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EFFECT OF GUANETHIDINE DESYMPATHIZATION ON CARDIAC FUNCTION IN YOUNG RATS

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Guanethidine inhibits release of noradrenalin from terminals of adrenergic neurons [10-12] and thereby disturbs equilibrium in the catecholamine concentrations in the tissues of many organs [4]. It is accordingly interesting to study functional changes in the sympathetic regulatory apparatus of the heart in the growing animal before puberty.

In the present investigation the effect of chemical desympathization by guanethidine on the functional state of the sympathico-adrenal system and activity of the developing heart was studied.

EXPERIMENTAL METHOD

Experiments were carried out on noninbred albino rats aged 3 weeks. Starting from the 1st day of life, the animals were given guanethidine (Isobarin, from Pliva, Yugoslavia) by daily subcutaneous injection in a dose of 30 mg/kg, which was sufficient to block sympathetic neurons completely [3]. Physiological saline was injected into rats of the control group. The rats were used in the acute experiments on the 21st day of life, and were anesthetized with urethane (600 mg/kg). To determine the chronotropic sensitivity of the heart, solutions of adrenalin and noradrenalin in concentrations of 10^{-6}-10^{-5} M were injected into the jugular vein through a vinyl chloride catheter, and the ECG was then recorded. The heart rate was calculated by measurement of 10 R-R intervals. The sensitivity of the heart was judged by the maximal changes in heart rate (HR) from its initial values before injection of the drugs. To determine the state of the catecholamines in the blood and tissues the rats were decapitated. Blood was collected in small jars, into each of which 5 ml of an 8% solution of perchloric acid had first been poured. The heart and both adrenals were removed, dried with filter paper, and used in the fresh state for investigation of their catecholamine content. The concentration of adrenalin and noradrenalin was determined fluorometrically [5] and expressed in nanograms/ml of blood and in micrograms/gram wet weight of tissue in the heart and adrenals.

EXPERIMENTAL RESULTS

HR in 3-week-old rats chemically desympathized with guanethidine was higher by 21.4 beats/min ($P < 0.05$), than in the control (Table 1). Relative tachycardia has been observed by other workers also in older desympathized rats [7, 9]. However, this fact has not been explained. HR in the growing organism depends on relations between the autonomic nerves. High functional activity of the sympathetic nervous system in the growing organism gives rise to high values of HR [1, 8]. In this case, in desympathized 3-week-old rats the influence of the sympathetic nerves on the heart was greatly weakened, and HR, on the contrary, was considerably higher than in the control animals. How can the correlation between these parameters be explained? In desympathized rats the total peripheral vascular resistance of the systemic circulation was 1.7 times less than in normal rats [7]. Consequently, the tone of their blood vessels was depressed. Under these conditions the heart must contract more frequently and expel more blood in order to maintain the necessary blood pressure in the peripheral ves-

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TABLE 1. Changes in HR (beats/min) in 3-Week-Old Rats After Injection of Noradrenalin

Catecholamine injection	Type of determination	Desympathization	Control
Noradrenalin	Before injection	516,8±7,5 (9)	495,4±6,8 (10)
	After injection	563,4±8,5* (9)	515,57±7,5* (10)
	Difference	46,6±8,7* (9)	20,1±5,8 (10)
Adrenalin	Before injection	494,5±9,5 (9)	481,3±5,1 (10)
	After injection	534,8±8,9 (9)	497,4±6,0 (10)
	Difference	40,3±7,8* (9)	15,9±7,1 (10)

Legend. Here and in Table 2: *) difference significant ($P < 0.05$). Number of animals given in parentheses.

TABLE 2. Changes in Catecholamine Concentration in Blood, Myocardium, and Adrenals of 3-Week-Old Rats after Chemical Desympathization with Guanethidine

Organ	Parameter	Desympathization	Control
Heat	Weight, mg	131,1±11,5	115,3±14,8
	Adrenalin, μg/g	0,13±0,03	(17) 0,178±0,1 (17)
	Noradrenalin, μg/g	—	(17) 0,274±0,08 (17)
Adrenals	Weight, mg	8,06±0,9	(18) 6,02±0,8 (17)
	Adrenalin, μg/g	178,4±18,1*	256,6±13,7
	Noradrenalin, μg/g	1426,9±64,3	(18) 1442,4±72,01 (17)
	Mg/organ	192,3±11,5*	276,9±13,7
Blood	Adrenalin, mg/ml	1538,2±75,1	(18) 1661,9±78,8 (17)
	Noradrenalin, mg/ml	2,1±0,2	(18) 2,5±0,2 (17)
		1,8±0,3	(18) 5,5±0,4 (18)

sels. The cardiovascular system attempts to maintain constancy in its own system [6], and compels the desympathized heart to work faster. In turn, this causes an increase in the volume of plasma in the desympathized organism [13]. The veins are dilated considerably. The plasma volume may be increased by 25%. All these changes evidently cause an increase in the body weight and the weight of the individual organs after desympathization. The body weight of 3-week-old desympathized rats (18.0 g) was 1.1 g more ($P < 0.05$) than that of control rats (16.9 g). The weight of the heart of desympathized rats also was greater than that of control animals ($P < 0.05$). While accepting this mechanism of tachycardia in the desympathized organism, we suggested a possible effect of extracardial neurohumoral factors, which can maintain high values of HR. Accordingly the catecholamine concentrations were studied in the heart and adrenal tissues and in the blood, i.e., the functional state of the sympathicoadrenal system as a whole was determined. No significant difference could be found in the catecholamine concentrations in the adrenals of the control and desympathized rats (Table 2). Meanwhile the adrenalin and noradrenalin concentrations in desympathized rats were lower than in the controls ($P < 0.05$). There is information in the literature that chemical desympathization by guanethidine has no significant effect on cathecholamine concentrations in chromaffin tissue, including the adrenals [10-12]. In the developing organism, a decrease in the catecholamine concentration in the adrenals was found after desympathization. Other workers [4] also have observed some decrease in catecholamine concentrations in the adrenals of desympathized rats aged 2.5 months compared with the control. In the present experiments the fall in catecholamine concentrations in the adrenals after chemical desympathization was much greater than was observed in [4].

The blood adrenalin concentration in desympathized and intact 3-week-old rats was about equal in level. Meanwhile the blood noradrenalin concentration in desympathized rats was only one-third of that in the control animals ($P < 0.05$). Finally, the adrenalin concentration in the heart of desympathized rats was 30% lower than in the control. No noradrenalin could be found in the heart tissues of desympathized 3-week-old rats, whereas in control animals of the same age its concentration was 0.274 ± 0.08 μg/g.

Consequently, noradrenalin is not present in the heart tissues of desympathized rats, and its concentration in the blood also is considerably reduced. This may be due to the following causes. First, the desympathized heart is no longer able to take up noradrenalin with its adrenergic nerve endings and to store it. Second, release of catecholamines from the adrenals also is reduced, as is shown by the fall in its blood concentration. We consider that noradrenalin in the heart of young developing rats is taken up only by nerve endings. In the present experiments, immediately after adrenergic nerve endings had been inactivated by chemical desympathization with guanethidine, noradrenalin disappeared from the heart. Adrenalin is taken up mainly by heart muscle and only to a very small extent by nerve endings. Possibly because of weakening of this last mechanism the adrenalin concentration in the myocardium also was depressed a little in desympathized rats.

The sensitivity of the adrenoreceptors of the heart underwent significant changes as a result of chemical desympathization with guanethidine, as shown by changes in the heart rate after injection of catecholamines (Table 1). The heart rate in desympathized rats was higher after injection of noradrenalin than in the resting state by 46.6 beats/min, but in normal animals by only 20.1 beats/min. Changes in HR after injection of adrenalin into desympathized rats also were greater than in normal rats ($P < 0.05$). Consequently, the sensitivity of the heart in desympathized 3-week-old rats was much greater than that of normal animals of the same age. Evidently the few remaining nerve endings [3] become hypersensitive and capable of reacting several times more strongly than those in the heart of normal animals. The sensitivity of the adrenoreceptors of the desympathized heart to adrenalin also was increased somewhat. The adrenalin concentration in the myocardium of the desympathized rats was lower than in normal animals.

Consequently, the reciprocal relationship discovered in these experiments between the concentration of the catecholamine present in the heart and the sensitivity of adrenergic receptors is in agreement with the relationship of their interaction described in the literature [4]. This may be of great importance in regulation of the chronotropic function of the developing heart. Under the influence of the same portion of noradrenalin, the desympathized heart responds by an increase in heart rate that is 2.2 times greater than the increase in control rats. The increased sensitivity of the heart to catecholamines can maintain a high heart rate, and in turn, this reduces the range of reserve capacity of the heart with respect to its frequency, i.e., to a reduction of its functional lability. This situation has a direct bearing on the parameters of muscular working capacity. Probably for this reason the duration of swimming of desympathized rats carrying a load, until exhaustion, is much shorter than that of intact animals.

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