Pharmacology Biochemistry & Behavior, Vol. 9, pp. 499–508. Printed in the U.S.A.

Effects of P-Chloroamphetamine and 5,7-Dihydroxytryptamine on the Sexual Behavior of Gonadectomized Male and Female Rats[1]

P. SÖDERSTEN, O. G. BERGE AND K. HOLE

Departments of Physiological Psychology and Physiology, University of Bergen Arstadveien 21, N-5000 Bergen, Norway

(Received 30 June 1978)

SÖDERSTEN, P., O. G. BERGE AND K. HOLE. *Effects of p-chloroamphetamine and 5,7-dihydroxytryptamine on the sexual behavior of gonadectomized male and female rats.* PHARMAC. BIOCHEM. BEHAV. 9(4) 499–508, 1978.—Treatment with the 5-HT neurotoxins *p*-chloroamphetamine (PCA, 2×10 mg/kg) or 5,7-dihydroxytryptamine (5,7-DHT, 2×6 μg intracerebrally) stimulated the display of all aspects of sexual behavior, including ejaculations, by castrated male rats in the absence of testosterone (T) treatment and increased the behavioral sensitivity to a low level of T stimulation. The reduction of the (^{3}H) 5-HT uptake after PCA treatment was more pronounced in the cortex than in the hypothalamus. 5,7-DHT treatment reduced the (^{3}H) 5-HT uptake in the septum, hippocampus, amygdala, hypothalamus and cortex but the behavioral effects produced by the 5,7-DHT treatment could not be correlated to the biochemical effects in any of these brain areas. Since the behavioral effect of PCA appears to be stronger than that of 5,7-DHT, the 5-HT neurotoxins may exert their effect on sexual behavior in forebrain structures rather than in the hypothalamus. PCA treatment had a very small effect on mounting behavior but 5,7-DHT treatment stimulated the display of mounts and intromission patterns by ovariectomized female rats given no hormone treatment. Neither PCA nor 5,7-DHT had any effect on lordosis behavior tested before and after treatment with estradiol benzoate alone or in combination with progesterone. The observations support the conclusion that 5-HT is involved in the control by T of sexual behavior in male rats, but argue against a role of 5-HT in the neural control of lordosis behavior.

p-Chloroamphetamine 5,7-Dihydroxytryptamine 5-HT Testosterone Estradiol Progesterone Sexual behavior

BRAIN monoamines have been implicated in the neural control of sexual behavior in rats [13, 17, 42]. Special attention has been paid to the suggestion that 5-hydroxytryptamine (5-HT) exerts an inhibitory effect on the sexual behavior of both males and females. Evidence in support of an inhibitory role for 5-HT in the sexual behavior of female rats came from the observation that treatment with the 5-HT synthesis inhibitor *p*-chlorophenylalanine (PCPA, [29]) or with the 5-HT neurotoxic substances *p*-chloroamphetamine (PCA, [23]) and 5,7-dihydroxytryptamine (5,7-DHT, [3]) facilitated the display of sexual receptivity by ovariectomized female rats given low doses of estradiol benzoate, EB [1, 12, 14, 15, 41, 55, 56]. There are as yet no reports demonstrating induction of sexual receptivity by drugs in the hormonally untreated ovariectomized rat. Similarly, it was found that treatment with PCPA in combination with low doses of testosterone propionate (TP) facilitated sexual behavior in castrated male rats [36, 37, 51], but several of the initial reports found no behavioral effects of PCPA unless the animals were given simultaneous treatment with TP [10, 16, 17, 52]. A recent study showed that treatment with 5,7-DHT of castrated male rats stimulated the induction of sexual behavior by TP, but only after a very long period of TP treatment [33]. However, in one study PCPA treatment of castrated rats induced sexual behavior in the absence of TP treatment [49]. About 60% of castrated male rats showed the complete pattern of sexual behavior, including ejaculations, in response to daily treatment with PCPA [49]. The same PCPA treatment stimulated the display of masculine copulatory behavior, i.e., mounting behavior, by hormonally untreated ovariectomized female rats but exerted no effect on the display of feminine copulatory behavior, i.e., lordosis behavior, by these females even

[1]Supported by the Swedish Council for Research in the Humanities and Social Sciences (531/76P), the Swedish Medical Research Council (K76-6OF-4855-01) and the Norwegian Council for Research in the Sciences and Humanities. Professor F. Neuman of the Schering AG kindly supplied estradiol benzoate and progesterone. We are grateful to Dr. Ch. Köhler of Astra Läkemedel for donating Zimelidine (H 102/09), for expert neurochemical guidance and for critically commenting on the manuscript. Dr. B. Srebro of the University of Bergen assisted with highly valuable neuroanatomical advice. We also wish to thank Professor H. Ursin of the University of Bergen for his enthusiasm and inspiring support.

when exogenous EB was supplied [50]. Similarly, it was recently reported that the ergot derivative lisuride stimulated mounting behavior of gonadectomized hormonally untreated male and female rats [7]. These results showed that reduced 5-HT levels in the brain of gonadectomized male and female rats stimulated masculine but not feminine sexual behavior, i.e., that the two patterns of rat reproductive behavior can be neurochemically dissociated. The effect of the 5-HT neurotoxins PCA and 5,7-DHT on sexual behavior in gonadectomized rats of both sexes have been studied in the present study to further study the role of 5-HT in rat sexual behavior.

GENERAL METHODS

Animals

Male and female Wistar rats (Möllegård Breeding Laboratories, Denmark) were maintained with ad lib access to food and water in an air-conditioned temperature-controlled colony room in which the lights were off between 1200–2400. Male rats were castrated at 55–60 days of age and they were given 3 tests for sexual behavior 30 days later (approximate weight: 330 g) before all drug treatments to ensure that they were not sexually active. Female rats were ovariectomized at 80 days of age and they were used 7 days later (approximate weight: 210 g).

Tests of Sexual Behavior in Male Rats

The males were allowed to adapt briefly in a test cage (a 50 cm wide circular Plexiglas cage with a sawdust covered floor). A sexually receptive stimulus female (treated with 20 μg estradiol benzoate 48 hr and 0.5 mg progesterone 6 hr before testing) was thereafter presented to each male and the following behavioral parameters were recorded: *Mount*: mount with pelvic thrusting but without intromission, *intromission*: mount with intromission, and *ejaculation*: mount with a final deep intromission, slow dismounting and genital grooming. The latency to the first intromission, *intromission latency*, the interval from the first intromission to ejaculation, *ejaculation latency*, and the time from ejaculation to the next intromission, *postejaculatory interval*, were measured. Tests were ended if the intromission latency was >15 min, if the ejaculation latency was >30 min or if the postejaculatory interval was >15 min. Behavioral testing started 4 hr after lights off.

Tests of Mounting Behavior in Female Rats

When tested with a sexually receptive female, normal female rats show the overt behavior patterns corresponding to mounts and intromissions in male rats [48]. Under some experimental conditions females also display the behavior typical of an ejaculating male [50]. The display of mounts and intromission patterns, i.e., mounting behavior, was tested in female rats using the above described procedure for males. Ejaculation patterns were not observed in female rats in this study.

Tests of Lordosis Behavior in Female Rats

The females were tested for lordosis behavior (concave back flexion, lateral tail deviation and neck extension) immediately after the tests for mounting behavior. Each rat was presented to a cage-adapted sexually vigorous male rat and remained with the male until mounted 10 times. The number of lordosis responses were recorded and a lordosis quotient: (no. lordosis responses/10 mounts)×100, was calculated.

Surgery

5,7-Dihydroxytryptamine creatinine sulphate (5,7-DHT, Regis Chemicals), dissolved in 0.9% NaCl containing ascorbic acid (0.1 mg/ml), was injected stereotaxically into the ascending 5-HT pathways [24] in the mesencephalon using an infusion pump set at 1 μl/min. The rats were anesthetized with Equithesin (2 ml/kg) and pretreated with protriptyline hydrochloride [20 mg/kg IP, Merck, Sharp and Dohme) about 20 min before being placed in a Kopf stereotaxic instrument with the bite bar 2.4 mm above the interaural plane. The injection coordinates in males were: 5.6 mm posterior to the bregma, + 0.6 mm lateral, and 7 and 8 mm ventral to the surface of the cortex. Three μl of 5,7-DHT (1 μg base/μl) were injected 7 mm and the injection needle was thereafter lowered 1 mm and an additional 3 μl were injected. The coordinates in females were the same with the exception that 4 μl of 5,7-DHT were injected 7.5 mm ventral to the surface of the cortex. Controls were injected with the vehicle or received no injection.

Drug and Hormone Treatment

p-Chloroamphetamine hydrochloride (PCA, Sigma Chemicals), dissolved in 0.9% NaCl (10 mg/ml), was injected IP at 1000 hr at a dose of 10 mg/kg. Both males and females received 2 injections separated by one day. The mortality rate was high in males (50%) but low in females (0%).

The 5-HT uptake inhibitor H 102/09 ((Z)-3-(4-bromophenyl-N, N-dimethyl-3-(3-pyridyl) allylamide dihydrocyloride, Zimelidine, Astra Läkemedel), dissolved in 0.9% NaCl (20 mg/ml), was injected IP at a dose of 20 mg/kg 30 min before the PCA. H 102/09 was only used in experiments on males.

Testosterone (T, Sigma Chemicals) was administered to male rats in SILASTIC® (Dow Corning, No. 602–285) capsules, which were filled with T as described in [34] and incubated in 0.9% NaCl at least 1 day before use. The T implants were inserted under light ether anesthesia through a small incision in the midthoracic region. Unless stated otherwise the T implants were 10 mm long. T implants of this size produce constant plasma T levels of about 0.7 ng/ml for at least 21 days, i.e., about 20–30% of the T levels on intact rats [6].

Female rats were treated with estradiol benzoate (EB, Schering Company), dissolved in peanut oil (4 μg/ml), injected SC at a dose of 2 μg/kg (unless stated otherwise), and progesterone (P, Schering Company), given SC at a dose of 0.5 mg/rat in 0.1 ml oil.

Biochemical Methods

After completion of behavioral testing the animals were sacrificed and their brains were rapidly removed. The following structures were dissected out: the amygdala (including parts of the surrounding lateral cortex; weight approximately: 25 mg), hippocampus (weight approximately: 55 mg), septum (weight of each side approximately: 7–8 mg) and hypothalamus (including the preoptic area and parts of the ventral thalamus; approximate weight: 55 mg). Crude synaptosomal fractions were prepared from the hypothalamus and amygdala as described in [25]. Slices (3 mm in dia.) were punched out of the dorsal hippocampus and cerebral cortex. The septum from each hemisphere was used as 1 slice. The uptake of (^{3}H)5-HT (23.9 Ci/mmol) and (^{3}H)NA (10.3

Ci/mmol, New England Nuclear) in slices and synaptosomal preparations was measured as described previously [25,26].

Organ Weights

At the time of sacrifice some of the males were weighed and the ventral prostate, seminal vesicles and adrenals were removed, blotted dry on filter paper and weighed. Similarly, at sacrifice some females were weighed and 2 cm of each uterine horn from the cervix and the adrenals were removed, blotted dry on filter paper and weighed.

Statistical Tests

The number of animals showing ejaculations in the different treatment groups were compared with the Chi^2 test or the Fisher exact probability test. Group differences in the frequencies of the various parameters of mounting behavior, in latencies and lordosis quotients were compared with the Kruskal-Wallis one-way analysis of variance and between group comparisons were made with the Mann-Whitney U test. The effects of the drug treatments on brain (^{3}H)5-HT and (^{3}H)NA uptake and on organ weights at autopsy were evaluated with *t* tests.

EXPERIMENT 1: EFFECTS OF PCA ON THE SEXUAL BEHAVIOR OF CASTRATED MALE RATS

METHOD

Twenty castrated rats received 2 daily injections of 10 mg/kg PCA. Nine of these rats survived the treatment. Nine other rats received injections of 20 mg/kg H 102/09 30 min before the PCA treatment. None of these rats died. Ten rats were given control injections of saline. The rats were given 3 daily tests for sexual behavior starting 7 days after the PCA treatment. On the day after the last test all rats were implanted with 10 mm long T implants and then given 3 additional behavioral tests 3, 5 and 7 days after T implantation, i.e., on Days 13, 15 and 17 after PCA treatment.

Within 3 days after completion of behavioral testing the rats were killed and the uptake of (^{3}H)5-HT in the cortex and hypothalamus was estimated.

Another group of 8 rats received 2 daily injections of 20 mg/kg H 102/09 and 8 more rats were treated with saline. All of these rats were implanted with two 20 mm long T implants at the time of H 102/09 or saline treatment and they were tested on Days 7, 8, 9, 13, 15 and 17 after the treatment.

RESULTS

Behavior

Figure 1 shows that the PCA treatment stimulated display of ejaculations in some of the rats prior to T treatment. Four of the PCA treated but none of the saline treated rats ejaculated before T treatment ($p<0.05$). The figure also shows that all PCA treated rats but only 3 of the saline treated rats ejaculated in response to T treatment ($p<0.01$). Additionally, the figure shows that the effect of PCA was prevented by H 102/09 pretreatment.

Treatment with H 102/09 had no inhibitory effect on the induction of sexual behavior by the longer T implants (Fig. 2).

Behavioral details for ejaculating rats treated with PCA before and after T treatment and for rats treated with two 20

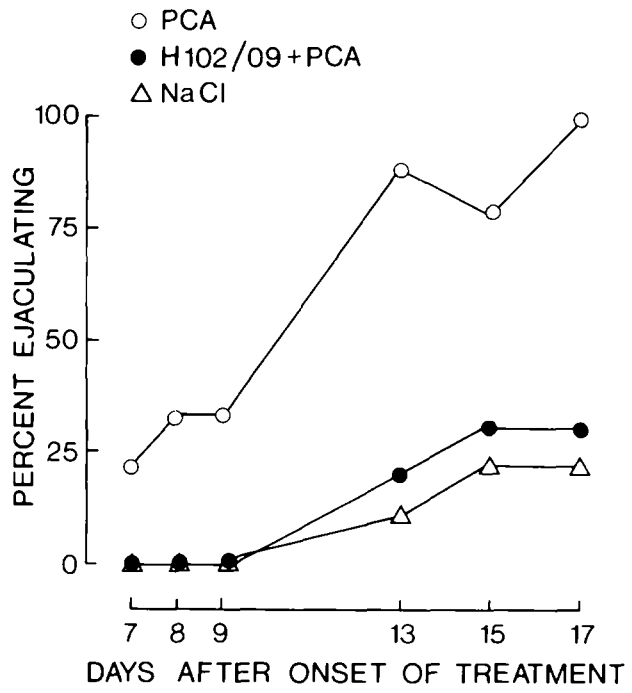

FIG. 1. Percent of castrated male rats ejaculating after treatment with *p*-chloroamphetamine (PCA, 2×10 mg/kg), H 102/09 (2×20 mg/kg) in combination with PCA, or NaCl. Ten mm long testosterone implants were given to all rats 10 days after PCA or NaCl treatment.

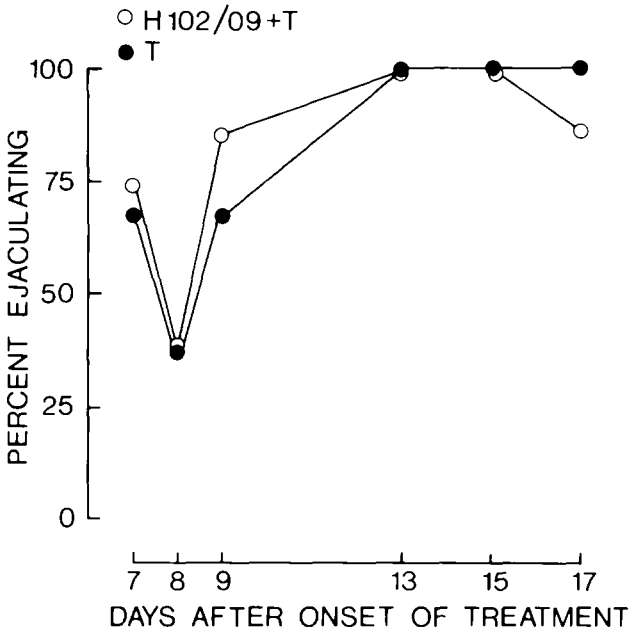

FIG. 2. Percent of castrated male rats ejaculating after treatment with two 20 mm long testosterone (T) implants in combination with H 102/09 (2×20 mg/kg at the time of T implantation).

TABLE 1

SEXUAL BEHAVIOR DISPLAYED BY CASTRATED MALE RATS TREATED WITH P-CHLOROAMPHETAMINE (PCA, 2 × 10 MG/KG), 5,7-DIHYDROXYTRYPTAMINE (5,7-DHT, 2 × 6 μG INTRACEREBRALLY) OR TESTOSTERONE (T, 2 × 20 MM LONG T IMPLANTS). THE VALUES ARE MEANS + S.E.M. OF 3 TESTS GIVEN 7, 8 AND 9 DAYS AFTER DRUG TREATMENT.

			Behavior Pattern				
Treatment	No. of rats	% ejac	Mounts	Intromissions	Intromission latency (min)	Ejaculation latency (min)	Postejaculatory interval (min)
PCA (Expt. 1)	9	44.4	26.5 ± 5.6	25.9 ± 3.0	4.7 + 2.3	18.6 + 3.8	12.1 ± 7.0*
5,7-DHT (Expt. 2a)	12	25.0	48.7 + 16.6	20.8 + 1.5	1.8 ± 0.9	19.9 + 4.7	11.9 + 0.2*
5,7-DHT (Expt. 2b)	9	44.4	30.5 + 8.4	27.6 ± 3.2	3.2 + 1.0	18.6 ± 3.8	13.1 ± 0.8*
2 × 20 mm T	8	62.5	18.0 + 2.4	36.0 + 2.8	1.3 + 0.9	17.7 ± 1.8	6.9 + 0.09

*$p < 0.05$ compared to 2 × 20 mm T.

TABLE 2

SEXUAL BEHAVIOR DISPLAYED BY CASTRATED MALE RATS TREATED WITH P-CHLOROAMPHETAMINE (PCA, 2 × 10 MG/KG) OR 5,7-DIHYDROXYTRYPTAMINE (5,7-DHT, 2 × μ G INTRACEREBRALLY) IN COMBINATION WITH 10 MM LONG TESTOSTERONE IMPLANTS (10 MM T) IMPLANTED 10 DAYS AFTER DRUG TREATMENT OR WITH 2 20 MM LONG T IMPLANTS (2 20 MM T). THE VALUES ARE MEANS + S.E.M. OF 3 TESTS GIVEN 13, 15 AND 17 DAYS AFTER DRUG TREATMENT.

			Behavior Pattern				
Treatment	No. of rats	% ejac	Mounts	Intromissions	Intromission latency (min)	Ejaculation latency (min)	Postejaculatory interval (min)
PCA × 10 mm T (Expt. 1)	9	100.0	7.9 ± 1.5	30.0 ± 2.7	2.2 + 1.0	8.4 + 0.3	4.9 + 0.2
5,7-DHT × 10 mm T (Expt. 2a)	12	66.7	14.7 + 6.1	15.4 ± 2.0	0.4 ± 1.8	8.3 + 1.5	5.6 + 0.3
5,7-DHT (Expt. 2b)	9	44.4	17.3 + 5.7	22.5 ± 3.7	3.7 ± 2.1*	10.0 + 3.4	11.8 + 0.9*
2 20 mm T	8	100.0	14.1 + 4.6	20.8 ± 1.4	0.5 + 0.3	9.2 + 1.7	5.4 + 0.1

*$p < 0.05$ compared to 2 20 mm T.

mm long T implants are shown in Tables 1 and 2. There were no differences in any behavior parameter between rats treated with two 20 mm long T implants in combination with H 102/09 or saline (data for the H 102/09 treated rats are not shown) and the only statistically significant difference between the PCA treated rats and the rats given two 20 mm long T implants was that the PCA treated rats showed longer postejaculatory intervals before T treatment.

Biochemistry

PCA treatment reduced the (^{3}H)5-HT uptake in the hypothalamus to 45 ± 7% and in the cortex to 13 ± 4% of the value for the saline injected controls ($p < 0.01$). Treatment with H 102/09 partly prevented the effect of PCA on hypothalamic (^{3}H)5-HT uptake (59 + 7%, $p < 0.01$) and completely prevented the effect on cortical (^{3}H)5-HT uptake (108 ± 3%, NS).

EXPERIMENT 2: EFFECTS OF 5,7-DHT ON THE SEXUAL BEHAVIOR OF CASTRATED MALE RATS

METHOD

Two experiments were made using 5,7-DHT. In Experiment 2a 12 castrated rats received intracerebral injections of 5,7-DHT plus protriptyline IP, 6 rats received vehicle and protriptyline and 6 rats were anesthetized, treated with protryptyline and placed in the stereotaxic apparatus but received no intracerebral injection. The rats were tested for sexual behavior before and after T treatment as the PCA treated rats described in Experiment 1. Within 3 days after completion of behavioral testing the rats were killed and the uptake of (^{3}H)5-HT in the cortex and hypothalamus and of (^{3}H)NA in the cortex was estimated.

In Experiment 2b a group of 9 castrated rats was treated with 5,7-DHT as described above and 10 rats served as uninjected controls. No vehicle injections were performed since this treatment had no behavioral effect in the first experiment. The rats were tested for sexual behavior 7, 8, 9, 13, 15 and 17 days after 5,7-DHT treatment but no T was given. The rats were killed within 3 days after the last behavioral test and the uptake of (^{3}H)5-HT was assayed in synaptosomal preparations from the hypothalamus and amygdala and in slices from the septum and hippocampus. The brain stems from 5 5,7-DHT and 5 vehicle injected rats were saved and 30 μm frozen sections at the injection sites were prepared and subsequently stained from thionine for microscopic examination.

RESULTS

Behavior

Since there were no behavioral differences between the

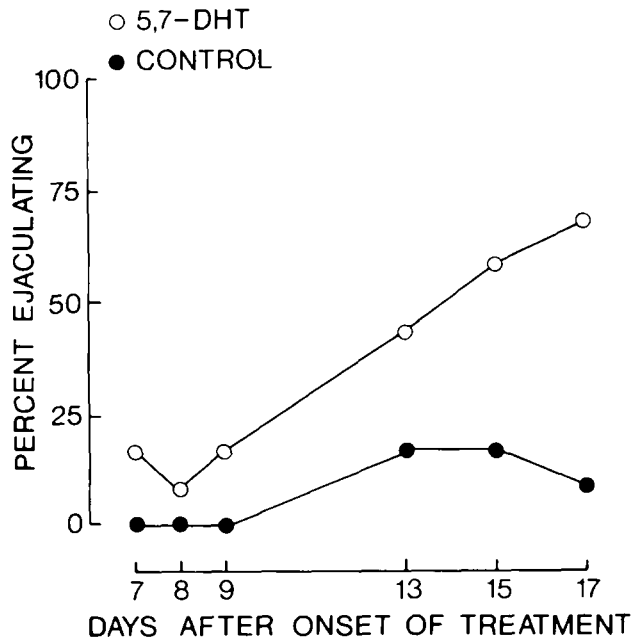

FIG. 3. Percent of castrated male rats ejaculating after treatment with 5,7-dihydroxytryptamine (5,7-DHT, 2×6 μg intracerebrally) or vehicle. Ten mm long testosterone implants were given to all rats 10 days after 5,7-DHT or vehicle treatment.

vehicle and the noninjected rats either before or after T treatment in Experiment 2a the results from these 2 control groups were combined. Figure 3 shows that some of the 5,7-DHT treated rats ejaculated before T treatment. However, since only 3 rats ejaculated the difference is not statistically significant. Figure 3 also shows that more of the 5,7-DHT treated rats (8 rats) than the controls (3 rats) ejaculated after T treatment ($p<0.05$).

Behavioral details for ejaculating 5,7-DHT treated animals before and after T treatment are given in Tables 1 and 2. No statistically significant differences in the behavior were found between the 5,7-DHT treated rats and the rats given two 20 mm long T implants except that the 5,7-DHT treated rats showed longer postejaculatory intervals before T treatment.

Four of the 5,7-DHT treated rats in Experiment 2b ejaculated in 4.5 ± 0.3 of the 6 tests but none of the controls showed any sexual response ($p<0.05$). There was no tendency for the 5,7-DHT treated rats to become less sexually active during the end of the 17 days testing period, all 4 rats ejaculated in the final test. However, the 5,7-DHT treated rats showed longer postejaculatory intervals than the rats implanted with two 20 mm long T implants and longer intromission latencies in the final 3 tests (Tables 1 and 2).

Biochemistry

In Experiment 2a the (^{3}H)5-HT uptake of the 5,7-DHT treated rats were reduced to 11 ± 4% of the value for the uninjected controls in the hypothalamus ($p<0.01$) and to 13 ± 4% in the cortex ($p<0.01$). Vehicle injections caused a moderate reduction of the (^{3}H)5-HT uptake in the hypothalamus (69 ± 5%, $p<0.01$) and cortex (65 ± 12%, $p<0.01$). The 5,7-DHT and vehicle injections did not significantly reduce the (^{3}H)NA uptake in the cortex (95 ± 8% and 89 ± 8%, NS).

In Experiment 2b significant reductions of the (^{3}H)5-HT uptake were found in the septum (14 ± 3% of uninjected controls, $p<0.01$), hippocampus (12 ± 5%, $p<0.01$), amygdala (2 ± 1%, $p<0.01$) and hypothalamus (4 ± 2%, $p<0.01$). An attempt to correlate the sexual behavior with the (^{3}H)5-HT uptake in any of these structures was unsuccessful.

Histology

In the 5,7-DHT and vehicle injected rats visible brain damage of approximately 100–300 μm size was observed in the needle track and its immediate surrounding. There was no detectable difference between the 5,7-DHT and vehicle injected rats. Fluorescence histochemistry of brains with similar 5,7-DHT lesions has been described in [24].

EXPERIMENT 3: EFFECTS OF PCA AND 5,7-DHT ON THE SEXUAL BEHAVIOR OF OVARIECTOMIZED FEMALE RATS

METHOD

Twenty ovariectomized rats received 2 daily injections of 10 mg/kg PCA and 20 other rats received saline injections. In contrast to male rats, no PCA treated female died. Nine ovariectomized rats received intracerebral 5,7-DHT injections, 6 rats were injected with the vehicle and 6 rats received no injections. All rats were tested for mounting behavior 7, 8 and 9 days later. Immediately after each test for mounting behavior the rats were tested for lordosis behavior with stimulus male rats. On day 10 after PCA or 5,7-DHT treatment all rats received a SC injection of 0.5 mg P and they were tested for lordosis behavior 6 hr later. Ten of the PCA, 10 of the saline and all 5,7-DHT, vehicle and noninjected rats then received daily SC injections of 2 μg/kg EB commencing on Day 11 after the drug treatment and they were tested for lordosis behavior with male rats on Days 3, 4, 5 and 6 of EB treatment. On the following day 0.5 mg P was given to all rats and they were again tested for lordosis behavior 6 hr after P treatment.

The rats were killed within 3 days after completion of behavioral testing and the uptake of (^{3}H)5-HT was estimated in the hypothalamus and cortex and, additionally, the uptake of (^{3}H)NA in the cortex in the 5,7-DHT treated rats.

Two groups of ovariectomized rats were treated daily with 2 (N=10) or 100 (N=11) μg/kg EB for 6 days and they were tested for lordosis behavior on Days 3, 4, 5 and 6 of EB treatment. Another group of ovariectomized rats (N=11) received daily injections of 2 μg/kg EB for 6 days in combination with 0.5 mg P 6 hr before behavioral testing on Days 3, 4, 5 and 6 of EB treatment.

RESULTS

Mounting Behavior

Table 3 shows that the PCA treated rats showed only slightly more mounting behavior than the saline injected controls, which was reflected in a significantly higher frequency of mounts/min among the rats that mounted. Table 3 also shows that more of the 5,7-DHT treated rats than controls showed mounts and intromissions and that those rats that mounted showed more mounts/min. (The data from vehicle and uninjected rats were combined, since no behavioral differences were found between these 2 groups.)

TABLE 3

MOUNTING BEHAVIOR DISPLAYED BY OVARIECTOMIZED FEMALE RATS TREATED WITH P-CHLOROAMPHETAMINE (PCA, 2 × 10 MG/KG), NACL, 5,7-DIHYDROXYTRYPTAMINE (5,7-DHT, 2 × 6 μG INTRACEREBRALLY) OR VEHICLE. THE VALUES ARE MEANS ± S.E.M. OF 3 TESTS GIVEN 7, 8, AND 9 DAYS AFTER DRUG TREATMENT.

Treatment	No. of rats	% showing Mounts	% showing Intromission patterns	Mounts/min*	Intromission patterns/min*
PCA	20	50	25	1.4 ± 0.2	0.4 ± 0.1
NaCl	20	30	5	0.4 ± 0.1	0.6
p		NS	NS	< 0.02	NS
5,7-DHT	9	88.9	66.7	1.2 ± 0.1	0.5 ± 0
Vehicle	12	33.3	0.	0.7 ± 0.1	0.0
p		< 0.05	< 0.01	< 0.05	—

*Non-responders excluded.

Lordosis Behavior

None of the rats showed lordosis behavior before EB treatment, even when P was given before testing.

Figure 4 shows that there was no significant effect of either PCA or 5,7-DHT treatment on the display of lordosis after initiation of EB treatment. Administration of 0.5 mg P before testing resulted in maximum lordosis quotients in all rats. The figure also shows that a high dose of EB (100 μg/kg) or administration of 0.5 mg P 6 hr before testing to rats given 2 μg/kg EB daily produced significantly higher lordosis quotients ($p < 0.01$) than daily treatment with 2 μg/kg EB.

Biochemistry

The PCA treatment reduced the (^{3}H)5-HT uptake in the hypothalamus to 58 ± 4% of the value for the saline injected controls ($p < 0.01$) and to 15 ± 6% in the cortex ($p < 0.01$). The 5,7-DHT treatment produced a reduction of the (^{3}H)5-HT uptake in the hypothalamus to 17 ± 3% ($p < 0.01$) and to 16 ± 2% in the cortex ($p < 0.01$). Vehicle injections did not reduce the (^{3}H)5-HT uptake in the hypothalamus (97 ± 10%, NS), however, uptake in the cortex was somewhat reduced (76 ± 8%, $p < 0.05$). The (^{3}H)NA uptake in the cortex was only marginally affected by the 5,7-DHT (95 ± 8%, NS or vehicle (89 ± 8%, NS) injection procedures.

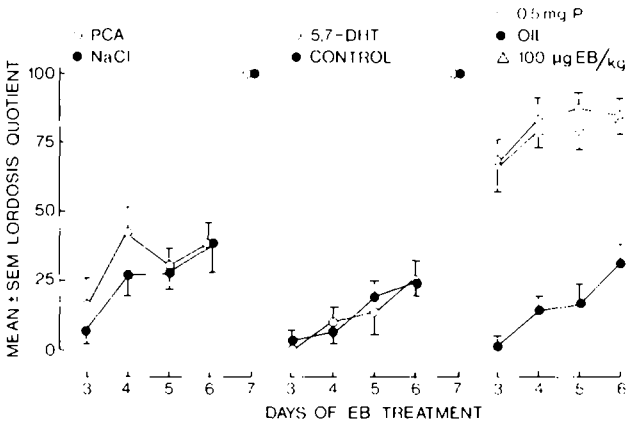

FIG. 4. Mean ± SEM lordosis quotients displayed by ovariectomized female rats treated with p-chloroamphetamine (PCA, 2 × 10 mg/kg), NaCl, 5,7-dihydroxytryptamine (5,7-DHT, 2 × 4 μg intracerebrally), or vehicle in combination with daily injections of 2 μg/kg estradiol benzoate (EB) starting 11 days after PCA or 5,7-DHT treatment. Five tenths (0.5) mg progesterone (P) was given to all rats on Day 7, 6 hr before testing. Additional groups of rats were given daily injections of 2 μg EB/kg in combination with oil or 0.5 mg P 6 hr before testing or daily injections of 100 μg EB/kg.

EXPERIMENT 4: EFFECTS OF PCA AND 5,7-DHT ON ANDROGEN AND ESTROGEN SENSITIVE ORGANS IN GONADECTOMIZED RATS

METHOD

Groups of 5 PCA, saline, 5,7-DHT or untreated castrated male rats were killed 10 days after the drug treatments and the weight of the accessory sex organs and adrenals glands was determined. One additional group of 9 castrated rats was implanted with 3 mm long T implants and these rats were tested for sexual behavior according to the previously described procedure. They were then killed and the weight of their accessory sexual glands and adrenals was determined.

RESULTS

Body weights in male rats ranged from 320 to 360 g and in females from 250 to 280 g with no significant differences related to drug treatment. Tables 4 and 5 show that the drugs treatments did not stimulate any of the androgen or estrogen sensitive organs or adrenals. Three mm long T implants did not stimulate any sexual response in any of the males but the ventral prostate and seminal vesicles of these rats were heavier than those of the drug treated animals.

DISCUSSION

This study has shown that treatment with the 5-HT neurotoxins PCA and 5,7-HDT reduces the high affinity uptake of (^{3}H)5-HT in the brain and facilitates the induction of sexual behavior by low doses of T in castrated male rats, thus supporting the conclusion reached in many previous experiments using PCPA, that central 5-HT neurotransmission is involved in the control of sexual behavior in male rats

TABLE 4

MEAN ± S.E.M. WEIGHTS OF THE ACCESSORY SEXUAL GLANDS AND ADRENAL GLANDS OF CASTRATED MALE RATS TREATED WITH P-CHLOROAMPHETAMINE (PCA, 2 × 10 MG/KG), NACL, 5,7-DIHYDROXYTRYPTAMINE (5,7-DHT, 2 × 6 μG INTRACEREBRALLY) OR VEHICLE AND KILLED 10 DAYS LATER. A GROUP OF RATS WAS TREATED WITH 3 MM LONG TESTOSTERONE IMPLANTS (3 MM T) AND KILLED 17 DAYS LATER.

Treatment	No. of rats	Ventral prostrate (mg)	Seminal vesicles (mg)	Two adrenals (mg)
PCA	5	15.0 ± 2.0*	52.0 ± 4.5	85.3 ± 18.7
NaCl	5	17.0 ± 2.0*	50.4 ± 2.9*	93.5 ± 10.5
5,7-DHT	5	12.7 ± 2.5*	41.6 ± 3.3*	96.8 ± 7.8
Vehicle	5	14.0 ± 1.6*	42.1 ± 2.1*	83.5 ± 4.3
3 mm T	9	35.6 ± 2.5	63.3 ± 2.6	96.8 ± 4.8

*$p < 0.05$ compared to 3 mm T.

TABLE 5

MEAN ± S.E.M. WEIGHT OF THE UTERUS AND ADRENAL GLANDS OF OVARIECTOMIZED FEMALE RATS TREATED WITH P-CHLOROAMPHETAMINE (PCA, 2 × MG/KG), NACL, 5,7- DIHYDROXYTRYPTAMINE (5,7-DHT, 2 × 4 μG INTRACEREBRALLY) OR VEHICLE AND KILLED 10 DAYS LATER

Treatment	No. of rats	Uterus (mg)	Two adrenals (mg)
PCA	5	70.5 ± 3.3	84.0 ± 2.8
NaCl	5	80.5 ± 5.8	94.7 ± 4.7
5,7-DHT	5	73.8 ± 6.4	97.7 ± 5.2
Vehicle	5	79.0 ± 6.0	101.7 ± 6.3

[10, 16, 36, 37, 51, 52]. More important, however, it was found that PCA or 5,7-DHT treatment induced sexual behavior in a significant proportion of castrated males in the absence of exogenous T and that the pattern of sexual behavior induced by PCA or 5,7-DHT differed only slightly from that induced by T. This effect is probably not due to activation of adrenal androgen secretion because no stimulation of the accessory sexual glands or adrenals was noted in animals treated with PCA or 5,7-DHT. A low level of T stimulation was shown to stimulate the peripheral androgen sensitive organs but not the sexual behavior. Also, we can be reasonably sure that the behavioral effect of 5,7-DHT was not due to interference with NA mechanisms since the (^{3}H)NA uptake in the cortex was only marginally affected. However, we cannot exclude the possibility that the ventral NA bundle might have been somewhat damaged by our 5,7-DHT treatment. A recent study [33] failed to induce sexual behavior by 5,7-DHT treatment, perhaps because less 5,7-DHT was injected in that study. Preliminary experiments in this study also indithat study. Preliminary experiments in this study also indicated that rather extensive lesions of the ascending 5-HT pathways were necessary to obtain behavioral effects. These and similar results with PCPA [49] show that drugs affecting 5-HT neurotransmission activate the sexual behavior of castrated male rats directly and do not merely serve to modulate the behavioral response to T. Implicit in this line of reasoning is the assumption that T activates the sexual behavior of male rats via an action on 5-HT neurons. On this hypothesis it would be predicted that castration should have measurable effects on 5-HT biosynthesis. Yet Kizer *et al.* [28] were unable to detect any effects on hypothalamic tryptophan hydroxylase activity 7 days after castration. However, recent experiments indicate that about 20 days after castration there is a significant increase in the synthesis of 5-HT, which can be reversed by T treatment, in the brain areas which are involved in the control of sexual behavior [11]. These observations strengthen the idea that 5-HT is involved in the control of sexual behavior by T. However, we have never been able to induce sexual behavior in the 100% of castrated male rats either by PCPA, PCA or 5,7-DHT treatment, which, of course, is easily done with T. Therefore, T must control the sexual behavior of male rats by additional, as yet unspecified, mechanisms.

Larsson *et al.* [33] found a correlation between the intensity of sexual behavior and the reduction of the (^{3}H)5-HT uptake in the hypothalamus in 5,7-DHT treated male rats and suggested that it is in this brain area that 5-HT acts to control sexual behavior. However, correlations between sexual behavior and (^{3}H)5-HT uptake in other brain areas might have been obtained had the uptake of (^{3}H)5-HT been measured elsewhere. We were unable to relate the behavioral effects of 5,7-DHT to the reduction of (^{3}H)5-HT uptake in either the hypothalamus, septum, hippocampus or amygdala, brain areas which may play a role in the neural control of sexual behavior [9]. However, the behavioral effects of PCA seemed to be more potent than those of 5,7-DHT. One hundred percent of the PCA treated rats compared to 66.7% of the 5,7-DHT treated rats ejaculated after T treatment. Yet the effect of PCA on the hypothalamic uptake of (^{3}H)5-HT (45 ± 7% of controls) was less pronounced than that of 5,7-DHT (11 ± 4%, Experiment 2a, 4 ± 2%, Experiment 2b). Moreover, the behavioral effect of PCA was completely reversed by pretreament with the 5-HT uptake inhibitor H 102/09, although the H 102/09 treatment did not completely prevent the effect of PCA on hypothalamic (^{3}H)5-HT uptake. The reversal of the behavioral effect of PCA by H 102/09 was not due to a non-specific effect of the H 102/09, since the induction of sexual behavior by two 20 mm long T implants was unaffected by H 102/09 treatment. These results are in agreement with a recently published detailed study of the biochemical effects of PCA [30] which showed that the most pronounced effect of PCA on 5-HT neurons is not in the

hypothalamus. Thus, the neural site at which 5-HT controls the sexual behavior of male rats remains to be determined.

In contrast to its pronounced effect in male rats, PCA had an almost negligible effect on mounting behavior in ovariectomized female rats. No improvement of the effect of PCA was obtained by giving 4 daily injections of 10 mg/kg (unpublished results). Also, whereas the mortality rate was high in males, females tolerated the PCA treatment. Although the effect of PCA on the (^{3}H)5-HT uptake in the hypothalamus and cortex was less marked in females than in males, it seems unlikely that this difference can explain the dramatic sex difference in the behavioral response to PCA. We are unable to explain this sex difference.

5,7-DHT treatment had a clear stimulatory effect on the mounting behavior of ovariectomized hormonally untreated female rats and produced a marked reduction of the uptake of (^{3}H)5-HT in the hypothalamus and cortex while having a very small effect on the uptake of (^{3}H)NA in the cortex. As with male rats, it seems unlikely that this behavioral effect was due to release of adrenal androgens or estrogens, since no stimulation of uterine or adrenal weights was noted by the treatment. Thus, as is the case with PCPA [49,50] 5,7-DHT treatment of gonadectomized male and female rats stimulates the display of masculine sexual behavior in the absence of exogenous supply of T.

No PCA or 5,7-DHT treated ovariectomized female rat showed lordosis, even if P was given before testing and there was no effect of the PCA or 5,7-DHT treatment on the subsequent behavioral response to daily treatment with 2μg/kg EB. Control experiments showed that ovariectomized female rats show high lordosis quotients in response to daily treatment with 100 μg/kg EB or 2 μg/kg EB in combination with 0.5 mg P 6 hr before testing. These results agree with our previous results using PCPA [50] and suggest that drugs affecting 5-HT neurotransmission cannot replace the behavioral effects of EB or P in ovariectomized rats. In the case of P this is perhaps not surprising since the neural sites at which P affects lordosis behavior [35, 38, 53, 54] do not coincide with the location of the 5-HT cell bodies or the major 5-HT projection areas in the brain [19] and since no consistent effects of P on central 5-HT biosynthesis have been reported [15, 18, 31, 32, 40, 41]. Similarly, whereas a central nervous estrogen—5-HT interaction seems likely [19], it is not clear whether this may be important for the regulation of lordosis. The ventromedial nucleus of the hypothalamus seems to be the main site at which EB acts to induce lordosis behavior [2, 8, 39, 46], but this nucleus has the lowest concentration of 5-HT of all hypothalamic nuclei [4] and the major 5-HT projection areas in the hypothalamus seem to be the preoptic—anterior area and the suprachiasmatic and arcuate nuclei [19], brain areas which do not play an indispensable role for the induction of lordosis behavior by EB [20,44]. Moreover, one study [45] failed to detect an effect of PCPA treatment or midbrain raphe lesions on hypothalamic estradiol retention and only little information is available on the effects of EB treatment on central 5-HT biosynthesis [27]. However, it must be added that 5-HT cell bodies were recently described in the ventromedial hypothalamus [5], but their physiological role remains to be determined.

Zemlan *et al.* [56] found that PCA treatment facilitated the display of lordosis behavior by ovariectomized females given EB and P 5, but not 3, days after injection of 10 mg/kg and 3, but not 5, days after injections of 20 mg/kg of the drug. Ovariectomized EB treated females did not respond to the PCA, P had to be given in addition to the EB. Zemlan *et al.* [56] and Michanek and Meyerson [43] also showed that lordosis behavior activated by EB and P treatment was inhibited 20–30 min after administration of 10 or 2.5 mg/kg PCA, but this observation can hardly be taken as evidence for involvement of 5-HT in the control of lordosis behavior per se, since PCA treatment produces rigid immobile postures, tremor, myoclonus, salivation and piloerection within 5 min of administration ([21], several of the males in the present study even died.) Everitt *et al.* [14] found that 5,7-DHT treatment of ovariectomized EB treated female rats facilitated the display of lordosis behavior 1–7 days after injection in a first experiment, but not after 7–13 days in a second experiment. The most pronounced facilitation of lordosis was observed 20–160 days after injection of 5,7-DHT in a third experiment. It is not clear why such a long time had to elapse before the behavioral effect appeared, particularly as a 75% reduction of the (^{3}H)5-HT uptake in the hypothalamus was evident already 14 days after the injection. Taken together these results with PCA and 5,7-DHT are rather variable and could not be replicated with our procedures. The results of previous studies on the effects of PCPA on lordosis behavior have also yielded inconsistent results, perhaps due to differences in procedures [1, 12, 15, 22, 41, 47, 55]. We conclude, therefore, that whereas 5-HT clearly plays a role in the control of masculine sexual behavior, conclusive evidence for a role of 5-HT in lordosis behavior remains to be presented.

REFERENCES

1. Ahlenius, S., J. Engel, H. Eriksson, K. Modigh and P. Södersten. Involvement of monoamines in the mediation of lordosis behavior. In: *Sexual Behavior: Pharmacology and Biochemistry*, edited by M. Sandler and G. L. Gessa. New York: Raven Press, 1975, pp. 137–145.
2. Barfield, R. J. and J. J. Chen. Activation of estrous behavior in ovariectomized rats by intracerebral implants of estradiol benzoate. *Endocrinology* **101**: 1716–1725, 1977.
3. Björklund, A., H. G. Baumbarten and A. Nobin. Chemical lesioning of central monoamine axons by means of 5,6-dihydroxytryptamine and 5,7-dihydroxytryptamine. In: *Advances in Biochemical Psychopharmacology*, edited by E. Costa, G. L. Gessa and M. Sandler. New York: Raven Press, 1974, pp. 13–33.
4. Brownstein, M. Biogenic amine content of the hypothalamic nuclei. In: *Anatomical Neuroendocrinology*, edited by L. D. Grant and W. E. Stumpff. New York: S. Karger, 1976, pp. 393–396.
5. Chan-Palay, V. Indoleamine neurons and their processes in the normal rat brain and in chronic diet induced thiamine deficiency demonstrated by uptake of ^{3}H serotonin. *J. comp. Neurol.* **176**: 467–494, 1977.
6. Damassa, D. A., D. Kobashigawa, E. R. Smith and J. M. Davidson. Negative feedback control of LH by testossterone: a quantitative study in male rats. *Endocrinology* **99**: 736–741, 1977.
7. DaPrada, M., E. P. Bonetti and H. H. Keller. Induction of mounting behaviour in female and male rats by lisuride. *Neurosci. Lett.* **6**: 349–353, 1977.

8. Davis, P. G., B. S. McEwen and D. W. Pfaff. Localized effects of tritiated estradiol implants in the ventromedial hypothalamus of female rats and behavioral correlates. Paper presented at the Eastern Conference on Reproductive Behavior, Madison, Wisconsin, 1978.
9. Davidson, J. M. Neurohumoral bases of male sexual behavior. In: *International Review of Physiology, Reproductive Physiology II*, edited by R. O. Greep. Baltimore: University Park Press, 1977, pp. 225–254.
10. DelFiacco, M., W. Fratta, G. L. Gessa and A. Tagliamonte. Lack of copulatory behaviour in male castrated rats after p-chlorophenylalanine. *Br. J. Pharmac.* **51:** 249–251, 1974.
11. Engel, J., S. Ahlenius, O. Almgren, A. Carlsson, K. Larsson and P. Södersten. Effects of gonadectomy and hormone replacement on monoamine synthesis in male rats. *Pharmac. Biochem. Behav.*, 1978, in press.
12. Eriksson, H. and P. Södersten. A failure to facilitate lordosis behavior in adrenalectomized and ovariectomized estrogen-primed rats with monoamine synthesis inhibitors. *Hormones Behav.* **4:** 89–98, 1973.
13. Everitt, B. J. Cerebral monoamines and sexual behavior. In: *Handbook of Sexology*, edited by J. Money and H. Mustaph. Amsterdam: Excerpta Medica, 1977, pp. 429–448.
14. Everitt, B. J., K. Fuxe and G. Jonsson. The effects of 5,7-dihydroxytryptamine lesions of ascending 5-hydroxytryptamine pathways on the sexual and aggressive behaviour of female rats. *J. Pharmac., Paris* **6:** 25–32, 1975.
15. Everitt, B. J., K. Fuxe, T. Hökfelt and G. Jonsson. Role of monoamines in the control by hormones of sexual receptivity in the female rat. *J. comp. physiol. Psychol.* **89:** 556–572, 1975.
16. Gawienowsky, A. M. and G. D. Hogden. Homosexual activity in male rats after p-chlorophenylalanine: effects of hypophysectomy and testosterone. *Physiol. Behav.* **7:** 751–755, 1971.
17. Gessa, G. L. and A. Tagliamonte. Role of brain serotonin and dopamine in male sexual behavior. In: *Sexual Behavior: Pharmacology and Biochemistry*, edited by M. Sandler and G. L. Gessa. New York: Raven Press, 1975, pp. 117–128.
18. Greengrass, P. M. and S. R. Tonge. Brain monoamine metabolism in the mouse brain during the immediate postpartum period. *Br. J. Pharmac.* **46:** 533P–534P.
19. Grant, L. D. and W. E. Stumpf. Hormone uptake sites in relation to CNS biogenic amine systems. In: *Anatomical Neuroendocrinology*, edited by W. E. Stumpf and L. D. Grant. New York: S. Karger, 1976, pp. 445–463.
20. Gray, G. D., P. Södersten, D. Tallentire and J. M. Davidson. Effects of lesions in various structures of the suprachiasmatic-preoptic region on LH regulation and sexual behavior in female rats. *Neuroendocrinology* **25:** 174–191, 1978.
21. Growdon, J. H. Postural changes, tremor, and myoclonus in the rat immediately following injections of p-chloroamphetamine. *Neurology* **27:** 1074–1077, 1977.
22. Gorzalka, B. B. and R. E. Whalen. Inhibition not facilitation of sexual behavior by PCPA. *Pharmac. Biochem. Behav.* **1:** 511–513, 1975.
23. Harvey, J. A., S. E. McMasters and L. M. Yunger. p-Chloroamphetamine: selective neurotoxic action in brain. *Science* **187:** 841–843, 1975.
24. Hole, K., K. Fuxe and G. Jonsson. Behavioral effects of 5,7-dihydroxytryptamine lesions of ascending 5-hydroxytryptamine pathways. *Brain Res.* **107:** 385–399, 1976.
25. Jonsson, G., Ch. Pycock, K. Fuxe and Ch. Sachs. Changes in the development of central noradrenaline neurons following neonatal administration of 6-hydroxydopamine. *J. Neurochem.* **22:** 621–626, 1974.
26. Jonsson, G. and Ch. Sachs. Actions of 6-hydroxydopamine catecholamine neurons. *J. Neurochem.* **25:** 509–516, 1975.
27. Kizer, J. S. Endocrine-induced alterations of monoamine metabolism in brain. In: *Anatomical Neuroendocrinology*, edited by W. E. Stumpf and L. D. Grant. New York: S. Karger, 1976, pp. 401–408.
28. Kizer, J. S., M. Palkovitz, I. J. Kopin, J. M. Saavedra and M. J. Brownstein. Lack of effect of various endocrine manipulations on tryptophan hydroxylase activity of individual nuclei of the hypothalamus, limbic system, and midbrain of the rat. *Endocrinology* **98:** 743–747, 1976.
29. Koe, B. K. and A. Weissman. p-Chlorophenylalanine: a specific depletor of brain serotonin. *J. Pharmacol. exp. Ther.* **154:** 499–516, 1966.
30. Köhler, Ch., S. B. Ross, S. Srebro and S. O. Ögren. Longterm biochemical and behavioral effects of p-chloroamphetamine in the rat. *Ann. N.Y. Acad. Sci.* **305:** 645–663, 1978.
31. Ladisich, W. Effect of progesterone on regional 5-hydroxytryptamine metabolism in the rat brain. *Neuropharmacology* **13:** 877–883, 1974.
32. Ladisich, W. Influence of progesterone on serotonin metabolism: a possible causal factor for mood changes. *Psychoneuroendocrinology* **2:** 257–266, 1977.
33. Larsson, K., K. Fuxe, B. J. Everitt, M. Holmgren and P. Södersten. Sexual behavior in male rats after intracerebral injections of 5,7-dihydroxytryptamine. *Brain Res.* **141:** 293–303, 1978.
34. Legan, S. J., G. A. Coon and F. J. Karsch. Role of estrogen as initiator of the daily LH surges in the ovariectomized rat. *Endocrinology* **96:** 50–56, 1975.
35. Luttge, W. G. and J. R. Huges. Intracerebral implantation of progesterone: re-examination of the brain sites responsible for facilitation of sexual behavior in estrogen-primed ovariectomized rats. *Physiol. Behav.* **17:** 771–775, 1976.
36. Malmnäs, C. O. Monoaminergic influences on testosterone-activated copulatory behaviour in the castrated male rat. *Acta Physiol. scand.*, Suppl. **395**, 1973.
37. Malmnäs, C. O. and B. J. Meyerson. p-Chlorophenylalanine and copulatory behavior in the male rat. *Nature* **232:** 398–400, 1971.
38. Marrone, B. L., J. F. Rodriguez-Sierra and H. H. Feder. Intrahypothalamic implants of progesterone inhibit lordosis behavior in ovariectomized, estrogen-treated rats. *Neuroendocrinology*, 1978, in press.
39. Mathews, D. and D. A. Edwards. The ventromedial nucleus of the hypothalamus and the hormonal arousal of sexual behavior in the female rat. *Hormones Behav.* **8:** 40–51, 1977.
40. Meyerson, B. J. Central nervous monoamines and hormone induced estrous behaviour in the spayed rat. *Acta Physiol. scand.*, Suppl. **241**, 1964.
41. Meyerson, B. J. and T. Lewander. Serotonin synthesis inhibition and estrous behavior in female rats. *Life Sci.* **9:** 661–671, 1970.
42. Meyerson, B. J. and C. O. Malmnäs. Brain monoamines and sexual behavior. In: *Biological Determinants of Sexual Behaviour*, edited by J. B. Hutchison. New York: John Wiley & Sons, 1978, pp. 521–554.
43. Michanek, A. and B. J. Meyerson. A comparative study of different amphetamines on copulatory behaviour and stereotype activity in the female rat. *Psychopharmacology* **53:** 175–183, 1977.
44. Powers, J. B. and E. S. Valenstein. Sexual receptivity: facilitation by medial preoptic lesions in female rats. *Science* **175:** 1003–1005, 1972.
45. Rotsztejn, W. H., F. Gogan, B. Mess, E. Laplante, E. Pattou, M. Faudon and C. Kordon. Brain serotonin and estradiol retention in the hypothalamus and pituitary of the rat. *Neuroendocrinology* **21:** 88–96, 1976.
46. Rubin, B. S. and R. J. Barfield. A refined localization of the site of action of estradiol in the regulation of estrous behavior in the rat. Paper presented at the Eastern Conference on Reproductive Behavior, Madison, Wisconsin, 1978.
47. Segal, D. S. and R. E. Whalen. Effect of chronic administration of p-chlorophenylalanine on sexual receptivity in the female rat. *Psychopharmacologia* **16:** 434–438, 1970.
48. Södersten, P. Mounting behavior in the female rat during the estrous cycle, after ovariectomy, and after estrogen of testosterone administration. *Hormones Behav.* **3:** 307–320, 1972.

49. Södersten, P., K. Larsson, S. Ahlenius and J. Engel. Sexual behavior in castrated male rats treated with monoamine synthesis inhibitors and testosterone. *Pharmac. Biochem. Behav.* **5**: 319–327, 1976.
50. Södersten, P., K. Larsson, S. Ahlenius and J. Engel. Stimulation of mounting behavior but not lordosis behavior in ovariectomized female rats by p-chlorophenylalanine. *Pharmac. Biochem. Behav.* **5**: 329–333, 1976.
51. Tagliamonte, A., P. Tagliamonte, G. L. Gessa and B. B. Brodie. Compulsive sexual activity induced by p-chlorophenylalanine in normal and pinealectomized male rats. *Science* **166**: 1433–1435, 1969.
52. Tagliamonte, A., W. Fratta, G. Mercuro and G. L. Gessa. Failure of p-chlorophenylalanine (PCPA) to restore copulatory behavior in male castrated rats. *Riv. Farmac. Ter.* **3**: 399–403, 1972.
53. Yanase, M. and R. A. Gorski. Site of estrogen and progesterone facilitation of lordosis behavior in the spayed rat. *Biol. Reprod.* **15**: 536–543, 1976.
54. Yanase, M. and R. A. Gorski. The ability of the intracerebral exposure to progesterone on consecutive days to facilitate lordosis behavior: an interaction between progesterone and estrogen. *Biol. Reprod.* **15**: 544–550, 1976.
55. Zemlan, F. P., I. L. Ward, W. R. Crowley and D. L. Margules. Activation of lordotic responding in female rats by suppression of serotonergic activity. *Science* **179**: 1010–1011, 1973.
56. Zemlan, F. P., M. E. Trulson, R. Howell and B. G. Hoebel. Influence of p-chloroamphetamine on female sexual reflexes and brain monoamine levels. *Brain Res.* **123**: 347–356, 1977.