# EFFECT OF PSYCHOPHARMACOLOGICAL AGENTS ON THE GONADS OF FEMALE RATS

N. M. Smol'nikova, S. N. Strekalova, and N. S. Artem'eva

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The effect of compounds of the phenothiazine series (fluacizine, chloracizine, trifluoroperazine, and chloromazine) on the sex cycle was studied in female rats. The compounds were found to depress the estrous cycle and to alter the ratio between the generative elements in the gonads. The link between the chemical structure of the compounds and their action on the sex cycle is discussed.

It is stated in the literature that psychotropic drugs can affect the reproductive function. Chlorpromazine, for instance, can inhibit the estrous cycle and suppress ovulation in animals [1, 5] and delay ovulation and menstruation in women [2, 9]. A disturbance of the estrous cycle has been described following the administration of haloperidol [8], imipramine, and desmethylimipramine [7] to rats. According to Cranston [4], depression of gonadal function and a decrease in the number of estrous cycles are found in mice after administration of reserpine, chlorpromazine, promethazine, promazine, meprobamate, phenobarbital, and ethyl alcohol.

In the opinion of most workers the action of the psychotropic drugs on the estrous cycle takes place at the level of the central nervous system and consists essentially of a disturbance of the neurohormonal regulation of the sex cycle. Because of the extensive use of psychopharmacological agents in clinical practice this fact deserves the closest attention.

The object of this investigation was to study the action of derivatives of the phenothiazine series – fluacizine, chloracizine, and trifluoperazine – on the hormonal and generative function of female rats. Chlorpromazine, as the compound which has been studied the most from this standpoint, was used for comparison. Except chloracizine, all the compounds studied are psychopharmacological agents. Fluacizine and chloracizine are original preparations synthesized in the Institute of Pharmacology, Academy of Medical Sciences of the USSR. The effect of these compounds on the gonads and their functions has not been studied. So far as trifluoperazine is concerned, it is stated that this has an inhibitory action on the estrous cycle in mice [3]. In experiments on rats, trifluoperazine has also been shown to have a lactogenic action [6].

## EXPERIMENTAL METHOD

Experiments were carried out on 50 sexually mature noninbred rats weighing 180-200 g. The periods of the estrous cycle were first determined in the animals. The stages of the cycle were identified from the cytological picture of vaginal smears. The vaginal smears were taken daily for 2 weeks. Animals with normal cycles, with a duration of 4-5 days, were chosen for the experiments.

Trifluoperazine, fluacizine, chloracizine, and chlorpromazine were given to the animals by gastric tube in a dose of 10 mg/kg body weight daily for 15 days (this is equivalent to about 1/80 $LD_{50}$ for oral administration). The animals of the control group received water.

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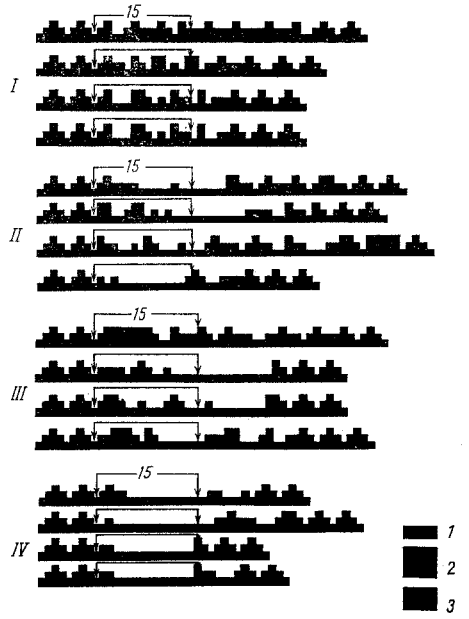


Fig. 1. Effect of compounds of the phenothiazine series on the estrous cycle: I) fluacizine; II) chloracizine; III) chlorpromazine; IV) trifluoperazine. 1) Diestrus, 2) estrus, 3) intermediate stages.

The vaginal smears were studied daily throughout the period of administration of the drugs and thereafter until the animals' normal cycle was restored. For the histological study of the gonads the ovaries were taken from some of the animals immediately after the end of administration of the drug and from others after restoration of the normal rhythm of the estrous cycles. The ovaries were fixed in formalin, and serial sections, 7 $\mu$ in thickness, were stained with hematoxylin and eosin. For the histological study of the gonads the number of structural components of the organ also was counted in order to obtain a more accurate determination of its morphological changes. The number of follicles (primary, ripening, atretic) and of corpora lutea was counted in every fifth section through the ovary, and the total number of generative elements was determined as the mean value per section.

Rats with an experimentally produced permanent estrus also were used in the experiments. For this purpose, on the second-fourth day after birth, newborn rats were given a subcutaneous injection of 0.25 ml of a 1% oily solution of testosterone propionate. Nine weeks later, rats with permanent estrus as shown by the cytological picture of the vaginal smears were chosen. The compounds were given to these animals by gastric tube in a dose of 10 mg/kg daily for 15 days.

## EXPERIMENTAL RESULTS AND DISCUSSION

The study of the rhythm of the estrous cycles in the experimental and control animals by examination of vaginal smears showed that fluacizine, chloracizine, and trifluoperazine, like chlorpromazine, induce disturbances of the estrous cycle expressed as changes in the alternation and duration of the individual phases of the cycle or as lengthening of the diestrus phase (Fig. 1). Depending on the intensity of their inhibitory action and on the rate of its development, the compounds could be arranged in the following order: fluacizine, chloracizine, trifluoperazine. Fluacizine disturbed the regular rhythm of the estrous cycle in all the rats. Chloracizine, in addition, induced lengthening of diestrus in four of the six rats. Trifluoperazine produced continuous diestrus in all the animals.

The action of fluacizine was weaker and that of trifluoperazine stronger than the action of chlorpromazine. The inhibitory action of chloracizine on the estrous cycle was similar in intensity to that of chlorpromazine.

Changes in the estrous cycle occurred after the first-third doses of the compounds and were reversible, for the normal cycle was restored 2-30 days after administration of the compounds ended. The procedure of introducing the tube into the stomach of the control animals did not cause any disturbance of the estrous cycle. No significant change in the weight of the animals was observed during the period of administration of the compounds. The weight of the ovaries and uterus (calculated per 100 g body weight) was virtually the same in the experimental and control animals. The histological study of the ovaries showed that, after administration of the compounds, the functional disturbances and changes in the rhythm of the estrous cycles were accompanied by some changes in the structure of the gonads and in the ratio between the numbers of generative elements. Ripening of the follicles was inhibited, the number of primary follicles was reduced, the number of corpora lutea was increased, and their reduction was inhibited (Table 1). The intensity of these changes after administration of the various compounds was about the same. During the action of chlorpromazine, considerable atresia of the follicles was, however, observed.

After the end of administration of the compounds and restoration of the normal rhythm of the estrous cycles, the ratio between the numbers of structural components of the ovary was partly restored to normal, and the number of ripening follicles increased although reduction of the corpora lutea was delayed by comparison with the ovaries of the control animals.

TABLE 1. Number of Generative Elements in the Ovaries After Administration of Compounds of the Phenothiazine Series

| Compound | No. of follicles | | | No. of corpora lutea | Total No. of generative elements |
|---|---|---|---|---|---|
| | primary | ripening | atretic | | |
| Control | 4,0±2,2 | 4,5±1,42 | 5,0±0,89 | 7,3±2,44 | 20,8 |
| Trifluoperazine | | | | | |
| A | 3,0±0,24 | 2,0±0,53 | 5,0±0,93 | 15,0±3,2 | 25,0 |
| P | <0,05 | <0,02 | <0,05 | <0,02 | |
| B | 2,0±0,28 | 4,0±1,53 | 6,0±0,94 | 12,0±1,8 | 24,0 |
| Fluacizine | | | | | |
| A | 1,8±0,46 | 2,8±1,45 | 6,6±2,01 | 13,8±2,78 | 25,0 |
| P | <0,02 | <0,05 | <0,02 | <0,02 | |
| B | 2,0±0,08 | 5,0±1,23 | 4,0±1,42 | 14,0±3,2 | 25,0 |
| Chloracizine | | | | | |
| A | 1,93±0,35 | 2,8±0,69 | 4,2±1,53 | 8,04±1,82 | 17,03 |
| P | <0,05 | <0,05 | <0,02 | <0,02 | |
| B | 2,0±0,07 | 4,22±0,78 | 5,5±1,28 | 9,33±0,8 | 21,05 |
| Chlorpromazine | | | | | |
| A | 2,4±0,2 | 2,5±0,98 | 17,0±1,92 | 16,0±1,84 | 37,9 |
| P | <0,02 | <0,02 | <0,02 | <0,05 | |
| B | 1,5±0,62 | 5,5±1,2 | 11,0±1,84 | 10,0±1,28 | 28,0 |

Legend: A) after end of administration of compound; B) after recovery of normal estrous cycles.

The compounds had no detectable action on the animals with permanent estrus.

The investigations showed that fluacizine, chloracizine, and trifluoperazine, like chlorpromazine, inhibit the hormonal function of the gonads in females: the rhythm of the gonads is disturbed, the duration and sequence of the individual phases of the cycle are upset, and the period of diestrus is lengthened. In the ovaries of the experimental animals the number of primary follicles was reduced, ripening of the follicles was inhibited, the number of ripening follicles was reduced, reactive changes were found in the corpora lutea, and the number of corpora lutea was increased through inhibition of reduction of the luteinizing cells.

The compounds had no action on the animals with permanent estrus, i.e., with a disturbed hypothalamic function. These observations, together with an analysis of the literature, suggest that the changes in the sex cycle under the influence of these compounds were due, inter alia, to a disturbance of the neurohormonal regulation of the sex cycle at the hypothalamic level.

The results indicate that the intensity of the inhibitory action of compounds containing a chlorine atom in position 2 (chlorpromazine, chloracizine) on the sex cycle was virtually equal, despite different substituents in position 10 (chlorpromazine is an aminoalkyl derivative, chloracizine an aminoacyl derivative). Replacement of Cl by the $CF_3$ group reduces the action of the compound somewhat. However, replacement of the aminoacyl group by a piperazinopropyl group in position 10 leads to a marked increase in the inhibitory effect (trifluoperazine).

These results agree with those obtained by Khazan et al. [6], who studied the mammotropic effect of tranquilizers, and with the conclusions reached by Bhargava et al. [3], namely that a parallel exists between the intensity of action of compounds of the phenothiazine series on the sex cycle and their neuroleptic properties. In fact, trifluoperazine is a more active neuroleptic than chlorpromazine, and in the present experiments it had a stronger action on the sex cycle.

These results must be borne in mind during the clinical application of these drugs.

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