The Pharmacology of Sexual Function and Dysfunction
J. Bancroft, editor

Monoamine influences on male sexual behavior of nonhuman primates

S.M. Pomerantz[1]

Department of Cell Biology and Physiology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania 15261, U.S.A.

Introduction

Over the years there has been considerable interest in investigating the neurotransmitter mechanisms underlying male sexual behavior. Although much progress has been made in this area, thus far most of the research has been conducted on laboratory rats with comparatively few studies being performed on humans and other primates. Consequently, many hypotheses and conclusions that have been formulated regarding neurotransmitter regulation of male sexual behavior have been generated from rat studies and need to be validated in primates. This paper will review recent progress that has been made investigating neurotransmitter influences of nonhuman primate male sexual behavior. More specifically, it will focus on studies exploring the possible role played by monoaminergic neurotransmitters in regulating male sexual behavior of nonhuman primates.

Development of a Nonhuman Primate Model to Study Neurotransmitter Regulation of Male Sexual Behavior

Prior to our research, the traditional method for evaluating neurotransmitter influences on nonhuman primate male sexual behavior was one in which the male was injected with a test compound or vehicle control and then paired with a battery of different females in separate behavioral tests. This acute pair test paradigm was used successfully in studies aimed at characterizing gonadal hormone influences on male sexual behavior of castrated males, since these animals tend to exhibit consistently low levels of sexual behavior prior to hormone treatment [1-3]. In contrast, this approach has not proven successful in elucidating neurotransmitter influences on male sexual behavior of gonadally intact males [4-5]. These animals, both prior to pharmacological treatment and during baseline vehicle testing, tend to show high levels of sexual behavior with a great deal of intertest variability. As a result, it has been extremely difficult to detect any effects of drug treatment on male sexual behavior using this acute pair testing paradigm in gonadally intact nonhuman primates.

In order to remedy this situation, we developed two novel sex behavior testing paradigms which have proven to be quite effective in characterizing neurotransmitter influences on male sexual behavior. The first paradigm, **the sexual stimulus test** [6], involves observing the sexual responses of a male rhesus after presenting him with a sexually receptive female monkey that he can see, hear, and smell, but is unable to physically contact. In this simple test setting, we can directly evaluate the effects of various drug treatments on noncopulatory measures of male sexual behavior including penile erection, masturbation, and courtship behavior. The second experimental paradigm, **the copulatory behavior test** [7], involves evaluating male sexual behavior in tests in which an experimental male and his female partner are paired together daily in the same cage for up to two ejaculations. Monkeys establish a stable level of baseline sexual performance under this chronic pair test arrangement in which they are continually tested over successive days with the same partner. As a result, when chronic pair tests are employed, the sensitivity of detecting drug effects on male copulatory performance is improved over that obtained through the use of acute pair testing procedures.

Dopamine Regulation of Male Sexual Behavior of Rhesus Monkeys

Initial studies in our laboratory used the sexual stimulus test to examine the effects of DA receptor agonists on male sexual responding [6,8]. As shown in Table 1, both the mixed D_1/D_2 receptor agonist, apomorphine, and the D_2 receptor agonist, quinelorane, markedly facilitated penile erections and masturbation of male rhesus monkeys. By contrast, the specific D_1 receptor agonist, SKF 81297, did not significantly affect male sexual performance in this testing paradigm. Additional experiments revealed that apomorphine had little effect on male penile erections and masturbation, when the males were tested in the absence of a stimulus female [6]. This finding indicates that the stimulation of male sexual responding by D_2 receptor agonists depends upon additional psychological factors, such as those produced by the presence of the female in the behavioral test. In order to evaluate whether DA agonists act centrally or peripherally to stimulate male sexual behavior, the ability of the peripherally-active DA antagonist, domperidone, and the centrally-active DA antagonist, haloperidol, to block the facilitation of sexual behavior produced by quinelorane treatment was examined [8]. Administration of domperidone (50-200 μg/kg), failed to block quinelorane's effects on sexual behavior, whereas treatment with haloperidol (5-20 μg/kg), prevented quinelorane from stimulating male sexual responding. These results indicate that D_2 receptor agonists act centrally to stimulate male penile erections and masturbation.

Table 1
Effects of DA Agonists on Behavior of Rhesus Monkeys

Drug (μg/kg)	Penile Erections (# of 10-sec periods)	Masturbation (# of 10-sec periods)
Apomorphine		
0	4.2±1.9	0.3±0.3
25	15.4±4.5	2.5±1.6
50	25.3±9.7	5.3±4.6
100	22.7±5.3	8.8±4.6
200	18.8±7.9	1.9±0.6
400	3.9±2.1	0.1±0.1
Quinelorane		
0	4.0±1.4	0.1±0.1
1	9.0±2.8	0.6±0.5
2.5	21.0±6.5	3.1±1.6
5	22.7±6.9	4.9±1.7
10	14.9±3.0	3.5±1.4
25	10.1±4.0	0.9±0.6
SKF 81297		
0	3.5±1.2	0.0±0.0
500	4.5±2.2	0.2±0.2
1000	3.0±2.1	0.0±0.0

Values represent mean (±SEM) of eight monkeys for apomorphine and quinelorane and four monkeys for SKF 81297.

DA influences on primate male sexual behavior were further evaluated by assessing the effects of DA agonists on male copulatory behavior of rhesus monkeys [7]. As shown in Figure 1, treatment with either the mixed D_1/D_2 agonist apomorphine, or the D_2 agonist, quinelorane, shortened the monkeys' postejaculatory interval (PEI) and increased their ejaculation latency. Interestingly, the doses of apomorphine and quinelorane which shortened the monkeys' PEI were comparable to those which had previously been found to stimulate male penile erections. By contrast, higher doses of these compounds were generally required to inhibit ejaculation. It should be noted that monkeys were assigned maximum PEI scores of 30 min if they failed to reinitiate copulation during the 30 min period allotted. As a result, our analysis understated the magnitude of the PEI facilitation, since none of the monkeys receiving 2.5 or 5 μg/kg quinelorane and only two of nine monkeys receiving 100 μg/kg apomorphine failed to reinitiate copulation, whereas monkeys failed to reinitiate copulation in 60% of the tests following vehicle administration.

In contrast to the effects observed with DA agonists that exhibit high affinity for D_2 receptors, the D_1 agonist, CY 208-243, did not significantly influence any measure of male copulatory performance. More recently, we have evaluated a more specific D_1 agonist, SKF 81297, in the copulatory behavior test paradigm and confirmed our previous finding that male copulatory performance of rhesus monkeys is not affected by exogenous D_1 receptor stimulation.

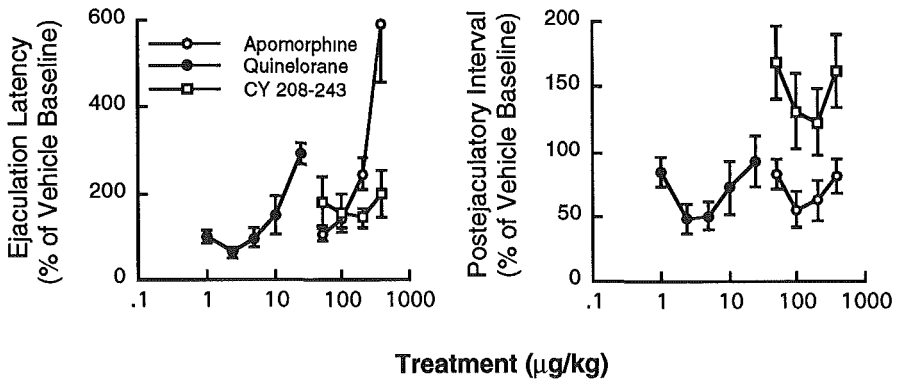

Figure 1. Mean ±SEM ejaculation latency and postejaculatory interval of male rhesus monkeys following treatment with varying doses of apomorphine (50-400 μg/kg, n=9), quinelorane (1-25 μg/kg, n=9), or CY 208-243 (50-400 μg/kg, n=9). Values are expressed as a percentage of vehicle baseline performance.

These experiments demonstrate that although male sexual behavior of rhesus monkeys is affected by exogenous DA stimulation, the direction of the effect depends on the behavior being evaluated and on the dosage and receptor subtype of the DA agonist being administered. In order to further examine the role of DA in regulating primate male sexual behavior, we proceeded to study the effects of blocking endogenous DA stimulation with DA antagonists. Several DA antagonists have been evaluated that exhibit varying specificity for D_1 and D_2 receptor subtypes including: SCH 23390 (D_1 specific); raclopride (D_2 specific); haloperidol (active at both D_1 and D_2 receptors, but greater selectivity for D_2), and cis-flupentixol (mixed D_1/D_2).

The most striking sexual behavior effect that was observed following DA antagonist administration occurred with the D_1 receptor antagonist, SCH 23390. As seen in Figure 2, SCH 23390 reliably reduced the monkeys' ejaculation latency. The effects of other DA antagonists on ejaculation latency were quite erratic with haloperidol, raclopride and cis-flupentixol only interfering with ejaculation at high doses that produced other more generalized deficits in the monkeys' behavior. These data are in marked contrast to the effect of DA agonists on this behavioral measure. Taken together, the results from the two studies on DA regulation of male copulation indicate that both D_1 and D_2 receptor stimulation can exert an inhibitory influence on ejaculation. Male ejaculatory threshold can be raised by either endogenous D_1 or exogenous D_2 receptor stimulation. By contrast, ejaculation is not affected by either exogenous D_1 or endogenous D_2 receptor stimulation.

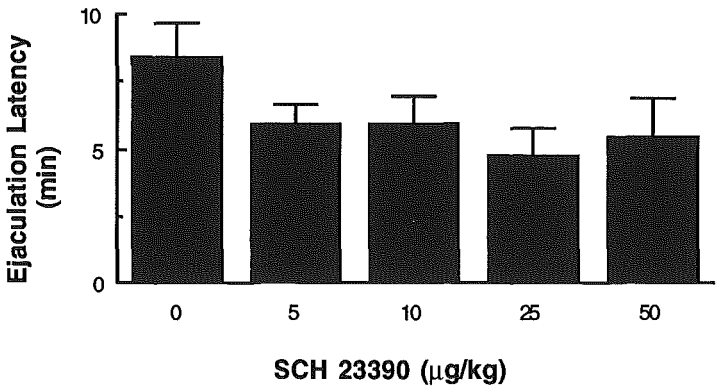

Figure 2. Mean ±SEM ejaculation latency of male rhesus monkeys (n=8) following administration of varying doses of SCH 23390 (5-50 µg/kg) or vehicle.

Based upon our research with D_2 agonists, it was expected that blocking D_2 receptor stimulation would produce an increase in the males' mount latency and postejaculatory interval. Although the D_2 receptor antagonists, haloperidol, raclopride and cis-flupentixol, produced dose-dependent increases in mount latency and postejaculatory interval, the effects were not specific for sexual behavior. Rather a generalized debilitative effect of these compounds occurred in conjunction with any impairments in male sexual function. Our failure to observe a more specific effect of D_2 antagonism on male sexual behavior may indicate that male sexual interest is not influenced by endogenous D_2 receptor stimulation. Alternatively, the copulatory behavior testing paradigm may not be ideally suited for detecting adverse consequences of D_2 inhibition on male sexual motivation. Since monkeys reinitiated copulation in less than 40% of vehicle tests, there was little opportunity for drug treatment to elicit a further significant reduction of PEI from vehicle baseline levels. Although we had hoped that mount latency would serve as an effective measure of male sexual interest in these studies, under the present testing conditions many male monkeys performed a perfunctory mount almost immediately once the cage partition was removed. Failure to do so often indicated that the monkeys were experiencing a more generalized behavioral impairment. Thus, as the results of these experiments indicate, alternative methodologies may need to be developed to further examine neurochemical influences on male sexual interest of rhesus monkeys.

We recently developed a third testing paradigm, a place conditioning procedure [9], which may prove useful in assessing neurotransmitter influences on male sexual motivation. Such a paradigm has been widely used in rats to study the rewarding effects of drugs [10-11] and has been more recently employed in rat studies of male sexual motivation [12-13]. A U-shaped test/conditioning cage, comprised of a central neutral compartment and two distinctively different end compartments, was used for these studies. In this paradigm, male monkeys were conditioned on alternate days in the two different end compartments. In one compartment they were left alone and in the other compartment they were paired with a receptive female monkey. Following eight days of conditioning, the males were given the opportunity to explore the entire test/conditioning cage alone. As shown in Figure 3, the effects of conditioning appeared to depend on the sexual behavior that was exhibited during the conditioning sessions. Males developed a conditioned place preference for the compartment with the sexually receptive female (i.e. spent >50% of compartment time), if they copulated to ejaculation with her. By contrast, they did not exhibit a conditioned place preference for the compartment with the sexually receptive female, if they either did not have sex with her or had sex but did not achieve an ejaculation. Thus, when sex served as the rewarding stimulus, males only exhibited a sex behavior-based conditioned place preference if they copulated to ejaculation. Since the place conditioning paradigm may enable us to overcome some of the problems associated with studying drug effects on primate sexual motivation, we plan on using it to examine the neurochemical mechanisms associated with the acquisition and expression of sex behavior-induced conditioned place preference in rhesus monkeys.

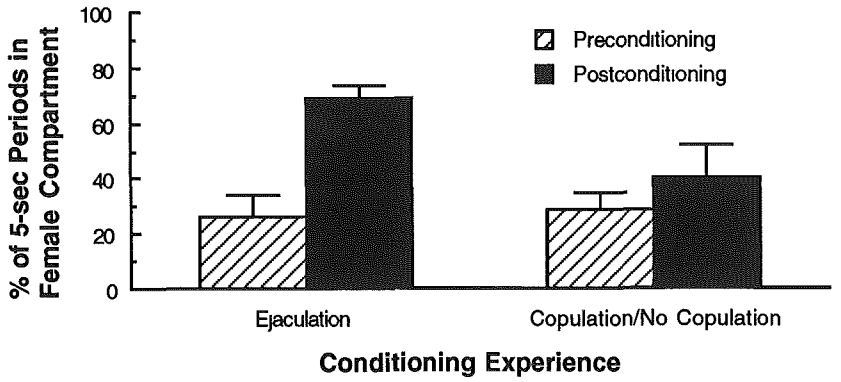

Figure 3. Mean ±SEM % of 5-sec periods during preconditioning and postconditioning tests that male rhesus monkeys spent in a compartment in which they ejaculated (n=6) or did not ejaculate with a sexually receptive female (n=7).

Serotonin Regulation of Male Sexual Behavior of Rhesus Monkeys

Several studies have examined 5-HT influences on penile erection of rhesus monkeys. In initial studies in which monkeys were restrained in primate chairs, the 5-HT_{2C} receptor agonist, m-chlorophenylpiperazine (m-CPP), elicited penile erections, whereas the 5-HT_{1A} receptor agonist, 8-OH-DPAT, did not have any effect on penile erections [14]. We replicated these results in subsequent research in which unrestrained monkeys were administered the

same 5-HT agonists [15]. Moreover, when we introduced a stimulus female into the testing situation, we found that her presence had an additive effect on m-CPP's ability to stimulate penile erections. By contrast, when males were tested in the presence of a female conspecific, an inhibitory effect of 8-OH-DPAT on penile erections was observed.

We initially characterized 5-HT influences on male copulatory behavior of rhesus monkeys by examining the effects of 8-OH-DPAT, ipsapirone, and m-CPP [16]. As shown in Figure 4, 8-OH-DPAT had a biphasic effect upon ejaculation latency, with low doses (5-10 μg/kg) producing a shortening of ejaculation latency and the highest dose (100 μg/kg) producing a lengthening of ejaculation latency. Administration of the partial 5-HT_{1A} agonist, ipsapirone, led to a shortening of ejaculation latency at all doses tested. By contrast, administration of m-CPP resulted in a dose-dependent increase in ejaculation latency. These treatments also affected intromission frequencies of the monkeys, with 5-HT_{1A} receptor stimulation generally reducing intromission frequency and 5-HT_{2C} receptor stimulation increasing intromission frequency. None of the 5-HT agonists were found to exert any effect on postejaculatory performance of the monkeys.

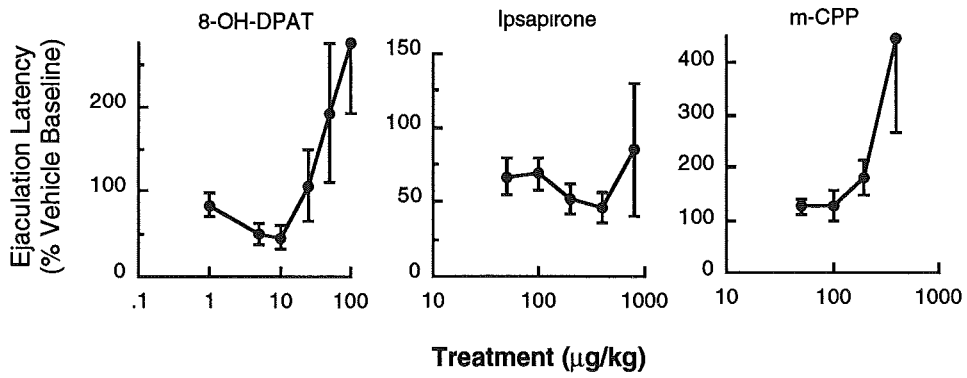

Figure 4. Mean ±SEM ejaculation latency of male rhesus monkeys following treatment with varying doses of 8-OH-DPAT (1-100 μg/kg, n=9), ipsapirone (50-800 μg/kg, n=8), or m-CPP (50-400 μg/kg, n=9). Values are expressed as a percentage of vehicle baseline performance.

The results of our studies with 5-HT receptor agonists indicated that a reciprocal relationship may exist between 5-HT_{2C} and 5-HT_{1A} receptor stimulation. Exogenous stimulation of 5-HT_{2C} receptors seems to facilitate penile erections and interfere with ejaculation, while exogenous stimulation of 5-HT_{1A} receptors inhibits penile erections and promotes ejaculation. Interestingly, a similar reciprocal relationship between 5-HT_{2C} and 5-HT_{1A} receptor stimulation and male sexual behavior also appears to exist in rats, with penile erection [17] and ejaculation [18-19] being influenced in opposite directions by the same 5-HT agonist treatment.

In order to determine the influence of endogenous 5-HT stimulation on male sexual behavior of rhesus monkeys, experiments have examined the effects of several 5-HT antagonists on male copulatory behavior including: mesulergine (5-HT_{2C}), LY53857 (5-HT_{2C}), ketanserin (5-HT_{2A}) and pindolol (5-HT_{1A}). As shown in Figure 5, 5-HT_2 antagonists elicited markedly different effects depending on their affinity for 5-HT_{2A} versus 5-HT_{2C} receptors. Ketanserin, which possesses a high affinity for 5-HT_{2A} receptors [20],

interfered with ejaculation. Mesulergine and LY53857, which possess a high affinity for 5-HT_{2C} receptors [20-21], lowered the monkeys' ejaculatory threshold, as evidenced by a shortening of the ejaculation latency and a reduction in intromission frequency (data not shown). Although the positive effects of 5-HT_{2C} antagonists on male ejaculation were expected, the inhibitory effect of the 5-HT_{2A} antagonist, ketanserin, was not anticipated. However, since ketanserin exhibits high affinity for α_1 adrenergic receptors as an antagonist [20], it may be possible that its α_1 antagonist properties are responsible for mediating its inhibitory effect on ejaculation. As a result, future studies will need to examine the generality of the 5-HT_{2A} receptor effect by assessing other more selective 5-HT_{2A} receptor antagonists. Although rodent studies have reported that pindolol adversely affects male sexual behavior performance [22-23], this compound did not significantly affect male sexual behavior of rhesus monkeys.

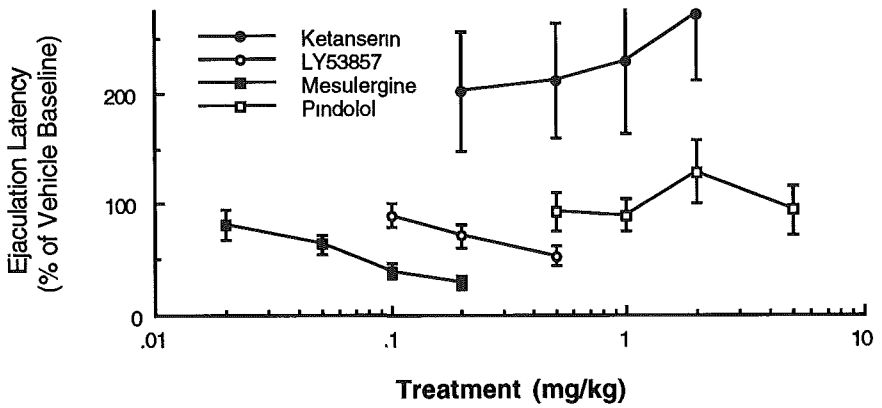

Figure 5. Mean ±SEM ejaculation latency of male rhesus monkeys following treatment with varying doses of ketanserin (0.2-2.0 mg/kg, n=9), LY53857 (0.1-0.5 mg/kg, n=8), mesulergine (0.02-0.2 mg/kg, n=8), or pindolol (0.5-5.0 mg/kg, n=9). Values are expressed as a percentage of vehicle baseline performance.

In summary, the results from our studies of 5-HT agonists and antagonists indicate that activation of 5-HT receptors may either serve to inhibit or facilitate male sexual behavior, depending upon the 5-HT receptor subtype being stimulated, the level of stimulation being provided, and the behavior being evaluated. A reciprocal relationship seems to exist between 5-HT_{2C} and 5-HT_{1A} receptor stimulation. Exogenous stimulation of 5-HT_{2C} receptors facilitates penile erections and interferes with ejaculation, while exogenous stimulation of 5-HT_{1A} receptors inhibits penile erections and promotes ejaculation. Moreover, recent preliminary data suggest the possibility that whereas endogenous 5-HT_{2C} stimulation raises the males' ejaculatory threshold, endogenous 5-HT_{2A} stimulation may lower the males' ejaculatory threshold.

Norepinephrine Regulation of Male Sexual Behavior of Rhesus Monkeys

Much of the research examining NE influences on rat male sexual behavior has been concerned with the facilitation of male copulatory performance following the administration of α_2 adrenergic receptor antagonists, such as yohimbine and idozoxan [24-26]. In initial studies dealing with NE influences on male sexual behavior of primates, the α_2 receptor antagonist, yohimbine, did not affect male copulatory performance of rhesus monkeys when administered in an acute pair test setting [5]. However, a later study reported that stumptail monkeys exhibited an increased number of ejaculations when they were chronically paired with the same female and administered the highly selective α_2 receptor antagonist, atipamezole [27]. Atipamezole was found to stimulate ejaculations occurring through either masturbation or copulation. When the positive effect of atipamezole is contrasted with the failure of yohimbine to produce a similar effect in rhesus monkeys, a question emerges regarding whether these differences in drug effects are due to species differences, testing differences, or drug differences. Recently, we have begun to address this issue, using the chronic pair test in rhesus monkeys to study the effects of the α_2 adrenergic receptor antagonists, yohimbine and idazoxan. As shown in Figure 6, we have not witnessed a facilitation of male copulatory performance. On the contrary, these compounds produced a lengthening of male ejaculation latency. These data indicate that the ability of α_2 receptor antagonists to facilitate primate male sexual behavior is specific either to compounds such as atipamezole or species such as stumptail monkeys.

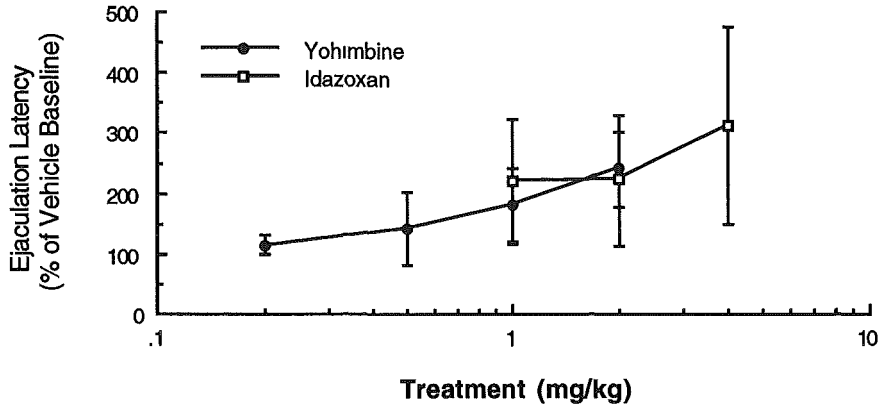

Figure 6. Mean ±SEM ejaculation latency of male rhesus monkeys following treatment with varying doses of yohimbine (0.2-2.0 mg/kg, n=8) or idazoxan (1.0-4.0 mg/kg, n=4). Values are expressed as a percentage of vehicle baseline performance.

Monoamine Reuptake Influences on Male Sexual Behavior of Rhesus Monkeys

Reports in the human clinical literature indicate that a number of monoamine reuptake inhibitors influence male sexual behavior. Cocaine, which nonspecifically inhibits reuptake of all monoamine neurotransmitters, has been reported to both facilitate [28] and inhibit male sexual function [29-30]. Several studies have reported deficits in sexual function as a side-effect of antidepressants which inhibit 5-HT reuptake [31-33]. In addition, facilitation of male sexual function has been reported following administration of the DA and NE reuptake

inhibitor, buproprion [34]. We have evaluated the potential of different monoamine reuptake inhibitors to influence male copulatory performance of rhesus monkeys including: cocaine (nonspecific) [35], nomifensine (NE), buproprion (DA and NE) and fluoxetine (5-HT). As shown in Figure 7, all of the monoamine reuptake inhibitors adversely affected male copulatory performance by lengthening the males' ejaculation latency. Although cocaine treatment also lengthened the mount latency of the monkeys, none of the other compounds affected other components of male copulatory behavior. Experiments are currently in progress to evaluate the effects of a highly specific DA reuptake inhibitor, GBR 12909 [36]. By acting selectively to stimulate DA activity, this compound may mimic the effects of direct-acting DA agonists, shortening males' postejaculatory interval at low doses and lengthening their ejaculation latency at higher doses.

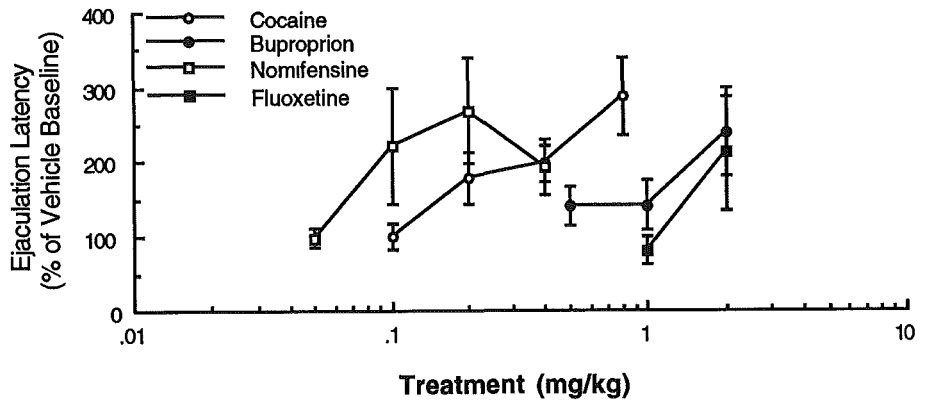

Figure 7. Mean ±SEM ejaculation latency of male rhesus monkeys following treatment with varying doses of cocaine (0.1-0.8 mg/kg, n=9), nomifensine (0.05-0.4 mg/kg, n=8), fluoxetine (1.0-2.0 mg/kg, n=8), or buproprion (0.5-2.0 mg/kg, n=5). Values are expressed as a percentage of vehicle baseline performance.

Effects of Treatments which Stimulate Multiple Monoamine Systems

Studies with D_2 and 5-HT_{1A} receptor agonists indicate that these two types of compounds act in a reciprocal fashion to affect male sexual behavior. D_2 agonists facilitated penile erection and postejaculatory interval, and inhibited ejaculatory performance at high doses. By contrast, 5-HT_{1A} agonists facilitated ejaculation and interfered with penile erection. Given the fact that both types of agents facilitated and inhibited different aspects of male sexual function, we became interested in evaluating the sexual effects of compounds that act as agonists at both 5-HT_{1A} and D_2 receptor sites. One compound that possesses such a receptor binding profile is lisuride [37]. When administered to rats, lisuride was initially viewed as facilitating sexual behavior through D_2 receptor mechanisms [38]. However, subsequent research revealed that lisuride's agonist activity at 5-HT_{1A} receptors was also involved in mediating its effects on sexual behavior [39]. In nonhuman primates, it is not clear whether the positive and negative effects on sexual function associated with activity at both 5-HT_{1A} and D_2 receptor sites will cancel one another out leaving male sexual behavior

unaffected, or whether at certain doses either the positive or negative effects on sexual function will predominate.

We have conducted preliminary investigations aimed at examining the effects of the 5-HT_{1A}/D_2 agonist, lisuride, on male copulatory behavior and penile erections (see Table 2). The results thus far indicate that administration of 2.5 μg/kg lisuride produced a broad-based facilitation of penile erections, ejaculation latency and postejaculatory interval. By contrast, when lisuride was administered at doses greater than or equal to 10 μg/kg, it induced a generalized serotonin-like syndrome which tended to interfere with male sexual behavior performance (e.g. ejaculation latency). Although these data with lisuride support the possibility that effective treatments for male sexual function may depend on the development of drugs that simultaneously act at a number of different neurotransmitter systems, they also point out the difficulty of properly titrating the drug dosage so that its activity at different neurotransmitter systems facilitates rather than compromises sexual functioning.

Table 2
Effects of Lisuride on Male Sexual Behavior of Rhesus Monkeys

Dose (μg/kg)	Penile Erections (% of 10-sec Periods)	Ejaculation Latency (min)	Postejaculatory Interval (min)
0	2.1±1.7	5.2±0.8	27.6±1.4
1	11.8±9.3	6.0±2.0	25.5±2.1
2.5	36.6±8.6	3.9±1.6	21.9±2.0
5	28.5±9.0	7.1±2.1	25.2±2.1
10	3.3±2.2	16.0±4.0	25.2±3.3

Values represent mean (±SEM). Penile erection data and copulatory behavior data are based on six monkeys.

Conclusions

A general finding of our research on monoamine influences on primate male sexual behavior is that the effects of drug treatments vary greatly, depending upon the neurotransmitter receptor subtype being manipulated, the dose of the drug being administered, and the behavior being evaluated. Several examples have been presented in which a drug treatment has a beneficial effect on a specific component of primate male sexual function at one dose, and at either the same dose or different dose, the drug interfered with another component of male sexual behavior. The clinical implication of this research finding is that although it may be possible to use selective pharmacological agents to treat discrete deficits in male sexual function, it is possible that any such treatment may also compromise a different functional component of male sexual behavior.

References

1. Michael RP, Wilson MI. Endocrinology 1974; 5: 150-159.
2. Phoenix CH, Slob AK, Goy RW. J. Comp. Physiol. Psychol. 1973; 84: 472-481.
3. Pomerantz SM, Goy, RW, Roy MM. Horm. Behav. 1986; 20: 483-500.

4. Everitt BJ, Herbert J, Keverne EB, Martensz ND, Hansen S. In: Fuxe K, Gustafsson J-A, Wetterberg L, eds. Steroid Hormone Regulation of the Brain. Oxford: Pergamon Press, 1981; 317-330.
5. Chambers KC, Phoenix CH. Behav. Neurosci. 1989; 103: 816-823.
6. Pomerantz SM. Pharmacol Biochem Behav 1990; 35: 659-664.
7. Pomerantz SM. Pharmacol Biochem Behav 1992; 41: 511-517.
8. Pomerantz SM. Pharmacol Biochem Behav 1991; 39: 123-128.
9. Pomerantz SM, Hepner B, Wertz J, Waslo L, Piazza J. Abstr. Soc. Neurosci. 1992; 18: 1572.
10. Carr GD, Fibiger HC, Phillips AG. In: Liebman JM, Cooper SJ, eds. The Neuropharmacological Basis of Reward. New York: Clarendon Press, 1989; 264-319.
11. Schecter MD, Calcagnetti DJ. Neurosci Biobehav Rev 1993; 17: 21-41.
12. Everitt BJ. Neurosci Biobehav Rev 1990; 14: 217-232.
13. Mehrara BJ, Baum MJ. Psychopharmacology 1990; 101: 118-125.
14. Szele FG, Murphy DL, Garrick NA. Life Sci 1988; 43: 1297-1303.
15. Pomerantz SM, Hepner BC, Wertz JM. Eur J Pharmacol 1993; 243: 227-234.
16. Pomerantz SM, Hepner BC, Wertz JM. Psychopharmacology 1993; 111: 47-54.
17. Berendsen HHG, Jenck F, Broekkamp CLE. Psychopharmacology 1990; 101: 57-61.
18. Ahlenius S, Larsson K, Svensson L, Hjorth S, et al. Pharmacol Biochem Behav 1981; 15: 785-792.
19. Fernandez-Guasti A, Escalante A, Agmo A. Pharmacol Biochem Behav 1989; 34: 811-816.
20. Van Wijngaarden I, Tulp M, Soudijn W. Eur J Pharmacol Molec Pharmacol Sect 1990; 188: 301-312.
21. Hoyer D. TIPS 1988; 9: 89-94.
22. Ahlenius S, Larsson K. J Neur Trans 1989; 77: 163-170.
23. Smith ER, Maurice J, Richardson R, Walter T, Davidson JM. Pharmacol. Biochem. Behav 1990; 36: 713-717.
24. Clark JT, Smith ER, Davidson JM. Science 1984; 225: 847-849.
25. Sala M, Braida D, Leone MP, Calcaterra P, et al. Physiol Behav 1990; 47: 165-173.
26. Smith ER, Lee RL, Schnur SL, Davidson JM. Physiol Behav 1987; 41: 7-14.
27. Linnankoski I, Gronroos M, Carlson S, Pertovaara A. Pharmacol Biochem Behav 1992; 42: 197-200.
28. Gay GR, Sheppard CW. Med Aspects Hum. Sex 1972; 6: 28-50.
29. Cocores JA, Dackis CA, Gold MS. J. Clin Psychiat 1986; 47: 384-385.
30. Siegel RK. J Psych Drugs 1982; 14: 71-74.
31. Doogan DP, Caillard V. J Clin Psychiat 1988; 49(8): 46-51.
32. Herman JB, Brotman AW, Pollack MH, Falk, WE, et al. J Clin Psychiat 1990; 51: 25-27.
33. Meston CM, Gorzalka BB. J Psych Drugs 1992; 24: 1-40.
34. Crenshaw TL, Goldberg JP, Stern WC. J Sex Marit Ther 1987; 13: 239-252.
35. Pomerantz SM, Hepner BC, Wertz JM. Life Sci 1994; 54: 917-924.
36. Andersen PH. Eur J Pharmacol 1989; 166: 493-504.
37. Rosenfeld MR, Makman MH. J Pharmacol Exp Ther 1981; 216: 526-531.
38. Ahlenius S, Larsson K, Svensson L. Eur J Pharmacol 1980; 64: 47-51.
39. Ahlenius S, Larsson K. In: Rodgers RJ, Cooper SJ, eds. 5-HT_{1A} Agonists, 5-HT_3 Antagonists and Benzodiazepines. Chichester: John Wiley & Sons, Ltd, 1991; 281-315.

Discussion - MONOAMINE INFLUENCES ON MALE SEXUAL BEHAVIOR OF NONHUMAN PRIMATES

J.T. Clark

Would you care to comment on the terms ejaculation latency and ejaculatory threshold?

S.M. Pomerantz

Let me start by saying the drugs that we have evaluated do not seem to affect the monkeys' copulatory rate. Thus, when a drug, such as the 5-HT_{1A} agonist, DPAT, enables monkeys to achieve an ejaculation in less time and with fewer intromissions, we view that compound as lowering the monkeys' ejaculatory threshold. By contrast, we view compounds, such apomorphine and quinelorane, as raising the monkeys' ejaculatory threshold, since they increase the monkeys' ejaculation latency and intromission frequency without affecting the monkeys' rate of copulation.

J.T. Clark

For DPAT you gave the index of percent of males showing an erection. Some of the males showed erection, those males that showed erections when treated with DPAT, did they have a normal number or was the number reduced?

S.M. Pomerantz

They had a normal number of erections. However, we only observed erections in two of nine monkeys receiving 0.1 mg/kg DPAT and one of nine monkeys receiving 0.2 mg/kg DPAT.

J. Bancroft

In the 1970s there was a butyrophenone called benperidol, I am not sure what its D-1 / D-2 characteristics were but it was marketed specifically for reducing sexual interest in humans and in fact we carried out a placebo controlled study of its effects. I wonder whether you were aware of that drug and whether there was any chance of evaluating that in your dopamine antagonist category.

S.M. Pomerantz

I am not very familiar with that compound, but I believe that it is predominately classified as a D_2 antagonist. I have spent a great deal of time working with dopamine antagonists, and with D_2 antagonists in particular, because I truly expected them to elicit a reciprocal effect from what we saw with D_2 agonists. However, I think we have a methodological problem in evaluating D_2 antagonists using the chronic pair test paradigm. We have developed the conditioned place preference paradigm to try to address this issue. This paradigm is designed to enable us to investigate whether or not drugs, such as D_2 antagonists, are affecting male sexual motivation. Using this paradigm the monkeys exhibit a conditioned place preference for the compartment in which they exhibited sexual behaviour. It is important to emphasize here that this preference is not just for the compartment in which the monkeys exhibited sexual behavior, rather the males have to actually ejaculate in that compartment. If they just copulate, then they do not exhibit a conditioned place preference. Now, we feel we have a paradigm which will enable us to look exactly at the sexual motivation issues that you are referring to.

J. Herbert

The situation used is one of maximized sexual interaction. You use males which are proficient and compatible and females treated with oestrogen. I am wondering whether an alternative strategy would be to pick males who are incompatible or indeed test your males with females that are not oestrogen-treated. That would allow us to see whether these drugs can show effects in situations which are not optimal.

S.M. Pomerantz

Yes it would be possible to employ such a strategy. However, up to this point we have been more interested in using our existing methodologies to screen a number of different compounds with varying biological activities. We need to get a library of standardized basic facts and then from that point see where we want to go. I have not discussed the role of the female in the copulatory behavior tests, however, it is important to stress that she still exerts a powerful influence on sexual interactions. For example, there are times when a female will not exhibit sexual receptivity even when

she is oestrogen-treated and sexually attractive to the male. This obviously compromises our ability to evaluate the drug effects. Moreover, in situations in which the female is not receptive, the male generally ceases sexual attempts regardless of the drug treatment that he has received.

B.D. Sachs

You did not tell us anything about the ejaculation of rhesus monkeys in a non-contact situation. Which drugs led them to masturbate to ejaculation during the observation period?

S.M. Pomerantz

Although we will often find ejaculatory plugs in the pans of monkeys that are housed in solitary cages, we have rarely witnessed the monkeys masturbating to ejaculation under our testing conditions. I did observe a few monkeys masturbating to ejaculation following treatment with the dopamine agonists, apomorphine and quinelorane. However, the effect was not statistically significant with either compound. Additionally, we did not check to see whether sometime later in the day the monkeys who had masturbated but not ejaculated in the test situation did ejaculate. In the case of 8-OH-DPAT, which interfered with erection, we did not observe any incidents of spontaneous emission or ejaculation.

J.G. Pfaus

That also raises another interesting issue. Do the monkeys get sick or at least nauseous at the doses that you use?

S.M. Pomerantz

It is hard to determine whether a monkey is nauseous or not. The best evidence that we have that they do not become nauseous with dopamine agonists is that when we offer them food they will generally eat it. If humans are nauseous they rarely eat food. Thus, from an anthropomorphic perspective we can suggest that these compounds are not causing nausea in monkeys.