EFFECT OF SYMPATHOLYTIN (DIBENAMINE) ON THE DEVELOPMENT OF THE HEMODYNAMIC ACTION OF THE THYROID HORMONES

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The hypothetical role of the sympathetic nervous system in the genesis of the symptoms of thyrotoxicosis [5, 10] has led to attempts to relieve these symptoms by means of sympatholytic drugs. The results of investigations along these lines are highly conflicting and in most cases they are not concerned with hemodynamic changes [11, 13, 15].

The object of the present investigation was to study the effects of sympatholytin—an analogue of the well known sympatholytic dibenamine, possessing a marked and prolonged peripheral action [6]—on the hemodynamic changes arising in experimental thyrotoxicosis.*

EXPERIMENTAL

Experiments were conducted on male rabbits weighing 2.5-3.5 kg. The animals were subdivided into four groups: group 1—20 control rabbits; group 2—9 rabbits receiving sympatholytin subcutaneously in a dose of 6 mg/kg every 2 days for 14 days; group 3—20 rabbits receiving thyroid by mouth in doses of 0.4-1.2 g once daily for 14 days; group 4—21 rabbits receiving sympatholytin by the same program as the animals of group 2 and, at the same time, thyroid by the same program as the animals of group 3. The first injection of sympatholytin was given one day before the administration of thyroid began. The degree of blocking of the adrenergic receptors in the rabbits of group 2 was estimated from the severity of the pressor reaction to adrenalin. The animals of the remaining groups were anesthetized with urethane (1 g/kg intravenously) and the pressure was measured by means of an electromanometer in the common carotid artery, the jugular vein, and the left ventricle before and after clamping of the aorta. The heart rate was obtained from the ECG, and the circulation time from the left jugular vein to the left femoral artery measured. The minute volume of the heart [9] and the arterio-venous oxygen difference [8] were determined. Several derivatives were calculated, including the "intensity of functioning of the structures" [4] (the IFS index of Meerson) of the myocardium, determined from the maximal pressure in the left ventricle before and after clamping of the aorta.

EXPERIMENTAL RESULTS AND DISCUSSION

The arterial pressure in the rabbits of groups 1 and 2 was practically identical (95 and 90.8 mm respectively). In response to the intravenous injection of adrenalin in a dose of 2.5 μg/kg, the mean pressure in the control rabbits rose to 136.2 mm, or by 43.3%, while in the animals receiving sympatholytin it rose to only 115.4 mm, or by 27%. Both in absolute terms and as a percentage, the difference between the increases in pressure in these two groups is significant ($P = 0.003$ and 0.001 respectively). Besides the increase in the mean arterial pressure, adrenalin produced a marked increase in the pulse pressure in the rabbits of group 1 (by 14 mm; $P < 0.001$). In the rabbits of group 2 this index remained unchanged ($p = 0.27$). It thus follows that although in these experimental conditions sympatholytin blocked the specific adrenergic receptors incompletely, it considerably weakened the effects of adrenalin. The hemodynamic changes arising under the influence of an excess of thyroid hormones in the rabbits of groups 1, 3, and 4 are compared in the table.

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Some Hemodynamic Indices in the Experimental Animals (M±m)

Index	Group 1 (control)	Group 3 (thyroid)	Group 4 (thyroid + sympatholytin)	P	
				Groups 1-3	Groups 1-4
Minute volume of the heart (in ml/ min/ kg)	268,2±5,6	445,4±23,6	430,0±23,3	<0,001	0,61
Pulse (beats/ min)	283±9,2	417,0±7,8	403±6,7	<0,001	0,61
Stroke volume (in ml)	2,76±0,12	2,77±0,13	2,53±0,13	0,9	0,19
Mean pressure (in mm Hg)	95,0±1,4	118,5±4,2	130,5±4,1	<0,001	<0,05
Work of the left ventricle (in kg/m/ min^{-1})	1,05±0,06	1,91±0,1	1,97±0,12	<0,001	0,69
Peripheral resistance (in dyn. sec. cm^{-5})	9 916±201	8 714±453	10 244±463	<0,02	<0,02
Arteriovenous oxygen differences (in % saturation Hb)	18,6±1,08	22,0±1,98	27,1±1,4	0,4	<0,05
IFS of left ventricle before clamping of the aorta (in mm Hg · g^{-1})	18,1±1,04	22,4±1,26	26,1±1,32	<0,01	<0,05
IFS of left ventricle after clamping of aorta (in mm Hg · g^{-1})	50,1±1,7	39,8±2,1	42,5±1,0	<0,001	0,23
Circulation time (in sec)	3,83±0,11	3,1±0,17	3,29±0,24	<0,007	0,55
Circulating blood volume (in ml)	166,0±1,9	173,6±4,3	151,0±4,1	0,13	0,13
Venous pressure (in mm Hg)	3,9±0,24	3,6±0,26	3,8±0,36	>0,1	0,5
Weight of left ventricle (in g/kg)	1,48±0,05	1,75±0,07	1,74±0,02	<0,001	1
Loss of body weight (in %)	—	18,7±1,6	20,5±1,1	<0,05	0,3

The minute volume of the heart in the rabbits of group 4 exceeded this index in the control group by an amount only a little less than its value in group 3. Sympatholytin not only did not prevent an increase in the mean arterial pressure in the animals receiving excess thyroid, but it actually made the increase greater still. Because of this, the external work of the heart was identical in the rabbits of groups 3 and 4. In the animals of both experimental groups the increase in the minute volume of the heart was due to the tachycardia; the stroke volume in the rabbits receiving thyroid together with sympatholytin actually showed a tendency to fall. The peripheral resistance in the systematic circulation of these animals increased by a greater degree than in the rabbits receiving thyroid alone. In contrast to this last group, the arterio-venous oxygen difference was much higher in the rabbits of group 4 than in the controls. The values of the IFS showed that sympatholytin did not prevent the increase in the contractile function of the heart and the decrease in its functional reserve arising under the influence of an excess of thyroid hormones. The other hemodynamic parameters showed commensurate changes in the rabbits of group 4 with those in the animals receiving thyroid alone. Sympatholytin prevented neither the loss of weight of the animals under the influence of excess of thyroid, nor the increase in the weight of the heart.

The weakening of the sympathetic influences thus prevented neither the onset, nor the development of the hemodynamic changes characteristic of experimental thyrotoxicosis in rabbits.

A fundamental question which arises in the course of the analysis of the hemodynamic changes in animals receiving an excess of thyroid hormones, against the background of weakening of the sympathetic influences is as follows: does this weakening reduce the load falling on the circulatory apparatus in experimental thyrotoxicosis, and does it thereby improve the functional state of the heart muscle?

Sympatholytin very slightly moderated the increase in the minute volume. However, the mean pressure increased by a greater amount, so that the work of the left ventricle increased equally in the rabbits of both experimental groups. In the animals of both groups the functional reserves of the heart evidently fell by the same degree. These findings thus demonstrate that in the present experiments sympatholytin did not reduce the load on the heart and did not facilitate its work. The arterio-venous oxygen difference increased in the animals of group 4, whereas in the animals receiving thyroid alone this increase was observed only in the late and severe stages of thyrotoxicosis, when the heart was evidently no longer able to satisfy the increasing demands of the tissues by an increase in the minute volume [2]. The possibility is not ruled out here that the somewhat smaller increase in the minute volume in the animals of group 4 may reflect the greater exhaustion of the heart muscle, while the larger increase in the systemic pressure is a measure of the compensation for the decrease in the coronary blood flow in the conditions when, as a

result of the reduction in the minute volume, the myocardium is not adequately supplied with oxygen, for the coronary arterio-venous oxygen difference is very small even in normal conditions.

In the present experiments sympatholytin only partly blocked the adrenergic receptors. Its influence could, therefore, be masked by an excessive secretion of endogenous catecholamines or by an increase in the sensitivity or the receptors to these substances in experimental thyrotoxicosis. However, the authors' earlier results [7] do not permit these explanations.

Although some authors [15, 17, 18, 20] have reported alleviation of the manifestations of hyperthyroidism under the influence of procedures and drugs lowering sympathetic tone, others [3, 12, 13, 19, 21, 22] did not observe this effect. The findings described by Yater [16, 23] have apparently provided the solution to the problem of the direct effect of thyroid hormones on the circulatory system. According to Brewster and co-workers [11], for example, many of the cardiovascular manifestations of experimental thyrotoxicosis in dogs could be reversed by epidural procaine block. Yet even in these experimental conditions, it was impossible to restore the normal arterial pressure and oxygen consumption. Furthermore, in these conditions the regulatory and metabolic processes were so disturbed that the body temperature and respiration of the experimental animals had to be maintained artificially. It is obviously difficult here to speak of a specific blocking of the flow of sympathetic impulses [20, 21]. According to de Groot and co-workers [13], neither guanethidine nor reserpine alters the minute volume of the heart when raised in thyrotoxicosis. In relation to the clinical observations that reserpine and other sympathicolytics alleviated the symptoms of thyrotoxicosis to some extent, as V. G. Baranov and co-workers have rightly pointed out [1], the possibility that these agents may possess a thyrostatic action has not been ruled out.

The hypothesis of Brewster and co-workers, according to which the manifestations of thyrotoxicosis "are the result of the physiological effects of adrenalin and noradrenalin," is in conflict with many observed facts including those described in the present paper, and it explains neither the clearly defined effect of the thyroid hormones in vitro, nor the failure of the attempts to use the catecholamines therapeutically in myxedema.

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