

SPONTANEOUS TRANSITORY HYPERTENSION  
IN WISTAR RATS

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By inbreeding between a hypertensive Wistar male and normotensive Wistar female rat a colony of rats was obtained in which arterial hypertension was observed between the ages of 1.5 and 4 months (maximal arterial pressure 145-170 mm Hg compared with the normal 100-120 mm Hg). In the males the mean values of the arterial pressure were higher than in the females. By the age of 5-6 months the arterial pressure was at the normal level. At the period of maximal arterial pressure no macroscopic changes in the internal organs nor changes in their weight were seen compared with normotensive Wistar rats. No differences were found in the plasma concentrations of sodium, potassium, and chlorides or in the distribution of sodium and potassium between the intra- and extracellular fluid in the heart. In rats with spontaneous transitory hypertension there was a larger increase in the plasma 11-hydroxycorticosteroid concentration after injection of the dopamine- $\beta$ -oxidase inhibitor sodium diethyldithiocarbamate.

Inherited arterial hypertension in animals is a model suitable for use when studying the genetic basis and pathophysiological mechanisms of this state. Strains of rabbits [4], dogs [16], and rats [7, 13, 15] with hereditary arterial hypertension have been described. Rats are the most interesting of these animals because of their relatively short reproductive cycle and because it is possible to investigate large groups of animals. Rats with hereditary hypertension are distinguished by a number of features: elevation of the

arterial pressure in animals of the Dahl strain arises only after administration of an excess of NaCl, whereas in rats of the Okamoto strain the hypertension is independent of the salt intake [10]. Animals of the Smirk strain differ in the increased reactivity of their vessels to the action of pressors [9, 12], which is not found in rats of other strains [6].

In the investigation described below an attempt was made to breed a colony of rats with hereditary hypertension and to study some indices of electrolyte and corticosteroid metabolism in these animals.

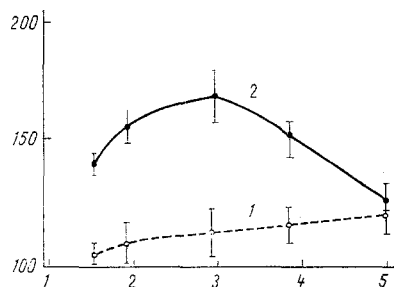


Fig. 1. Age changes in arterial pressure in male Wistar rats with normal (1) and raised (2) arterial pressure. Short vertical lines represent limits of variations of parameter at different age periods. Abscissa, age of animals (in months); ordinate, maximal arterial pressure (in mm Hg).

## EXPERIMENTAL METHOD

The maximal arterial pressure was measured by means of a piezoelectric pulse sensor on the tail in animals lightly anesthetized with ether [3]. The sodium and potassium concentrations in the blood plasma and tissues were determined by flame photometry. The distribution of electrolytes between the intra- and extracellular fluid, allowing for the chloride space [2, 11], was calculated by the equations of Cort and Fencle [5]. The plasma

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TABLE 1. Sodium and Potassium Concentrations in Blood Plasma and Heart of Rats of Different Groups ( $M \pm m$ )

Group of animals	Arterial pressure (in mm Hg)	Blood plasma			Heart			
		sodium	potassium	chlorides	Na <sub>e</sub>	Na <sub>i</sub>	K <sub>e</sub>	K <sub>i</sub>
		meq/liter			meq/100 g weight of dry, defatted tissue			
Intact (n=12)	100±2,2	131±3,1	5,4±0,8	100±4,5	11±0,4	2,2±0,5	0,43±0,03	25±4,6
Spontaneous transitory hypertension (n=13)	158±4,8	140±4,1	5,9±0,7	107±2,2	14±2,3	3,1±0,4	0,42±0,01	31±4,2
Suprarenal hypertension (n=8)	145±9,0	136±5,8	5,1±0,8	103±5,8	10±0,6	5,7±0,2*	0,43±0,02	26±1,9
Metopirone hypertension (n=8)	160±6,6	127±6,2	5,1±0,9	106±6,4	10±0,6	7,1±0,3*	0,43±0,12	24±1,8

Legend: Na<sub>e</sub>, K<sub>e</sub>) extracellular; Na<sub>i</sub>, K<sub>i</sub>) intracellular sodium and potassium.

\* Difference between indices for intact rats significant ( $P < 0.01$ ).

TABLE 2. Effect of Sodium Diethyldithiocarbamate on 11-Hydroxycorticosteroid Level (in g%) in Blood Plasma of Rats ( $M \pm m$ )

Group of animals	Untreated	3 h after injection of sodium diethyldithiocarbamate	P
Intact . . . . .	28±3,6	75±2,0	<0,001
Spontaneous transitory hypertension . . . . .	30±4,2	92±3,4	<0,001
P	>0,1	<0,05	

11-hydroxycorticosteroid level was determined fluorimetrically [1]. Suprarenal hypertension in rats was produced by piercing both adrenals with a silk thread soaked in turpentine. The animals were studied four weeks after the operation. Metopirone hypertension was induced by intraperitoneal injection of 100 mg/kg metopirone (Ciba) once a day for 6-8 days. The rats of this group received 1% NaCl solution to drink.

## EXPERIMENTAL RESULTS

Examination of the group of Wistar rats at the age of two months revealed a male with a maximal arterial pressure of 170 mm Hg. (The normal pressure for rats of the corresponding age and weight is  $100 \pm 2.2$  mm Hg.) This parameter remained unchanged for two months, although the animals showed no external pathological feature. Four litters (first generation) numbering 22 individuals (12 males and 10 females) were obtained from this male and a Wistar female with normal arterial pressure. Arterial hypertension was found in 50% of the animals at the age of two to four months: the maximal arterial in the males was  $165 \pm 4.6$  mm, in the females  $145 \pm 3.1$  mm Hg.

It was hoped by selective inbreeding to obtain two colonies consisting of hypertensive and normotensive rats of the same clan, but the results showed that in the second generation hypertensive individuals were found equally frequently (67%) in both groups. Subsequently the normotensive individuals were rejected. In the third and fourth generations the frequency of arterial hypertension came close to 75%.

The most characteristic feature of this colony was the transitory character of the hypertension (Fig. 1), which was observed starting from 1.5 months (when the arterial pressure could first be measured by the method used) and not beyond the age of five months. This type of pathology was described as "spontaneous transitory hypertension." It is interesting to note that in the male ancestor of this colony the arterial pressure at the age of six months, i.e., at the time when the progeny was obtained, also was normal.

At necropsy on the animals no macroscopic changes were found in the internal organs. The weight of these organs was the same as that of the normotensive rats.

In spontaneous transitory hypertension, unlike in other types of experimental hypertension in rats (when the level of intracellular sodium in the heart is increased), there was no change in the concentration of electrolytes in the plasma or in their distribution between the intra- and extracellular fluid in the heart (Table 1).

In rats with spontaneous transitory hypertension the initial plasma 11-hydroxycorticosteroid level was unchanged although the response to injection of sodium diethyldithiocarbamate was considerably increased (Table 2).

Activation of the pituitary-adrenocortical system by substances blocking catecholamine biosynthesis, including the dopamine- $\beta$ -oxidase inhibitor sodium diethyldithiocarbamate, is associated with inhibition of hypothalamic noradrenergic mechanisms [8, 14]. These results are indirect evidence that the activity of these mechanisms is increased during spontaneous transitory hypertension.

A colony of rats was thus obtained with significant elevation of the arterial pressure at an early age and with disturbance of the reactivity of at least one link in the chain of central regulation of endocrine functions.

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