of the test, if the animal was on the OFF side it was removed immediately; if on the ON side, it was not removed until it crossed over to the OFF side. The animals received no signal indicating the end of the 5- or 10-minute session.

In the empty shuttle box the median preferred ON durations were 4 to 20 seconds for seven of the rats and 45 seconds for one rat (*13*). The introduction of appropriate goal objects into the box produced a dramatic change in all the animals' behavior. Instead of the restless searching, rearing, and sniffing which was characteristic of their behavior on the ON side of the empty box, each rat calmly engaged in feeding, drinking, or gnawing behavior while the current was on in the presence of appropriate goal objects. Their median ON times increased by at least 50 percent and in most cases by more than 100 percent. Their range was now 12 to 233 seconds (Table 1). While eating the food or drinking the water, the rats would typically stroll slowly around the box, occasionally appearing to accidentally enter deep into the OFF side, thereby terminating the current. In fact one of the feeders (rat No. 89) and one of the drinkers (rat No. 67) seemed never to terminate the stimulation intentionally, but only accidentally by wandering into the OFF side while feeding or drinking (*14*). The combined median ON duration for all the rats was 14 seconds under the empty condition and 33.5 seconds under the goal-object condition (*15*).

Thus for all the rats the onset of the aversive effects of the brain stimulation was delayed, and for two of them it appeared to be almost completely suppressed by performance of the behavior facilitated by the stimulation. To evaluate the role of sensory input in suppressing these aversive effects, three of the feeders were given additional tests with powdered foods containing 0, 33, and 80 percent sugar (*16*). Each rat was given three 10-minute tests per day, one with each concentration of sugar. The tests were separated by 3 hours. One hour before each test, the food mixture to be used in the test was placed into the rat's cage to insure that the rat would be satiated on the test food. Each rat was tested for six consecutive days; each day the tests were administered in a different order. The results were clear for all animals: the greater the concentration of sugar in the food, the longer the preferred ON duration (Fig. 1). This trend was statistically significant for each rat (*17*). Thus the greater the palatability of the food, the greater the inhibition of the aversive effects of hunger-inducing brain stimulation.

These data are consistent with the hypothesis that the aversive effects of hypothalamic stimulation are due to an excessive arousal of a drive, and that these effects can be inhibited by the engagement of the consummatory behavior facilitated by the drive. Most previous studies have emphasized the role of stimulation parameters and brain locus as the primary determinants of the reinforcing effects of brain stimulation (*1*). However, four experiments have shown that the affective tone of hypothalamic stimulation is also a function of the environment in which the subjects are tested (*18*): if the environment lends support to activities facilitated by the stimulation, then its rewarding effects are augmented. The present experiment complements the previous ones by demonstrating that in such environments the aversive effects of stimulation are diminished.

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10. Histological analysis of the brains of four of the rats revealed that the electrode tips were located in hypothalamic areas whose stimulation has been previously reported to induce feeding, drinking, and gnawing [see J. Mendelson, *J. Comp. Physiol. Psychol.* **62**, 341 (1966); G. H. Mogenson and J. A. F. Stevenson, *Exp. Neurol.* **17**, 119 (1967); W. W. Roberts and R. J. Carey, *J. Comp. Physiol. Psychol.* **59**, 317 (1965)].
11. This testing apparatus was designed for the experiment because it provided for simplicity of the responses for initiating and terminating the stimulation and for freedom of movement for the rat while the stimulation was on or off.
12. There were three exceptions to this. Rat No. 91 dislodged its electrode after two tests in the empty box and one test with wood, and rats Nos. 89 and 120 stopped engaging in stimulation-induced feeding and gnawing, respectively, after their second pair of tests.
13. Rat No. 89 initially had much shorter ON times (median, 29 seconds), but then developed the habit of chasing and chewing its hind legs. This greatly increased its ON times (median, 60 seconds), presumably because chewing decreased the aversive effects of the stimulation.
14. Rat No. 67 appeared to intentionally terminate the stimulation on only one of its food tests, but only accidentally on the other three tests. All its terminations on the water tests appeared to be accidental.
15. It should be noted that this result is obtained with food and wood only if they are not easily transportable. However, if food pellets or small pieces of wood are used, then the preferred ON times decrease by more than 50 percent and the animals transport the food or wood from the ON side to the OFF side. This is probably related to the fact that in the rat's natural environment "hoarding" successfully competes with feeding when hungry rats find food in an insecure place. In this experiment the ON side is insecure or potentially dangerous (the stimulation becomes aversive if allowed to continue too long); so the rats hoard portable objects to the OFF side (where there is never any aversive stimulation), thus obscuring the present phenomenon.
16. Purina rat food powder was thoroughly mixed with various amounts of brown sugar. For rats Nos. 47 and 67 these tests were conducted about 6 months after the first experiment, by which time their preferred ON durations had slightly changed.
17. $P < .001$ by a nonparametric trend analysis [G. A. Ferguson, *Nonparametric Trend Analysis* (McGill Univ. Press, Montreal, 1965)].
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19. This research was begun at the Massachusetts Institute of Technology, continued at the University of Michigan and McGill University, and completed at Rutgers University. Supported in part by NIH grants to S. L. Chorover (MH-07923), S. E. Glickman (MH-13253), D. Bindra (MH-03238), and J. Olds and J.M. (MH-31258 and MH-14410), and by NSF grant GB-7370 to J.M.

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Compulsive Sexual Activity Induced by p-Chlorophenylalanine in Normal and Pinealectomized Male Rats

Abstract. p-*Chlorophenylalanine depletes brain serotonin and induces long-lasting sexual excitation in male rats. The effect of* p-*chlorophenylalanine is potentiated by pargyline. Administration of 5-hydroxytryptophan to rats treated with* p-*chlorophenylalanine plus pargyline blocks the sexual excitation.* p-*Chlorophenylalanine also elicits sexual excitation in pinealectomized rats; this effect is not mediated by the lack of indole hormones in the pineal but may be the consequence of depletion of 5-hydroxytryptophan in the brain and the resulting imbalance between 5-hydroxytryptophan and catecholamine activity in the central nervous system.*

Several studies suggest that brain serotonin (5-hydroxytryptamine, 5-HT) and the pineal hormones (melatonin and 5-methoxytryptophol) inhibit the estrous cycle and sexual behavior in female rats. Thus, Meyerson concluded that serotoninergic mechanisms inhibit the copulatory behavior (lordosis re-

flex) displayed by the female rat during estrus (*1*). Administration of the pineal 3-methoxyindoles decreased the incidence of estrus and the rate of ovarian growth in rats (*2*). Conversely (*3*), *p*-chlorophenylalanine (PCPA), an inhibitor of serotonin synthesis (*4*), increases the incidence of estrus in rats and is suggested to act by inhibiting the formation of methoxyindoles in the pineal. Finally, 2-propyldopacetamide, another inhibitor of tryptophan hydroxylase (*5*), in combination with reserpine activates the mating behavior in female rats (*6*).

A casual observation that the administration of PCPA and pargyline to male rats produced sexual excitement prompted us to study the influence of the selective inhibition of 5-HT synthesis on the sexual behavior in male rats. The study was extended to pinealectomized animals since PCPA also inhibits the formation of serotonin in the pineal gland (*7*), resulting in a decreased formation of 5-methoxyindoles (*3*). Finally, since 5-HT and catecholamines have been proposed as mediators for opposite neuronal functions in brain (*8*), we studied sexual behavior in male rats after lowering brain 5-HT concentration by blockade of synthesis and raising that of the catecholamines by inhibition of monoamine oxidase.

Sprague-Dawley male rats, NIH strain, weighing 200 to 250 g (about 60 days old) were used. The animals were housed in individual cages. The lighting schedule consisted of 14 hours of light (6 a.m. to 8 p.m.) and 10 hours of darkness. The behavior studies were conducted in a quiet room with adequate ventilation and lighting; 30 control rats underwent the same isolation schedule and were treated with saline. None of them exhibited sexual excitement during the observation period. The animals were treated with DL-PCPA, methyl ester hydrochloride (100 mg/kg, injected intraperitoneally, daily at 11 p.m. for 4 days). This dosage schedule is optimum for eliciting sexual excitement. Thirteen hours after the fourth administration of PCPA, a number of the animals were treated with pargyline (100 mg/kg, injected intraperitoneally). The animals were put in groups of six in observation cages and observed for 12 hours.

The same procedure was followed with pinealectomized animals. These were Sprague-Dawley rats weighing 250 to 300 g (about 80 days old), pinealectomized 1 week previously by the Zivic Miller Laboratory. Some of the animals were decapitated; the brains were removed, frozen, and assayed for biogenic amines. Norepinephrine (NE) was extracted from brain homogenates by absorption onto alumnia (*9*) and assayed fluorometrically (*10*). Brain serotonin was also assayed (*11*).

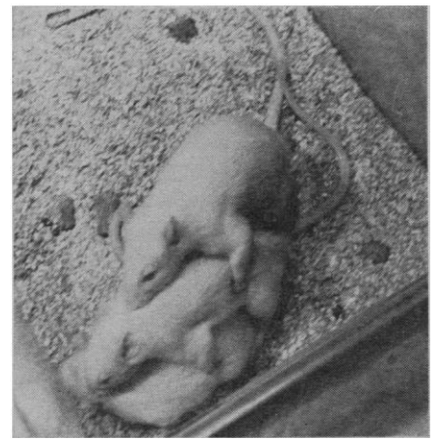

Fig. 1. Male rats treated with *p*-chlorophenylalanine and pargyline.

The sexual behavior of 60 animals treated with PCPA was compared with that of 80 animals treated with PCPA and pargyline. At 12 noon, the rats were placed in groups of six in a cage and observed until 12 midnight. The rats treated with PCPA began to show sexual excitement at various times from 30 minutes to several hours after they were placed together. This was characterized by repeated mountings and rapid copulatory movements. Each mounting consisted of several pelvic thrusts, after which the rats quickly dismounted, usually lying on their haunches and licking their genitalia. Mountings were usually accompanied by erection, but these phenomena also occurred independently. Between mountings, the animals exhibited other signs of sexual stimulation (*12*), such as excessive grooming, scratching, and mutual smelling of the genitalia. Of the 60 rats treated with PCPA, 16 attempted at least one mounting in the 12-hour period and 10 of them mounted 10 or more times (Table 1).

Table 1. Effect of *p*-chlorophenylalanine (PCPA) alone and in combination with pargyline on sexual activity in male rats. *p*-Chlorophenylalanine (100 mg/kg) injected intraperitoneally daily for 4 days.

Animals treated (No.)	Animals showing mounting behavior in 12 hours (No.)	Animals mounting at frequencies of		
		1–5 times (No.)	6–10 times (No.)	>10 (No.)
p-Chlorophenylalanine				
60	16	3	3	10
p-Chlorophenylalanine plus pargyline				
80	58	4	16	38

Table 2. Effects of *p*-chlorophenylalanine (PCPA) alone and in combination with pargyline on content of brain amines in male rats. Rats were killed 18 and 6 hours after PCPA and pargyline, respectively. Values are the average ± S.E. of 10 determinations. 5-HT, 5-hydroxytryptamine; NE, norepinephrine. *p*-Chlorophenylalanine (100 mg/kg) injected intraperitoneally daily for 4 days.

Treatment	Brain monoamines	
	5-HT (μg/g)	NE (μg/g)
Control	0.58 ± 0.01	0.46 ± 0.01
PCPA	0.06 ± 0.01	0.33 ± 0.01
PCPA and pargyline	0.16 ± 0.02	0.45 ± 0.02
Pargyline	1.46 ± 0.03	0.60 ± 0.01

The rats that were treated with PCPA plus pargyline showed far more sexual excitation, although the overt signs were not observed for 5 to 10 hours. Compared to the rats given PCPA alone, a much larger percentage of animals displayed mounting behavior, coital movements, and other signs of sexual excitement (Table 1). Moreover, the frequency of mounting was much greater. The sexual excitation lasted for several hours and usually reached a climax with all the animals in one cage attempting to mount each other at the same time (Fig. 1). To decide whether the sexual excitation was related to deficiency of 5-HT, L-5-hydroxytryptophan (25 mg/kg intravenously) was injected into ten of the animals treated with PCPA and pargyline while they were exhibiting sexual excitation. Within 10 minutes all signs of sexual excitation disappeared. All the animals given PCPA with or without pargyline were isolated for 12 hours and then retested for sexual activity. None of the animals showed any further signs of sexual excitement.

To determine the role of the pineal gland in the sexual behavior, similar experiments were carried out with pinealectomized animals. No episodes of sexual excitation occurred in control pinealectomized rats, but 7 out of 12 pinealectomized rats treated with PCPA displayed sexual excitement at about the same frequency as the animals treated with PCPA and pargyline.

As expected, PCPA treatment lowered the concentrations of 5-HT to about 10 percent of that in control animals, whereas concentrations of NE fell to 71 percent of that in normal animals (Table 2). After administration of pargyline to the animals treated with PCPA the 5-HT and NE concentrations rose to 20 and 100 percent of that in normal animals, respectively.

Brain serotonin inhibits sexual behavior in male rats. The increase in sexual excitement elicited by inhibition of monoamine oxidase suggests that the relative balance of serotoninergic and noradrenergic tone in brain may control sexual behavior in male animals. The demonstration that PCPA elicits sexual excitation in pinealectomized rats rules out the possibility that action of PCPA is mediated by inhibition of pineal indole hormones derived from 5-HT. The above considerations and the finding that sexual excitation is blocked by 5-hydroxytryptophan suggest that the changes in sexual behavior produced by PCPA alone or by PCPA with pargyline are the consequence of the depletion of 5-HT in the brain and of the secondary unbalance between 5-HT and catecholamine activity in brain. *p*-Chlorophenylalanine increases the number of copulations and ejaculations in male animals exposed to receptive females.

After we completed these studies, an abstract appeared which refers to the sexual stimulating effect of PCPA in male rats (*13*). The sexual stimulation produced by PCPA alone and in combination with pargyline is not restricted to male rats. Rabbits injected with PCPA and pargyline also displayed a compulsive sexual behavior that lasted up to 3 days.

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Avoidance Learning: Long-Lasting Deficits after Temporal Lobe Seizure

Abstract. *Microinjections of carbachol (carbamylcholine chloride) into the amygdaloid complex of rats produced behavioral and electrophysiological seizures which subsided within 24 hours. A persisting functional change caused a deficit in avoidance learning 1 to 3 weeks after the seizure. A cholinergic system is implicated by the fact that cholinergic blockade (scopolamine) of the amygdala during training reversed the effects of the seizures induced by carbachol.*

Microinjections of chemicals which initiate, facilitate, or inhibit synaptic transmission have been used extensively to produce temporary changes in the activity of discrete brain areas (*1*). In general, the induced changes are reversible, and the organism appears electrophysiologically and behaviorally normal within a few hours after the drug application. A notable exception has been reported after chemical stimulation of the amygdala with cholinergic substances such as acetylcholine or carbamylcholine chloride (carbachol). In the cat, highly abnormal electroencephalographic patterns have been seen in the affected region as long as 5 months after a single injection. This is accompanied by pronounced "personality changes" (extreme viciousness and aggressiveness) which make it essentially impossible to study in detail other behavioral reactions to the injection (*2*).

Long-lasting behavioral and electrophysiological changes have been seen after electrical stimulation of the amygdaloid complex (*3*), and a permanent reduction in amygdaloid seizure threshold has been produced by repeated electrical stimulation (*4*). The apparent lability of amygdaloid neurons is particularly intriguing in view of the evidence which suggests that this portion of the temporal lobe may play an important role in the acquisition of new responses (*5*). We therefore investigated the possibility that a carbachol-induced change in amygdaloid function might specifically affect an animal's ability to learn a novel conditioned response. We elected to perform these experiments on the albino rat in the expectation that behavioral testing might be possible in this species even after the expected changes in emotional reactivity.

Double-walled cannulas were stereotaxically implanted bilaterally into the ventral aspects of the amygdaloid complex of male albino rats of the Holtzman Sprague-Dawley strain. The surgical procedure and construction of the implant have been described (*6*). For some of the animals, the cannulas were insulated with a vinyl enamel except for the cross section of their tip, and an additional silver wire electrode was implanted into a third brain structure. A silver ball, embedded in the skull, served as the reference electrode.

The training apparatus consisted of a box, 92.5 by 92.5 by 61 cm, with a grid floor, white Plexiglas walls, and transparent Plexiglas top. The box was partitioned into four equal compartments. The middle of each partition contained an opening (10 by 10 cm) covered with a black door which opened in one direction only. The doors were locked by a solenoid until the beginning of a trial. The conditoned stimulus (CS) consisted of the illumination of a light bulb mounted in the center of the ceiling of each compartment. The unconditioned stimulus (USC) was a 300-μa grid shock supplied by a high-voltage, vacuum-tube-controlled constant-current source (*7*).

Immediately before training, the animals were shaped, by a series of successive approximations, to open the doors between compartments. The CS and UCS were not presented during these habituation trials. After an animal was habituated, all the doors were locked, and the animal was confined in one compartment. After 60 seconds the door to the next compartment was un-