ARTERIAL PRESSURE CORRECTION IN RATS WITH INHERITED HYPERTENSION BY MODIFICATION OF CATECHOLAMINE METABOLISM IN EARLY ONTOGENY

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It has been shown on SHR rats with inherited hypertension that changes in catecholamine mechanisms take place in the relatively early period of individual development [1] and that persistent hypertension may be formed as early as the 8th-10th week of life [7, 12]. It is claimed that an essential role in the pathogenesis of the raised blood pressure (BP) of such animals may be played by weakening of the sympathicoinhibitory tone of central noradrenergic mechanisms [13]. Profound changes in the function of central noradrenergic structures have been found by the writers in rats of a different line, with inherited arterial hypertension (inherited stress-sensitive arterial hypertension, ISSAH), which is evidently one of the leading causes of the lasting elevation of BP in these animals [3]. The writers showed previously that changes in catecholamine metabolism at certain periods of early ontogeny are accompanied by long-term modification of the noradrenergic system of the brain [14].

The aim of this investigation was to seek to obtain possible normalization of BP in rats with inherited hypertension by short-term intervention in catecholamine metabolism in early ontogeny.

EXPERIMENTAL METHOD

The investigation was conducted on rats with inherited hypertension (ISSAH line) belonging to the 16th, 17th, and 18th generations of breeding. This line was obtained by breeding Wistar rats on the basis of their BP level under conditions of emotional stress [2]. On the 7th-9th, 14th-16th, 21st-23rd, or 21st-25th days after birth the young rats were given daily intraperitoneal injections of an aqueous suspension of the dopamine precursor L-dopa (Reanal, Hungary) in a dose of 1 mg/10 g body weight. Intact animals or young rats receiving injections of 0.1 ml distilled water/10 g body weight served as the control. To inhibit noradrenalin synthesis, some rats were given an injection of a suspension of the dopamine-β-hydroxylase inhibitor SLA-59 (Serva, West Germany) in a dose of 0.15 mg/10 g body weight, made up in 0.5% Tween-80 (Ferak, West Germany) at the age of 21-25 days, 3 h before the injection of L-dopa. The control animals of this group received injections of 0.1 ml Tween, followed by distilled water, in a volume of 0.1 ml/10g body weight, 3 h later. On the 30th day after birth the young rats (6-8 in a litter) were weaned. At the age of 40 days the young rats were separated by sex and formed into randomized groups with eight animals in each group. Experiments were carried out on males aged 4-4.5 months, placed in individual cages 1 week before the experiment began.

BP was measured with a sphygmomanometer in the tail at rest and after emotional stress, as described previously [2]. Emotional stress was induced by immobilizing the rats in a constraining wire cylinder for 30 min. The results were subjected to statistical analysis by Student's t test.

EXPERIMENTAL RESULTS

Daily injections of the dopamine precursor L-dopa into young rats aged 7-9 or 14-16 days, belonging to the 16th generation of breeding, were not accompanied by any change in BP of these

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TABLE 1. BP in Adult ISSAH Rats after Modification of Catecholamine Metabolism on the 21st-25th Days of Life (M ± m)

Experimental conditions	BP, mm Hg	
	initial	during stress
Intact rats	171±3,0 (27)	200±2,7 (28)
Water	173±2,5 (25)	198±3,2 (27)
L-dopa	156±2,2 (30)*	179±2,6 (30)*

Legend. Number of animals shown between parentheses. *p < 0.001 compared with corresponding control.

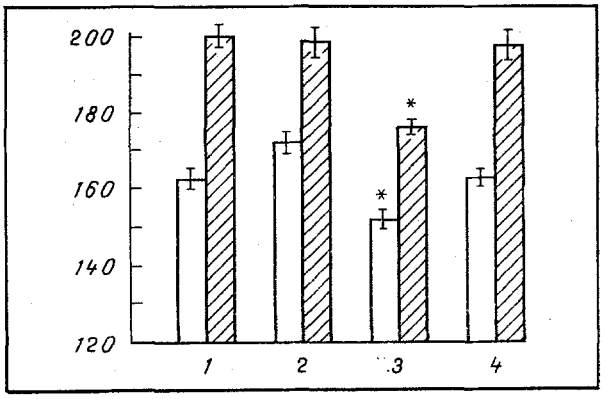

Fig. 1. BP (in mm Hg) of adult ISSAH rats after blocking of noradrenalin synthesis on the 21st-25th days after birth. Unshaded columns — initial BP, shaded — during emotional stress. 1) Intact rats; 2) injection of solvent; 3) L-dopa; 4) FLA-59 + L-dopa. Each group contained 18 animals. *) Significant differences from 1, 2, and 4.

animals at the age of 4-4.5 months compared with rats receiving injections of water at the same times. All the animals had an equally high BP. Meanwhile injection of L-dopa on the 21st-23rd day of postnatal development caused a significant fall of BP in the adult rats compared with the hypertensive control (152 ± 3.4 and 178 ± 6.8 mm Hg respectively, $p < 0.01$). A similar tendency also was observed under conditions of emotional stress.

The results are evidence that, in principle, BP can be lowered in adult hypertensive rats by intervention in catecholamine metabolism in early ontogeny. On the basis of these data it can also be postulated that the 4th week of postnatal development of rats is a sensitive period when intensification of catecholamine synthesis may lead to prolonged lowering of BP. Incidentally, by this age the catecholamine systems of the brain [5] and sympathetic nervous system [1] are not yet completely formed in rats.

In the next experiments the effects of modification of catecholamine metabolism in young ISSAH rats at the 4th week of life were studied. The duration of intervention was increased to 5 days.

Daily injections of the dopamine precursor into rats of the 17th breeding generation on the 21st-25th days after birth likewise were accompanied by a distinct and prolonged effect on BP. In these animals the initial BP at the age of 4-4.5 months was significantly lower than in intact hypertensive rats and in animals receiving injections of water at the same times. Under these experimental conditions the response of BP to emotional stress also was depressed. A similar pattern was observed in experiments on rats of the next breeding generation. The similarity between results obtained on hypertensive animals of the 17th and 18th breeding generations enabled these data to be pooled (Table 1). The results are evidence that potentiation of catecholamine synthesis in the 4th week of life of ISSAH rats is accompanied by prolonged and lasting lowering of BP both at rest and during emotional stress.

Positive attempts to lower BP in rats with spontaneous inherited hypertension by intervention during early ontogeny also were undertaken previously. However, neurotoxic poisons were injected for this purpose: 6-hydroxydopamine [8, 10], which, if administered centrally, destroys nerve endings predominantly of brain noradrenergic neurons, and sodium glutamate [9], which causes degeneration of neurons of the hypothalamic arcuate nuclei, or guanethidine, peripheral administration of which, together with antibodies to nerve growth factor, is accompanied by destruction of the sympathetic nervous system in rats with hypertension [6]. The use of the natural dopamine precursor, which is also used in clinical practice, is therefore undoubtedly more appropriate.

Since injection of L-dopa is accompanied by potentiation of dopamine synthesis, and dopamine is easily converted into noradrenalin, these experiments could not give the answer to the question of the role of each endogenous catecholamine in the weakening of arterial hypertension in ISSAH rats. In the next series of experiments, rats of the 18th breeding generation received, together with L-dopa, the dopamine-β-hydroxylase inhibitor, preventing conversion of dopamine into noradrenalin, on the 21st-25th days after birth. Administration of FLA-59 3 h before injection of L-dopa completely blocked the BP-normalizing effect of the dopamine precursor. In these animals BP at the age of 4-4.5 months, both in the initial state and during emotional stress, was significantly higher than in animals receiving L-dopa alone in the early period of development, and was indistinguishable from BP in intact hypertensive rats (Fig. 1).

Thus, both at rest and during emotional stress, lowering BP in animals with inherited hypertension, the effect of L-dopa, injected in early ontogeny, is realized through intensification of noradrenalin synthesis in the 4th week of the postnatal period of individual development.

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