

## PHYSIOLOGY

### CHARACTERISTICS OF HYPOTHALAMIC NEURONS CONTROLLING THE PITUITARY GONADOTROPIC FUNCTION IN OLD FEMALE AND MALE RATS

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In old rats with an intact estrous cycle the sensitivity of neurons of the preoptic and arcuate regions of the hypothalamus to estradiol is reduced although neurons of the arcuate region remain more sensitive than those of the preoptic region. Old rats with constant estrus or diestrus had equally low sensitivity of the neurons of both these hypothalamic regions. In old male rats the sensitivity of neurons of the arcuate region to testosterone was reduced while neurons of the preoptic region did not respond at all to injection of the hormone.

The leading role of the hypothalamic region in regulation of the sex cycle in reproductive animals has been proved conclusively [1, 2, 6, 12]. Presumably age disturbances of the sex cycle, with omission of various stages or even with permanent estrus or diestrus are the result of primary changes in the function of the hypothalamic centers regulating the tonic and cyclic liberation of gonadotropins. Clinical data and the study of pituitary-ovarian relations in women at the menopause confirm the view that there is a primary disturbance of the activity of the hypothalamic centers [3-5, 7-9].

The object of this investigation was to study the functional state of neurons of the preoptic and arcuate regions of the hypothalamus in old female and male rats.

#### EXPERIMENTAL METHOD

Rats of both sexes aged 24-36 months were used. On the basis of a study of vaginal smears the females were divided into groups with a regular cycle, with an irregular but persistent cycle (the duration of the cycle was disturbed, with prolongation of estrus or diestrus), and animals with permanent estrus or permanent diestrus. Altogether 84 rats (59 females and 25 males) were used, and the activity of 318 neurons was studied in the preoptic and arcuate regions of the hypothalamus. Unit activity of the dorsomedial nuclei was studied as the control. For the experiment the animals were immobilized with tubocurarine (0.2 ml of a 0.1% solution/100 g body weight), and artificial respiration was applied. Unit activity was recorded extracellularly by glass microelectrodes filled with 2.5 M KCl solution saturated with potassium ferricyanide to mark the electrode. The mean frequency (spikes per second) and mean interspike interval (in msec) were determined for each neuron. A histogram of distribution of interspike intervals before and after injection of the hormones was plotted from the results; the relative percentages of neurons responding unidirectionally compared with the total number of neurons tested was determined. The technique was described fully elsewhere [1, 2].

#### EXPERIMENTAL RESULTS AND DISCUSSION

In the old rats with an intact normal cycle the sensitivity of neurons of the arcuate region of the hypothalamus to estradiol was considerably higher than that of neurons of the preoptic region. Meanwhile the sensitivity of both regions to endogenous hormones was lowered in the old animals of all groups. As Table 1

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TABLE 1. Unit Responses in Regions of the Hypothalamus to Intravenous Injection of Hormones in Old Rats

Region studied	Females										Males	
	with normal cycle		with lengthened cycle		with permanent cycle		Dose of testosterone (in $\mu$ g)				Dose of testosterone (in $\mu$ g)	
	proestrus	estrus	metestrus	diestrus	estrus	diestrus	estrus	diestrus	estrus	diestrus		
Preoptic	++(82) ++(71) ---(90)	0 ++(69)	0 ++(73)	0 ++(72)	0 ++(78)	0 ++(73)	0 ++(76)	0 ++(80)	0 ++(86)	0 ++(80)	20,0 30,0 50,0	0 0 0
Dorsomedial nuclei	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	20,0 30,0 50,0	0 0 0
Arcuate region	++(68) ++(70) ---(84)	0 0 ++(90)	0 0 ++(75)	0 0 ++(68)	0 0 ++(78)	0 0 ++(83)	0 0 ++(85)	0 0 ++(93)	0 0 ++(86)	0 0 ++(80)	3,0 20,0 30,0 50,0	++(66) ++(63) ---(78) ---(72)
	---(72)	---(66)	---(73)	---(74)	---(74)	---(83)	---(85)	---(93)	---(86)	---(80)	---	---

Legend: + + excitation; 0 no response; -- inhibition; -- no response. Percentage of responding neurons shown in parentheses.

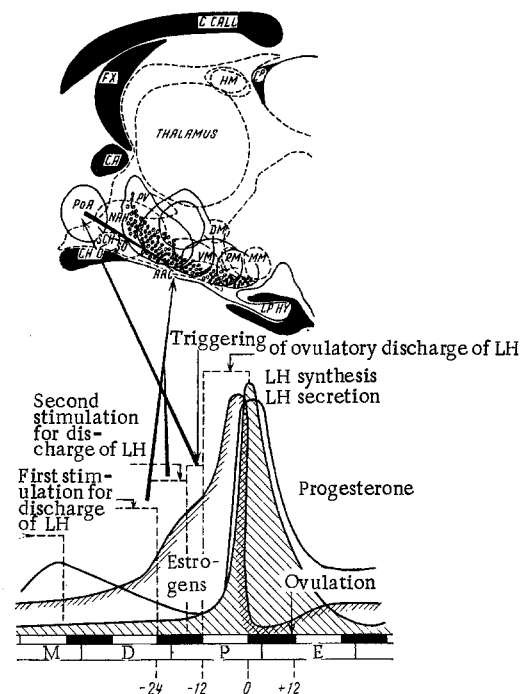


Fig. 1. Scheme of hypothalamic regulation of the sex cycle. Numbers below graph represent time (in h). M) Metestrus; D) Diestrus; P) Proestrus; E) Estrus; LH) Luteinizing hormone; POA) Preoptic region of hypothalamus; SCH) Suprachiasmatic region; SO) Supraoptic region; CHO) Optic chiasma; NAH) Anterior hypothalamus; PV) Paraventricular nuclei; ARC) Arcuate nuclei of hypothalamus; VM) Ventromedial nuclei; DM) Dorsomedial nuclei; PM) Premamillary nuclei; MM) Mamillary nuclei; LPHY) Anterior lobe of pituitary. Remainder of legend in text.

shows, neurons of the arcuate region of the hypothalamus in old rats in proestrus react by increased activity to injection of estradiol only if injected in a dose of 0.3  $\mu$ g or more, whereas in young, sexually mature rats a similar response could be obtained by injection of a dose of 0.1  $\mu$ g. Neurons of the preoptic region responded by increased activity at this same stage of the cycle to injection of 1  $\mu$ g estradiol (compared with 0.5  $\mu$ g for young sexually mature rats). In other stages of the cycle, in order to obtain an analogous response from neurons of the arcuate region, not less than 3  $\mu$ g estradiol had to be injected, and for a response from neurons of the preoptic region the dose required was 5  $\mu$ g. Neurons of the dorsomedial nuclei did not respond at all to injection of the hormone, indicating that the response of neurons of the preoptic and arcuate regions of the hypothalamus is specific. In rats with prolonged or permanent estrus or diestrus, with reduced sensitivity of both regions of the hypothalamus to estradiol, no difference could be observed between the sensitivity of the neurons in the arcuate and preoptic regions.

Analysis of unit activity in the corresponding regions of the hypothalamus of old male rats showed significant changes in their sensitivity in response to injection of testosterone. Neurons of the preoptic region did not respond in general to testosterone, while the sensitivity of the neurons of the arcuate region was lower by two to three times than in young sexually mature males. The results suggest a scheme of hypothalamic regulation of the gonadotropic function of the pituitary and changes in it with age (Fig. 1). In rats with a stable 4-day cycle, in the stage of metestrus, diestrus, and the initial phase of proestrus the effect of estrogens and progesterone extends chiefly to neurons of the arcuate region, which are significantly more sensitive than neurons of the preoptic region. Stimulation of the arcuate region is accompanied by secretion of releasing factors (LH-RF) and by discharge of luteinizing hormone from the pituitary. As the blood estrogen concentration rises in the second half of proestrus [10, 11], the effects spread to the preoptic region, which stimulates the arcuate region to give a further, ovulatory, discharge of LH-RF, thereby bringing about ovulation. With age the sensitivity of these hypothalamic region falls, and one of the most important components of the feedback mechanism, in which nervous impulses are switched to hormonal, is lost. Essential changes in the sensitivity of neurons in the corresponding hypothalamic regions develop before changes are found in the vaginal smears and in the concentration of sex hormones or gonadotropins. Intensification of these changes leads to permanent estrus or diestrus.

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