Pharmacology Biochemistry & Behavior, Vol. 23, pp. 831–836, 1985. © Ankho International Inc. Printed in the U.S.A. 0091-3057/85 $3.00 + .00

Locomotor Effects of Cocaine, Cocaine Congeners, and Local Anesthetics in Mice[1]

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Received 2 November 1984

REITH, M. E. A., B. E. MEISLER AND A. LAJTHA. *Locomotor effects of cocaine, cocaine congeners, and local anesthetics in mice.* PHARMACOL BIOCHEM BEHAV 23(5) 831–836, 1985.—Spontaneous locomotor activity of mice was stimulated by IP administration of cocaine and its closely related phenyltropane analogs. In contrast, locomotion was inhibited by IP administration of cocaine congeners such as norcocaine, (+)-pseudococaine, and tropacocaine, and of isomers of phenyltropane analogs. Also inhibitory were the local anesthetics procaine, tetracaine, benzocaine, lidocaine, and prilocaine. The locomotor inhibition induced by IP norcocaine or tetracaine could be reversed by subsequent treatment with cocaine. Both cocaine and norcocaine were centrally stimulatory when injected intracerebroventricularly. The rank order of potencies of cocaine congeners and local anesthetics in depressing locomotion was similar to that of their potencies in interacting with sodium channels. From these results we infer that the locomotor depression induced by systemic administration of cocaine congeners results from a local anesthetic action involving inhibition of the ion conductance of sodium channels.

Locomotion Cocaine Cocaine congeners Local anesthetics Dopamine uptake Sodium channels Mice

COCAINE is a potent local anesthetic [2], and it also has remarkable stimulatory effects on the CNS [22,28]. Recent work on sodium channels [4, 13, 16] has shown that there is a strongly positive correlation between the local anesthetic potency of various compounds related to cocaine and their potency in inhibiting sodium channel function measured by electrophysiological or biochemical techniques. Much less is known about the structural requirements for central stimulation, mainly because there is no single mechanism underlying the various central effects of cocaine [22]. In contrast to cocaine, procaine and lidocaine do not stimulate locomotor activity in rats [30]. The ester linkage between the tropane and phenyl rings in cocaine is not a prerequisite for affecting various kinds of centrally controlled behavior [3, 5, 8, 9, 25–27]. In this respect N-demethylated derivatives are two to ten times less potent than their parent compounds [25,27]; WIN 35,065-2, a phenyltropane analog of cocaine is very potent, whereas its enantiomer, WIN 35,065-3, is inactive [24,25]. There is no information on the behavioral effects of stereoisomers and epimers of cocaine, and of the related compounds tropacocaine (benzoylpseudotropine) and benzoyltropine.

The present work was undertaken to determine the structure-activity relationships of the effects of cocaine related compounds on spontaneous locomotor behavior of BALB/cBy mice, as part of a more general project on behavioral and biochemical effects of cocaine congeners in these animals [18,19]. We observed that most cocaine congeners, including norcocaine, inhibited rather than stimulated spontaneous locomotor activity upon systemic administration. To test the hypothesis that these inhibitory effects were due to local anesthetic action, an effort was made to determine the potency of locomotor inhibition by many cocaine congeners and of the local anesthetics tetracaine, prilocaine, lidocaine, procaine, and benzocaine; subsequently the potency of locomotor inhibition was compared with the degree of local anesthesia reported in the literature. In addition, we investigated whether the inhibitory effects on locomotion were also observed after intracerebroventricular injection. Finally, we determined whether the locomotor inhibition induced by intraperitoneal norcocaine, procaine, or tetracaine could be counteracted by subsequent administration of cocaine.

METHOD

Subjects

Male BALB/cBy mice, 5–8 weeks of age, weighing 19–21 g, from the breeding colony of our Institute were used. The animals were kept on a 12-hour light/dark cycle (7 a.m./7 p.m. light), with food and water available ad lib.

Spontaneous Locomotor Activity

Mice were housed in separate plastic cages (27×17×12 cm) from one to three days prior to testing, in the same room in which the behavioral measurements were made. Shades were drawn to reduce the light from the windows, and no artificial light was used. A constantly humming window air conditioner kept the temperature at 22–24°C. Behavioral

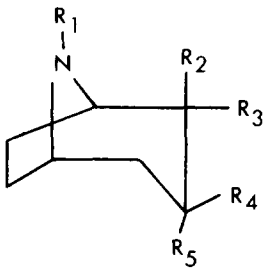
[1]Supported by USPHS grant DA 03025.

TABLE 1

LOCOMOTOR EFFECTS OF COCAINE AND COCAINE CONGENERS

No.	Drug	Group substituents* R_1	R_2	R_3	R_4	R_5	Locomotor stimulatory or inhibitory dose (μmol/kg)
1.	Cocaine	CH_3	CO_2CH_3	H	OOCPh†	H	70 stim††
2.	WIN 35,428	CH_3	CO_2CH_3	H	PhF‡	H	5 stim
3.	WIN 35,065-2	CH_3	CO_2CH_3	H	Ph	H	17 stim
4.	WIN 35,140	CH_3	H	CO_2CH_3	Ph	H	116 inh**
5.	WIN 35,004§	CH_3	H	CH_2OAc	Ph	H	68 inh
6.	WIN 35,065-3¶	CH_3	CO_2CH_3	H	Ph	H	93 inh
7.	Norcocaine	H	CO_2CH_3	H	OOCPh	H	7 inh
8.	N-allylnorcocaine	CH_2CHCH_2	CO_2CH_3	H	OOCPh	H	6 inh
9.	(+)-pseudococaine	CH_3	H	CO_2CH_3	OOCPh	H	15 inh
10.	(+)-neopseudococaine	CH_3	H	$CO_2C_3H_7$	OOCPh	H	65 inh
11.	benzoylpseudotropine	CH_3	H	H	OOCPh	H	252 inh
12.	benzoyltropine	CH_3	H	H	H	OOCPh	8 inh

*General structure.



†Ph=phenyl.
‡PhF=phenyl with F in para position.
§Ethylene bridge between C_1 and C_5 in tropane ring is removed.
¶Compound 6 is enantiomer of 3.
**IP dose that gives a stimulation ratio of 0.5.
††IP dose that gives a stimulation ratio of 2.0 (see the Method section).

testing was performed between 9 a.m. and 5:30 p.m. and was started by placing the animal in its home cage in an Opto-Varimex-Minor acivity monitor (Columbus Insturments) and replacing the cover with a flat one without food and water. After an exploratory period of 10 min, the animal was monitored for 40 min. The animal was then injected (see below), placed back in the home cage, and monitored for another 40 min. The number of activity counts produced in the second 40-min period over those in the initial 40-min period was defined as the stimulation ratio [6]. This method takes into account the somewhat varied baseline levels of spontaneous activity in different animals. In preliminary experiments it was found that the 10-min exploratory period was sufficiently long for our animals to return to steady baseline activities. The behavioral data presented in this paper are based on activity counts produced by the animals by interrupting consecutive infrared beams only; interruptions of one beam are not included. The activity counts therefore mainly represent ambulation. Each animal was used only once. The same drug was administered at various times of the day to minimize the effects of time-related phenomena on the behavioral results.

Analysis of Locomotor Effects of Drugs Injected Intraperitoneally

For dose-response curves, logarithm-transformed values of the stimulation ratios were plotted against the log dose. The dose that produced a stimulation ratio of 2.0 or 0.5 and its confidence interval were estimated by linear regression analysis on the rising or falling portion of the dose-response curve. For all compounds shown in Fig. 5, the 90% confidence interval of the ID_{50} (inhibitory dose in μmol/kg decreasing locomotion by 50%) ranged from one-third (or more) of the ID_{50} to three (or less) times the ID_{50}, except for compounds 11 and 17, which had much wider intervals. The slopes of the dose-response curves for compounds 8 and 12–15 were similar to the slope for norcocaine (see Fig. 1); for the remaining compounds (except No. 17) shown in Fig. 5, the curves were steeper. We did not observe convulsive effects of the higher doses (around ten times the ID_{50}) of any of the drugs used in this study. Similar estimates of ID_{50} values were obtained when log-probit analysis was applied to locomotor inhibitions expressed as percent of baseline.

The statistical significance of observed effects was determined with the test of Wilcoxon (two-tailed) for independent samples, or the sign-rank test of Wilcoxon (two-tailed) for paired samples.

Intracerebroventricular Administration and Sniffing/Biting

Mice were implanted under chloral hydrate (380 mg/kg) anesthesia with 22-gauge stainless steel guide cannulas containing 28-gauge dummy cannulas the tips of which were aimed at the third ventricle. The stereotaxic coordinates of the intended microinjection sites were 0.3 mm posterior to the bregma and 3.0 mm below the skull surface. The mice were allowed one week for postsurgical recovery. They were kept in individual cages. After receiving an injection of 5 μl, the animal was placed in a 27×17×12 cm plastic cage just like its home cage; the floor of the observation cage was covered with a layer of shavings. The animal was then ob-

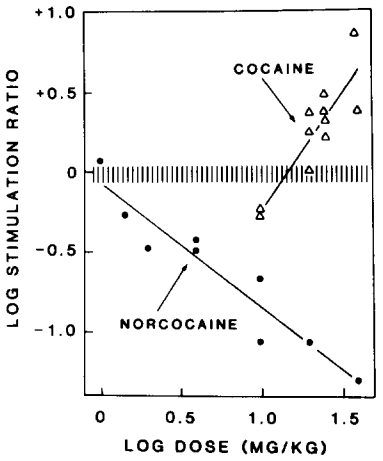


FIG. 1. Effects of IP administration of cocaine and norcocaine on spontaneous locomotor activity. The stimulation ratio is defined as the ratio of the number of activity counts produced during 40 min after injection over those in the 40-min period preceding injection (see the Method section). Each point represents one animal. The hatched area depicts the mean±SEM for six animals treated with saline alone.

served by one of the authors (MEAR) for a period of 10 min. After postsurgical recovery, animals were used over a 2-week period, and were injected more than once (at least one day apart). We are aware of reports of sensitization to certain effects of cocaine in the rat upon prolonged treatment [15, 17, 21], but we have not found evidence for this phenomenon in the mouse under the conditions of our experiments. Correct placement of the cannulas was verified by injecting Evans blue before killing the animal.

Drugs

The following persons or companies generously donated the drugs indicated: Dr. S. B. Ross, Astra (Sweden), benzoyltropine and benzoylpseudotropine; Dr. K. A. Nieforth (Storrs, CT), N-allylnorcocaine hydrochloride; Merck (Darmstadt, Germany), (+)-pseudococaine and (+)-neopseudococaine hydrogen tartrate; Sterling-Winthrop Research Institute (Rensselaer, NY), WIN 35,428, WIN 35,065-2, WIN 35,140, WIN 35,004, WIN 35,065-3, and tetracaine hydrochloride; Astra Pharmaceuticals (Worcester, MA), prilocaine hydrochloride and Xylocaine® (lidocaine hydrochloride); and National Institute on Drug Abuse, Research Triangle Institute (Research Triangle Park, NC), norcocaine, Mallinckrodt Chemical Corp. (St. Louis, MO) was the source of cocaine hydrochloride, and Sigma of procaine hydrochloride and benzocaine.

For the studies on locomotor behavior, drugs were dissolved in appropriately diluted saline to accomodate the contribution (if any) of the drug to the osmolarity. Compounds that came as free bases were dissolved as described below for intracerebroventricular (ICV) injections. Solutions were injected intraperitoneally (IP) in a volume of 0.15 ml per 20 g body weight. Benzocaine was dissolved in ethanol, and warm saline was added; the final ethanol concentration of 3–6% (v/v) did not by itself affect the locomotor activity. Lidocaine solutions were prepared by diluting Xylocaine® with saline.

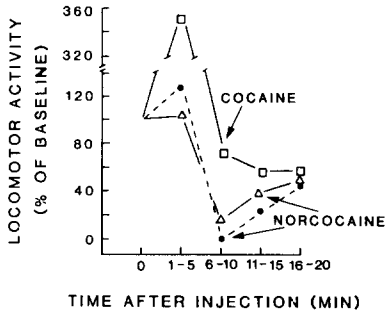


FIG. 2. Effects of IV administration of cocaine and norcocaine on spontaneous locomotor activity. The activity in each 5-min period is expressed as percent of baseline activity monitored for 20 min before injection. Note the break in the ordinate between 140 and 320%. Each curve represents one animal. □—□, 1 mg/kg cocaine; △—△, 1 mg/kg norcocaine; and ●——●, 6 mg/kg norcocaine.

For ICV and intravenous (IV) (tail vein) injection, the drugs were dissolved in an isotonic solution (vehicle) of 0.12 M NaCl and 6.2 mM sodium phosphate buffer, pH 6.7. Compounds that came as free bases were first dissolved in 25 mM sodium phosphate buffer, pH 6.7; then 0.15 M NaCl was added to obtain the above concentrations.

RESULTS

Locomotor Stimulation and Depression Following Systemic Administration

Of all cocaine congeners tested by IP administration (Table 1), only WIN 35,428 and WIN 35,065-2 increased the spontaneous locomotor activity, with potencies stronger than that of cocaine itself. The other compounds depressed locomotion; at severely inhibitory doses the animals spent most of the post-injection time sitting in one corner, with their backs curved and eyes open. The animals were less alert but did not assume postures normally associated with sleep. The inhibition of locomotion was dose-related. Doses that gave a two-fold decrease in locomotion were far lower than the lethal doses. Interestingly, the dose at which norcocaine reduced locomotion by a factor of two (2 mg/kg) was ten times lower than the dose of cocaine required for a two-fold stimulation (24 mg/kg) (Fig. 1) ($p<0.05$, no overlap in 95% confidence intervals). Low doses of cocaine of 0.5, 2, and 4 mg/kg resulted in stimulation ratios of 0.71±0.10, 0.76±0.02, and 0.64±0.03 (average ±SEM for 3 or 4 animals) respectively. Thus, although there was a tendency for decreased activity after low doses of cocaine, the effects were far weaker than those produced by comparable doses of norcocaine.

After IV injection of 1 mg/kg of cocaine, the onset of the stimulation was earlier, and the duration was appreciably shorter than after IP administration (Fig. 2). The same dose of norcocaine IV had little or no stimulatory effect; it produced an almost complete inhibition of locomotion from 6 to 10 min after injection (Fig. 2), an effect of shorter duration than that observed after IP administration. A higher IV dose of 6 mg/kg of norcocaine did not produce locomotor stimulation; again a severe locomotor inhibition was observed (Fig. 2).

Sniffing and Biting Following ICV Administration

Opposite effects of cocaine and norcocaine on locomotion

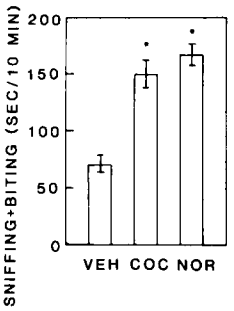


FIG. 3. Effects of ICV administration of cocaine and norcocaine. The duration of sniffing and biting was measured for 10 min after injection of vehicle (VEH), 0.05 mg/kg cocaine (COC), or 0.05 mg/kg norcocaine (NOR) as described in the Method and Results sections. The results are the average±SEM of 9 (vehicle) or 6 (drug) behavioral sessions. The entire experiment involved 5 animals that received vehicle, cocaine, and norcocaine in different sequences. *$p<0.01$, test of Wilcoxon, two-tailed.

were not found after intracerebroventricular injection. Observation revealed an increase in stereotyped behavior. Both drugs at 0.05 mg/kg produced a two-fold increase ($p<0.01$) in the total duration of sniffing and biting, measured for 10 min after injection, as compared with that after vehicle alone (Fig. 3). Further experimentation showed the increases to be dose dependent (data not shown); the drugs did not produce licking and did not consistently increase grooming. The sniffing occurred not only on the spot, with the nose up, but also included sustained forward head searching movements. Episodes of biting of skin or paws, though vigorous, usually lasted less than 15 sec, and the total time spent biting was far less than that spent sniffing.

Reversal of Locomotor Depression

The locomotor inhibition produced by IP norcocaine could be reversed by IP administration of cocaine (Fig. 4). When injected 20 min after 10 mg/kg of norcocaine, a dose of 40 mg/kg of cocaine produced a significant stimulation as compared with saline following norcocaine ($p=0.02$). Although the average activity after cocaine in animals pretreated with norcocaine was higher than their initial baseline (Fig. 4), this difference was not statistically significant, in contrast to the increase above baseline after cocaine in saline-pretreated animals ($p<0.01$).

Norcocaine has local anesthetic activity, and is in fact a more powerful local anesthetic than cocaine [10,13]. The observed reversal of norcocaine-induced inhibition by cocaine raises the question of whether other local anesthetic drugs can produce locomotor inhibition, and if so, whether cocaine can reverse that as well. Indeed, all local anesthetics tested (Fig. 5) were found to be inhibitory. Behaviorally, the effects were indistinguishable from those produced by cocaine congeners (see above). Locomotion was inhibited significantly $p\leq0.02$) by 75 mg/kg of procaine, one and a half times the ID_{50}, or 25 mg/kg of tetracaine, seven times the ID_{50}, in the experiments shown in Fig. 4. Treatment with 40 mg/kg of cocaine did not reverse the procaine-induced inhibition, but it did reverse the tetracaine-induced inhibition, as shown by the significant increase of locomotion after cocaine in comparison with the group that received saline following tetracaine ($p=0.02$).

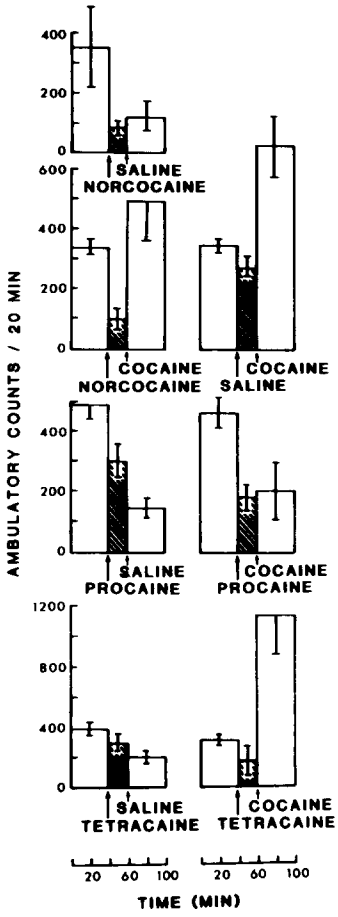


FIG. 4. The effect of IP cocaine (40 mg/kg) on animals having locomotor depression induced by IP norcocaine (10 mg/kg), procaine (75 mg/kg), or tetracaine (25 mg/kg). Arrows indicate the injections. The results are the average±SEM for 6 animals, except for the third row left panel (procaine-saline, 5 animals), the bottom left panel (tetracaine-saline, 5 animals), and the bottom right panel (tetracaine-cocaine, 4 animals).

Relationship Between Locomotor Depression Upon IP Aministration and Local Anesthetic Potency

The above results with procaine and tetracaine suggest that local anesthetic action is responsible for the locomotor depression observed after IP administration of cocaine congeners. To test this possibility, we compared the rank order of the locomotor inhibitory potencies of various drugs with the rank order of their local anesthetic potencies (Fig. 5). The latter activities, taken from the literature and averaged, were determined by measuring suppression of reflexes in the dog for compounds 1 and 9 [2], block of sensitivity after intradermal application in the guinea pig for 1–4 and 6 [3], block of conduction in frog sciatic nerve for 11, 13, 15 and 16 [1,23], and interaction with sodium channels in *in vitro* uptake or binding assays for 1, 7–9, and 14–17 [4, 12, 13, 16]. The rank order of estimates from the *in vitro* assays corresponds well with the rank order of potencies derived from (electro)physiological experiments [4, 11, 16]. There was a significant correlation between the potencies of cocaine congeners and of local anesthetics in depressing spontaneous locomotor activity and their local anesthetic potencies

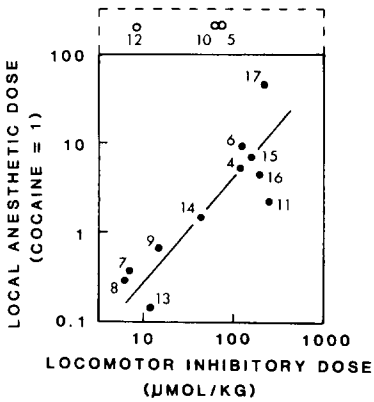


FIG. 5. Relationship between potencies in inhibiting locomotion and local anesthetic potencies. The locomotor inhibitory dose (ID_{50}) is the dose that produces a stimulation ratio of 0.5 (see the Method section). The local anesthetic dose is the dose required for a certain local anesthetic effect as compared with cocaine; these values were taken and averaged from the literature (see the Results section). The open symbols in the upper hatched box represent the locomotor inhibitory doses of drugs for which the local anesthetic potencies are unknown. The numbering of the cocaine congeners is as in Table 1. Additional local anesthetics shown: 13, tetracaine; 14, prilocaine; 15, lidocaine; 16, procaine, and 17, benzocaine.

($r=0.87$, $N=10$, $p<0.002$, Fig. 5). Benzocaine was not included in this analysis, because its dose-response curve was unusually flat; this is probably related to the different absorption kinetics reflecting its insolubility in water [20]. The 95% confidence interval of the ID_{50} of compound 14 in inhibiting locomotion did not overlap with that of 7, 8, 9, or 13, indicating a significant difference (Fig. 5). There was also no overlap in the 95% confidence intervals of the ID_{50}'s of compounds 7, 8, 9, and 13 on the one hand, and those of 4, 6, 15, and 16 on the other.

DISCUSSION

Structure-Activity Relationships

The structure-acitivity relationships observed in the present work for depression of spontaneous locomotion differ from those reported for various central activities [3, 5, 8, 9, 24–27], but generally correspond to those for local anesthetic activity. Thus, removal of the ester linkage between the tropane and phenyl rings of cocaine (compounds 4 and 6) appreciably reduces locomotor inhibitory potency (Fig. 5) and anesthetic potency [3]. Moving the carbomethoxy group (R_2) on C_2 of cocaine from an axial (compound No. 1) to an equatorial (No. 9) position, or N-demethylation (No. 7) gives potent compounds. Increasing the negativity associated with the oxygen atom of the carbonyl group of procaine (No. 16) by adding C_4H_9 to the p-NH_2 group on the phenyl ring (No. 13) greatly enhances the potency. Introduction into lidocaine (No. 15) of more aliphatic groups (No. 14) also increases the potency. The local anesthetic activity of compound 5 has not been determined [3], but it can be expected to be similar to that of its close congener, 4; the two drugs are also close in potency of locomotor inhibition (Fig. 5). The stronger effects on locomotion of 12 as compared to 11 (Fig. 5) suggests that it is a potent local anesthetic. If this is the case, moving the O-benzoyl group (R_4) on C_3 of tropacocaine from an equatorial (No. 11) to an axial (No. 12) position results in a change in local anesthetic activity opposite to that produced by C_3 epimerization of cocaine (allococaine) or pseudococaine (allopseudococaine) [13]. Extension of the carbomethoxy group in (+)-pseudococaine (yielding No. 10) reduces the inhibitory effect on locomotion (Fig. 5); it is of interest that this extension increases the potency in inhibiting high-affinity binding of imipramine and cocaine in the cerebral cortex [18] and in blocking uptake of monoamines into central neurons (manuscript submitted).

Peripheral Versus Central Sodium Channels

Needless to say, the above comparisons between drug effects under various conditions have to be interpreted with extreme caution. Drugs applied in vivo must be transported to their presumed sites of action, are susceptible to metabolizing enzymes, and may have multiple effects. Yet, the correlation between potency of locomotor inhibition and local anesthetic activity of cocaine-related structures is impressive and is consonant with the implication of sodium channels in observed locomotor depression. It is a matter of speculation whether centrally located channels are involved. Suggestive evidence against this is our observation that intracerebroventricularly applied norcocaine has no locomotor depressive effect. In addition, if IP norcocaine or tetracaine did block sodium channels on central neurons, the increase in central monoamines by subsequent administration of cocaine, a monoamine uptake inhibitor, would be expected to have no effect on such neurons with blocked sodium channels. Since norcocaine penetrates the brain as rapidly as cocaine itself [14], IP administration of 2 mg/kg of norcocaine, which is the ID_{50} for locomotor inhibition, could result in brain levels as high as 1 μM after 10 min [7], when the behavioral depression is evident; IC_{50} values of 2 and 6 μM have been reported for norcocaine and cocaine in inhibiting the uptake of sodium in preparations of sodium channels from brain [13]. However, appreciably higher concentrations of cocaine and other local anesthetics are required for inhibition of binding of batrachotoxinin-A20-α-benzoate to sodium channel preparations from brain [4,16] and for inhibition of batrachotoxin-induced depolarization of such preparations [4]. Since local anesthetics interfere with the function of all organs in which conduction of impulses occurs [20], it is conceivable that multiple targets at the peripheral level are involved, such as the cardiovascular system (decrease in force of contraction and arteriolar dilation), the neuromuscular junction (decrease in conduction), and the lungs (depression of respiration). In this context it is of interest that notable side effects of lidocaine in humans are sleepiness and dizziness [20]. Perhaps the local anesthetic effects at multiple sites may sometimes add up to locomotor inhibition so severe that subsequent central stimulation by cocaine is ineffective, as found with procaine-induced depression (Fig. 4). The behavioral depression observed in this study by IP administration of cocaine congeners is strikingly similar to that described after IV injection of lidocaine into rabbits and cats [29], and is therefore not an unusual response displayed by the particular mouse strain used in the present work. It has been shown that the lidocaine-induced behavioral depression in rabbits and cats is accompanied by changes in the electrical activity of the amygdala, and is usually followed by a slowing of the EEG; Wagman *et al.* leave the question open of whether the locomotor depression is in fact caused by such central "sedative" effects or is caused by block of conduction in peripheral motor and sensory systems [29].

Local Anesthetic Effect Versus Inhibition of Dopamine Uptake

Most of the present results are consonant with the suggestion that the locomotor depression induced by cocaine congeners results from their peripheral or central local anesthetic actions on sodium channels, whereas the locomotor stimulation involves a central mechanism of action. Dopaminergic systems in the brain have been implicated in the locomotor stimulation induced by cocaine and its phenyltropane analogs [8, 9, 22], and indeed the locomotor stimulants, WIN 35,428 and WIN 35,065-2 (see Table 1) inhibit the neuronal uptake of dopamine in mouse striatum with a potency more than 30 times higher than that of the locomotor depressants 4–6 and 9–12 (manuscript submitted), whereas the local anesthetic potency of the former drugs is similar to or weaker than that of the latter. In contrast, norcocaine is only two times weaker than cocaine in inhibiting striatal dopamine uptake, and yet does not induce locomotor stimulation at any dose tested IP (Fig. 1). This may be the result of the fact that norcocaine is a stronger local anesthetic than cocaine [10,13], so that upon systemic administration of norcocaine (and also N-allyl-norcocaine) to mice, the local anesthetic activity of the drug outweighs its capability in interfering with central dopamine. Conversely, upon systemic administration of cocaine, the central stimulatory effect dominates.

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