

CONCENTRATION OF LUTEINIZING HORMONE IN THE HYPOPHYSIS OF RATS WITH PROLONGED ESTRUS

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In studying the mechanism for various disorders in women's menstrual cycles, great assistance may be gotten from investigating disturbances in the function of the sexual system of laboratory mammals.

One of these disturbances is known as prolonged, or so-called permanent, estrus. This disorder arises spontaneously (more accurately speaking, it arises for reasons as yet unknown), predominantly in aging females, but occasionally, although more rarely, it is encountered in young animals [5]. A similar disturbance may be caused experimentally. The genesis of permanent estrus has been described under the influence of prolonged light exposure (in the course of several weeks) [3,4,5].

Experimental prolonged estrus may also be caused by bilateral injury of certain areas of the hypothalamus (the region situated between the paraventricular nuclei and the median eminence) [7].

The state of the sexual system in "spontaneous" prolonged estrus and that caused experimentally are very similar. In both cases, there are many huge, often cystically enlarged, follicles in the ovaries, but ovulation does not occur and, correspondingly, there are absolutely no fresh yellow bodies.

A large number of cornified squamous cells are noted in the vaginal smears for prolonged periods, sometimes in the order of several months, these cells being characteristic of the estrus stage. On individual days the cellular composition of the smear changes, becoming comparable to the picture characteristic for metaestrus or proestrus, but never (or very rarely) is diestrus observed.

The administration of progesterone leads to ovulation, and the formation of yellow bodies, with corresponding interruption of the vaginal estrus [3,6].* This action of progesterone cannot be explained solely as an interaction with the estrogen hormone; it may be postulated that progesterone manifests its effect via the gonadotropic function of the hypophysis. Actually, it has been shown that the introduction of a preparation of luteinizing hormone causes this same action [2].

On this basis, it was postulated [3,6] that the phenomenon of permanent estrus is caused by insufficient production of luteinizing hormone by the hypophysis. The purpose of this work was to test the hypothesis experimentally by determining the luteinizing activity of the hypophyseal hormone in females with prolonged estrus.

EXPERIMENTAL METHOD

We investigated the hypophyses of female rats with prolonged estrus, both of the "spontaneous" type and the type caused by traumatization of the hypothalamus, plus the hypophyses of individuals with normal cycles. In order to obtain comparative data, in the females with normal cycles and the females whose sexual cycle was not disturbed by the operation, the hypophysis was taken in the estrus stage for determination of the luteinizing activity.

In addition to the observations on the vaginal smears, the animals were opened, the state of the ovaries was recorded, and these glands were then fixed for subsequent histological investigation.

*There are reports [3,6] that, after administration of progesterone, the normal, cyclic, functioning of the ovaries is subsequently restored, but the interpretation of these observations is still unclear, particularly in females with hypothalamic injury.

TABLE 1. Luteinizing Activity of the Hypophysis from Rats with Normal Cycles, During the Estrus Period

Expt. No.	No. of fem. donors	No. of recipients in which the ovulation reaction was:				
		negative	positive			
			total	weak	interm.	strong
16	1	—	1	1	—	—
17	1	—	1	1	—	—
18	3	2	1	1	—	—
22	2	2	—	—	—	—
23	7	7	—	—	—	—
25	1	—	1	—	1	—
27	3	1	2	2	—	—
Total	18	12	6	5	1	—

TABLE 2. Luteinizing Activity of the Hypophysis in Rats with "Spontaneous" Prolonged Estrus

Expt. No.	No. of fem. donors	No. of recipients in which the ovulation reaction was:				
		negative	positive			
			total	weak	interm.	strong
18	2	—	2	—	1	1
19	2	—	2	—	2	—
20	3	2	1	—	—	1
21	3	2	1	1	—	—
23	2	—	2	1	1	—
24	2	1	1	—	—	1
25	2	—	2	1	1	—
27	1	—	1	—	—	1
Total	17	5	12	3	5	4

TABLE 3. Luteinizing Activity of the Hypophysis in Females with Prolonged Estrus Caused by Injury to the Hypothalamus

Expt. No.	No. of fem. donors	No. of recipients in which the ovulation reaction was:				
		negative	positive			
			total	weak	interm.	strong
22	2	—	2	—	1	1
23	2	—	2	—	1	1
24	2	—	2	—	—	2
25	1	1	—	—	—	—
26	4	1	3	2	1	—
27	1	—	1	—	—	1
Total	12	2	10	2	3	5

TABLE 4. Luteinizing Activity of the Hypophysis in Females in which Injury to the Hypothalamus Failed to Cause a Disturbance in the Sexual Cycles

Expt. No.	No. of fem. donors	No. of recipients in which the ovulation reaction was:				
		negative	positive			
			total	weak	interm.	strong
21	2	2	—	—	—	—
22	3	3	—	—	—	—
26	3	3	—	—	—	—
27	2	—	2	—	2	—
Total	10	8	2	—	2	—

Note. In Tables 1-4, a positive reaction was appraised as weak with observation in the oviducts of the recipients of 1-10 ova; as intermediate, with observation of 11-19 ova; and as strong, with observation of 20 ova and more.

The concentration of luteinizing hormone (LH) in the hypophysis was determined by a somewhat modified version of the method of Zarrow and co-workers [7]. The basis of this method lies in causing ovulation in infantile females by serial administration of follicle stimulating and luteinizing hormones (FSH and LH). Gonadotropin, from the serum of pregnant mares (PMS), was used as the FSH preparation, and the hypophysis being tested served as the source of LH.

Females weighting 35-40 g were initially injected subcutaneously with 34 IU of the PMS preparation, and then, after 56 h, with an aqueous suspension of the test hypophysis, intraperitoneally; 24 h after this second injection, the animal was opened in order to appraise the results of the reaction.

The hypophyses were tested individually, which was accomplished by injecting each female-recipient with a suspension of one hypophysis from a female donor. The degree of the reaction was appraised from the number of ovulating infantile females, and from the average number of ova found in the oviducts. In a positive reaction, easily distinguished, thickened, translucent, segments were seen in the oviducts, corresponding to the sites where ova had collected. On autopsy, a gelatinous mass was removed from each such thickening, containing ova surrounded by follicular cells.

The animals with "spontaneous" prolonged estrus were selected by mass investigation of the females in the vivarium: for the experiment, females were selected in which uninterrupted estrus had been observed for not less than 2 weeks.

For experimental production of prolonged estrus, females weighing 175-200 g were subjected to surgery, using a stereotaxic apparatus [1]; investigation of the vaginal smears began 2 weeks after the operation, and the duration of observation was from 1-5 months.

EXPERIMENTAL RESULTS

The concentration of LH in the hypophysis of females with normal cycles, during the estrus stage, was so low that even injection of a suspension of the entire hypophysis caused only a weak reaction in the infantile females, and even that in no more than one-third of the cases (Table 1).

In rats with spontaneous prolonged estrus, the concentration of LH in the hypophysis was higher than that seen in the females with normal cycles, as shown by both the increased number of ovulating recipients and the degree of the reaction, i.e., the number of ova observed in the oviducts (Table 2).

As can be seen from Table 2, a positive reaction was noted in 12 of the 17 recipients, and the intermediate and strong reactions predominated.

In the females with prolonged estrus, caused by injury to the hypothalamus, the concentration of LH in the hypophysis was also greater than in the control animals (Table 3). Out of 12 hypophyses investigated, 10 caused a positive reaction, and in half the female-recipients the reaction was manifested to a strong degree.

In those females in which the surgical procedure on the hypothalamus failed to cause disturbances in the sexual cycle, the hypophyses did not differ from the hypophyses of the control animals in their LH concentration, i.e., were significantly less active than in the females with "spontaneous" and "hypothalamic" prolonged estrus (Table 4).

Thus, a comparative study of the luteinizing activity of the hypophysis showed that, in females with prolonged estrus, they doubtlessly contain more LH than in individuals with normal cycles during the estrus period. This pertains to both females with "spontaneously" prolonged estrus, and females in which this disturbance was caused by electrolytic injuries of specific areas of the hypothalamus.

We have already noted that the ovaries of females with prolonged estrus retain the capacity to ovulate, which has been proven by experiments with injection of exogenous LH or of progesterone, which apparently stimulates the secretion of endogenous LH.

The absence of ovulation, with retention of the reactivity of the ovaries to LH and an elevated concentration of this hormone in the hypophysis, provides a basis for postulating that the investigated disturbance in the sexual cycle is not caused by an insufficiency in the production of the luteinizing hormone, but by a disturbance in the neural regulation of its secretion from the hypophysis.

SUMMARY

Luteinizing hormone (LH) content was studied in the hypophysis of female rats with permanent estrus occurring both spontaneously or caused by electrolytic hypothalamic injury. To determine the LH content, suspensions of hypophyses, examined individually, were administered to infantile female rats to which folliculostimulating hormone prepared of the blood serum of a pregnant mare (PMS) had been administered.

This reaction was assessed by the number of ovulating recipients and by the average number of ova in the oviducts. In females with a permanent estrus, both spontaneous and caused by hypothalamic injury, the LH content in hypophysis was much greater than in the animals with a normal cycle during the estrus.

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