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REACTIVITY OF THE HYPOTHALAMO-HYPOPHYSEO-ADRENOCORTICAL SYSTEM IN RATS WITH INHERITED ARTERIAL HYPERTENSION

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In the study of the causes and pathogenesis of arterial hypertension, great attention has been paid in the literature to analysis of stressor reactivity [2, 10, 11]. In many publications a setate of stress is regarded as an important factor leading to the development of arterial hypertension [2-4, 8, 12]. This is connected with the fact that stress hormones such as adrenalin and gluco- and mineralocorticoids play a direct part in the regulation of blood pressure (BP). Increased stressor reactivity may therefore by one of the most important causes of development of essential hypertension. It has been shown [5] that the level of stressor reactivity in populations of experimental animals (rats or mice) is highly variable, largely due to genetic factors. Consequently, selection for raised BP under conditions of stressor stimulation has been possible [7]. As a result a population of rats with inherited stress-induced arterial hypertension (ISIAH) has been obtained, in which the systolic BP in the 15th generation of selection was 183 ± 2.9 mm Hg. With the appearance of this model of essential hypertension, the way was open for experimental research in several directions [6, 7].

The aim of this investigation was to study reactivity of the hypothalamo-hypophyseo-adrenocortical system (HHAS) to stress and to stimulation of the neurochemical mechanisms of the brain in rats with ISIAH.

METHODS

Experiments were carried out on male rats aged 5-6 months of two genetic groups: with ISIAH (15th generation of selection) and Wistar rats, from which rats with ISIAH were obtained by selection.

One week before the experiment the animals were put into single cages. Emotional stress was induced by placing the animal for 1 h in a cylindrical wire cage, which restricted the movements of the rat drastically (restriction). Combined stress was induced as follows: for 2 min the rat was exposed to ether vapor and 1 ml blood was quickly taken from the tip of the tail, after which the rat was placed in an unfamiliar situation for 1 h. In both the 1st and the 2nd cases, 1 h after the beginning of exposure to stress blood samples were taken from the tip of the tail to measure the concentration of 11-hydroxycorticosteroids (11-HCS). After a recovery period of 5 days, steel guiding microcannulas were inserted into the lateral ventricle of the brain, and 4 days later the response of the HHAS to intraven-

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TABLE 1. Plasma 11-HCS Concentration (in μg %) of Wistar and ISIAH Rats ($\bar{S} \pm m$)

Experimental conditions	Wistar rats	Rats with ISIAH
Resting state (basal level)	10,0±1,45 (10)	11,4±1,68 (13)
Restriction of movements (emotional stress)	29,4±2,00 (11)	18,2±2,26*(15)
Combined stress	26,3±3,03 (9)	36,6±3,23*(10)
Intraventricular injection of		
Physiological saline	9,9±1,04 (9)	10,0±1,11*(8)
Noradrenalin	25,3±2,56 (9)	17,1±2,36*(7)
Carbachol	37,7±4,16 (6)	40,5±4,16*(6)
Serotonin	18,1±3,22 (4)	20,7±2,20*(8)

Legend. Number of animals shown in parentheses. *P < 0.05 for interlinear differences.

tricular injection of substances simulating the action of one of the three neurotransmitters was investigated: 10 μg noradrenalin bitartrate, 100 μg serotonin creatinine-sulfate, or 1.5 μg carbachol in 10 μl of physiological saline. Rats receiving an injection of physiological saline alone, at pH values corresponding to the experimental series, served as the control. The animals were decapitated 1 h after the intraventricular injection and blood samples were taken for measurement of the 11-HCS concentration in the plasma by a fluorometric method [15] and on a Specol (East Germany) spectrofluorometer fitted with FÉU-36 photoelectric multiplier.

RESULTS

The results of the study of adrenocortical function of the experimental animals are given in Table 1. The plasma 11-HCS concentration of the rats at rest was virtually the same. During stress, however, significant differences were noted. Differentiation of the genotypes is mainly linked with the fact that rats with ISIAH respond differently depending on the nature of stressor stimulation. Under conditions of emotional stress induced by limitation of movement, their response was less marked than that of Wistar rats. Combined stress, on the other hand, led to higher elevation of the 11-HCS level in rats with ISIAH. Consequently, selection for a raised BP under conditions of emotional stress is accompanied by changes in the response of the adrenal cortex; these changes, however, differ qualitatively and their trend is largely determined by the characteristics of stressor stimulation.

An experimental model of arterial hypertension, namely rats of the SHR (spontaneously hypertensive rats) line, is widely used to investigate the pathogenesis of essential hypertension.

Investigation of the adrenocortical response of these animals revealed a picture very similar to that described above for rats with ISIAH. Compared with WKY rats, from which the SHR line was obtained, showed that the response of SHR rats to immobilization is relatively depressed [13], whereas the corticosteroid response to stressor stimulation of SHR rats by electric shocks was higher than that of WKY rats [13, 14].

As in investigations by other workers, so also in the present study the effect of the character of stressor stimulation on the magnitude of genetically determined differences in adrenocortical function could be identified. This effect is evidently linked with differences in the neurochemical mechanisms of activation of the pituitary adrenal system in different types of stress [9] and with differences in the correlated changes of these mechanisms as a result of selection. This hypothesis is confirmed by data obtained in the present investigation after intraventricular injection of the preparations (Table 1).

Injection both of carbachol and of serotonin into the lateral ventricle was accompanied by marked and similar changes in HHAS function in the animals of these two genetically different groups. Meanwhile, in response to injection of noradrenalin under the same conditions the blood 11-HCS level of the rats with ISIAH was significantly lower than in Wistar rats.

It can therefore be tentatively suggested that depression of the response of the HHAS to excitation of noradrenergic mechanisms of the brain may be the cause of weakening of the adrenocortical response in these animals to emotional stress induced by restriction of movement in a constricting cage. Significant correlation between the response of the rat HHAS to intraventricular injection of noradrenalin and the reaction of these animals to emotional stress, induced by restriction of movements [1], was demonstrated previously. Meanwhile no such correlation was present after intraventricular injection of serotonin and carbachol [1]. Consequentely, it can be postulated that as a result of selection for raised BP, under conditions of emotional stress.

The fact that the noradrenergic system of the brain can be considerably modified by selection for BP is confirmed by abundant data in the literature [6]. It is considered that this mechanism may lie at the basis of formation of hypertensive states in SHR rats, and also at the basis of changes in other physiological functions and, in particular, behavior in animals with hereditarily determined arterial hypertension.

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