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Effect of Cocaine on Sexual Behaviour in Male Stumptail Macaques (*Macaca arctoides*)[1]

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LINNANKOSKI, I., M. GRÖNROOS, S. CARLSON AND A. PERTOVAARA. *Effect of cocaine on sexual behaviour in male stumptail macaques* (Macaca arctoides). PHARMACOL BIOCHEM BEHAV 52(1) 211–216, 1995.—The effect of cocaine (0.01–1.0 mg/kg) on sexual behaviour was studied in four male stumptail macaques (*Macaca arctoides*). Following drug–saline control administration, the behaviour of the male monkey with a female was observed for 30 min in two different behavioural conditions; in one of the conditions the baseline sexual activity was low, and in the other it was high (partial or complete separation of the male and the female between the sessions, respectively). The reversal of the cocaine-induced effects was attempted by haloperidol (0.003–0.01 mg/kg), a dopamine-2-receptor antagonist. Cocaine (0.1–1.0 mg/kg) produced a highly significant dose-dependent suppression in the number of ejaculations. The cocaine-induced suppression of ejaculatory behaviour was completely reversed by haloperidol. Haloperidol at the dose range used did not in itself influence ejaculatory behaviour. The effect of cocaine on grooming, nonejaculatory mounting, aggression, or perineal investigations did not reach statistical significance. The possibility that cocaine at very low doses (0.01–0.1 mg/kg) might increase sexual activity was excluded in the behavioural condition with a low basal sexual activity. The results indicate that cocaine dose-dependently suppresses ejaculatory behaviour as a result of dopamine-2-receptor–mediated mechanisms. The cocaine-induced suppression of ejaculatory behaviour might be explained by the strong rewarding effect of cocaine alone.

Cocaine Dopaminergic antagonist Ejaculation Haloperidol Monkey Sexual behaviour

THERE is a considerable amount of data indicating that dopamine is important for male sexual behaviour. Most of the evidence indicates that dopamine agonists facilitate various aspects of sexual activity in male rats (2), monkeys [(18); however, (4)], and humans (11). Cocaine activates dopaminergic mechanisms as a result of a nonselective reuptake block of monoaminergic neurotransmitters (9). Cocaine has a reputation as an aphrodisiac in humans, although there is no verified experimental data on its effect on sexual behaviour in humans or nonhuman primates. There is little data on the effect of cocaine on sexual behaviour in male rats. In one study cocaine at low doses enhanced sexual activity of male rats, whereas at high doses sexual activity was suppressed (12). According to another rat study cocaine did not affect sexual behaviour (1). The current study is the first attempt to examine the effect of cocaine on sexual behaviour in nonhuman primates, male stumptail macaques (*Macaca arctoides*). The effect of cocaine was tested in two different behavioural conditions, in one of which the basal sexual activity was high and the other low. The reversal of possible cocaine-induced effects was attempted by haloperidol, the prototype dopamine-2-receptor antagonist.

METHOD

Four adult male and two adult female stumptail macaques were studied in the experiments. One of the females monkeys and three of the males were used in our preceding study on the effect of atipamezole on sexual behaviour (13). The females were sexually mature with normal hormonal cycles. There were no signs of pregnancy during the experiments. During the testing period, the monkeys were housed individually in

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stainless-steel cages. All monkeys were fed commercially available food twice each day, and water was always available. The experimental protocol was approved by the Institutional Ethics Committee of the University of Helsinki.

Males were weighed before the first injection of each series of tests. Doses were adjusted accordingly when appropriate. Sexual behaviour was tested between 1100 and 1600 h. The same test cage and testing procedure were used in all experiments. Two experienced observers, one at a time, viewed the animals at a distance of about 0.5 m from the cage.

During the testing period the couple being tested was housed in a single cage (0.6 × 0.9 × 1.2 m) with two compartments. During the first 10 min of each session, a sliding wall made of steel bars separated the male and the female in the test cage. The monkeys could see and touch each other through this wall. There were two behavioural conditions; the housing of the female between the sessions depended on the behavioural condition. In one of the conditions the aim was to find possible increases in sexual activity and therefore to have a low basal sexual activity in the test session. This was accomplished when the female was housed in the test cage between the sessions, separated, however, by the sliding wall from the male (partial separation of the male and the female between sessions). In the other condition the aim was to find possible decreases in sexual activity and therefore to have a high basal sexual activity during the test session. This was accomplished by housing the female between the sessions in another cage in another room, with no visual contact with the male being tested (complete separation of the male and the female between sessions).

After intramuscular (IM) administration of the studied drug dose–saline control to the male, observation of the sexual behaviour began as described subsequently. Ten minutes after drug administration, the sliding wall between the male and the female was pulled away and the observation of sexual activity continued for the next 20 min. At the end of the observation period (30 min after drug administration), the sliding wall was replaced. During complete separation between sessions, the female was taken after the test session to her home cage in the other room, whereas during partial separation between sessions, the female remained in the test cage, separated by the sliding wall from the male.

The time of occurrence and duration of the following behaviours were observed: perineal investigation, mounting, masturbation, ejaculation, tying, male and female grooming, direct aggression toward the female, yawning, self-scratching, and teeth grinding. Ejaculation obtained by masturbation and copulation were registered separately. Ejaculation obtained by copulation was divided into that obtained in uninterrupted copulation and that obtained in interrupted copulation. A single mount leading to ejaculation was considered to be an uninterrupted ejaculation. An interrupted ejaculation was defined as ejaculation obtained following two or more mounts. If the interval between mounts was >30 s, the mount was considered to be separate and not part of interrupted ejaculation even when followed by a mount leading to ejaculation.

In stumptail macaques, male ejaculation reached in copulation or masturbation can be recognized clearly on the basis of its stereotypic manifestations. This has been described earlier in detail (14–16) and is only briefly described here. Following ejaculation, the male displays momentary rigidity; full body inertia usually followed by body spasms; a frowning, round-mouthed look; and rhythmic expiration vocalizations. The male remains coupled to the female for about 20–30 s. After masturbation ejaculation, the male keeps its hand around the penis for about 20–30 s.

The doses of cocaine were selected on the basis of previous publications indicating that doses of 0.1 and 1.0 mg/kg, IM, are effective in modulating the behaviour of monkeys (10). In addition, one dose lower than these was used (0.01 mg/kg) when exploring the hypothesis that at very low doses, cocaine might increase sexual behaviour as reported in an earlier rat study (12). Haloperidol at the dose range used (0.003–0.01 mg/kg, IM) has proved not to influence significantly the behaviour of monkeys when administered alone (10). In our preliminary tests haloperidol alone at a dose of 0.03 mg/kg proved to be too high a dose for these experiments, because at that dose it suppressed sexual behaviour in itself.

The experiments were performed once a day for 5 days/week. Cocaine (dissolved in physiologic saline) was administered IM at a concentration of 0.25, 2.5, or 25 mg/ml when the dose was 0.01, 0.1, or 1 mg/kg, respectively. The order of testing the two behavioural conditions was counterbalanced between the subjects. In the behavioural condition of complete separation between sessions (high basal sexual activity), we studied the effect of two cocaine doses (0.1 and 1.0 mg/kg). The order of testing was: saline, cocaine 1 mg/kg, saline, saline, cocaine 0.1 mg/kg. This test series was repeated five times for each monkey. Furthermore, in complete separation between sessions, the impact of two haloperidol doses (0.003 and 0.01 mg/kg) on the cocaine-induced effects was studied. The order of testing was: saline, haloperidol alone, saline, saline, haloperidol combined with cocaine (0.1 mg/kg). This test series was repeated twice at each haloperidol dose. Some of the test series with cocaine alone were performed between and following the test series with haloperidol. In the haloperidol plus cocaine condition, these two drugs were administered into the opposite gluteal regions to avoid possible peripheral interactions between the drugs. In partial separation between sessions (low basal sexual activity), the effect of two low cocaine doses (0.01 and 0.1 mg/kg) was evaluated. The order of testing was: saline, cocaine 0.01 mg/kg, saline, saline, cocaine 0.1 mg/kg. This series was repeated five times with each monkey. According to previously published data the interval between the two cocaine doses was long enough to prevent possible interactions between two cocaine administrations (10).

In each condition, the mean numbers or durations of the observed behavioral indexes were calculated. The effects of the studied compounds (cocaine with or without haloperidol) were compared with the effect of saline control. One-way analysis of variance (ANOVA) and Student's *t*-test (with Bonferroni correction for multiple comparisons, when appropriate) were used in statistical evaluation of the data. $p < 0.05$ was considered to represent a significant difference.

RESULTS

General

There was significantly more sexual activity (total number of ejaculations) when the test session took place after complete separation (the male and the female were in different rooms between sessions) than when the test session took place after partial separation (the male and female were in the same cage between sessions, but without the possibility of copulation). This was shown by the difference in the total number of ejaculations obtained with saline control in these two conditions [$t(df = 3) = 5.084$, $p < 0.02$; paired *t*-test; compare the saline condition in Fig. 1A with that in Fig. 3A].

In two monkeys all ejaculations were obtained in copulation. Only in two monkeys and only in the saline control conditions were a few ejaculations obtained by masturbation (an average of 0.03 and 0.2 masturbation ejaculations per session with saline). Ejaculation obtained by masturbation was left out in the following results because of their low incidence in this study. Thus, in this report the total number of ejaculations consisted of ejaculations obtained in uninterrupted and interrupted copulations.

Complete Separation Between the Sessions Condition

We explored the hypothesis of a possible suppressive effect of cocaine on sexual behaviour as well as its reversibility by haloperidol in the behavioural condition producing a high sexual activity in control conditions (i.e., the condition complete separation between sessions). Cocaine produced a highly significant dose-dependent (0.1 and 1.0 mg/kg) decrease in the total number of ejaculations [$F(6, 27) = 12.36$, $p < 0.0001$; ANOVA], and this cocaine-induced suppressive effect could be completely reversed by haloperidol at doses (0.003 and 0.01 mg/kg) that did not in themselves have any effect on the total number of ejaculations (Fig. 1A). The effect of cocaine and haloperidol treatment was also significant when the number of uninterrupted and interrupted ejaculations were separately evaluated [$F(6, 27) = 10.22$, $p < 0.0001$, and $F(6, 27) = 3.37$, $p = 0.021$, respectively; ANOVA; Fig. 1B and C]. The effect of cocaine and haloperidol treatment was not significant for the number of nonejaculatory mounts [Fig. 1D, $F(6, 27) = 1.43$; ANOVA] or the incidence of perineal investigation [Fig. 2A, $F(6, 27) = 1.58$; ANOVA]. There was also a lack of significant effect of drug treatment for the incidence of aggressions [Fig. 2B, $F(6, 27) = 1.28$; ANOVA] and the duration that the male groomed the female [Fig. 2C, $F(6, 27) = 1.34$; ANOVA]. However, it should be noted that there was a very low baseline level of these activities. Only one of the males showed a considerable amount of grooming activity with saline (523 ± 45 s/session, mean ± SEM); and this individual had a marked dose-dependent decrease of activity following cocaine (7 ± 6 s/session following 1 mg/kg of cocaine). The drug treatments had no significant effect on the duration of grooming by the female [Fig. 2D, $F(6, 27) = 2.03$; ANOVA], although the duration of grooming by the

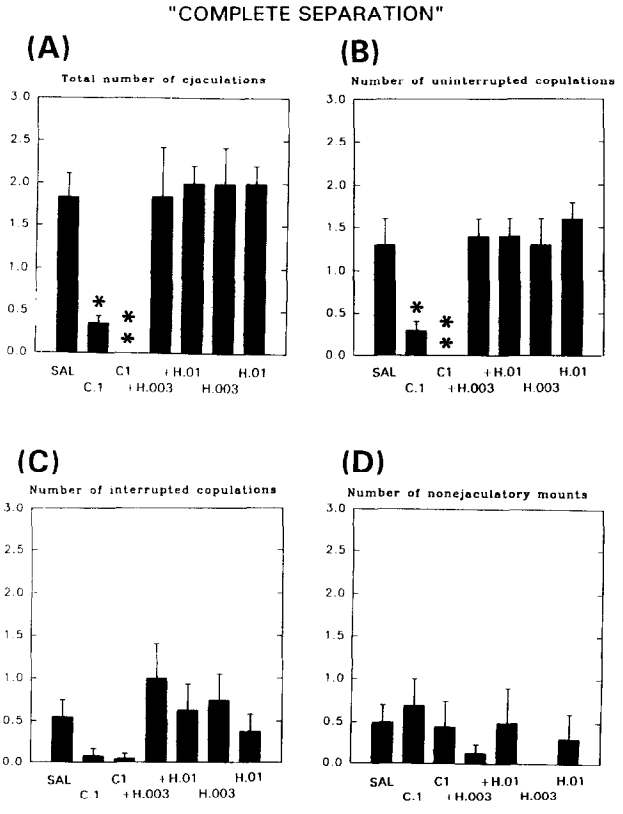

FIG. 1. Hypothesis of a decrease in sexual behaviour by cocaine was tested in a behavioural condition producing a high basal sexual activity in saline control sessions [i.e., between the test sessions the male and the female were completely separated (in different rooms)]. (A) Total number of ejaculations/session (B) Number of uninterrupted ejaculations obtained by copulation/session. (C) Number of interrupted copulations leading to ejaculation/session. (D) Number of mounts not leading to ejaculation/session. SAL, Saline control; C.1 and C1, cocaine at the dose of 0.1 or 1 mg/kg, respectively; +H.003 and +H.01, cocaine 0.1 mg/kg + haloperidol at the dose of 0.003 or 0.01 mg/kg, respectively; H.003 and H.01, haloperidol alone at respective doses. The vertical error bars represent SEM ($n = 4$). *$p < 0.05$; **$p < 0.01$ (t-test with Bonferroni correction for multiple comparisons; reference = SAL).

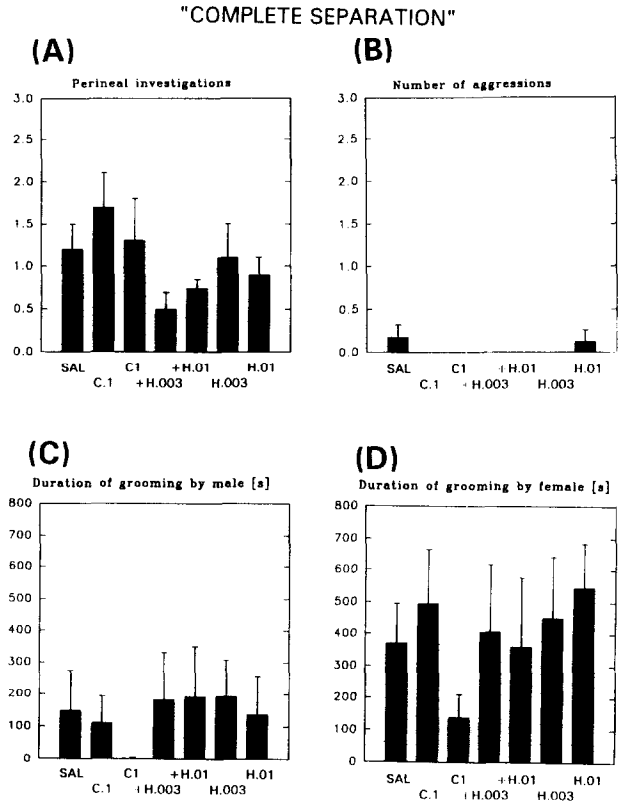

FIG. 2. (A) Number of perineal investigations/session. (B) Number of aggression toward female/session. (C) Duration of grooming by male/session. (D) Duration of the grooming by female/session. For further explanations, see Fig. 1.

female was slightly briefer when the male was under the influnce of the higher dose of cocaine.

Partial Separation Between the Sessions Condition

The hypothesis that cocaine at low doses (0.01 and 0.1 mg/kg) might increase sexual activity was tested in the behavioral condition with low basal sexual activity (partial separation between sessions). There was no cocaine-induced increase of the low baseline ejaculatory activity. If anything, there was a tendency to decrease in the total number of ejaculations (Fig. 3A). This cocaine-induced decrease from the low baseline value, however, was not significant [$F(2, 11) = 1.34$; ANOVA]. None of the studied parameters (number of uninterrupted or interrupted ejaculations, number of aggressions or nonejaculatory mounts, duration of grooming by the male or the female, or incidence of perineal investigations) was significantly influenced by cocaine in the partial separation between sessions condition (ANOVA; Figs. 3 and 4).

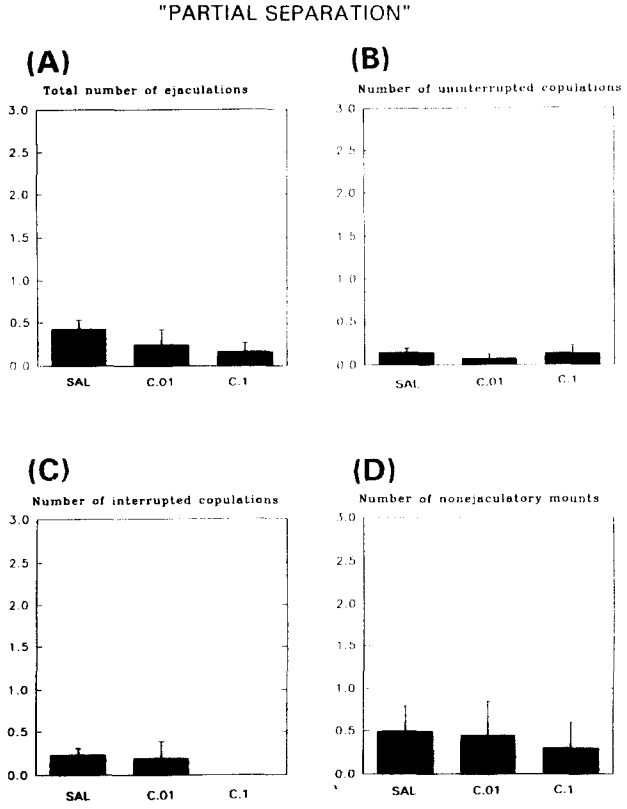

FIG. 3. Hypothesis of an increase in sexual behaviour by cocaine tested in a behavioural condition producing a low sexual activity in saline control sessions [i.e., between the test sessions the male and female were in the same room, but with no possibility of copulating (partial separation)]. (A) Total number of ejaculations/session. (B) Number of uninterrupted ejaculations obtained by copulation/session. (C) Number of interrupted copulations leading to ejaculation/session. (D) Number of mounts not leading to ejaculation/session. SAL, Saline control; C.01 and C.1, cocaine doses 0.01 and 0.1 mg/kg, respectively. The error bars represent SEM ($n = 4$).

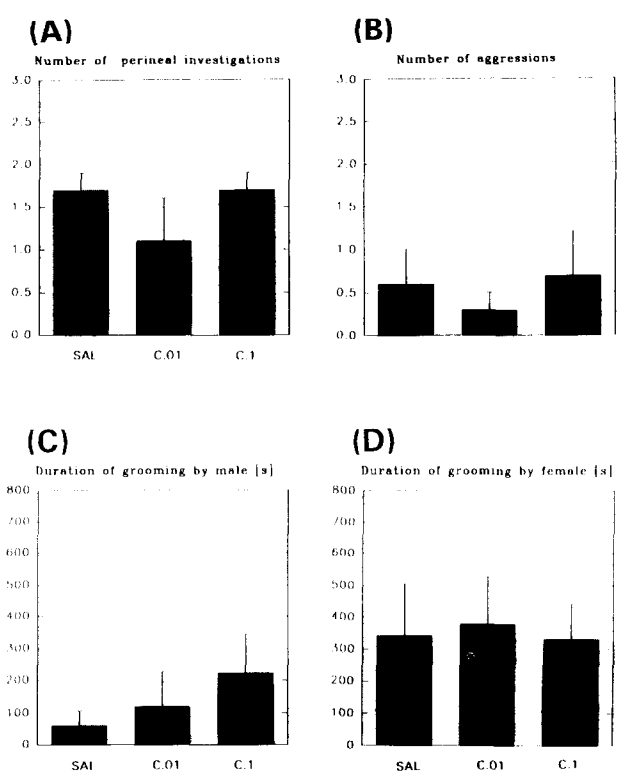

FIG. 4. (A) Number of perineal investigations/sessions. (B) Number of aggressions toward female/session. (C) Duration of grooming by male/session. (D) Duration of grooming by female/session. For further explanations, see Fig. 3.

DISCUSSION

The choice of behavioural paradigms for the study of drug effects proved to be successful. With complete visual and tactual separation between the test sessions there was more sexual activity than when the male and the female were between test sessions in the same room without the possibility of copulation. These two behavioural conditions allowed us to find possible decreases and increases in sexual activity, respectively. Thus, it was possible to eliminate, for example, sexual exhaustion as a cause of failure to find increased activity, or a low basal sexual activity as a cause of a failure to find a drug-induced suppression.

There is a considerable amount of evidence indicating that dopamine agonists increase sexual activity in males of various species, including rats (2), monkeys [(18); however, (4)] and humans (11). Also, amphetamine which, like cocaine, produces activation of dopaminergic system through a nonselective reuptake block of monoamines (9), has been reported to be effective in increasing sexual activity in male rats, at least when applied at low doses (5,12). The present failure to produce an increase in sexual activity in male stumptail macaques by cocaine, a dopaminergic compound, may depend on various reasons. Cocaine nonselectively activates dopamine receptors, and the direction of effect on sexual behaviour (increase vs. decrease) depends on the dopamine receptor subtype activated (7,18). The fact that cocaine in addition to its dopamin-

ergic effect has a number of other neurochemical effects [e.g., noradrenergic and serotoninergic (9)] may be another explanation. Accordingly, it has been suggested earlier that a nonselective increase of monoamines inhibits copulatory behaviour [cf. (2)]. A nonselective coactivation of serotoninergic system may also have contributed to the lack of cocaine-induced increase in sexual activity in the present study, because depending on the serotoninergic receptor subtype the serotoninergic influence may suppress sexual activity in primates (19) and possibly mask the cocaine-induced increase. The possibility that cocaine at a very low dose might increase sexual acitivity as reported with male rats (12) was also excluded in the low basal sexual activity condition of the present study.

The main finding of this study was that cocaine dose dependently suppressed ejaculatory activity in male stumptail macaques. Also, in a previous rat study, cocaine at high but not low doses decreased sexual activity (12), although another study reported no effects by cocaine on the sexual behaviour of male rats (1). The cocaine-induced suppression of ejaculatory activity in male stumptail macaques was due to activation of dopamine-2-receptors as indicated by the complete reversal of the suppression by haloperidol. Importantly, haloperidol at the dose range used (0.003–0.01 mg/kg) did not in itself influence sexual behaviour in this study. At higher doses haloperidol alone can markedly influence sexual behaviour as also shown by our preliminary results using haloperidol at a dose of 0.03 mg/kg. The suppressive effect of cocaine on schedule-controlled behaviour in squirrel monkeys was attenuated by identical doses of haloperidol in a recent study (10). However, in contrast to sexual behaviour observed in our study, haloperidol at the dose range 0.03–0.01 mg/kg did have an effect on schedule-controlled behaviour in squirrel monkeys. The locomotor stimulant effects of cocaine and its analogs as well as the discriminative effects of cocaine have been attenuated by haloperidol in earlier investigations [e.g., (6,8)]. Thus, a number of behavioural effects of cocaine may be mediated by haloperidol-sensitive receptors. This conclusion is hampered by the fact that some of the previously reported reversals of cocaine-induced effects by haloperidol have been achieved at haloperidol doses which themselves influenced behaviour [cf. (10)], which was not the case in the present study.

The most simple and plausible explanation for the current cocaine-induced decrease in the number of ejaculations is the high rewarding effect of cocaine. In other words, the pleasure produced by cocaine may have been stronger that that produced by copulation. However, we cannot exclude a decrease in libido or sexual ability as contributing factors. The decrease in ejaculatory behaviour with the lack of significant cocaine-induced changes in the other behavioural parameters observed (nonejaculatory mounts, grooming, aggressions, perineal investigations) might be considered to give support to the interpretation that sexual ability was decreased by cocaine. Against this interpretation it could be argued that these other behavioural parameters are not always related to sexual activity but to other functions as well (e.g., showing of dominance by aggression and nonejaculatory mounts). Furthermore, the very low basal activity of nonejaculatory behaviour may underlie the lack of cocaine-induced suppression in these behavioural parameters. Interestingly, morphine, another compound with strong rewarding effects but with underlying neurochemical mechanisms different from those of cocaine, has been reported to decrease sexual activity in male rats (17). Similarly, it has been previously shown that male rats prefer to self-stimulate the medial forebrain bundle, a structure presumably important for mediating the rewarding properties of cocaine, rather than mating with females when given the choice (3). These observations support the hypothesis that a compound with strong intrinsic rewarding properties, such as cocaine or morphine, can suppress male sexual activity by substituting for the copulation-induced reward value.

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REFERENCES

1. Abel, E. L.; Moore, C.; Waselewsky, D.; Zajac, C.; Russell, L. D. Effects of cocaine hydrochloride on reproductive function and sexual behavior of male rats and the behavior of their offspring. J. Androl. 10:17–27; 1989.
2. Bitran, D.; Hull, E. M. Pharmacological analysis of male rat sexual behavior. Neurosci. Biobehav. Rev. 11:365–389; 1987.
3. Carlsson, S. G.; Larsson, K. Self-stimulation and mating behavior in the male rat. Scand. J. Psychol. 16:7–10; 1975.
4. Chambers, K. C.; Phoenix, C. H. Apomorphine, deprenyl, and yohimbine fail to increase sexual behavior in rhesus males. Behav. Neurosci. 103:816–823; 1989.
5. Dallo, J.; Lekka, N.; Knoll, J. The ejaculatory behavior of sexually sluggish male rats treated with (−)deprenyl, apomorphine, bromocriptine and amphetamine. Polish J. Pharmacol. Pharm. 38:251–255; 1986.
6. Heikkilä, R. E.; Cabbat, F. S.; Manzino, L.; Duvoisin, R. C. Rotational behavior induced by cocaine analogs in rats with unilateral 6-hydroxydopamine lesions of the substantia nigra: Dependence upon dopamine uptake inhibition. J. Pharmacol. Exp. Ther. 211:189–194; 1979.
7. Hull, E. M.; Eaton, R. C.; Markowski, V. P.; Moses, J.; Lumley, L. A.; Loucks, J. A. Opposite influence of medial preoptic D_1 and D_2 receptors on genital reflexes: Implications for copulation. Life Sci. 51:1705–1713; 1992.
8. Järbe, T. U. C. Cocaine as a discriminative cue in rats: Interactions with neuroleptics and other drugs. Psychopharmacology 59: 183–187; 1978.
9. Johanson, C. E.; Fischman, M. W. The pharmacology of cocaine related to its abuse. Pharmacol. Rev. 41:3–52; 1989.
10. Katz, J. L.; Witkin, J. M. Behavioral effects of cocaine alone and in combination with selective dopamine antagonists in the squirrel monkey. Psychopharmacology 103:33–40; 1991.
11. Lal, S.; Ackman, D.; Thavundayil, J. X.; Kiely, M. E.; Etienne, P. Effect of apomorphine, a dopamine receptor agonist, on penile tumescence in normal subjects. Prog. Neuropsychopharmacol. Biol. Psychiatry 11:235–242; 1984.
12. Leavitt, F. I. Drug-induced modifications in sexual behavior and open field locomotion of male rats. Physiol. Behav. 4:677–683; 1969.
13. Linnankoski, I.; Grönroos, M.; Carlson, S.; Pertovaara, A. Increased sexual behavior in male Macaca arctoides monkeys produced by atipamezole, a selective alpha-2-adrenoceptor antagonist. Pharmacol. Biochem. Behav. 42:197–200; 1992.
14. Linnankoski, I.; Grönroos, M.; Pertovaara, A. Eye contact as a trigger of male sexual arousal in stump-tailed macaques (*Macaca arctoides*). Folia Primatol. 60:181–184; 1993.
15. Linnankoski, I.; Hytönen, Y.; Leinonen, L.; Hyvärinen, J. Determinants of sexual behavior of *Macaca arctoides* in a laboratory colony. Arch. Sex. Behav. 10:207–222; 1981.
16. Linnankoski, I.; Leinonen, L. Compatibility of male and female

sexual behaviour in Macaca *arctoides*. Z. Tierpsychol. 70:115–122; 1985.
17. Pfaus, J. G.; Gorzalka, B. B. Opioids and sexual behavior. Neurosci. Biobeh. Rev. 11:1–34; 1987.
18. Pomeranz, S. M. Dopaminergic influences on male sexual behavior of rhesus monkeys: Effects of dopamine agonists. Pharmacol. Biochem. Behav. 41:511–517; 1992.
19. Pomeranz, S. M. 5-HT_{1A} and 5-HT_{1C}/1D receptor agonists produce reciprocal effects on male sexual behavior of rhesus monkeys. Eur. J. Pharmacol. 243:227–234; 1993.