STIMULATION OF GONADOTROPHIN SECRETION WITH THE PREGNANCY INHIBITOR D-6-METHYL-8-CYANOMETHYLERGOLINE (I)

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D-6-Methyl-8-cyanomethylergoline (I) (compound 6605 VÚFB) prevents pregnancy in rats when given orally up to the 7th day after copulation (Řežábek, Semonský & Kucharczyk, 1969). A similar effect was seen with the chemically related compounds, ergocristine, ergocryptine, ergocornine, ergosine and ergovaline (Shelesnyak, 1957; Kraicer & Shelesnyak, 1965). All the evidence shows that these drugs interfere with the secretion of hypophysial luteotrophic hormone (LTH), which is necessary for the correct function of corpora lutea (Shelesnyak, 1957; Zeilmaker & Carlsen, 1962; Lindner & Shelesnyak, 1967). Moreover, Lobel, Shelesnyak & Tic (1966) observed histological changes in the ovary associated with a drop in the levels of LTH and a rise in FSH and LH after ergocornine. This indicated that ergocornine might have a direct or indirect influence on the secretion of hypophysial gonadotrophins.

Since the action of compound 6605 VÚFB on pregnancy appears to resemble that of ergocornine, we decided to study the effects of the compound on the increase in the secretion of gonadotrophins which takes place after unilateral ovariectomy in rats. (Peterson, Edgren & Jones, 1964; Benson, Sorrentino & Evans, 1969). We also considered the possible interaction of compound 6605 VÚFB with methallibure (ICI 33828), which is known to inhibit gonadotrophin secretion (Paget, Walpole & Richardson, 1961).

Adult, nulliparous, female rats of the Wistar Konárovice strain, weighing 160 to 180 g, were allocated to five groups. Group 1 consisted of intact animals. Groups 2 to 5 consisted of animals which were unilaterally ovariectomized (left ovary removed) under light ether anaesthesia on the 1st experimental day. The animals of both control groups (1 and 2) received 1 ml of physiological saline. The animals of Group 3 received 0.5 mg, and those of Group 4, 1.0 mg of compound 6605 VÚFB. The rats in Group 5, received 12 mg of methallibure, followed 20 min later by 1.0 mg of compound 6605 VÚFB. These doses were administered by gavage once a day for 12 days, beginning on the day of unilateral ovariectomy. The daily doses of 6605 VÚFB were each dissolved in 1 ml of water and the dose of methallibure was suspended in 0.5 ml of vehicle SV 17874 (Dorfman, 1962). On the day following the twelfth dose, the animals were killed by cervical dislocation, the remaining ovary was extirpated, freed from adherent tissue and weighed on a torsion balance.

The left-sided ovariectomy resulted in hypertrophy of 47% of the remaining

right ovary. Compound 6605 VÚFB increased this hypertrophy, the dose of 1 mg being significantly more potent than the dose of 0.5 mg. When methallibure was added to the higher dose of compound 6605 VÚFB, hypertrophy of the remaining ovary did not occur. The ovarian weight in this last group corresponded to that of the intact control group. Ovarian hypertrophy following unilateral ovariectomy has been attributed to the elevated secretion of gonadotrophins (Peterson *et al.*, 1964; Benson *et al.*, 1969). We used this technique because when using the specific OAAD assay (Parlow, 1958), we observed that, following administration of another structurally similar derivative, a drop in the hypophysial LH content occurred in accordance with the results of the above-mentioned technique. We also observed a transient drop in hypophysial FSH content on the 4th day after unilateral ovariectomy when using Benson's modification of the Steelman & Pohley assay method (Benson *et al.*, 1969).

TABLE 1

THE EFFECT OF COMPOUND 6605 VÚFB AND METHALLIBURE ON THE WEIGHT OF THE RIGHT OVARY AFTER LEFT UNILATERAL OVARIECTOMY

Group*	Treatment	Wt of right ovary in mg (Mean $\pm$ S.E.)	Wt of ovary related to that of intact control	Significantly different from the groups ($P = 0.01$)
1 (20)	Intact controls 12 $\times$ 1 ml physiol. saline	25.3 $\pm$ 0.8	100%	2, 3, 4
2 (20)	Unilateral ovariectomy 12 $\times$ 1 ml physiol. saline	37.2 $\pm$ 1.1	147%	1, 3, 4, 5
3 (20)	Unilateral ovariectomy 12 $\times$ 0.5 mg 6605 VÚFB	46.4 $\pm$ 1.6	183%	1, 2, 4, 5
4 (17)	Unilateral ovariectomy 12 $\times$ 1.0 mg 6605 VÚFB	54.6 $\pm$ 1.6	215%	1, 2, 3, 5
5 (10)	Unilateral ovariectomy 12 $\times$ 1.0 mg 6605 VÚFB 12 $\times$ 12 mg methallibure	23.4 $\pm$ 1.6	92%	2, 3, 4

* No. of animals in parentheses.

The results of the present study indicate that compound 6605 VÚFB stimulates the secretion of hypophysial gonadotrophins. The inhibition of this effect by the previous administration of methallibure is in agreement with its known blocking action.

Unpublished observations show that compound 6605 VÚFB blocks the secretion of prolactin. The stimulation of hypophysial gonadotrophins of LH and FSH type and simultaneous inhibition of prolactin could hardly be explained by direct action on the hypophysis. It is more logical to assume that the compound stimulates the hypothalamus to release LH and FSH-releasing and prolactin-inhibiting factors. Our results seem to support the hypothesis of Lindner & Shelesnyak (1967), who suggested that the hypothalamus was responsible for the disturbed function of the hypophysis following the administration of ergocornine. The possibility of a stimulatory action of ergocornine on the hypothalamic secretion of prolactin-inhibiting factor was recently mentioned by Carpent & Desclin (1969).

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