Aldosterone and Stress-Dependent Arterial Hypertension

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Secretory activity of the adrenal cortex and hormonal reaction to emotional stress were examined in normotensive WAG and hypertensive ISIAH rats. Under nembutal narcosis (surgical stage), secretion of corticosteroid hormones and hormonal reaction to acute stress in hypertensive rats were enhanced. In these rats, the stress-induced elevation of aldosterone secretion was most pronounced, which indicates an important contribution of this hormone to the pathogenesis of stress-dependent arterial hypertension.

Key Words: *arterial hypertension; stress; adrenocortical hormones*

Discovery of aldosterone [8] and realizing its role as a vitally important hormone responsible for the maintenance of the basic parameters of the water and salt homeostasis and blood circulation culminated in the conception of its involvement in the pathogenesis of hypertension. Even the first reports on aldosterone [3] hypothesized that primary hypertension is the state caused by small albeit sustained overproduction of aldosterone (aldosteronism). In the following, enhanced secretion of aldosterone was considered as an attribute of the secondary forms of arterial hypertension initiated by the hormone–producing tumors of the adrenal glands (Conn's syndrome) or some renal diseases accompanied by aldosterone overproduction. Hypertonic patients do not demonstrate the overt signs of aldosteronism (hyperaldosteronism). At present, etiology of essential hypertension responsible for 90% cases of the disease is not established, although the risk factors that clearly promote the development of hypertension while not being its primary triggers are well known. These factors include genetic predisposition and numerous environmental factors such as dietary peculiarities, sedentary life, chronic stress, tobacco smoking, some related diseases (obesity, diabetes mellitus), *etc*. However, the role of aldosterone in the pathogenesis of essential hypertension again attracted much attention [2,5,9]. Admitting chronic stress as a key risk factor of the development of hypertension and cardiovascular diseases, the researchers [5] consider such hormones as epinephrine and to some extent cortisol as the basic triggers of numerous stress-induced cardiovascular complications, although aldosterone is also intensively produced during these pathologies probably in cooperation with ACTH as an agent promoting aldosterone synthesis. Still, by analyzing the mechanisms of stress effects on the hearts and blood vessels, the possible up-regulation of aldosterone synthesis is ignored [5].

Our aim was to assess possible contribution of aldosterone into pathogenesis of stress-dependent type of arterial hypertension in ISIAH rats.

MATERIALS AND METHODS

The experiments were carried out on male ISIAH (inherited stress-induced arterial hypertension) and WAG (normotensive control) rats aging 5-6 months. The ISIAH rats were obtained in Institute of Cytology and Genetics from the outbred Wistar line by selection according to AP level attained during the emotional stress. These rats demonstrate the baseline hypertension and attain a high AP upon mild emotional stress [6]. The animals were maintained under the standard vivarium conditions with natural day-night cycle and food and water *ad libitum*. They were randomized

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into three groups. The examined processes and indices were secretory activity of the adrenal glands (group 1 rats comprising 13 ISIAH and 7 WAG animals); reaction of the glucocorticoid and mineralocorticoid hormones to acute emotional stress (group 2 with 10 rats of every line); and the baseline (control) indices of hormone concentration in blood plasma (group 3 with 10 rats of every line).

Laparotomy was performed under intraperitoneal nembutal narcosis (50 mg/kg body weight). The left suprarenal vein was ligated in the place where it drains into the renal vein, thereafter a Teflon catheter was introduced into the suprarenal vein. After closing the operative wound, the blood samples flowing from the adrenal gland were collected into heparinized test tubes. The amount of drawn blood was 1.3-1.5 ml. Then the second (right) adrenal gland was excised for the following measurement of tissue hormonal concentration in the gland. The blood entered the test tube freely and without obvious obstacles. The duration of blood drawing procedure was recorded to calculate the volume flow across the adrenal gland. The value of plasma flow necessary to determine secretion of the plasma hormones was calculated from the venous hematocrit. Concentrations of corticosteroid hormones in blood plasma and adrenal glandular tissue were determined by HPLC in an Agilent 1260 chromatograph equipped with a photodiode array ultraviolet detector and a Zorbax Extend C18 column. This technique made it possible to measure concentration of aldosterone, corticosterone, 11-dehydrocorticosterone, and 11-deoxycorticosterone in the adrenal tissue and in the blood flushing it.

Group 2 rats were subjected to acute stress. The animals were placed into a large tank with a cotton soaked in ether on the bottom. After 7 minutes, the blood was drawn from the caudal vein to assay corticosterone and aldosterone.

In group 3 rats, the baseline (control) concentrations of corticosterone and aldosterone were determined after instantaneous decapitation. In groups 2 and 3 rats, the concentrations of corticosterone and aldosterone in blood plasma were measured using Aldosterone ELISA Kit and Corticosterone EIA Kit.

The data were processed statistically using Student's *t* test for small independent samples.

RESULTS

In ISIAH rats, the weight of right adrenal gland was significantly greater than that in normotensive WAG rats (Table 1). The left adrenal gland was not weighted because it was disturbed by manipulations needed to cannulate the suprarenal vein. It can be hypothesized that selection of the rats according to enhanced reaction of AP to stress was accompanied with potentiation of total functional activity of the adrenal glands. It is corroborated by the values of the secretory activity of the adrenal cortex assayed in rats under surgical stage narcosis with the help of cannulated suprarenal vein (Table 1). In ISIAH rats, secretion of corticosterone, 11-dehydrocorticosterone, and 11-deoxycorticosterone was significantly greater (almost 2-fold for the two latter hormones) than that in WAG rats. Thus, selection of rats resulted in pronounced up-regulation of adrenal hormone secretion. However, secretion of aldosterone was virtually identical in both strains. Paradoxically, the content of all examined hormones in adrenal tissue of ISIAH rats was only insignificantly higher than that in Wag rats. Probably it indicates that these hormones are not stored in the gland being secreted into the blood stream immediately after synthesis.

TABLE 1. Adrenal Gland Weight, Hormone Content in Adrenal Tissue (ng), and Hormone Secretion (ng/min) in WAG and ISIAH Rats ($X \pm m$)

Index	WAG rats	ISIAH rats	Significance of WAG/ISIAH line differences
Weight of right adrenal gland	20.4±0.7 (16)	24.4±1.3 (15)	T=2.71; $p<0.05$
Aldosterone, ng	11.8±2.0 (14)	18.3±2.7 (15)	NS
11-Dehydrocorticosterone, ng	27.3±2.5 (14)	30.7±4.8 (15)	NS
Corticosterone, ng	690±56 (14)	755±41 (15)	NS
11-Deoxycorticosterone, ng	175±12 (14)	201±11 (15)	NS
Aldosterone, ng/min	2.1±0.4 (7)	2.3±0.2 (13)	NS
11-Dehydrocorticosterone, ng/min	14.4±3.1 (7)	29.1±5.4 (13)	T=2.36; $p<0.05$
Corticosterone, ng/min	519±61 (7)	769±83 (13)	T=2.43; $p<0.05$
11-Deoxycorticosterone, ng/min	45.6±6 (7)	87±12 (13)	T=3.09; $p<0.01$

Note. The brackets show the number of animals; NS means "not significant".

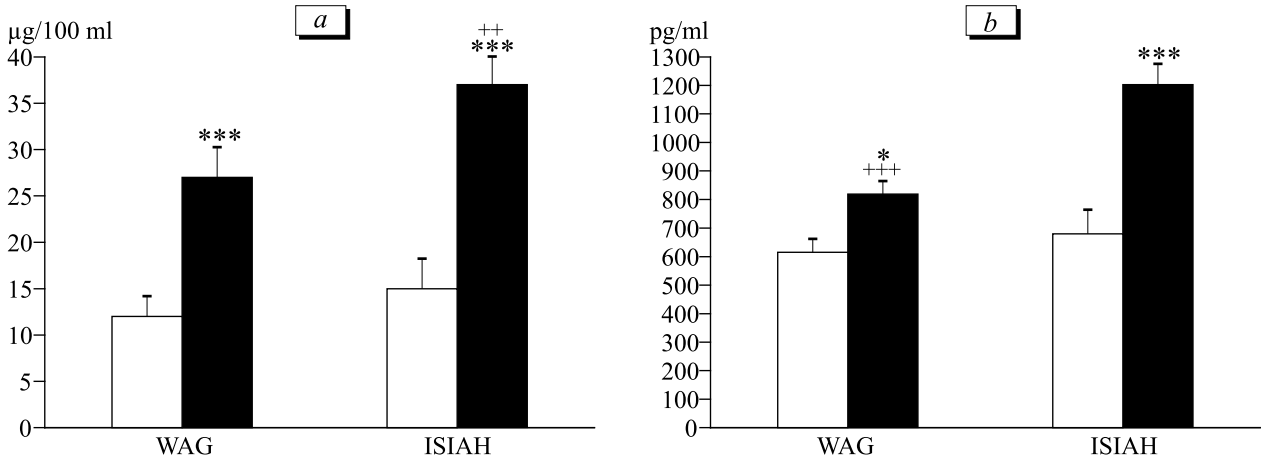

Fig. 1. Concentrations of corticosterone (*a*) and aldosterone (*b*) in blood plasma of WAG and ISIAH rats in control (open bars) and during acute stress (closed bars). **p*<0.05, ****p*<0.001 compared to the control; ++*p*<0.01, +++*p*<0.001 compared to the corresponding index of other rat strain.

The hormonal responses of ISIAH and WAG rats to a 7-min stress were instructive (Fig. 1). It is worthy to note that the baseline concentrations of corticosterone and aldosterone in the plasma of peripheral blood were virtually identical in both strains. In agreement with previous data [7], stress elevated the concentrations of both hormones in ISIAH and WAG rats, although there were certain peculiarities in the observed reaction. First, the increment of corticosteroid concentration in blood plasma of ISIAH rats was significantly greater than that in WAG rats. Second, the increment of concentration of the major mineralocorticoid (aldosterone) in WAG rats induced by acute and mostly emotional stress was smaller than elevation of corticosterone, while in ISIAH rats, the stress-induced increment of aldosterone concentration was pronounced and significantly greater than the corresponding response in WAG rats. This accentuated mineralocorticoid response to emotional stress in hypertensive rats indicates aldosterone as a key player in pathogenesis of stress-dependent arterial hypertension. Enhancement of mineralocorticoid function in ISIAH rats can be also supported by enhancement of 11-deoxycorticosterone secretion found in this study. The growing evidence appears in literature indicating an important role of elevation of aldosterone concentration in pathogenesis of essential arterial hypertension. The pronounced response of aldosterone to stress in hypertensive rats found in this study indicates the crucial role of this pathogenetic mechanism in the development of stress-dependent form of hypertension, which is reproduced in the genetically selected ISIAH rats.

Our data agree with some studies on humans. The research revealed an enhanced hormonal (mineralocorticoid included) reaction to psychological stress both in hypertensive patients and in the individuals with normal AP but with hypertensive parents [4]. Some researchers stated that despite the absence of established signs of hyperaldosteronism incommensurate to other indices of activated renin system, elevation of aldosterone is still involved in pathogenesis of primary hypertension [9]. Such cases are characterized by elevation of aldosterone that does not surpass the upper normal limit and an increase of aldosterone/renin ratio. This elevation of aldosterone (relative to the level of renin) probably indicates the greater role of ACTH in stimulation of aldosterone secretion in patients with stress-dependent hypertension, which agrees with enhanced response of aldosterone to stress and down-regulation of renin gene expression in renal tissue of ISIAH rats [1].

Thus, examination of corticosteroid profile in ISIAH rats characterized by stress-dependent arterial hypertension indicated pronounced contribution of enhancement of mineralocorticoid function of adrenal cortex into pathogenesis of stress-dependent type of arterial hypertension. Probably, a similar mechanism of the development of hypertension takes place in humans with enhanced responsiveness of AP to stress stimuli. Taken these data into consideration, the respective patients can be recommended to use more adequate therapy with the anti-aldosterone drugs.

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