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SOME ENDOCRINE EFFECTS OF TWO PHENOTHIAZINE DERIVATIVES, CHLORPROMAZINE AND PERPHENAZINE, IN THE FEMALE MOUSE

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The effects of chlorpromazine and perphenazine were studied with both immature and mature female mice. At a dose of 5 mg/kg daily, each drug delayed the onset of sexual maturity in immature animals. In mature mice, a daily dose of 10 mg/kg inhibited vaginal oestrus and reduced the weights of the ovaries, vagina and uterus. Each of the two drugs inhibited ovarian hypertrophy following unilateral ovariectomy, but only slightly diminished the responses to exogenous oestrogen and to exogenous gonadotrophin. In one experiment, pseudopregnancy, as shown by a positive deciduoma-test, was provoked by perphenazine, but this experiment could not be repeated. Chlorpromazine failed to evoke a positive deciduoma response. At a dose of 10 mg/kg, neither drug caused a fall in levels of adrenal ascorbic acid. In the rat, treatment for 1 week with 10 mg/kg daily of either drug led to a rise in pituitary gonadotrophic activity. It was concluded that both drugs inhibited the release of gonadotrophins by the pituitary gland, independently of any action in releasing corticotrophin.

In their original investigation of chlorpromazine, Courvoisier & Ducrot (1954) failed to demonstrate any effect of the drug upon sexual maturation in the young female rat, or upon ovulation, fertilization or lactation in the mature female. However, there have since been a number of reports of endocrine effects attributable to chlorpromazine. These effects include suppression of vaginal oestrus and inhibition of ovulation in experimental animals, delay of ovulation and menstruation in women, induction of pseudopregnancy in animals, and/or initiation of lactation in animals and in women and also stimulation of release of corticotrophin. It seems probable that other phenothiazine derivatives may have similar actions, but these drugs have been much less extensively studied than chlorpromazine.

The present work was undertaken to compare the effects of chlorpromazine with those of another phenothiazine derivative, perphenazine, in the female laboratory mouse, and to study the mode of action of the two compounds.

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METHODS

Albino mice, bred at Guy's Hospital Medical School, were housed in boxes containing five or less. Their food consisted of M.R.C. diet No. 41, supplemented by yeast, oats and water, all supplied *ad libitum*.

Vaginal smears were taken daily, except Sundays. They were reported as containing predominantly cornified cells (oestrus smears), predominantly leucocytes (dioestrus smears) or as mixed smears.

Organs were removed from animals immediately after death, placed in a Petri dish containing filter paper moistened with 0.9% saline, cleaned of connective tissue, blotted and then weighed on a torsion balance. They were then preserved in formol-saline for histological examination.

All operative procedures were carried out on animals anaesthetized with ether.

The pituitary glands. For assay, these were removed immediately after death, freed of adherent blood and weighed. Groups of five pituitaries were crushed between two glass slides, allowed to dry in air and then kept in a desiccator over calcium chloride. After storage for 4 weeks, the dried material was scraped off, ground to a fine powder in a glazed mortar, weighed and then taken up in 0.9% saline for injection. Gonadotrophic activity was assayed on 21-day-old female mice, weighing 8 to 10 g, by the method of Rothchild (1960).

Release of corticotrophin. This was estimated by the adrenal ascorbic acid depletion test. Adrenal ascorbic acid was measured by the method of Dekanski & Harvie (1960).

Chlorpromazine and perphenazine were injected subcutaneously in a volume of 0.1 ml., the stock solutions being diluted with 0.9% saline before injection. Control animals were injected subcutaneously with 0.9% saline only.

RESULTS

The effect of chlorpromazine on immature female mice

From two groups, each of eight 23-day-old mice, mice of one group were injected daily with 5 mg/kg of chlorpromazine, while mice of the second group served as a control. The experiment was terminated after 56 days, when four of the control animals had gone into oestrus, that is they had had one or more oestrus cycles. None of the treated animals had gone into oestrus by this time. At post-mortem, the mean weights of ovaries, vagina and uterus of the mice treated with chlorpromazine were significantly less than those of the controls (Table 1a). The body weights of the control and treated mice were not greatly different. Histological examination revealed that, compared with the controls, the uterus and vagina of the mice treated with chlorpromazine were undeveloped and infantile, with ovaries containing no corpora lutea, and with follicles relatively undeveloped, though apparently normal in number.

The effect of perphenazine on immature female mice

Twenty 23-day-old female mice were divided into two groups of ten. Mice of one group were injected with 5 mg/kg of perphenazine daily, and those of the other group served as a control. The experiment was terminated after 42 days, when three of the animals treated with perphenazine and eight of the controls had gone into oestrus. At post-mortem, the sex-organs of mice treated with perphenazine were significantly lighter than those of the controls. There was no effect on body weight (Table 1b).

TABLE 1

THE EFFECTS OF CHLORPROMAZINE AND OF PERPHENAZINE ON BODY AND SEX-ORGAN WEIGHTS OF FEMALE MICE

Values are means ± standard errors. For details of treatments see text

No. of animals	Treatment	Weights of Body (g)	Vagina (mg)	Uterus (mg)	Ovaries (mg)
(a) Chlorpromazine and immature female mice					
8	Chlorpromazine (5 mg/kg)	18·9±0·65	22·5±2·33	16·1±1·99	2·7±0·45
8	Saline (control)	19·8±1·12	55·6±13·2	75·3±23·8	4·4±0·57
	P	>0·4	<0·05	<0·05	<0·001
(b) Perphenazine and immature female mice					
10	Perphenazine (5 mg/kg)	19·4±0·58	31·3±6·57	30·8±6·94	3·2±0·37
10	Saline (control)	20·4±1·53	57·8±7·97	75·2±16·1	4·8±0·41
	P	>0·5	<0·02	<0·05	<0·01
(c) Treatment for 2 weeks with perphenazine and chlorpromazine on mature female mice					
10	Perphenazine (10 mg/kg)		21·6±0·94	32·8±1·63	8·83±0·69
10	Chlorpromazine (10 mg/kg)		28·6±1·86	39·5±2·18	8·25±0·53
10	Saline (control)		46·6±6·43	68·2±5·51	9·48±0·57
	P, perphenazine		<0·01	<0·001	>0·4
	P, chlorpromazine		<0·02	<0·001	>0·1
(d) Treatment for 6 weeks with perphenazine and chlorpromazine on mature female mice					
8	Perphenazine (10 mg/kg)		36·8±5·79	61·1±11·09	8·6±0·6
8	Chlorpromazine (10 mg/kg)		39·2±4·66	55·9±8·04	9·8±1·04
9	Saline (control)		63·1±4·88	104·2±10·5	11·3±0·91
	P, perphenazine		<0·01	<0·02	<0·05
	P, chlorpromazine		<0·01	<0·01	>0·02
(e) Perphenazine and adrenalectomized immature female mice					
8	Perphenazine (5 mg/kg)		16·1±1·4	13·5±1·56	2·7±0·2
8	Saline (control)		50·5±9·15	61·7±14·4	4·3±0·22
	P		<0·01	<0·01	<0·001

On histological examination, the vagina and uterus of the mice treated with perphenazine, other than those which had gone into oestrus, were undeveloped. The vaginal epithelium resembled that of pro-oestrus or dioestrus and the stroma was scanty. The uterine epithelium was columnar; there were few glands and scanty stroma. The ovaries contained no corpora lutea.

The effects of chlorpromazine and perphenazine on mature female mice

Thirty virgin mice, approximately 3 months old, were divided into three equal groups. During a preliminary period of 16 days, daily vaginal smears were taken to establish the regularity of the vaginal cycle. Then daily injections of 5 mg/kg of chlorpromazine, 5 mg/kg of perphenazine and of 0.9% saline, respectively, were begun for mice of each group and continued for 14 days. Each drug, but more particularly chlorpromazine, inhibited the vaginal cycle in some of the mice. Five of the perphenazine group and two of the chlorpromazine group went into oestrus during the second week of treatment, compared with eight of the controls. There was no effect on body weight. The weights of the sex-organs were smaller in mice of the treated groups than in the controls, but these differences did not reach the 5% level of significance.

With a dose of 10 mg/kg for 14 days, neither drug affected body weight, but vaginal oestrus was completely suppressed during the second week in mice treated with each drug. The mean weights of the vagina and uterus were significantly less than for the controls, but the ovaries, though lighter than for the controls, did not weigh significantly less (Table 1c).

The histological appearance of the organs was similar in treated mice of both groups. The vaginal epithelium resembled that of normal dioestrus, that is flattened and infiltrated with leucocytes. In the uterus, glands were few and those present were collapsed. The surface epithelium was low columnar and the nuclei of the stroma cells resembled those of fibroblasts. The striking feature of the ovaries was the absence of recent corpora lutea.

A similar experiment was performed, in which daily treatment with 10 mg/kg of either drug was continued for 6 weeks. The suppression of vaginal oestrus was maintained throughout this time, periods of cornification occurring only sporadically in the treated animals. The weight of the sex-organs after treatment for 6 weeks is shown in Table 1d. As in the shorter experiments, the vagina and uterus were significantly lighter than the organs for the control mice.

The effect of perphenazine on adrenalectomized, immature female mice

Sixteen 4-week-old immature mice were adrenalectomized by the dorsal route. Following the operation, they were given 0.5% saline to drink and a daily injection of 25 μg of cortisone acetate. This dose was based on the findings of Munford (1957), that doses above 25 μg of cortisone daily did not further decrease the mortality of adrenalectomized mice. After 3 days from the operation, the mice were divided into two groups of eight. Those of one group received 5 mg/kg of perphenazine daily, and the other 0.9% saline. After 38 days of treatment, five of the controls, but none of the treated animals had gone into oestrus. Table 1e shows that the post-mortem weights of the sex-organs of treated mice were all significantly lighter than those of the controls.

The effect of perphenazine and chlorpromazine on the uterotrophic action of oestradiol in ovariectomized mice

Thirty-three mature female mice, about 4 months old, were ovariectomized. Subsequent vaginal smears contained leucocytes only. The mice were divided into four groups, and 3 weeks later the following treatments were given:

Group A, chlorpromazine (10 mg/kg) daily for 4 days.

Group B, perphenazine (10 mg/kg) daily for 4 days.

Groups C and D, injections of 0.9% saline daily for 4 days.

On days 3 and 4 all mice, except those in Group D, were injected with 0.05 μg of oestradiol benzoate in 0.1 ml. of olive oil daily. Group D received control injections of 0.1 ml. of olive oil only. On days 3, 4 and 5, vaginal smears were taken from each animal and, on day 5, the animals were killed and the uteri removed and weighed (Table 2). All the animals receiving oestradiol had cornified smears on days 4 and 5. However, the mean weights of the uteri of the animals treated

TABLE 2

THE EFFECTS OF PERPHENAZINE AND CHLORPROMAZINE ON THE UTEROTROPHIC ACTION OF OESTRADIOL IN OVARIECTOMIZED MICE

Values are means ± standard errors. For details of treatments see text

Weight of uterus (mg) after treatment with			
Oestradiol	Olive oil	Perphenazine (10 mg/kg)	Chlorpromazine (10 mg/kg)
114·0±13·4	19·9±1·06	86·7±4·46	89·7±5·41
P		>0·05	>0·1

with a drug were less than for the oestradiol controls, although the difference did not quite reach significance ($0.1>P>0.05$ for perphenazine; $0.2>P>0.1$ for chlorpromazine).

The effect of perphenazine and chlorpromazine on ovarian compensatory hypertrophy

In this experiment, the groups of ten 23-day-old mice were treated according to the following procedure:

Group A, left oophorectomy; perphenazine (10 mg/kg) for 10 days.

Group B, left oophorectomy; chlorpromazine (10 mg/kg) for 10 days.

Group C, left oophorectomy; 0.9% saline for 10 days.

Group D, intact animal; 0.9% saline for 10 days.

The excised left ovaries were weighed. The drugs were then administered for 10 days and on the eleventh day the animals were killed and the remaining ovaries removed and weighed. The results are shown in Table 3. No compensatory hypertrophy occurred in the animals treated with a drug, whereas, in the ovariectomized controls, the right ovary was about 50% heavier than the left.

The effect of perphenazine and chlorpromazine on the response to exogenous gonadotrophin

In this experiment, groups of twelve 23-day-old mice were treated as follows:

Group A, perphenazine (10 mg/kg) daily for 10 days.

Group B, chlorpromazine (10 mg/kg) daily for 10 days.

Groups C and D, daily injections of 0.9% saline for 10 days.

TABLE 3

THE EFFECTS OF PERPHENAZINE AND CHLORPROMAZINE ON OVARIAN COMPENSATORY HYPERTROPHY, FOLLOWING LEFT OVARIECTOMY, IN IMMATURE MICE

Values are means for groups of ten mice. The left ovaries were excised and weighed before treatment, the right after eleven days with or without treatment

Treatment	Ovarian weight (mg)	
	Left	Right
A, perphenazine (10 mg/kg)	1·19	1·07
B, chlorpromazine (10 mg/kg)	1·12	1·06
C, ovariectomized only (control)	1·07	1·52
D, none (control)	1·24	1·29

TABLE 4

THE EFFECTS OF PERPHENAZINE AND CHLORPROMAZINE (10 MG/KG) ON THE RESPONSE TO EXOGENOUS GONADOTROPHIN (P.M.S.) IN IMMATURE MICE

Values are means ± standard errors, for groups of twelve mice. For the mice treated with chlorpromazine, differences were not significant. For details of treatments, see text

Treatment	Weights of Vagina (mg)	Uterus (mg)	Ovaries (mg)
A, perphenazine+P.M.S.	28·3±2·34	43·2±3·68	3·4±0·15
B, chlorpromazine+P.M.S.	33·5±2·78	57·3±6·29	4·1±0·25
C, saline (control)+P.M.S.	34·7±3·98	62·6±4·44	4·5±0·28
D, saline (control)	15·6±1·65	15·8±4·63	3·0±0·16
P, perphenazine	>0·1	<0·01	<0·01
P, chlorpromazine	—	—	—

On days 9 and 10 all the mice, except those in group D, were injected with 1 unit of pregnant mare serum, a preparation of gonadotrophin containing mainly follicle-stimulating activity. The animals were killed on the eleventh day and the sex organs removed and weighed. The results are shown in Table 4. In the mice treated with chlorpromazine there was no significant difference from the controls, but in the mice treated with perphenazine both the uterus and the ovaries responded to the gonadotrophin significantly less than did those of the controls.

A similar experiment was therefore performed with 5 mg/kg of perphenazine (Table 5). This time the vaginae, but not the uteri, were significantly lighter than for the controls. The ovaries were lighter, but the difference was not quite significant ($0.1>P>0.05$).

Induction of pseudopregnancy

In a preliminary experiment, daily vaginal smears were made from ten adult virgin mice for 7 days to determine the regularity of the vaginal cycle. From the eighth to eleventh days the mice were injected with 10 mg/kg of perphenazine daily. On the eleventh day, they were anaesthetized with ether and one horn of each uterus was traumatized by passing along it some silk thread, moistened with saline. The animals were killed on the fifteenth day and the uteri examined both macroscopically and microscopically for decidual tissue. One animal died under anaesthesia; of the remaining nine, four showed macroscopic (subsequently confirmed microscopically) and one showed microscopic deciduomata. In a control group of

TABLE 5

THE EFFECTS OF PERPHENAZINE (5 MG/KG) ON THE RESPONSE TO EXOGENOUS GONADOTROPHIN (P.M.S.) IN IMMATURE MICE

Values are means ± standard errors. For details of treatments, see text

Treatment	Weights of Vagina (mg)	Uterus (mg)	Ovaries (mg)
Perphenazine+P.M.S.	23·3±2·1	41·2±2·86	4·7±0·33
Saline (control)+P.M.S.	32·0±2·18	46·8±3·13	5·6±0·36
Saline (control)	15·8±2·88	16·1±1·69	2·9±0·2
P	<0·02	>0·2	>0·05

ten mice, following a similar operation, none showed any decidual tissue at post-mortem. The injections in this experiment were started arbitrarily on day 8 and not on a particular day in the oestrous cycle. If the injections had been started after ovulation, that is 24 hr after the appearance of cornified cells in the vaginal smears, then a higher score of positive responses might have been obtained.

In the next experiment, therefore, injections of drugs were started on day 2 or 3 of oestrus, that is the second or third day following the appearance of cornified cells in the vaginal smear. The injections were continued for 4 days, and the uteri were then traumatized and the animals killed 4 days later. Eight animals were injected with 10 mg/kg of chlorpromazine and nine with 10 mg/kg of perphenazine. No decidual reaction was obtained.

At this stage of the research, it was decided to repeat the experiments using mice which had previously borne one litter. Poulson (personal communication) found that, using the same colony of mice, virgin mice rarely became pseudopregnant following sterile mating, whereas in a series of over 150 mice which had borne one litter, sterile mating produced about 50% of pseudopregnancies. The same experimental procedure was therefore followed, except that trauma was induced by crushing the uterine horn at four sites with artery forceps. The animals treated with drugs again failed to produce deciduomata, while five of ten animals mated with sterile males formed deciduomata.

As Barraclough & Sawyer (1959) had induced pseudopregnancy in the rat with single large doses of chlorpromazine, single large doses of the drugs were next tried. Eight animals received 10 mg/kg of perphenazine, another eight received 30 mg/kg of perphenazine, six received 10 mg/kg of chlorpromazine and ten received 50 mg/kg of chlorpromazine. Again no decidual reaction was seen.

The effect of perphenazine and chlorpromazine on pituitary gonadotrophin levels in the rat

Female Sprague-Dawley rats weighing 150 to 200 g were used in this experiment. Regular oestrous cycles were first demonstrated by daily vaginal smears, and injections of drugs were then begun on the first day of the dioestrus and continued for 6 days. The rats were killed with ether vapour on the seventh day. The whole pituitary glands were removed, weighed and later assayed for gonadotrophic activity. The results of the assays are given in Table 6. There were five rats in each of the

TABLE 6

THE EFFECTS OF PERPHENAZINE AND CHLORPROMAZINE ON THE GONADOTROPHIC POTENCY OF THE RAT PITUITARY

Values are the mean uterine weights (in mg) of groups of three mice, treated with the indicated weights of powdered pituitary from rats treated as described in the text. There were five rats in each of the treated groups, and ten in the control group

	Weights of powdered pituitary (mg)			
Treatment of rats	0·3	0·5	0·7	1·0
Perphenazine	49·1	—	51·7	69·6
Chlorpromazine	50·5	—	54·1	66·9
Saline (control)	14·1	17·2	17·9	50·4

treatment-groups and ten in the control-group. The dose of the two drugs was 10 mg/kg/day. The uterine weights are each the mean from three mice.

The gonadotrophic activity of the pituitary glands from the animals treated with drugs was greater than that from the controls, a dose of 0.3 mg of powdered pituitary gland producing a response equivalent to that of 1.0 mg for the controls.

The depleting effect of perphenazine and chlorpromazine on adrenal ascorbic acid levels

To avoid possible variations in the levels of adrenal ascorbic acid associated with the different stages of the oestrous cycle in the female, the test animals were adult males of about 4 months of age. The animals were injected subcutaneously with either drug and killed 2 hr later by breaking their necks. The adrenals were removed immediately, weighed and then placed in freshly prepared metaphosphoric acid.

At a dose of 10 mg/kg, neither drug had any effect on the level of adrenal ascorbic acid. Ten mice received perphenazine, ten received chlorpromazine and fifty controls were injected with 0.9% saline only. The mean levels of adrenal ascorbic acid were 217 ± 8.1, 218.8 ± 12.6 and 218.1 ± 8.2 mg/100 g respectively.

DISCUSSION

Chlorpromazine and perphenazine, in doses of 5 to 10 mg/kg, each delayed the onset of sexual maturity (oestrous activity) in immature female mice, without affecting gain in weight during the period of growth, and suppressed vaginal oestrus in mature animals, with corresponding diminution in the weight of the ovaries, vaginae and uteri. The histological changes in the vaginae and uteri were consistent with deficiency of oestrogen, while the changes in the ovaries suggested lack of gonadotrophin or gonadotrophins. Each drug diminished slightly the response to exogenous gonadotrophin and exogenous oestrogen. In the experiment in which oestradiol was administered to ovariectomized mice, cornified vaginal smears were obtained from all those animals which received chlorpromazine or perphenazine, but the mean weights of the uteri were less than those of the control group. In the mice treated with perphenazine, this difference was almost significant ($0.1 > P > 0.05$). It is possible, therefore, that part of the action of these drugs is anti-oestrogenic. However, as cornification of the vagina did occur, it seems improbable that their major activity is anti-oestrogenic. Each drug prevented the compensatory ovarian hypertrophy which occurs because of increased release of gonadotrophin following unilateral ovariectomy, and also, in the rat, increased the gonadotrophic activity of the pituitary gland. This suggests that the chief mode of action of the two drugs is to diminish the release of gonadotrophin(s) by the pituitary gland, a hypothesis which is supported by the report of Barraclough & Sawyer (1957) that chlorpromazine blocked ovulation in the rat, probably by inhibiting the neurogenic release of luteinizing hormone.

Barraclough (1957) and Barraclough & Sawyer (1959) also found that chlorpromazine induced pseudopregnancy in the rat, presumably by stimulating the release of luteotrophin (prolactin). Similarly, Talwalker, Meites, Nicoll & Hopkins (1960) found that, under certain conditions, chlorpromazine initiated or maintained

lactation in the rat, effects at least partly attributable to release of luteotrophin. It is possible, also, that the galactorrhoea of human patients taking derivatives of phenothiazine can be due to release of prolactin (Polishuk & Kulczar, 1956 ; Winnik & Tennenbaum, 1955).

Except in one experiment with perphenazine, it was impossible to demonstrate release of luteotrophin by mice of the Guy's colony, using the deciduoma-test for pregnancy. However, this failure may be due to species differences between rat and mouse. In the lactating rat, deciduomata can be induced readily from 4 to 17 days *post partum* (Long & Evans, 1922 ; Lyon & Allen, 1938). In the mouse, however, the results have been variable. Thus Parkes (1929) was able to induce deciduomata during lactation, but the reaction was not as intense as in pregnancy or pseudopregnancy. Turpeinen (1941), however, could only provoke formation of deciduomata in two of twenty-three lactating mice, and Greenwald (1958) was successful with only one of thirty-one animals whose uteri were traumatized from 4 to 16 days *post partum*. However, in sixteen of eighteen *post partum* lactating mice of the same strain given 0.25 mg of progesterone daily for 3 days following uterine trauma, the deciduoma-test was positive. This dose of progesterone was smaller than that required to support formation of deciduoma in non-lactating mice, and the conclusion was that, in lactating mice, the progesterone levels in the blood were not normally high enough to support formation of deciduomata. Thus, for the mouse, induction or maintenance of lactation may be a more sensitive indication of release of luteotrophin than is the deciduoma-test.

There are many reports of drugs which appear to inhibit the release of follicle stimulating hormone, luteinizing hormone or both from the pituitary gland, but most of these drugs have also been shown, or may be suspected, to release corticotrophin from the gland. Selye (1949) suggested that when the hypophyseo-adrenal defence system was activated by stress, a shift in production of hypophyseal hormone occurred, with corresponding increase in corticotrophin and decrease in gonadotrophin production. However, this mechanism does not appear to be operative with the two derivatives of phenothiazine studied here, for the dose of 10 mg/kg, effective in inhibiting vaginal oestrus in the adult mouse, did not reduce the adrenal ascorbic acid level. Also, the effect on the reproductive tract was as great, or greater, after treatment for 6 weeks with the drugs, an unlikely finding if the effect were due to stress. Adaptation to a non-specific stress might be expected to occur after 2 to 3 weeks of exposure.

It therefore seems that both chlorpromazine and perphenazine may inhibit the release of gonadotrophin by the anterior pituitary gland, in doses which do not provoke release of corticotrophin.

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