CHANGE IN HYPOPHYSEAL ACTIVITY AND IN STRUCTURE AND FUNCTION OF THE OVARIES UNDER THE INFLUENCE OF HYPOTHALAMIC ELECTRICAL STIMULATION

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Experimental damage to various parts of the hypothalamus leads to structural and functional changes in the ovaries [5,6,7]. It has been found that certain conditions must be fulfilled in order for the hypothalamus to influence the ovaries. Thus, in experiments on rabbits electrical stimulation of the hypothalamus caused ovulation only when the infundibulum of the hypophysis remained intact [10], as well as the ovarian nerves [12].

It seemed interesting to determine how hypophyseal activity would be affected by prolonged hypothalamic stimulation and by what routes the influence of the hypothalamus is conveyed to the ovary.

EXPERIMENTAL METHOD

The experiments were carried out on 38 sexually mature white rats weighing from 80 to 100 g and on 60 immature rats weighing up to 40 g. An index of the change of ovarian activity was the sexual cycle which was recorded by means of vaginal smears [1]. To influence hypothalamic activity we used electrical stimulation applied by indwelling electrodes implanted by a method which differed from the means we used previously [4]. Instead of the electrodes being cemented to a perforated plate fixed to the skull, they were fastened to a platic strip introduced beneath the temporal muscles. Stimulation was effected by 50-cycle alternating potentials which were threshold for somatic and autonomic responses; they were applied three times daily for 45 sec at an interval of 3-5 min. At the end of the experiments the animals were killed, sections of the brain were impregnated with silver (Campos method). To determine the position of the end of the stimulating electrode we used the atlas of Krieg [11], and of Fifkova and Marsala [8].

Three sets of experiments were carried out.

In the first set on 20 rats stimulation was applied one day per week for three months. The sexual cycle was studied before and during the stimulus period, and the ovaries were examined microscopically.

In the second set of experiments on 18 rats the animals were stimulated daily for two months. Before and during the whole of the stimulus period the sexual cycle was followed (for 12 weeks altogether). After two months of stimulation the rats were killed, the ovaries were examined microscopically, and the tissue of the adenohypophysis of the immature rats was tested [2].

In the third set of experiments on sexually immature rats we studied the reactivity of the sexual apparatus to the injection of gonadotropins (FSH given to 34 rats and LH to 26 rats) which were given to the animals receiving hypothalamic stimulation. The source of FSH was a suspension of adenohypophyses of male rats, while the LH was obtained from the urine of pregnant women which was treated with ether to remove estrogens. As controls we used immature rats without electrodes and immature rats with implanted electrodes carrying no stimulus. All the control animals received the same suspension of hypophysis and the same treated urine as did the experimental group which were given these substances by subcutaneous injection.

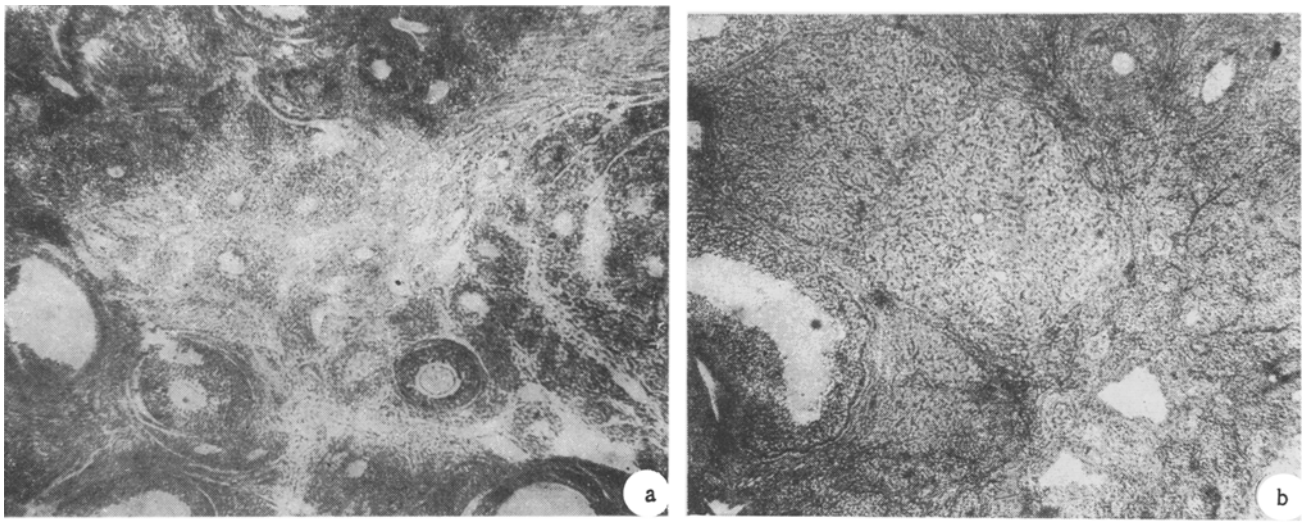

Fig. 1. Asymmetrical structure of the ovaries in an animal from the second series of experiments. a) Preponderance of follicles of various degrees of maturation, complete absence of corpora lutea; b) another ovary from the same animal; numerous corpora lutea, occasional follicles, hyperplasia of the estrous tissue. Micrograph. Hematoxylin-eosin. Magnification 3×7.

EXPERIMENTAL RESULTS

An analysis of the first series of experiments showed that in most cases electrical stimulation led to various disturbances of the sexual cycle. In six rats there was a marked and in four rats a small increase of estrus, which encroached on the resting period; in two estrus was shortened and the postestrus and resting periods extended, while in two the postestrus period was increased at the expense of the resting period. In sex rats there was no change of the sexual cycle. In certain cases threshold stimulation enabled an estrous period to appear, while stronger stimulation brought on a resting period.

In most animals of the second series daily prolonged threshold electrical stimulation of the hypothalamic region led to a marked prolongation of the active phase of the cycle, the stage of pre-estrus and estrus. In certain cases there was also a prolongation of the postestrous period. In almost all cases the resting stage was considerably shortened.

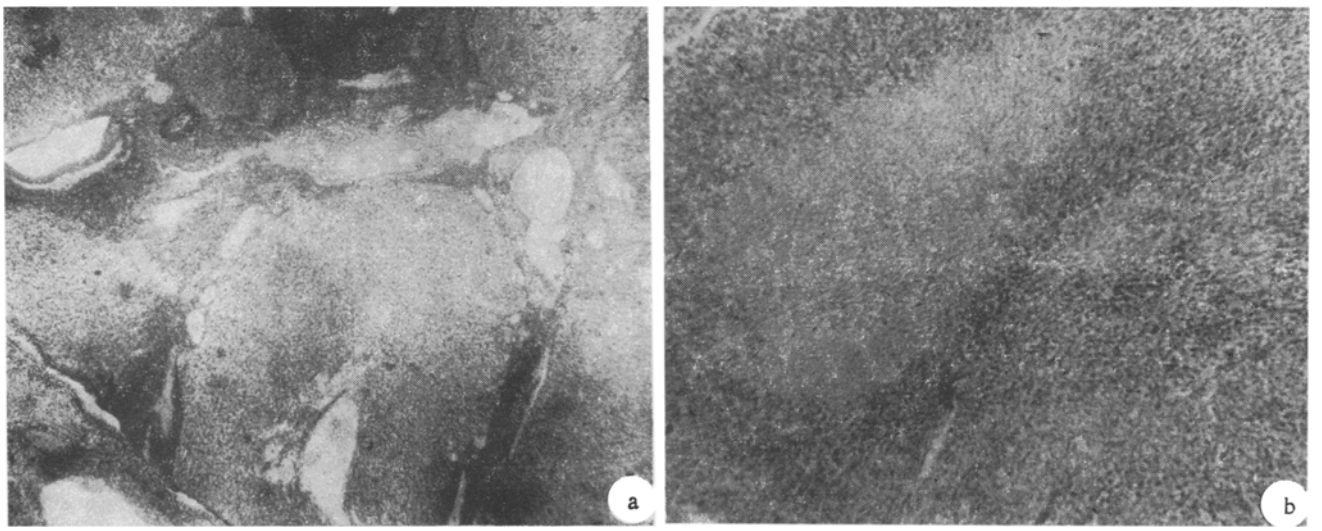

Fig. 2. Asymmetry of ovarian structures in an animal from the first set of experiments. a) Massive luteinization of the ovaries; b) the other ovary from the same animal: ovarian tissue considerably inflamed and necrotic. Micrograph. Hematoxylin-eosin. Magnification: a) 3×7; b) 9×7.

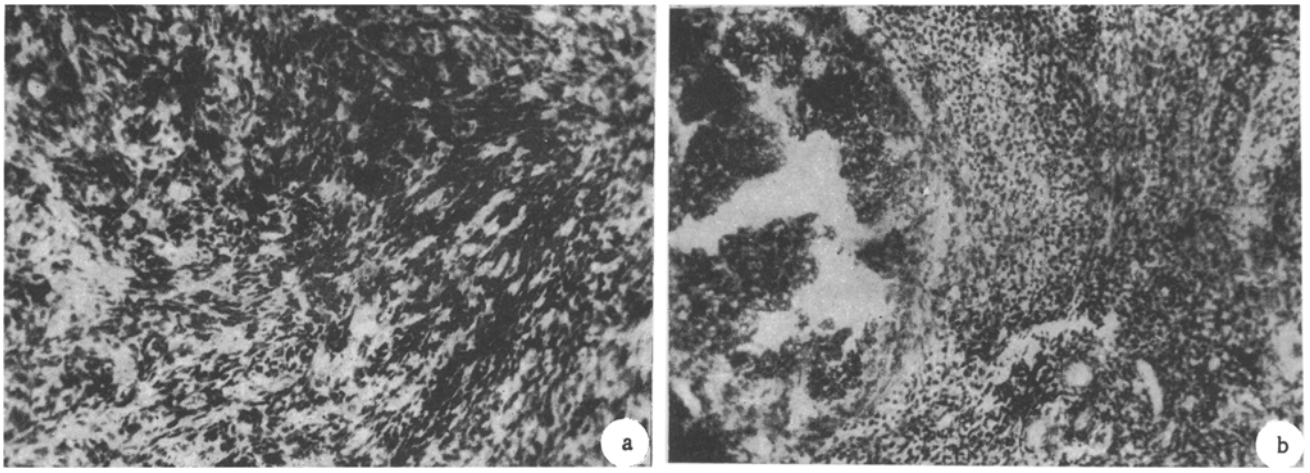

Fig. 3. Structural changes in the ovaries of rats of the first set of experiments after prolonged hypothalamic stimulation. a) Marked outgrowth of the cytogenous stroma of the corpus luteum, occasional lutein cells; b) focal necroses in an ovary infiltrated with leucocytes; complete absence of germinative elements and corpora lutea. Micrograph. Hematoxylin-eosin. Magnification a) 10×7; b) 9×7.

Neither in the first or second series of experiments could we determine any relationship between the changes observed and the position of the tip of the stimulating electrodes.

In connection with hypophyseal activity, in rats whose hypothalamus was stimulated daily for two months, at the end of the experiment gonadotropic activity of the adenohypophysis was higher than it was in intact rats of the same weight. Thus in the immature rats in which the adenohypophyseal tissue of the "stimulated" animals were tested the ovary weight to body weight ratio was 0.41 as compared with a ratio of 0.29 in the control rats which received a suspension of adenohypophyses of intact animals. The extension of the active periods of the sexual cycle therefore corresponds to an enhanced gonadotropic activity of the hypophysis.

In experiments to study the influence of electrical stimulation of the hypothalamus on the influence of injected gonadotropic hormones we found a statistically significant increase of the gonadotropic reaction in response to the injection of luteinizing hormone. Changes of the gonadotropic reaction in response to the injection of a suspension of hypophysis were not statistically significant. Stimulation of the cerebral cortex, or placement of the electrodes in the hypothalamic region but without application of a stimulus (control experiment) caused no change in the gonadotropic reaction.

A microscopical study of the ovaries (Figs. 1-3) revealed almost complete disappearance of the primordial follicles from most of the experimental animals of the second series; in some of them many maturing follicles appeared and there was some tendency to form clusters; in others there were a large number of corpora lutea. For the ovaries of this group of animals hyperplasia in estrus was very common. The vessels were engorged.

We tried unilateral stimulation of the hypothalamus, and to determine the possibility of some nervously conducted influence of the ovary we made a comparative study of the microscopical appearance of both ovaries in a single animal. We then found a structural asymmetry between right and left ovaries. In one ovary (rat No. 1) we found chiefly follicles at various stages of maturation, a marked hyperplasia of the estrous tissue, and small corpora lutea. In the ovary there were many corpora lutea, and occasional follicles; the estrous tissue showed no hyperplasia. In another animal (rat No. 9) in the left ovary there was a region where the granulosa cells were proliferating and showing occasional mitoses; in the right ovary, in the proliferating granulosa cells of the follicles a large number of mitoses could be seen.

This structural asymmetry was still more strongly shown in animals of the first series. Also, in a considerable proportion of the animals necrotic or inflammatory regions were to be found. Thus, in one ovary of rat No. 18 numerous necrotic areas were present and the tissue surrounding them was infiltrated with polymorphonuclear leucocytes; the estrous tissue showed hyperplasia; there was an infiltrating growth of granulosa cells; no corpora lutea or follicles were present in the ovary. In the other ovary there were numerous corpora lutea and primordial follicles; there was a marked proliferation of granulosa cells, and cluster formation.

The ovaries of a single animal showing such differences microscopically were also frequently different in size.

As is known [5,9,13] a long estrus occurs in response to electrolytic hypothalamic damage; the same effect is found on ligation of the infundibulum and transplantation of the hypophysis to a region remote from the hypothalamus. When nervous connection is interrupted near the ovary itself, again estrus is again arrested [3]. As far as functional disturbance of the hypothalamus is concerned it is known that estrus is of longer duration when rats are kept in prolonged illumination [5]. Thus in any form of disturbance of the neuro-humoral connection in the hypothalamo-hypophyseo-ovarian system there is a marked change in the duration of estrus.

Fundamentally the normal relationship between the hypophysis and ovary represents a condition of negative feed-back, because it is known that liberation of gonadotropic hormones by the hypophysis stimulates the production of ovarian sex hormones which in turn inhibit the gonadotropic activity of the hypophysis. From results which are generally known and from our own experiments we may conclude that the nervous structures of the hypothalamus play an important part in mediating this negative feed-back.

The fact which we have observed that there is a structural asymmetry of ovaries under conditions of unilateral hypothalamic stimulation gives reason to suppose that the mechanism of the sexual cycle is related not only to the rate of liberation of gonadotropic hormones by the hypophysis but also to the rhythm of parahypophyseal influences reaching the ovaries via the autonomic route.

SUMMARY

Prolonged unilateral electrical hypothalamic stimulation applied to albino rats prolonged the period of estrus, intensified hypophyseal gonadotropic activity, and induced structural ovarian changes. The ovaries showed structural asymmetry. The contribution of nervous conduction from the hypothalamus is discussed in relation to negative feed-back between the hypophysis and ovaries.

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