ON THE CHOLINERGIC REACTIONS AND SYMPATHOADRENAL ACTIVITY ASSOCIATED WITH EXPERIMENTAL HYPERTHYROIDISM IN WHITE RATS

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The participation of acetylcholine in the transmission of excitation within the sympathetic ganglia [3, 8], in the activation of the medullary substance of the adrenals [4, 6], its role in the liberation of adrenalin-like substances in the myocardium [9], and the methylation of noradrenalin [7], all serve as a basis for regarding this preparation as a physiological activator of sympathetic activity [1, 2]. In connection with this we considered it of interest to study the cholinergic reactions under pathological conditions during states characterized by manifest sympathoadrenal excitation.

In this work, for the study of the interrelationship between adrenergic and cholinergic reactions in the presence of elevated sympathoadrenal activity, we used the form represented by experimental hyperthyroidism. The adrenergic and cholinergic activity during the hyperthyroid state was judged from the reactions of the heart and respiration to adrenalin, ephedrine, acetylcholine, and proserine.

EXPERIMENTAL METHOD

The experiments were carried out on male white rats, weighing 180-300 grams. Hyperthyroidism was induced by l-thyroxin, which was injected subcutaneously in a dose of 0.007 micrograms/100 grams of body weight for a course of 3 days, and in a dose of 160-220 micrograms/100 grams of weight daily, for a course of 7-9 days.

Tests with acetylcholine (1.5 micrograms/100 g of body weight subcutaneously), proserine (25 micrograms per 100 g of body weight subcutaneously), adrenalin (100 micrograms/150 g of body weight subcutaneously), and ephedrine (2.5 mg/150 g of body weight subcutaneously), were set up after 3 injections with the small doses and 7-9 injections with the large doses of thyroxin. The action of the thyroxin, as well as the indicated preparations, was appraised from the change in the indices of the EKG and respiration frequency. The EKG and respiration were recorded on an "Officine Galileo" polycardiograph, at a rate of 100 mm/sec. The EKG was recorded from the standard I, II, and III, and CL leads, every ten minutes over the course of an hour following the injection of the preparations.

The results of the experiments were analyzed statistically, and the validity of the results was determined by the magnitude of the error P. The work was performed on 102 animals.

EXPERIMENTAL RESULTS

In connection with the fact that the rhythm of the cardiac activity and respiration were slowed due to the animal being kept in the chamber for an hour in an immobile, rest state (Table 1), the corresponding corrections were introduced in analyzing the results of the trials with the pharmacological samples.

It is apparent from Figs. 1 and 2 that adrenalin and ephedrine caused a minimal positive chronotropic effect in the normal animals, proserine caused a minimal negative chronotropic effect, and acetylcholine, in the given dose, gnerally did not possess any chronotropic activity. The remaining indices of the EKG remained essentally unchanged.

The respiration frequency changed to a significant degree only under the influence of ephedrine (increased frequency by 120%). The doses of the pharmacological preparations (except for ephedrine) were threshold level, as pertained to the majority of indices of the EKG and respiration.

TABLE 1. Change in the Rhythm of Cardiac Activity and Respiration in 5 White Rats Following Their Being Kept in a Chamber in an Immobile Rest State for a Period of 40-60 Minutes

Index	R–R						Respiration/min	
	control		following injection of small doses of thyroxin		following injection of large doses of thyroxin		control	following injection of small doses of thyroxin
	max.	min.	max.	min.	max.	min.		
M	+40,6	+38,5	+16,8	+19,6	+6,6	+6,7	−30	−16
m	±9,6	±6,6	±2,6	±4,2	±2,0	±2,7	±7,0	±4,5

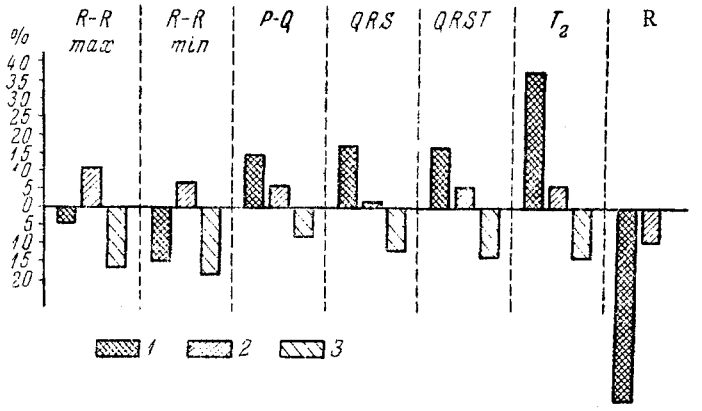

Fig. 1. The effect of ephedrine on indices of the EKG and respiration in the control (1), and also after injection of 0.021 mg of thyroxin in a period of 3 days (2) and 1100-2000 μg of thyroxin over the course of 7-9 days (3).

After 3 injections with small doses of thyroxin, no essential changes were observed in the indices of the EKG and respiration (Table 2). We noted only a prolongation of the QRS and QRST intervals by 0.0014 and 0.0040 sec, respectively.

In contrast to the control experiments, adrenalin and ephedrine, under these conditions, caused a negative chronotropic effect – lengthening of the $R–R_{max}$ and $R–R_{min}$ by 5.8 and 6.8% (adrenalin) and 11.8-8.6% (ephedrine).

The injection of adrenalin led to a more intense prolongation of auriculoventricular conduction (by 10.27%) than in the control, as well as to lengthening of the QRS rather than shortening, and a marked heightening of the positive T_2 (+57.1%). In addition, in contrast to the control experiments, adrenalin caused a more intense tachypnea (+45%). Ephedrine, in comparison with the control, caused a smaller elongation of the P–Q, QRST, and QRS, a smaller heightening of the positive T_2, and a minimal tachypnea (+8%).

The effect of acetylcholine and proserine against the background of small doses of thyroxin changed in the following manner. While in the control acetylcholine practically did not affect the magnitude of the R–R intervals, under these conditions it caused a prolongation of R–R by 31-23.7%, and, in addition, a more intense shortening of QRS (by 22% instead of 6%) and a clear bradypnea (−24% instead of +5%). In 6 of the 14 animals, on the 20th minute after injection, proserine caused lateral dissociation of the II–III degree, with ventricular extrasystoles, against a setting of bradycardia. In 4 rats, the block developed into an idioventricular rhythm, with marked suppression of respiration; the 4 rats died.

As pertains to the other indices, the action of proserine was almost identical with that seen in the control experiments.

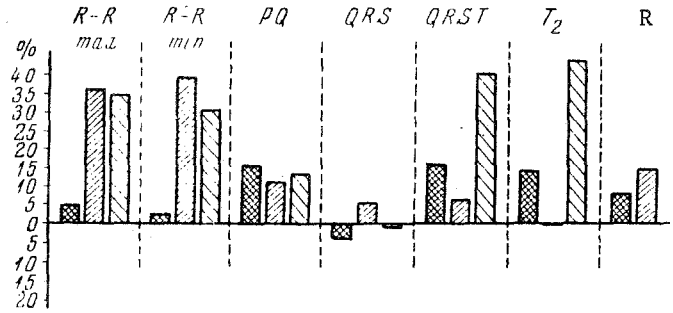

Fig. 2. The effect of proserine on the indices of the EKG and respiration in the setting of thyroxin administration. Symbols are the same as in Fig. 1.

TABLE 2. Changes in the EKG and Respiration of White Rats After Injection of Small and Large Doses of Thyroxin

Experimental conditions	Index	$R-R_{max}$	$R-R_{min}$	$P-Q$	QRS	$QRST$	T_2	Respiration (per min)
Normal	M	0,12	0,11	0,046	0,0144	0,064	+0,145	127
	m	±0,00002	±0,000015	±0,0005	±0,0002	±0,0008	±0,007	±4,0
	n	82	82	82	82	82	81	76
Small doses of thyroxin	M	0,12	0,11	0,046	0,0158	0,068	+0,15	129
	m	+0,0017	±0,0017	±0,002	±0,0003	+0,0012	±0,009	+6,5
	n	58	58	55	47	55	27	33
	P	—	—	—	1	1	60	60
Large doses of thyroxin	M	0,095	0,09	0,044	0,011	0,044	+0,11	159
	m	±0,002	±0,0018	±0,0009	±0,0041	±0,0009	±0,007	±5,0
	n	38	38	37	38	36	30	38
	P	1	1	20	30	1	1	1

The administration of large doses of thyroxin over a course of 7-9 days led, in all cases, to marked tachycardia (R–R = 0.095-0.090 sec), shortening of the P–Q by 0.002 - 0.003 sec, and of the electric systole (QRST) by 0.020 sec, to reduction of the positive T_2, and tachypnea (see Table 2). Thyroxin also caused marked changes in the behavior of the animals: the rats became more excitable. We noted a sharp loss in weight (by 20-30%).

Under these conditions adrenalin did not cause essential changes in the automatism of the heart over the course of 30-40 min after its injection, but in contrast to the control experiments it caused a shortening of auriculoventricular conduction (−5% instead of +6%). In comparison with the control experiments, its use led to a smaller prolongation of the QRST (9.7% instead of 17.5%).

In 7 out of 11 rats, 60-120 min after the beginning of the experiment, paroxysmal tachycardia and ventricular fibrillation developed, and they died. The action of ephedrine against the setting of large doses of thyroxin also changed. Out of 20 rats, 8 died 40-50 min after the beginning of the experiment. Paroxysmal tachycardia and ventricular fibrillation arose at the time of their deaths.

In analyzing the changes in the EKG preceeding the death of the animals we noted a more intense positive chronotropic action of ephedrine than in the control (shortening of the R–R by 16.7-17.8%), and a shortening of the P–Q, QRS, and QRST intervals, rather than the lengthening seen in the control. We also observed a smaller heightening of the positive T_2 than in the control.

In this series of experiments, acetylcholine caused a small negative chronotropic effect (less than after the small doses of thyroxin), and a more intense prolongation of the electric systole (23% instead of the 11% in the control).

In contrast to acetylcholine, proserine retained its sharply manifested negative chronotropic action in the setting of large doses of thyroxin: the R–R intervals were prolonged by 34-32%. In addition, both proserine and acetylcholine showed a more intense action on the electric systole than in the control or following small doses of thyroxin: the QRST interval was increased by 40% (normally by 11%, after small doses of thyroxin, by 7%).

The results of the experiments show that thyroxin in small doses causes essential changes in the neuro-humoral regulation of the heart and respiration.

The fact that, in the setting of injections of small doses of thyroxin, adrenalin and ephedrine caused a negative chronotropic effect, while acetylcholine and, especially, proserine, having intensified their negative chrono- and dromotropic action, led to the death of a portion of the animals, permits a conclusion to be drawn on the cholinergic direction of the heart's reaction subsequent to the action of small doses of thyroxin.

In the case of large doses of thyroxin, along with signs of elevated sympathoadrenal activity (tachycardia, shortening of the P – Q and QRST, tachypnea, elevation of sensitivity to the sympathomimetics, adrenalin and ephedrine, increased excitability, and weight loss), the cholinergic reactions to acetylcholine and proserine also were intensified, but not to the degree seen after small doses of thyroxin.

The data obtained permit advancing the hypothesis that the elevation in cholinergic activity, observed via the increased reaction to exogenous cholinomimetic preparations and cholinomimetics of endogenous origin, is an important condition for ensuring the elevated activity of the sympathoadrenal system during hyperthyroidism, and is one of its early phenomena.

The certain weakening of the cholinergic reactions that occurs under the influence of large doses of thyroxin may be explained by peculiarities in metabolic changes, characteristic for elevation in the activity of endogenous sympathetic catecholamines.

The simultaneous intensification of the adrenergic and cholinergic effects during hyperthyroidism has a definite pathogenetic significance. Thus, Wise and Hoff [10] explain the genesis of arrhythmias during hyperthyroidism by the "collision" of adrenergic and cholinergic effects.

The results of the experiments with "immobilization" are of interest: with progressive development of the hyperthyroidism the adaptation potentials of the cardiovascular system decreased – the bradycardia and bradypnea decreased in the animals at rest.

SUMMARY

As demonstrated by this work, thyroxin given in low doses (0.007 mg/100 g of weight) augmented the cholinergic reactions – intensified the negative chrono- and dromotropic effect of acetylcholine and especially of proserine. Threshold doses of proserine become fatal in these conditions. Against the low doses of thyroxin, adrenalin and ephedrine produce a vagal effect – a negative chronotropic effect. High doses of thyroxin (160-220 mg/100 g of weight) caused a rise in sympathicoadrenal activity (tachycardia, shortening of P – Q, QRST intervals, tachypnea, and loss of weight); cholinergic reactions in these conditions are also intensified as compared to control tests but not to such an extent as after low thyroxin doses. The role of increased cholinergic activity as a condition provoking intensification of sympathoadrenal reactions in hyperthyroidism is suggested.

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