD) was dissolved in distilled water. All compounds were injected IP in a volume of 0.01 ml/g body weight 16 min prior to apomorphine administration. The dose of apomorphine was selected on the basis of previous observations in which cocaine augmented apomorphine-induced gnawing (48). The other compounds were studied up to doses that either produced significant behavioral effects or reached the limits of toxicity.

Data Analysis

Because many means and variances were 0 or close to 0, fundamental assumptions for analysis of variance (especially homogeneity of variances) and most of the a priori tests (such as Dunn's test) could neither be met nor approached through transformation of raw data. Comparisons between means were, therefore, conducted using the Welch-Aspin test. This test is an a priori test for planned pairwise comparisons, which is a modified version of the Dunn's test, provides a robust correction for the heterogeneity of variances (25), and uses the Dunn table of critical values. Statistical significance was accepted at a probability level of < 0.05. Comparisons were conducted between the means of the experimental groups (test drug plus apomorphine or test drug plus saline) and the corresponding control groups (saline plus apomorphine or saline plus saline, respectively).

RESULTS

Under control conditions (saline + saline), gnawing and climbing occurred at relatively low levels (Figs. 1–4, solid bars above 0). Mean control values for gnawing and climbing were 2.84 ± 0.89 and 11.38 ± 0.77, respectively. Apomorphine (8 mg/kg) alone induced significant increases in gnawing and marked increases in climbing (Figs. 1–4, striped bars above 0). Mean effects of apomorphine on gnawing and climbing were 12.66 ± 1.98 and 58.27 ± 2.75, respectively.

Effects of a range of doses of (−)-cocaine alone (solid bars) and in conjunction with 8 mg/kg apomorphine (striped bars) are shown for all three measures in Fig. 1. In this experiment, (−)-cocaine alone had no significant effect on gnawing but increased climbing at 50 mg/kg. (−)-Cocaine did not increase gnawing when given alone; in fact, lower doses (3 and 10 mg/kg) produced small decreases. Nonetheless, (−)-cocaine dose dependently increased apomorphine-induced gnawing. Maxi-

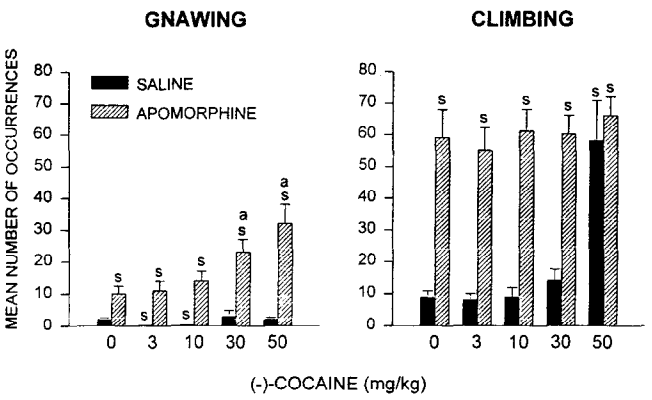

FIG. 1. Effect of (−)-cocaine on apomorphine-induced gnawing and climbing in C57Bl/6J mice. Cocaine was injected 16 min before either saline or 8 mg/kg apomorphine. Data are means ± SEM (n = 8). Solid bars represent effects of cocaine alone; striped bars represent effects of cocaine in the presence of 8 mg/kg apomorphine. Symbols: "s" designates effects significantly different than effects of saline alone (solid bar above 0); "a" represents effects significantly different than effects of apomorphine alone (striped bar above 0). Significance of effects was assessed by the Welch-Aspin test for $p < 0.05$.

mal potentiation occurred after 50 mg/kg (−)-cocaine. Apomorphine-induced climbing was not altered by (−)-cocaine pretreatment, despite a strong induction of climbing by 50 mg/kg (−)-cocaine alone.

Administration of either (+)-cocaine or (−)-cocaine methiodide did not affect either gnawing or climbing studied alone (Fig. 2). Further, these compounds also did not alter the behavioral effects of apomorphine.

Lidocaine, like (−)-cocaine, dose-dependently augmented

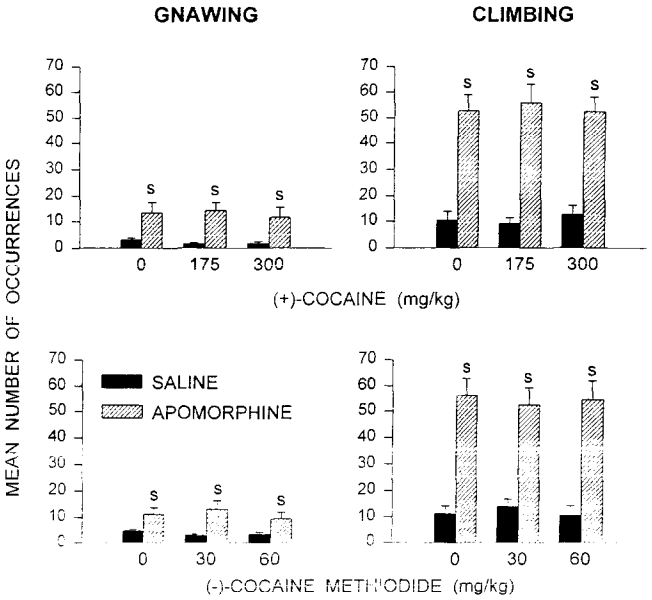

FIG. 2. Effect of (+)-cocaine and cocaine methiodide on gnawing and climbing directed toward the wire-mesh walls of the experimental cage in saline-treated (solid bars) or apomorphine-treated (striped bars) C57Bl/6J mice. Pretreatments were given 16 min before either saline or 8 mg/kg apomorphine. Other details as Fig. 1.

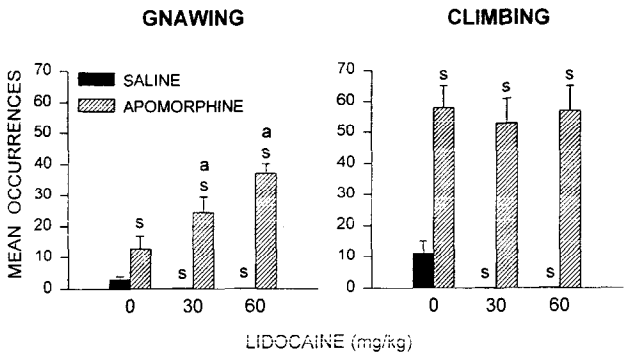

FIG. 3. Effect of lidocaine on gnawing and climbing directed toward the wire-mesh walls of the experimental cage in saline-treated (solid bars) or apomorphine-treated (striped bars) C57Bl/6J mice. Pretreatments were given 16 min before either saline or 8 mg/kg apomorphine. Other details as Fig. 1.

the gnawing response to 8 mg/kg apomorphine (Fig. 3, striped bars), but did not increase gnawing when given alone (Fig. 3, solid bars). Although lidocaine decreased climbing when studied alone, it did not alter the effects of apomorphine on climbing.

The effects of the psychomotor stimulants (+)-amphetamine and GBR 12909 alone and on apomorphine-induced behaviors are shown in Fig. 4. (+)-Amphetamine alone increased both gnawing and climbing at the highest dose. Apo-

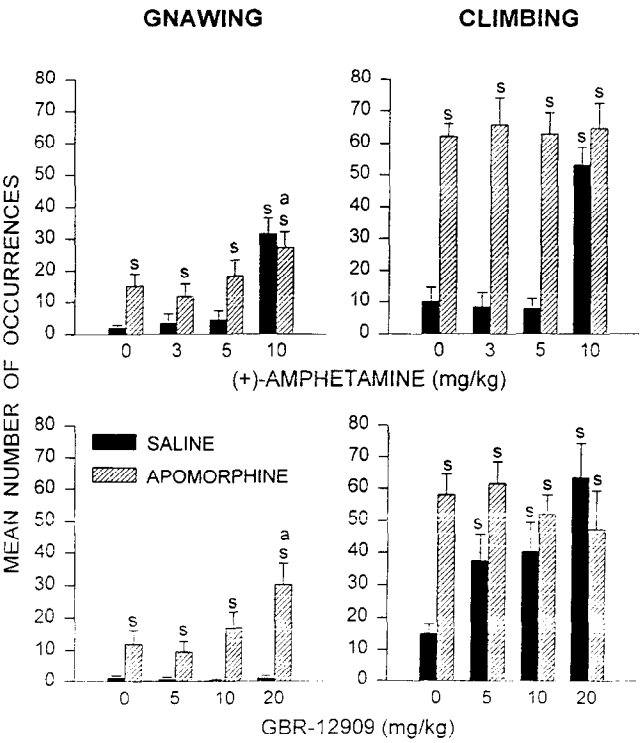

FIG. 4. Effect of (+)-amphetamine and GBR-12909 on gnawing and climbing directed toward the wire-mesh walls of the experimental cage in saline-treated (solid bars) or apomorphine-treated (striped bars) C57Bl/6J mice. Pretreatments were given 16 min before either saline or 8 mg/kg apomorphine. Other details as Fig. 1.

morphine-induced gnawing was enhanced by the highest dose of (+)-amphetamine, which increased gnawing when given alone. In contrast, apomorphine-induced modifications of climbing were not altered by (+)-amphetamine.

GBR 12909, like cocaine, did not increase gnawing when given alone. However, GBR 12909 produced a dose-dependent increase in climbing in the absence of apomorphine. Apomorphine-induced gnawing was facilitated by the highest dose of GBR 12909.

DISCUSSION

Cocaine augmented apomorphine-induced gnawing without increasing gnawing when given alone. This result replicates previous observations (9,10,47,48). The present study was designed to provide additional information on the behavioral and pharmacological mechanisms associated with this augmentation.

Augmentation of apomorphine-induced gnawing by cocaine was stereoselective. In contrast to (−)-cocaine, the (+)-isomer of cocaine did not change apomorphine-induced gnawing. These results extend previous findings on the stereoselectivity of behavioral effects of cocaine. The dextrorotatory form of cocaine lacks most of the typical behavioral effects of (−)-cocaine. In particular, (+)-cocaine does not stimulate locomotor activity, increase rates of operant responding, or produce cocaine-like discriminative stimulus effects (6,14,15,20,28, 31,44). Correspondingly, (+)-cocaine displays negligible affinity for the dopamine transporter (23,36,40). Finally, whereas (−)-cocaine inhibits the spontaneous activity of 5-HT neurons of the dorsal raphe nucleus, the (+)-isomer is inactive (8). In contrast, convulsant and lethal effects of (−)-cocaine are mimicked by (+)-cocaine (20). In the present experiment, higher doses of (+)-cocaine, therefore, could not be explored due to toxic consequences.

The contribution of peripheral nervous system synapses to the enhancement of apomorphine-induced gnawing was investigated using cocaine methiodide. This compound remains charged at physiological pH and thereby becomes relatively impermeable to the CNS (41,45,56). In congruence with this distribution, cocaine methiodide does not produce a host of pharmacological effects like those of cocaine. Cocaine methiodide does not increase locomotor activity (56), produce cocaine-like discriminative stimulus effects (57), inhibit neuronal firing of serotonergic neurons of the dorsal raphe (8), or produce convulsions (56). Cocaine methiodide did not alter any of the behaviors measured here nor did it modify these behaviors in the presence of apomorphine. Cocaine methiodide is ~10-fold less potent than cocaine in its cardiovascular (noradrenergic) effects and local anesthetic actions (41,45) and ~30 times less potent than cocaine as an inhibitor of binding to the dopamine transporter (36). Although the somewhat lower potency of cocaine methiodide requires higher doses to be given to fully mimic the peripheral actions of cocaine, higher doses of cocaine methiodide are toxic. The doses of cocaine methiodide studied here approached those which are lethal (56).

Of the compounds tested, only cocaine and lidocaine selectively augmented the gnawing response to apomorphine. Both compounds increased apomorphine-induced gnawing at doses that did not increase gnawing or climbing when given alone. Although GBR 12909 and (+)-amphetamine also enhanced apomorphine-induced gnawing, this effect was not selective. GBR 12909 increased climbing at doses fourfold lower than those effective in augmenting the gnawing response while (+)-amphetamine increased both gnawing and climbing at the dose that enhanced apomorphine-induced gnawing. The differential behavioral effects observed among these closely related compounds is interesting in light of the generally comparable behavioral effects of these and related drugs reported previously [cf. (13,19,49,55,57)]. The method may prove useful for dissociating subtle behavioral differences among dopaminergic agents.

Although GBR 12909 only augmented gnawing induced by apomorphine at doses that also increased climbing, climbing was not responsible for the augmentation of gnawing. Climbing occurred at lower doses than those augmenting the gnawing response. Because the induction of climbing by GBR 12909 is not responsible for the augmentation of apomorphine-induced gnawing, the dopamine uptake-blocking effects of this compound cannot be ruled out as a potential mechanism of action for this effect on gnawing.

The ability of lidocaine to augment apomorphine-induced gnawing suggests a possible role for the local anesthetic actions of cocaine in the cocaine-augmentation of apomorphine-induced gnawing. Like most of the other local anesthetics, including (−)-cocaine, lidocaine exerts its anesthetic effects through the inhibition of voltage-gated sodium channels and consequent blockade of neuronal excitability (34). Cocaine is approximately five times more potent than lidocaine in its affinity for voltage-sensitive sodium channels (27). Therefore, the doses of lidocaine studied here were sufficient to produce local anesthesia comparable to that produced by the range of doses of cocaine investigated. However, unlike a host of other local anesthetics, lidocaine has negligible affinity for the dopamine transporter (35) and there is no serious evidence for a dopaminergic involvement in the expression of the neurobehavioral or toxicological effects of acutely injected lidocaine [e.g., (12,32,34,56)]. Lidocaine is completely inefficient in increasing the extracellular concentration of dopamine in the nucleus accumbens (17). At best, only when injected chronically can lidocaine produce dopamine-like neurobehavioral effects: progressive, stepwise, kindling followed by increases in both apomorphine stereotypies and mesolimbic D_2 receptor density (7,26). Lidocaine is, therefore, an ideal agent for investigating the role of local anesthesia in the absence of dopaminergic effects. In other behavioral tests, lidocaine does not produce any of the typical behavioral effects of psychomotor stimulants, such as hyperlocomotion or rotational behavior after either systemic or intracerebral administration in rodents (11,31,42,43), or self-administration in primates (58). However, van Dyck et al. (51) reported comparable subjective effects of intranasal cocaine and lidocaine in humans.

Cocaine methiodide is also a local anesthetic although about 10-fold weaker than that of (−)-cocaine (41); however, this compound did not augment the gnawing response to apomorphine. GBR 12909 also augmented gnawing induced by apomorphine. GBR 12909 selectively blocks the uptake of dopamine (18,50) and may also have weak local anesthetic properties (1). Whether dopamine agonism or local anesthetic actions of cocaine separately or together contribute to the augmentation of apomorphine-induced gnawing will require evaluation of a series of compounds with a range of each of these two effects. Notwithstanding, a resolution to this question, the potentiation by lidocaine of a dopamine-related psychopharmacological effect, is a matter for future investigation, the examination of other behavioral and toxicological effects being warranted.

Whereas apomorphine and (+)-amphetamine increased gnawing when given alone, none of the other compounds

tested produced this effect. This is true even of (−)-cocaine, GBR 12909, and lidocaine, all of which augmented the gnawing response to apomorphine. The absence of effects of these latter drugs on gnawing contrast with previous results indicating that indirect- but not direct-acting agonists can induce gnawing in this strain of mice (49). In that study, (−)-cocaine, GBR-12909, and (+)-amphetamine elicited dose-dependent increases in gnawing directed towards corrugated flooring; apomorphine did not. This work differed from the present study in the use of a different form of gnawing. In the form used here, gnawing is conditional on climbing (or verticalization of the body). In contrast, gnawing of corrugated paper is independent of body position and can be only primed, not elicited, by postsynaptic dopamine agonists like apomorphine (9,39,46–48). Importantly, both (−)-cocaine and (+)-amphetamine are able to dose-dependently potentiate apomorphine-primed gnawing of floor corrugations in mice [(9,10,39,46); E. Tirelli, unpublished observations]. While it is possible that the mechanisms underlying cocaine potentiation of apomorphine-induced gnawing differ depending upon the manner in which gnawing is assessed, the common potentiation of floor gnawing, just mentioned, and gnawing while climbing, as observed here, is at least suggestive of common mechanisms.

The enhancement of apomorphine-induced gnawing by cocaine was shown to be a behaviorally selective phenomenon as previously demonstrated. Apomorphine-induced gnawing was augmented by cocaine, whereas cocaine did not increase gnawing when given alone. Likewise, cocaine did not increase climbing at doses that were effective in enhancing apomorphine-induced gnawing. Although gnawing under these conditions is dependent upon climbing (i.e., the mice gnaw under apomorphine while climbing) (46,48,49), the increase in apomorphine-induced gnawing by cocaine is not due to increased amounts of climbing since climbing is maximally elicited by 8 mg/kg apomorphine (47,48). That drug effects on climbing per se were not responsible for the augmentation of apomorphine-induced gnawing is given further support by the effects of GBR 12909, as noted above. Further, lidocaine augmented the gnawing response at doses that decreased gnawing and climbing when given alone. However, high doses of caffeine (30 and 60 mg/kg) or nicotine (2 and 4 mg/kg), which also decreased climbing, did not augment apomorphine-induced gnawing (unpublished observations).

In summary, the augmentation of apomorphine-induced gnawing by cocaine was shown to be stereospecific and data from a stable-charged analog suggest that it was due to a central action of cocaine. The augmentation by both lidocaine and GBR 12909 indicate that both local anesthetic actions and dopamine uptake-blocking effects of cocaine may be important mechanisms whereby cocaine augments this behavioral effect of apomorphine.

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