Disintegration is due to a decrease in the resistance of small thymocytes to hydrocortisone. The biochemical nature of this phenomenon is not yet clear. It may be associated also with inhibition of enzymes which inactivate hydrocortisone and with an increase in binding of the hormone through slowing of catabolism of specific protein receptors in the thymocytes. Coincidence of the peak of the cortisone-like action of OT with the maximum of hypovitaminosis in the liver (72 h) indicates a contribution of metabolic changes in the liver to thymocyte disintegration. Such a contribution is in agreement with the fact that the thymolytic effect of hydrocortisone is abolished in hepatectomized rats [7].

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ROLE OF NORADRENALIN IN SECRETION OF LUTEINIZING HORMONE

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KEY WORDS: luteinizing hormone; noradrenalin; ovariectomy; estradiol; rausedil.

Monoamines, as a class of neuromediators, participate in the regulation of hormonal functions and exert their action through releasing hormones, located in different parts of the CNS and, in particular, in the hypothalamus. Recently considerable attention has been paid to the study of the role of adrenergic mediators in gonadotrophin secretion. The noradrenergic and adrenergic systems of the hypothalamus have been shown to control processes such as the rhythmic type of secretion in ovariectomized rats and the preovulatory liberation of luteinizing hormone (LH) in intact female rats [5, 15].

The writers previously demonstrated correlation between changes in the monoamine content in individual regions of the hypothalamus and the LH level in female rats in various physiological states [1]. However, the results did not give any clear idea of the concrete participation of each monoamine in the regulation of pituitary gonadotrophin function.

The object of the present investigation was to study the role of noradrenalin (NA) in the mechanism of gonadotrophin secretion, specifically: to determine the LH concentration in the pituitary and blood after injection of NA into the preoptic region of the hypothalamus, which is functionally connected with the cyclic liberation of gonadotrophins in female rats [3], and which, as the writers showed previously, is characterized by the greatest changes in NA concentration in the course of the estrous cycle [1].

EXPERIMENTAL METHOD

Experiments were carried out on 120 sexually mature female rats weighing 200-250 g with a stable 4-day estrous cycle. The animals were kept under standard conditions (daylight from 5 to 19 h, temperature 20-23°C).

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TABLE 1. Effect of Injection of NA into PR of Hypothalamus of Female Rats in Various Stages of Estrous Cycle on LH Levels in Blood (in ng/ml) and Pituitary (in ng/mg tissue)

Stage of cycle	Time of expts.	Plasma (M ± m)		Pituitary (M ± m)	
		control	NA	control	NA
D_1	9—11	51,1±5,5 (6)	46,0±6,1 (6)	552,0±32,0 (6)	628±49,2 (6)
	14—16	49,0±4,8 (7)	49,4±4,9 (7)	569,8±27,1 (7)	567,1±30,2 (7)
D_2	9—11	80,2±6,5 (4)	96,8±17,4 (4)	706,2±48,2 (5)	893,4±75,4 (5)
	14—16	63,0±5,8 (4)	118,5±17,0 (6)	698,5±44.8 (6)	678,7±37,6 (6)
P	9—11	70,2±8,3 (5)	336,3±91,0 (4)	803,6±57,9 (5)	1117,6±57,4 (5)
	14—16	199,0±21,5 (5)	189,2±22,0 (5)	956,7±88,7 (6)	977,2±67,9 (5)
E	9—11	47,4±7,1 (6)	49,2±14,4 (5)	438,5±22,3 (6)	571,5±89,2 (5)
	14—16	47,4±7,1 (5)	42,1±5,9 (7)	660,8±84,1 (6)	646,1±66,6 (6)

Legend. Here and in Table 2, number of experiments shown in parentheses. E) Estrus.

TABLE 2. Effect of Injection of NA into PR of Hypothalamus of Ovariectomized Female Rats, Treated or Untreated with Estradiol, on LH Concentration in Blood (in ng/ml) and Pituitary (in ng/mg tissue)

Conditions of expt.	Plasma (M ± m)		Pituitary (M ± m)	
	control	NA	control	NA
Ovariectomy	277,5±25,4 (9)	317,9±29,1 (8)	5590,0±98,0 (9)	4773,0±46,0 (6)
Ovariectomy + rausedil	219,6±13,0 (5)	300,9±33,7 (8)	4007,3±82,0 (10)	5120,0±49,0 (14)
Ovariectomy + estradiol	111,2±6,1 (5)	405,6±72,2 (10)	2712,0±24,0 (5)	2700,0±20,0 (6)
Ovariectomy + estradiol + rausedil	98,5±10,1 (9)	185,0±34,6 (9)	2260,0±17,0 (5)	2150,0±16.0 (6)

Intact female rats, into which NA was injected during the first (9-11 a.m.) or the second (2-4 p.m.) half of the day at each stage of the estrous cycle, were used in one series of experiments.

Experiments on ovariectomized animals were performed 3-4 weeks after castration. Some of the ovariectomized animals were given estradiol benzoate subcutaneously in a dose of 4 mg/kg body weight 24 h before the experiment began. Instead of estradiol, the rest of these animals were given rausedil intraperitoneally in a dose of 4 mg/kg body weight 18 h before the experiment. The experiments of this series were carried out at 9-11 a.m.

The operation was performed on the animals under urethane–chloralose anesthesia (40 and 5 mg/100 g body weight respectively) and the rats were fixed in a stereotaxic apparatus. A freshly prepared solution of NA (1 μg in 4 μg physiological saline) was injected into the preoptic region (PR) of the hypothalamus by means of a microinjector. Animals of the control group received an injection of 4 μl physiological saline. The animals were decapitated 30 min after the injection, the pituitary glands were removed, and blood was taken for obtaining serum. The material was kept at −30°C. The LH concentrations in the pituitary and blood were determined by a radioimmunologic method [2].

EXPERIMENTAL RESULTS

In the experiments of series I the effect of NA on LH secretion was investigated in intact female rats (Table 1). Changes in the blood LH concentration were observed only in the second half of stage diestrus-2 (D_2) and in the morning of the proestrus stage (P). Injection of NA in these phases of the cycle caused an increase in the blood LH concentration compared with that in control animals (for D_2, $P < 0.05$; for P, $P < 0.01$). In other stages of the cycle, and also at other time intervals of the D_2 and P stages, no significant changes in the LH concentration were observed. Determination of the LH concentration in the pituitary showed no change after injection of NA in any phase of the estrous cycle except in phase P during the mornings, when an increase in the LH concentration in the pituitary was observed in response to injection of NA ($P < 0.01$).

The results of these experiments confirm the view that NA has an important role in the central regulation of pituitary gonadotrophic function [11, 13]. The influence of NA on LH secretion, incidentally, was noted at a time when the peripheral blood estrogen level was beginning to rise [8], suggesting that circulating sex hormones play a role in the neuromediator–releasing hormone–gonadotrophins regulating system.

To study this problem a series of experiments was carried out on ovariectomized rats either without injection of estradiol or with its preliminary injection (Table 2). Injection of NA into ovariectomized rats caused an increase in the blood LH concentration to 317.0 ng/ml (control 277.5 ng/ml, difference not statistically significant). Exhaustion of the brain monoamines by rausedil in ovariectomized rats led to a fall in the LH concentration in the blood ($P < 0.05$) and pituitary ($P < 0.01$), which was also observed in investigations by other workers [4]. Injection of NA into such animals caused an increase in the LH level in the blood ($P < 0.01$) and pituitary ($P < 0.01$).

In the next series of experiments the ovariectomized rats were given estradiol benzoate. This treatment caused the blood LH level in the control animals to fall to 111.2 ng/ml. NA caused an increase in the blood LH concentration in the rats of this group ($P < 0.01$). Exhaustion of the brain monoamine by rausedil in this case led to a very small decrease in LH level in the blood and pituitary ($P > 0.5$). Injection of NA into PR of these animals caused the blood LH level to rise ($P < 0.05$).

The results obtained on ovariectomized rats thus demonstrate the important role of NA in the mechanism of the central regulation of gonadotrophic function. Experiments in which NA was shown to increase the LH concentration in ovariectomized rats receiving rausedil demonstrated the specific role of NA in this process. Moreover, the experiments showed that estrogens can potentiate the response of LH to injection of NA. This dependence of the action of NA on pituitary gonadotrophic function on the circulating estrogen level may be due to two factors: the ability of estrogens to modify the sensitity of the pituitary to the action of LH releasing hormone and (or) the property of estrogens of modulating NA effects at the hypothalamic level. It can be concluded from the results described above that estrogens, in turn, modify the sensitivity of the pituitary, for the effects of NA were identical in direction on ovariectomized rats, whether receiving rausedil or estradiol. The absence of changes in the LH concentration in ovariectomized and otherwise untreated rats in response to injection of NA was evidently due to the rhythmic character of LH secretion in these animals [6]. However, a tendency for the LH level to rise after injection of NA was observed in these animals also. After injection of estradiol, however, the response of these animals to NA was much higher.

The following question arises from a consideration of these data: what is the role of NA in the mechanism of the ovulatory discharge of LH and how does NA interact with LH releasing hormone? It must first be pointed out that the localization of noradrenergic terminals coincides with the topography of LH releasing hormone (LHRH) distribution in the hypothalamus [9, 10, 12, 14]. Moreover, experiments [7] have shown that the highest LHRH concentration in PR in the course of the estrous cycle corresponds to the period between 18 and 22 h of the D_2 stage. Later [8] an increase in the LHRH concentration was found in the mediobasal hypothalamus in the morning in the P stage, when it was accompanied by elevation of the blood LHRH level and led to a change in sensitivity of the pituitary to LHRH. Previously [1] the present writers observed the greatest changes in NA concentration in the anterior zone of the hypothalamus in the period between 18 h of the D_2 stage and 10 h of the P stage. It can be postulated that changes in the LHRH concentration in the hypothalamus are connected with the more intensive secretion of NA from presynaptic endings and the more intensive stimulation of perikarya containing LHRH by them. Under these circumstances sex steroids facilitate the activation process.

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EFFECT OF THE STATE OF CELLULAR IMMUNITY ON PHARMACOLOGICAL IMMUNOCORRECTION OF WOUND HEALING BY PHYTOHEMAGGLUTININ IN RABBITS

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Great importance in the prevention of suppurative complications and in the treatment of wound has been attached in recent years to local and general mechanisms of immune defense of the body [3, 10, 11]. It has been shown [11] that a positive intradermal test to Thielmann's stain, tuberculin, and other bacterial antigens is associated with a low percentage of complications of wound healing (suppuration in 4% of cases), whereas a negative or weakly positive test is associated with a complicated course (suppuration in 21.5% of cases, development of infiltration in 59.2%). The change in the state of the wound from bacterial contamination to infection depends on the level of the body's immunologic defense [5].

In the last 10 years three principal trends in immunocorrection in vivo have been determined: hormones and mediators of the immune system, immune engineering, and pharmacological correction of immunity. The problem of wound healing and wound infection is also being tackled in accordance with these same three approaches [2, 6, 9]. A few investigations devoted to methods of immunologic stimulation of wound regeneration with the aid of the plant lectin phytohemagglutinin (PHA) have been published [1, 7]. The absence of any experimental justification for the use of this new immunostimulant for wound treatment prevents any objective evaluation of the method, still less any recommendation for PHA under clinical conditions.

Preliminary investigations to determine the PHA dose–effect relationship by the use of ointments and emulsions on 183 inbred C57BL/6 mice showed that a dose of 3 μg/g ointment base is optimal, when the times of wound healing are reduced by 33% compared with the control. The dose of PHA of under 3 μg/g had a suppressor effect; the times of wound healing during treatment with these doses were significantly longer than in the controls (25.5 ± 1.12 compared with 12.4 ± 0.55 days; $P < 0.001$). It has been shown [12, 13] that PHA (from Difco, USA, or Wellcome, England), in a dose of 3 μg/ml, causes maximal stimulation of DNA synthesis in a lymphocyte culture, raises the cyclic GMP level, and lowers the cyclic AMP concentration, effects which reflect maximal mitotic and functional activity of the lymphocytes.

The object of the present investigation was to study the stimulating effect of local application of PHA ointment and emulsion in a dose of 3 mg/g on wound healing in rabbits depending on the intensity of the reaction of cellular immunity revealed by the intradermal test to the same mitogens.

EXPERIMENTAL METHOD

The reaction of delayed-type hypersensitivity (DTH) objectively reflects the state of T cell immunity [8] and correlates with the reaction of blast transformation of lymphocytes in culture [4].

The intradermal test with PHA [1] was carried out on 255 rabbits of different breeds and of both sexes, weighing 3.2 ± 0.07 kg. All the rabbits were divided into three groups: those reacting strongly to PHA (32.9%;

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