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Serotonin Antagonist Pirenperone Inhibits Sexual Behavior in the Male Rat: Attenuation by Quipazine[1]

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MENDELSON, S. D. AND B. B. GORZALKA. *Serotonin antagonist pirenperone inhibits sexual behavior in the male rat: Attenuation by quipazine.* PHARMACOL BIOCHEM BEHAV **22**(4) 565–571, 1985.—Peripheral administration of the serotonin (5-HT) antagonist pirenperone produced a dose dependent inhibition of sexual behavior in sexually naive and experienced male rats. In Experiment 1, both 75 μg/kg and 150 μg/kg pirenperone significantly reduced the proportion of naive males mounting, while 150 μg/kg also reduced the proportion of naive males intromitting and ejaculating. In Experiment 2, both 75 μg/kg and 150 μg/kg pirenperone significantly increased mount and intromission latencies in sexually experienced males, as well as decreased intromission frequency, with 150 μg/kg more potent in each regard. The 150 μg/kg dose also increased the post-ejaculatory interval, and decreased both mount frequency and copulatory efficiency. In Experiment 3, both 150 μg/kg pirenperone and 3 mg/kg of the 5-HT agonist quipazine produced significant inhibition of male sexual behavior; however, when co-administered, inhibitory effects of each drug were significantly attenuated. The mutual attenuation of effects by a 5-HT agonist and a 5-HT antagonist suggests that the observed effects of both of these drugs were serotonergically mediated. In the final experiment, the 5-HT antagonist ketanserin was shown to inhibit sexual behavior in a manner similar to that of pirenperone. Results suggest a facilitatory, as well as an inhibitory role for 5-HT in male sexual behavior.

Sexual behavior Pirenperone Ketanserin Quipazine Serotonin

EVIDENCE suggests that serotonin (5-HT) serves an inhibitory role in the sexual behavior of the male rat. A variety of treatments which decrease 5-HT activity, such as the administration of the monoamine storage depletors tetrabenazine and reserpine [11,32], the 5-HT synthesis blocker p-chlorophenylalanine (PCPA) [21, 30, 33], and 5-HT receptor blockers methysergide, mesorgydine, and WA 335-B5 [9], as well as lesions of central 5-HT pathways with the neurotoxin 5, 7-dihydroxytryptamine (5,7-DHT) [20,31] have been reported to facilitate male sexual behavior. Furthermore, stimulation of 5-HT activity by administration of either the 5-HT precursor 5-hydroxytryptophan (5-HTP) [35], 5-HT agonists quipazine and LSD [16, 22], or the MAO inhibitor pargyline [34], has been reported to impair male sexual performance.

Despite evidence supporting an inhibitory role of 5-HT in male sexual behavior, the literature is not entirely consistent with this notion. At least one study failed to find any enhancement of male heterosexual behavior following PCPA administration [36]. It has been noted that PCPA has relatively little effect in sexually vigorous males, but facilitates mating activity in naive or sexually sluggish animals [37]. Similarly, the sexual behavior of vigorous, intact males is not facilitated following 5,7-DHT lesions which lower central 5-HT levels to one third of normal, although the sexual behavior of castrated animals is significantly facilitated by this treatment [20]. 5-HT agonists have not been consistent in their effects on male sexual behavior. For example, lisuride enhances sexual behavior in intact male rats [2], while 5-methoxy-N,N-dimethyltryptamine is ineffective in castrates maintained with estradiol and dihydrotestosterone [7]. Based on a simple inhibitory role for 5-HT, both agonists would have been expected to attenuate male sexual activity.

Current evidence suggests that 5-HT receptors exist in multiple forms in the central nervous system [27]. In a recent study, we attempted to elucidate differential roles for the 5-HT_1 and 5-HT_2 receptor subtypes in the modulation of sexual behavior in the female rat. Following the administration of the putative 5-HT_2 receptor specific antagonists pirenperone or ketanserin, we observed a profound inhibition of sexual receptivity, with no apparent illness or sedation [23]. This result was surprising in view of the hypothesis that 5-HT activity inhibits sexual receptivity [24], although it is not the first time that contrary evidence has been obtained in the female rat [15].

The following experiments were designed to determine if

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pirenperone produces an inhibition of mating behavior in sexually naive and experienced males in a manner similar to that observed in females. To test for specificity and attenuation of a potential pirenperone effect, the 5-HT_2 agonist quipazine was co-administered. Furthermore, to determine whether the effect of pirenperone holds for another 5-HT_2 antagonist, ketanserin was administered.

GENERAL METHOD

Animals

Male Long-Evans rats were obtained from Charles River Canada Inc., Montreal, at 60 days of age. Upon arrival, these males were group housed in standard laboratory wire mesh cages in a room maintained under a reversed 12 hr dark/12 hr light cycle at 21±1°C. Animals had free access to food and water.

Behavioral Testing

Behavioral testing involved presentation of a stimulus female to an experimental male in a cylindrical Pyrex testing arena measuring 45 cm in height, and 29 cm in diameter. Tests commenced 4–6 hr after onset of the dark cycle. Sexual receptivity was induced in Sprague-Dawley females by the administration of 10 μg estradiol benzoate (Steraloids) 48 hr, and 500 μg progesterone (Steraloids) 4 hr prior to testing. Females were rotated from male to male at 10 min intervals.

Behavioral parameters recorded and analyzed included: mount latency, i.e., time from presentation of the female to the first mount with pelvic thrusting; intromission latency, i.e., time from presentation to the first intromission; ejaculation latency, i.e., time from the first intromission to ejaculation; and post-ejaculatory interval, i.e., time from ejaculation to the next intromission. Furthermore, the number of mounts (M) and intromissions (I) from presentation to ejaculation were recorded, and used to derive mount frequencies, intromission frequencies, and copulatory efficiencies, i.e., I/I+M. Animals were allowed 1 hr to progress through the complete behavioral sequence of mounting, intromission, ejaculation, and the first post-ejaculatory intromission. Animals failing within 1800 sec to mount, intromit after the last mount, or ejaculate after the last intromission, or failing within 900 sec to intromit after an ejaculation, were removed from the testing arena at that time, and assigned the highest scores observed for those specific behaviors independent of the treatment groups.

EXPERIMENT 1

The first two experiments were designed to test the effects of pirenperone on male sexual behavior. Because PCPA treatment is apparently more effective in sexually naive rats [37], inexperienced rats were used in the initial study.

Method

One hr prior to testing, each of three groups of 10 naive males received either 150 μg/kg pirenperone, 75 μg/kg pirenperone, or 0.05 ml of the citrate vehicle administered intraperitoneally (IP). Pirenperone was initially dissolved in a warm solution of physiological saline and citrate (0.0007 M), and concentrations were adjusted with saline such that both doses were delivered in approximately 0.05 ml of solvent. Prior to behavioral testing, animals were allowed 10 min to habituate to the testing arenas.

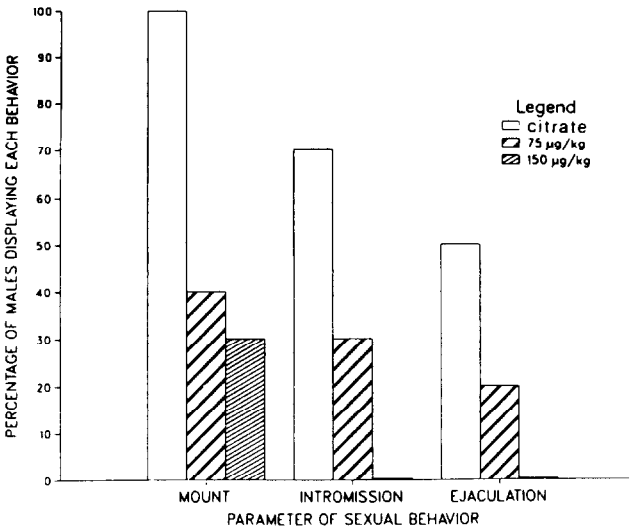

FIG. 1. Proportion of sexually naive males exhibiting mounting, intromission, and ejaculation following administration of 75 μg/kg or 150 μg/kg pirenperone, or the citrate vehicle 1 hr prior to behavioral testing.

Results and Discussion

Neither intromissions nor ejaculations were observed in the group of males receiving 150 μg/kg pirenperone. Those receiving 75 μg/kg pirenperone appeared more active than animals in the high dose group, but less active than control animals (Fig. 1). Chi square tests confirmed significant differences among control and treatment groups in the number of animals mounting, $\chi^2(2)=10.76$, $p<0.01$; intromitting, $\chi^2(2)=11.14$, $p<0.01$; and ejaculating, $\chi^2(2)=7.09$, $p<0.05$. Subsequent pair-wise comparisons further revealed a dose dependent inhibition of sexual behavior by pirenperone, with only the 150 μg/kg dose consistently producing inhibition. In comparison to the control group, a significantly smaller proportion of animals displayed mounting behavior in the 75 μg/kg group, $\chi^2(1)=8.57$, $p<0.01$, and the 150 μg/kg group, $\chi^2(1)=10.77$, $p<0.01$. However, in comparison to controls only the 150 μg/kg group had a significantly smaller proportion of animals intromitting, $\chi^2(1)=10.77$, $p<0.01$, and ejaculating, $\chi^2(1)=6.67$, $p<0.01$. The high and low dose groups were not significantly different in these three parameters.

In our experience, a significant number of male rats fail to copulate, even after repeated testing and exposure to receptive females. Therefore, to strengthen the conclusion that pirenperone was responsible for the inhibition of sexual behavior observed in the naive males, it was necessary to determine which, if any, of these males would remain non-copulators after further behavioral testing. It was found that 5 of the 30 males failed to ejaculate in four subsequent behavioral tests. Of these males, 2 had been control animals, 2 had received 75 μg/kg, and 1 had received 150 μg/kg pirenperone. This difference was not significant. Therefore, it appears reasonable to conclude that pirenperone was responsible for inhibiting the initial display of sexual behavior in the naive males.

Although these results indicate that pirenperone inhibits sexual behavior in naive male rats, it remains to be determined whether these effects are produced via a non-specific

TABLE 1

THE EFFECTS OF PIRENPERONE ON THE SEXUAL BEHAVIOR OF EXPERIENCED MALE RATS

Behavioral parameter	Pirenperone (μg/kg) 0	75	150
Mount latency	6.3 ± 1.1	104.7 ± 53.4	298.5 ± 80.7
Intromission latency	23.2 ± 6.2	161.2 ± 55.1	601.9 ± 133.4
Ejaculation latency	352.7 ± 37.2	548.5 ± 107.8	570.3 ± 105.9
Post-ejaculatory interval	382.5 ± 16.4	391.7 ± 15.5	430.9 ± 16.9
Mount frequency	1.32 ± 0.20	1.26 ± 0.20	0.72 ± 0.12
Intromission frequency	1.68 ± 1.02	1.02 ± 0.16	0.60 ± 0.10
Copulatory efficiency	0.58 ± 0.04	0.47 ± 0.03	0.44 ± 0.03

Values are untransformed means ± S.E.M. All latency and post-ejaculatory interval scores are in seconds; frequency scores are per minute; and copulatory efficiency scores are calculated from the formula I/I+M, where I=number of intromissions and M=number of mounts preceding the first ejaculation.

mechanism. The consistent observation of animals exhibiting sniffing, gnawing, and rearing behavior upon initial placement into testing arenas argues against this possibility. To further reduce the probability that pirenperone acted via a non-specific mechanism, the effects of the drug were examined on wheel-running activity and rearing in an open-field apparatus. Males that received 150 μg/kg pirenperone 1 hr prior to testing did not differ significantly from control animals in 1 hr of wheel-running activity, with each group making 63.9±16 and 83.6±35 revolutions, respectively (n=8). When placed for 3 min in an open-field apparatus, males that received 150 μg/kg 1 hr prior to testing did not differ significantly from control animals in rearing behavior, with 18.3±10.9 and 17.9±4.7 rearings, respectively (n=10). These results are consistent with a report that pirenperone does not disturb lever pressing performance [18]. Therefore, it appears unlikely that the observed inhibition of male sexual activity following the administration of pirenperone was due to illness, sedation, or motor impairment.

EXPERIMENT 2

In Experiment 1 it was demonstrated that pirenperone inhibited sexual behavior in naive male rats. Yet, as previously discussed, there have been instances of drugs producing effects in naive animals, but failing to produce significant effects in mature, sexually vigorous animals. The ability to generalize from such data is reasonably limited. Therefore, in the present experiment pirenperone was administered to sexually active male rats.

Method

Twenty-one sexually experienced adult male rats were tested once a week with stimulus females until they reached a criterion of ejaculating in three consecutive behavioral tests. Having achieved this criterion, each animal, in a repeated measures design, then received either 150 μg/kg pirenperone, 75 μg/kg pirenperone, or the citrate vehicle administered IP 1 hr prior to behavioral testing. Animals received the remaining treatments in random order during the following two test periods. The interval between successive test periods was one week.

Results and Discussion

As indicated by Table 1, pirenperone appeared to inhibit sexual behavior in a dose dependent fashion. Mean values for mount, intromission, and ejaculation latency, and post ejaculatory interval increased, while those for mount frequency, intromission frequency, and copulatory efficiency decreased as the pirenperone dose was raised. While the variance of post-ejaculatory interval, mount frequency, intromission frequency, and copulatory efficiency scores were at an acceptable statistical level, the variance encountered in the mount latency, intromission latency, and ejaculation latency scores violated the assumption of homogeneity, and a natural logarithmic transformation was performed. Heterogeneity of variance is common in male sexual behavior data, and transformations have been employed previously for this reason [20]. Moreover, transformation would tend to reduce any potential bias resulting from assigning scores when time-limited behavioral criteria are not achieved.

The apparent inhibition of sexual behavior by pirenperone was confirmed by analyses of variance which revealed significant treatment effects for the post-ejaculatory interval, $F(2,40)=6.90$, $p<0.003$; mount frequency, $F(2,40)=7.58$, $p<0.002$; intromission frequency, $F(2,40)=18.01$, $p<0.0001$; and copulatory efficiency, $F(2,40)=5.42$, $p<0.008$. The Newman-Keuls method of pair-wise comparisons further revealed that both 150 μg/kg and 75 μg/kg pirenperone significantly reduced intromission frequency ($p<0.05$), and that 150 μg/kg reduced intromission frequency significantly more than the 75 μg/kg dose

TABLE 2

THE EFFECTS OF PIRENPERONE, AND QUIPAZINE ON THE SEXUAL BEHAVIOR OF EXPERIENCED MALE RATS

Behavoral parameter	Treatment			
	Control	Pirenperone	Quipazine	Quipazine + Pirenperone
Mount latency	26.0 ± 14.0	310.5 ± 110.2	417.8 ± 119.7	143.7 ± 77.6
Intromission latency	64.0 ± 14.0	534.1 ± 133.6	602.6 ± 154.0	229.0 ± 92.7
Ejaculation latency	519.8 ± 105.6	611.5 ± 117.9	721.0 ± 144.4	768.2 ± 147.7
Post-ejaculatory interval	376.8 ± 25.5	429.9 ± 24.7	473.0 ± 26.8	441.6 ± 24.8
Mount frequency	1.68 ± 0.23	0.78 ± 0.16	0.90 ± 0.17	0.96 ± 0.17
Intromission frequency	0.96 ± 0.14	0.66 ± 0.13	0.66 ± 0.16	0.90 ± 0.16
Copulatory efficiency	0.43 ± 0.06	0.45 ± 0.05	0.36 ± 0.06	0.44 ± 0.04

Values are untransformed means ± S.E.M. All latency and post-ejaculatory interval scores are in seconds; frequency scores are per minute; and copulatory efficiency scores are calculated from the formula I/I+M, where I=number of intromissions and M=number of mounts preceding the first ejaculation.

($p<0.05$). Furthermore, 150 μg/kg, but not 75 μg/kg pirenperone, increased the post-ejaculatory interval ($p<0.05$), and decreased both the mount frequency and copulatory efficiency values ($p<0.05$). Analyses of variance of the transformed latency scores were consistent with a pirenperone-induced inhibition of sexual behavior. Significant treatment effects were found for mount latency, $F(2,40)=20.74$, $p<0.001$, and intromission latency, $F(2,40)=20.76$, $p<0.001$. The Newman-Keuls method further revealed that both doses of pirenperone had effects on the mount and intromission latencies ($p<0.05$), and that 150 μg/kg had greater effects than the 75 μg/kg dose on both parameters ($p<0.05$). Effects on the ejaculation latency scores were consistent with an inhibition, but did not reach significance, suggesting that this measure is less sensitive to the inhibitory effects of pirenperone. All analyses of variance that reached statistical significance for transformed latency scores were also significant for untransformed latency scores.

EXPERIMENT 3

Pirenperone significantly inhibited sexual activity in both naive (Experiment 1) and sexually experienced (Experiment 2) males. Given that pirenperone has been found to bind with high affinity to 5-HT_2 receptors, the results suggest that these receptors may serve a facilitatory role in the modulation of male sexual behavior. The traditional view that 5-HT serves an inhibitory role in male sexual function would require revision if the effects of pirenperone generalize to all 5-HT_2 antagonists. However, the possibility also exists that the results reflect a non-specific mechanism. If pirenperone inhibits sexual behavior by acting specifically upon 5-HT_2 receptors, then the co-administration of a 5-HT_2 agonist would be expected to attenuate this inhibition. It has been shown that the 5-HT agonist quipazine produces the head twitch response, a behavior believed to be mediated via 5-HT_2 receptors [17,28]. Furthermore, quipazine-induced head twitch is attenuated by pirenperone, suggesting that these drugs share a common site of action [17]. Therefore, to resolve the issue of specificity in the inhibition of sexual behavior by pirenperone, quipazine was co-administered with pirenperone prior to behavioral testing.

Method

In a 2×2 repeated measures design, 21 sexually experienced male rats received either 150 μg/kg pirenperone, 3 mg/kg quipazine, 150 μg/kg pirenperone plus 3 mg/kg quipazine, or the citrate vehicle 1 hr prior to tests of sexual activity. The sequence of treatments was randomized for each animal, and the interval between successive tests was 1 week.

Results and Discussion

As indicated by Table 2, pirenperone appeared to inhibit sexual activity relative to citrate-treated control animals. Mean values for mount, intromission, and ejaculation latencies, and post-ejaculatory interval increased; while those for mount and intromission frequencies decreased in animals receiving pirenperone alone. In quipazine treated males, mean values were consistent with an inhibition on every behavioral parameter. While both pirenperone and quipazine alone produced inhibition of mating behavior, the inhibitory effects of both of these drugs appeared to be markedly attenuated when they were administered together. These results suggest an interaction between pirenperone and quipazine.

Analyses of variance were performed after the mount, intromission, and ejaculation latencies were transformed to natural logarithms, as in Experiment 2. The analyses revealed a significant main effect of quipazine for mount frequency, $F(1,20)=5.86$, $p<0.024$. Although no main effects of pirenperone were revealed, significant interactions between

TABLE 3
THE EFFECTS OF KETANSERIN ON THE SEXUAL BEHAVIOR OF EXPERIENCED MALE RATS

Behavioral parameter	Control	Ketanserin
Mount latency	11.9 ± 2.3	60.6 ± 14.1
Intromission latency	57.3 ± 31.2	146.4 ± 44.9
Ejaculation latency	457.4 ± 79.2	542.0 ± 88.4
Post-ejaculatory interval	346.5 ± 22.7	451.0 ± 22.1
Mount frequency	1.56 ± 0.20	1.19 ± 0.20
Intromission frequency	1.66 ± 0.33	0.80 ± 0.09
Copulatory efficiency	0.50 ± 0.06	0.43 ± 0.05

Values are untransformed means ± S.E.M. All latency and post-ejaculatory interval scores are in seconds; frequency scores are per minute: and copulatory efficiency scores are calculated from the formula I/I+M, where I=number of intromissions and M=number of mounts preceding the first ejaculation.

pirenperone and quipazine were confirmed for mount latency, $F(1,20)=19.26$, $p<0.0003$, intromission latency, $F(1,20)=17.79$, $p<0.0005$, mount frequency $F(1,20)=8.88$, $p<0.007$, and intromission frequency, $F(1,20)=5.14$, $p<0.033$. The Newman-Keuls method of pair-wise comparisons further revealed that pirenperone and quipazine alone significantly increased mount and intromission latencies in comparison to control animals ($p<0.05$). Furthermore, the mount and intromission latencies of animals receiving quipazine plus pirenperone were found to be significantly lower than those of animals receiving quipazine alone ($p<0.05$), thus demonstrating an attenuation of the inhibitory effect of quipazine by pirenperone. The mean mount latency of animals receiving quipazine plus pirenperone was not significantly different from that of animals treated with either pirenperone or the citrate vehicle, suggesting at least a partial attenuation of the inhibitory effects of pirenperone by quipazine. Moreover, the mean intromission latency of animals receiving quipazine plus pirenperone was significantly lower than that of animals receiving pirenperone alone ($p<0.05$), thus confirming a mutual attenuation of inhibitory effects by pirenperone and quipazine. As in Experiment 2, all analyses that reached statistical significance for transformed latency scores were also significant for untransformed latency scores. The mutual attenuation of effects by a 5-HT agonist and a 5-HT antagonist does not unequivocally prove, but certainly suggests that the observed effects of both of these drugs were serotonergically mediated.

EXPERIMENT 4

The present series of experiments has demonstrated that pirenperone inhibits male sexual behavior. These results, which suggest a facilitatory role for 5-HT, are in contrast with much of the relevant literature. It may be that the inhibition observed after the administration of pirenperone is an atypical effect of that 5-HT_2 antagonist. However, if another 5-HT_2 antagonist were found to inhibit male sexual behavior, the probability that this inhibition was due to 5-HT_2 receptor blockade would be enhanced. Ketanserin has been shown to be a highly specific 5-HT_2 receptor antagonist [18]. If both ketanserin and pirenperone were shown to inhibit male sexual behavior, it would be reasonable to suggest that such inhibitory effects may be characteristic of 5-HT_2 antagonists.

Method

One hr prior to behavioral testing, one group of 10 sexually experienced males received 5.0 mg/kg ketanserin, and a second group of 10 males received the saline vehicle. Ketanserin had been dissolved in warm physiological saline immediately prior to administration, and all injections were made IP. Although ketanserin is a potent peripheral 5-HT_2 antagonist, doses considerably larger than those of pirenperone are required to produce central effects [18].

Results and Discussion

The results of Experiment 4 (Table 3) demonstrate that ketanserin inhibits male sexual behavior in a manner similar to that of pirenperone. The effects of ketanserin were consistent with an inhibition in every behavioral parameter. Data were analyzed in a series of Student's t-tests for independent groups. As in Experiments 2 and 3, natural logarithmic transformations were performed on mount latency, intromission latency, and ejaculation latency scores prior to statistical evaluation. Ketanserin was found to increase the post-ejaculatory interval, $t(9)=3.29$, $p<0.009$, and to reduce the intromission frequency, $t(9)=2.55$, $p<0.03$. Evaluation of transformed data revealed that ketanserin significantly increased mount latency, $t(9)=4.86$, $p<0.0009$, and intromission latency, $t(9)=2.66$, $p<0.026$. An evaluation of the untransformed mount latency data also reached statistical significance. However the untransformed intromission latency data did not generate significant differences.

The results of Experiment 4 confirm that ketanserin, like pirenperone, inhibits male sexual behavior. Indeed, the two drugs appear to be virtually indistinguishible in their effects on male sexual behavior. These findings strongly suggest that the inhibitory effects of ketanserin and pirenperone are due to an antagonism of 5-HT_2 receptors, an activity common to both drugs.

GENERAL DISCUSSION

In this series of experiments, the 5-HT_2 antagonist pirenperone consistently inhibited male sexual behavior. Quipazine was also found to attenuate male sexual behavior, confirming earlier reports of this effect [3,16]. Additionally, the complete attenuation of the quipazine effect by pirenperone was consistent with the attenuation of quipazine induced head twitch [17], as well as with the recent demonstration that pirenperone blocked the stimulus generalization of 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM) to quipazine [14]. While it was found that both pirenperone and the 5-HT_2 agonist quipazine alone inhibited sexual behavior, the two drugs administered together did not produce significant inhibitory effects. Assuming that the effects of the drugs taken together do not reflect an atypical interaction between a 5-HT agonist and antagonist, these findings argue against pirenperone acting simply in a toxic or non-specific manner. Rather, these data suggest that piren-

perone inhibits sexual behavior by acting as a 5-HT_2 receptor antagonist. Consistent with this suggestion was the demonstration of an inhibitory effect of ketanserin. Paradoxically, the finding that quipazine inhibits sexual activity, and that this inhibition is attenuated by the 5-HT_2 antagonist pirenperone, is consistent with the hypothesis that 5-HT is inhibitory. However, this hypothesis is contradicted by the observed inhibition of mating behavior with pirenperone alone.

Following completion of the present series of experiments, a paper was published in which, as part of a larger study, the effects of pirenperone upon male sexual behavior were examined [4]. In that study, an increase in the post-ejaculatory interval was reported as the only significant effect; however, the statistical analysis of the data was incomplete. Pirenperone appeared to have produced a dose dependent inhibition of ejaculation, though the proportions of animals ejaculating at each level of pirenperone dose were not compared statistically, and control data were not presented.

We believe that the observed inhibition of male sexual behavior following the administration of a 5-HT antagonist challenges the theory of a simple inhibitory role for 5-HT in male sexual behavior. The present data suggest a dual role for 5-HT activity in male sexual behavior.

A lack of drug specificity may have prevented earlier recognition of a dual role for 5-HT in the modulation of male sexual behavior. Pirenperone binds in a relatively specific manner to 5-HT_2 receptors [10], while the classical antagonists, such as methysergide, as well as the agonists LSD and lisuride readily bind to both 5-HT_1 and 5-HT_2 receptors [28,29]. Furthermore, while pirenperone may be considered a pure 5-HT_2 antagonist, the classical antagonists have been reported to display mixed agonist-antagonist activity [10]. Pirenperone does appear to bind with relatively high affinity to α-adrenergic receptors [18]; however, activity at these receptors is reported to have no specific effect upon male sexual behavior [22]. Another drug affecting 5-HT, PCPA, also acts in a non-specific manner, affecting catecholamine activity, adrenal activity, and possibly amino acid utilization, as well as inhibiting 5-HT synthesis [12,15]. The report that hypophysectomy eliminates the PCPA induced facilitation of homosexual mounting activity in the male rat [13] further complicates the notion of the drug's 5-HT specificity. Moreover, while the neurotoxin 5,7-DHT facilitates mating under some conditions [20,31], there is a question of 5-HT specificity, as it is reported to affect catecholaminergic as well as serotonergic systems [8].

Although problems of drug specificity may partially account for why the present results are at variance with a classical theory of 5-HT inhibition of male sexual behavior, it remains paradoxical that PCPA facilitates whereas pirenperone inhibits mating behavior. Whether or not PCPA acts specifically upon 5-HT, the fact remains that whole brain 5-HT levels are reported to be depleted following a course of PCPA treatment [19]. If, as the present results suggest, some component of 5-HT activity serves to facilitate the expression of male sexual behavior, then the profound inhibition of 5-HT synthesis following PCPA treatment should not necessarily facilitate mating. It may be that inhibitory 5-HT activity is simply more dominant than facilitatory activity. Alternatively, the apparent paradox may reflect regional brain differences in the extent of 5-HT depletion produced by PCPA. While whole brain 5-HT levels are often depleted by more than 80% following PCPA treatment [19], this depletion appears to take place primarily in forebrain structures; mesencephalic 5-HT levels are less disturbed by PCPA, and at least one area, the nucleus linearis, retains normal levels of 5-HT in perikarya and synaptic terminals following a regimen of PCPA administration [1].

Conclusions arising from the pirenperone data are significant in that we propose a facilitatory role for 5-HT in male sexual behavior. However, supporting evidence already exists in the literature. For example, the 5-HT agonist lisuride has been reported to facilitate sexual behavior in the male rat. While pre-synaptic inhibition of 5-HT activity may have contributed to this effect, the observation of hind limb abduction, a symptom of the serotonin syndrome, suggested the presence of post-synaptic 5-HT activity [2]. Furthermore, the increase in the incidence of penile erection observed in rats following the administration of lisuride is attenuated by the 5-HT antagonist methysergide [6]. The 5-HT agonists 8-methoxy-2-(di-n-propylamino)tetralin (8-OMeDPAT) and 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) have been reported to dramatically facilitate sexual behavior in the male rat [3,26]. The appearance of symptoms of the serotonin syndrome following the administration of 8-OMe-DPAT and 8-OH-DPAT, as well as *in vitro* receptor binding data, suggest that these two drugs were acting, at least in part, as 5-HT agonists [3, 5, 25]. A recent report suggested that these two drugs did not facilitate male sexual behavior via either a 5-HT_1 or a 5-HT_2 receptor. This suggestion was based on the failure of the 5-HT antagonists metergoline, methiothepine, and pirenperone to attenuate the effects of 8-OH-DPAT. However, while each of these antagonists did, at least partially, attenuate the inhibitory effects of 5-HTP, they produced little, if any, facilitation of mating behavior when administered alone. To the contrary, all were reported to increase post-ejaculatory intervals. These results are consistent with a dual role for 5-HT in male sexual behavior.

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