INCREASED ACTIVITY OF CENTRAL NORADRENERGIC STRUCTURES IN RATS WITH TRANSIENT SPONTANEOUS HYPERTENSION

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An increase in the excretion of noradrenalin, a decrease in the adrenalin/noradrenalin ratio, an increase in the combined excretion of metanephrine and normetanephrine, and a sharper decrease in the noradrenalin level in the hypothalamus, brain stem, and cerebral hemispheres were found after catecholamine biosynthesis had been blocked by sodium diethyldithiocarbamate in a colony of Wistar rats, aged from 1.5 to 4 months, with well-marked hereditary hypertension. The results, when examined in the light of reciprocity between central-nervous and adrenomedullary catecholamine mechanisms, indicate an increased rate of circulation of cerebral noradrenalin, which may point to the importance of changes in the central noradrenergic activity in the pathogenesis of arterial hypertension

Particular interest in the problem of the pathogenetic significance of changes in catecholamine (Ca) metabolism in hypertension [6, 18] is being paid to the study of the state of central noradrenergic structures [8, 12]. The investigation of these structures is concerned with the possibility of simulating this type of pathology. One of the most adequate experimental models of essential hypertension at the present time is hereditary spontaneous arterial hypertension in albino rats [19]. One of us (M. S. R.) has bred a colony of Wistar rats with the distinguishing feature of having marked hypertension at the age of 1.5 to 4 months, with subsequent return to a normal arterial pressure.

The object of the present investigation was to use this experimental model (described as "transient spontaneous hypertension" TSH) to investigate the biochemical parameters of activity of the central and peripheral catecholamine mechanisms and to examine the results in the light of the writers' views regarding reciprocity between central noradrenergic and peripheral adrenomedullary structures [2, 4].

EXPERIMENTAL METHOD

Experiments were carried out on 25 male rats of the TSH colony aged 3 and 5 months and on 20 normal Wistar rats. Blood pressure was measured by means of a piezoelectric transducer on the caudal artery [9]. The concentrations of adrenalin (A) and noradrenalin (NA) in the tissues and urine were investigated by the trihydroxyindole method [1, 7] with certain modifications [3], and the combined excretion of metanephrine and normetanephrine (MN + NMN) was determined by Pisano's method [20]. The rate of "circulation" of NA was determined from the degree of lowering of the mediator level in the tissues 3 h after intraperitoneal injection of the dopamine-β-oxidase inhibitor sodium diethyldithiocarbamate (DDCS) in a dose of 200 mg/kg.

EXPERIMENTAL RESULTS AND DISCUSSION

During the period of maximal elevation of the blood pressure in the rats of the TSH colony (at the age of 3 months) a higher level of excretion of NA and MN + NMN was found than in the control animals; these

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TABLE 1. Excretion (in μg/day/100 g body weight) of Free Catecholamines and of Combined Metanephrine and Normetanephrine (M±m)

Group of animals	Age (in months)	Weight (in g)	Blood pressure (in mm Hg)	A	NA	A/NA	MN + NMN
Control (6) . . .	3	180±4	103±7	0,07±0,004	0,12±0,016	0,59±0,06	2,8±0,16
TSH (6)	3	192±6	161±5	0,07±0,01 $P>0,5$	0,23±0,016 $P<0,05$	0,31±0,05 $P<0,05$	4,6±0,35 $P<0,05$
TSH (6)	5	230±5	125±9	0,07±0,01 $P>0,5$	0,13±0,03 $P>0,1$	0,54±0,05 $P>0,1$	3,0±0,35 $P>0,1$

TABLE 2. Concentration of Catecholamines in Organs of Rats Aged 3 Months and Effect of DDCS (M±m)

Organ tested	Noradrenalin			Adrenalin		
	control	TSH	P	control	TSH	P
Hypothalamus						
No treatment,	0,96±0,05 (14)	1,1±0,08 (6)	>0,1	0,03±0,01 (14)	0,04±0,01 (6)	>0,1
DDCS	0,66±0,04	0,48±0,07 (6)	<0,05	0,06±0,02 (6)	0,07±0,02 (6)	>0,5
P	<0,01	<0,001		>0,1	>0,1	
Brain stem	0,44±0,012 (4)	0,45±0,024 (3)	>0,5	—	—	—
No treatment,	0,29±0,002 (6)	0,22±0,028 (6)	<0,05	—	—	—
DDCS	<0,01	<0,01		—	—	—
P						
Cerebral hemispheres	0,20±0,01 (6)	0,22±0,02 (6)	>0,1	—	—	—
No treatment,	0,14±0,01 (6)	0,09±0,003 (6)	<0,01	—	—	—
DDCS	<0,05	<0,01		—	—	—
Heart						
No treatment,	0,61±0,04 (6)	0,62±0,07 (6)	>0,5	0,05±0,01 (6)	0,04±0,02 (6)	>0,5
DDCS	0,43±0,07 (6)	0,42±0,06 (6)	>0,5	0,04±0,02 (6)	0,09±0,002 (6)	<0,02
P	<0,05	<0,05		>0,5	<0,05	
Adrenals						
No treatment,	4,1±0,8 (6)	5,2±0,7 (6)	>0,1	19±2,9 (6)	18±2,1 (6)	>0,5
DDCS	3,8±0,5 (6)	4,9±6,4 (6)	>0,1	18±2,9 (6)	17±3,1 (6)	>0,5
P	>0,5	>0,5		>0,5	>0,5	

Note. Number of animals shown in parentheses; catecholamine concentration given in μg/g except in adrenals (in μg/organ).

changes were absent in animals aged 5 months (Table 1). No change in the concentrations of A and NA were observed in the hypothalamus, cerebral hemispheres, brain stem, heart, and adrenals of the TSH rats compared with the control (Table 2). An increase in the excretion of free NA and methoxycatecholamines in the urine, reflecting principally the extramural liberation of neurohormones [2, 16], is evidence of increased sympathico-adrenal activity [14]. Meanwhile the NA level in the tissues, which depends on several different aspects of CA metabolism, does not necessarily reflect changes in the functional activity of adrenergic mechanisms.

The most adequate parameter to reflect the activity of adrenergic structures when the CA concentration in the tissues is investigated is the rate of "circulation" of neuromediators [22]; one way of studying this parameter is by analyzing changes in the NA concentration after its biosynthesis has been blocked. The results given in Table 2 show that the NA concentration in all investigated tissues except the adrenals was lowered 3 h after the administration of DDCS both in the control animals and in rats of the TSH colony. However, the degree of this decrease in the hypothalamus, brain stem, and cerebral hemispheres in the TSH rats was significantly greater than in the control. Since after the blocking of CA synthesis the degree of lowering of the NA reserves depends on the intensity of its utilization, it can be taken that the utilization of NA in the parts of the brain investigated was increased in the TSH rats. With a normal NA level in the tissues the increase in utilization must be compensated by its more rapid biosynthesis. In TSH there is thus an increase in the rate of circulation of NA in the brain, indicating increased activity of the central noradrenergic structures.

The data on CA excretion also agree with this interpretation. One of us (A. M. B.) showed previously that, despite the peripheral genesis of the excreted CA, the direction of the changes in the ratio between A

and NA correlates closely with the state of the central noradrenergic structures, reflecting reciprocity of interaction between the peripheral (adrenomedullary) and hypothalamic catecholamine mechanisms [4]. In particular, a decrease in the relative content of A is regularly observed in emotional disturbances which are characterized by increased central noradrenergic activity. It may therefore be supposed that hereditary TSH is also connected with changes in central catecholaminergic activity, manifested by changes in certain somatic and central nervous functions. From this point of view it is interesting to note that in animals of the TSH colony an increased response to DDCS was found in the adrenomedullary and adrenocortical mechanisms, whose regulation is closely linked with the functional state of the central noradrenergic structures.

Changes in CA metabolism in other experimental models of hypertension (DOCA-salt [11], hemorenal [13], renoprival [21], and suprarenal [10]) differ considerably from those described in TSH, chiefly by the presence of changes in the NA level in the peripheral organs. This could be connected with the leading role of disturbances of water and salt balance in the pathogenesis of these forms of experimental hypertension. In genetically determined hypertension in a colony of rats bred by Japanese workers a decrease in the NA concentration was found in the lower levels of the brain stem [15, 16], and the circulation of NA in the heart was reduced [17]. The results now obtained confirm the view that central noradrenergic structures play an important role in the genesis of arterial hypertension.

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