Pharmacology Biochemistry and Behavior, Vol. 3, pp. 511–513. ANKHO International Inc., 1975. Printed in the U.S.A.

BRIEF COMMUNICATION

Inhibition not Facilitation of Sexual Behavior by PCPA[1]

BORIS B. GORZALKA[2] AND RICHARD E. WHALEN[3]

Department of Psychobiology, University of California
Irvine, CA 92664

(Received 16 August 1974)

GORZALKA, B. B. AND R. E. WHALEN. *Inhibition not facilitation of sexual behavior by PCPA.* PHARMAC. BIOCHEM. BEHAV. 3(3) 511–513, 1975. – It has been proposed that estrous behavior in the female rat may be under tonic inhibition by a central serotonergic system. Studies conbining estrogen priming and the pharmacological depletion of serotonin have provided some support for this hypothesis. Some evidence, however, is not consistent with this hypothesis. In the present study estrogen primed ovariectomized-adrenalectomized rats were administered p-chlorophenylalanine and were tested for lordosis behavior 66 and 70 hr later. Lordosis was not facilitated. The animals were then administered progesterone and retested at hour 74. PCPA inhibited progesterone-induced lordosis behavior in a dose dependent manner.

PCPA Lordosis Female sexual behavior Rat sexuality

IT HAS been proposed that estrous behavior in the female rat may be regulated by a central nervous serotonergic mechanism: high brain levels of serotonin inhibit estrous responses while low levels are facilitatory [4–7]. Consistent with this hypothesis are findings that a relatively specific depletor of brain serotonin, p-chlorophenylalanine (PCPA), facilitates sexual receptivity in estrogen-primed, ovariectomized rats [7]. Thus it would appear that a reduction of serotonin levels mimics the effects of progesterone in facilitating receptivity in estrogen-primed animals.

Although the serotonergic hypothesis is an attractive one, there are at least two studies which make it suspect. First, α-propyldopacetamide, a drug which is as effective as PCPA in depleting brain serotonin, was ineffective in facilitating estrous behavior in estrogen-primed, ovariectomized rats [7]. And second, PCPA failed to facilitate estrous behavior in adrenalectomized, ovariectomized rats [1]. PCPA may facilitate sexual receptivity in nonadrenalectomized animals by stimulating the secretion of sufficient adrenal progesterone.

Although the evidence supporting an inhibitory serotonergic system for estrous behavior seems open to serious questions, a recent study has generated new controversy. It has been reported that PCPA does indeed facilitate sexual receptivity in estrogen-primed, ovariectomized, adrenalectomized rats [11] when animals were administered a PCPA dosage appreciably higher than those used in previous studies [1,9] and when the animals were tested 66–74 hr after PCPA when maximum depletion of brain serotonin has been reported to occur [3]. Since this is the only report of PCPA effectiveness in adrenalectomized animals, we have now attempted to repeat the study using similar procedures. The present study also sought information about the effects of PCPA on sexual behavior in animals primed with both estrogen and progesterone since it has been reported that chronic PCPA treatment may inhibit receptivity induced by estrogen and progesterone [9].

METHOD

Twenty-four female Sprague-Dawley rats, 70 days old with a mean weight of 218 g supplied by Simonson were bilaterally ovariectomized and adrenalectomized while under light ether anesthesia. Animals were maintained on ad lib food and physiological saline throughout the experiment.

Behavioral testing began 3 hr after the onset of the dark period of a reversed lighting cycle (12 hr light, 12 hr dark). For mating tests, females were placed individually into cylindrical glass observation arenas with sexually experienced, vigorous male rats. Receptivity scores were calculated by determining the ratio of female lordotic

[1] This research was supported by Grant HD-00893 to R.E.W. from the National Institute of Child Health and Human Development.
[2] Current address: Department of Psychology, University of Western Ontario, London N6A 3K7, Canada.
[3] Requests for reprints should be sent to Richard E. Whalen, Department of Psychobiology, University of California, Irvine, CA 92664.

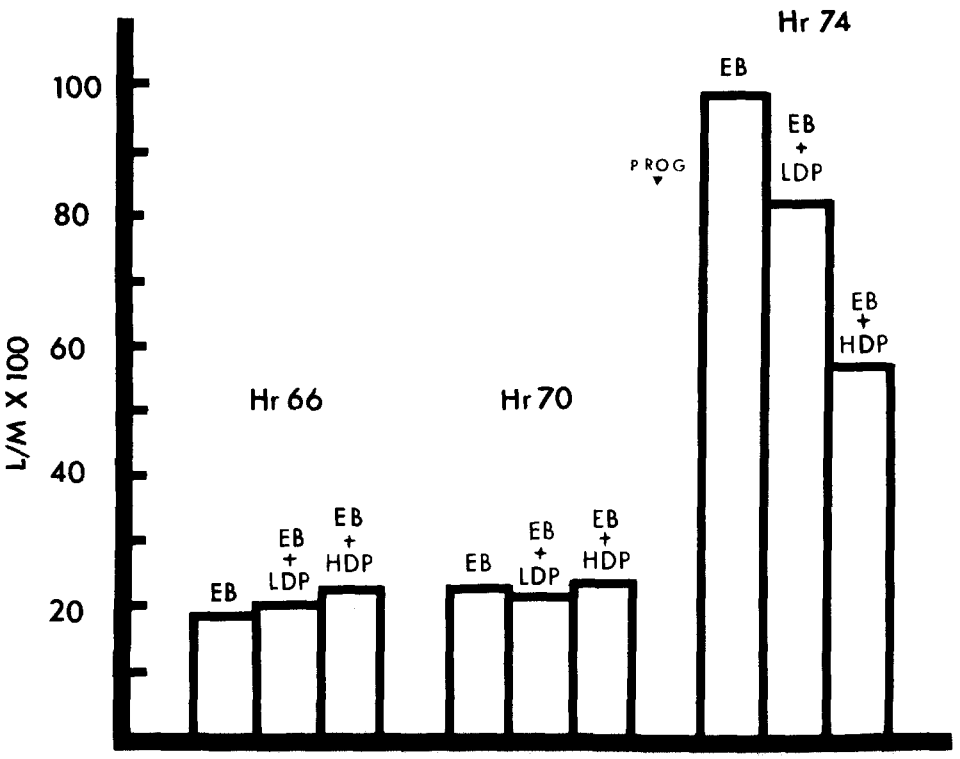

FIG. 1. Sexual receptivity in ovariectomized-adrenalectomized rats expressed as the ratio of lordosis responses to mounts by the male (L/M). At hour 0, 316 mg PCPA/kg (HDP), 100 mg PCPA/kg (LDP) or the vehicle was administered. All animals received 10 μg estradiol benzoate at hour 24, 500 μg progesterone at hour 71, and were tested at hours 66, 70 and 74.

responses to mounts with pelvic thrusting by the male. Scores were expressed as a lordosis quotient (LQ). A test was terminated when the male had mounted the experimental female 10 times.

It is known that ovariectomized female rats do not show maximum receptivity on the first administration of estradiol benzoate (EB) and progesterone. Therefore, as in the Zemlan *et al.* study [11], animals received a subcutaneous injection of 10 μg EB immediately after surgery followed 42 hr later by 1.0 mg progesterone. Two weeks after surgery, animals were divided into three treatment groups which received at hour 0, intraperitoneal injections of either 316 mg PCPA (p-chlorophenylalanine methyl ester hydrochloride)/kg body weight, 100 mg PCPA/kg body weight or the drug vehicle, 0.6 ml of 5% Tween 80 solution. All animals received 10 μg EB dissolved in 0.1 ml peanut oil at hour 24 and were tested for sexual receptivity at hours 66 and 70. In order to determine the possible effects of PCPA on progesterone action, animals were then administered 500 μg progesterone dissolved in 0.1 ml peanut oil at hour 71 and were retested for sexual receptivity at hour 74.

Brain serotonin levels return to normal two weeks following administration of 100 or 316 mg PCPA/kg body weight [3]. To ensure that the three experimental groups did not differ under conditions where serotonin levels are presumably normal, animals were retested for steroid-induced receptivity two weeks after the initial drug tests. All animals received 10 μg EB at hour 0 and were tested for sexual receptivity at hour 42. At hour 43, 500 μg progesterone were administered and sexual receptivity was retested at hour 46.

RESULTS

The results of the drug tests are shown in Fig. 1. Neither lower doses nor higher doses of PCPA facilitated lordosis behavior in estrogen-primed animals. Analyses of variance indicated no significant group differences for tests at hours 66 and 70. However, following progesterone administration, PCPA appeared to inhibit lordosis behavior in a dose-dependent manner. An analysis of variance confirmed significant differences in lordosis behavior ($p<0.01$) following progesterone treatment (hour 74). Using the Newman-Keuls procedure, *a posteriori* comparisons indicated that PCPA produced a significant inhibition of sexual receptivity of the 316 mg/kg dose ($p<0.01$) but not at the 100 mg/kg dose. Animals receiving PCPA did not appear impaired or unhealthy relative to animals receiving only the vehicle. Two weeks later, in the absence of drug treatment, there were no significant differences between the three groups of animals in either their response to estrogen (hour 42) or in their response to estrogen and progesterone (hour 46). At hour 42, mean LQ's were 24.5, 28.2 and 25.3 in the vehicle, 100 mg/kg and 316 mg/kg groups, respectively. At hour 46, mean LQ's were 98.8, 96.3 and 96.3 in the vehicle, 100 mg/kg and 316 mg/kg groups, respectively.

DISCUSSION

Our results provide no support for the hypothesis that suppression of serotonergic activity facilitates estrous behavior. On the contrary, our finding that PCPA inhibits sexual responses induced with estrogen and progesterone suggests that the opposite may be true. That is, suppression of serotonergic activity inhibits rather than facilitates estrous behavior. This finding is consistent with the results of our earlier study [9].

The failure of PCPA to facilitate receptivity in estrogen-primed, adrenalectomized rats is consistent with recent evidence that the facilitatory effects of monoamine depletors may be mediated by pituitary-adrenal activation. For example, reserpine is a monoamine depletor which both induces lordosis behavior and increases progesterone levels in estrogen-primed, ovariectomized rats [8]. These effects of reserpine can be prevented by the administration of dexamethasone, a drug which inhibits ACTH secretion by negative feedback [8]. Moreover, administration of ACTH alone both induces lordosis behavior and increases progesterone levels in estrogen-primed, ovariectomized rats [2]. Finally, adrenalectomy eliminates the facilitatory effects of reserpine [10], α-methyl-p-tyrosine [1] and PCPA [1] on lordosis behavior in estrogen-primed, ovariectomized animals. Thus most studies, including the present one are consistent with the idea that the facilitatory effects of monoamine depletors are dependent on the adrenal system. The only report in the literature of facilitatory effects of PCPA in adrenalectomized animals [11] was not replicated in the present experiment using systemic administration of the drug. The reasons for our failure to replicate Zemlan *et al.* [11] are not clear. Possibly genetic differences between the animals used or differences in effective dosage were involved. Nevertheless, it is clear that PCPA was an active pharmacological agent in the present study as evidenced by the dose-dependent inhibition of progesterone action.

Since PCPA apparently does not substitute for progesterone in the facilitation of estrous behavior in estrogen-primed animals but does inhibit receptivity induced by estrogen and progesterone, the concept of serotonergic involvement in lordosis behavior is still a viable hypothesis. The present data would suggest that for progesterone to be effective, brain serotonin levels must be within a normal range. Adequate functioning of progesterone sensitive neurons may be dependent on both appropriate levels of progesterone and appropriate levels of serotonin.

REFERENCES

1. Eriksson, H. and P. Södersten. A failure to facilitate lordosis behavior in adrenalectomized and gonadectomized estrogen-primed rats with monoamine-synthesis inhibitors. *Horm. Behav.* **4**: 89–98, 1973.
2. Feder, H. H. and K. B. Ruf. Stimulation of progesterone release and estrous behavior by ACTH in ovariectomized rodents. *Endocrinology* **91**: 738–746, 1969.
3. Koe, B. K. and A. Weissman. p-Chlorophenylalanine: A specific depletor of brain serotonin. *J. Pharmac. exp. Ther.* **154**: 499–516, 1966.
4. Meyerson, B. J. The effect of neuropharmacological agents on hormone-activated estrous behaviour in ovariectomized rats. *Arch. Int. Pharmacodyn.* **150**: 4–33, 1964.
5. Meyerson, B. J. Estrous behavior in spayed rats after estrogen or progesterone treatment in combination with reserpine or tetrabenazine. *Psychopharmacologia* **6**: 210–218, 1964.
6. Meyerson, B. J. Central nervous monoamines and hormone induced estrous behavior in the spayed rat. *Acta Physiol. scand.* **63**: *Suppl.* 241, 1964.
7. Meyerson, B. J. and T. Lewander. Serotonin synthesis inhibition and estrous behavior in female rats. *Life Sci.* **9**: 661–671, 1970.
8. Paris, C. S., J. A. Resko and R. W. Goy. A possible mechanism for the induction of lordosis by reserpine in the spayed rat. *Biol. Reprod.* **4**: 23–30, 1971.
9. Segal, D. S. and R. E. Whalen. Effect of chronic administration of p-chlorophenylalanine on sexual receptivity of the female rat. *Psychopharmacologia* **16**: 434–438, 1970.
10. Uphouse, L. L., J. R. Wilson and K. Schlesinger. Induction of estrus in mice: The possible role of adrenal progesterone. *Horm. Behav.* **1**: 255–264, 1970.
11. 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.