Endocrine Functions in Hypertensive Rats of the NISAG Strain Exposed to Epinephrine

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Endocrine functions were investigated in normotensive (Wistar) and hypertensive (NISAG) rats before and on days 3, 7, and 21 after subcutaneous epinephrine administration. Rats of the NISAG strain are characterized by elevated plasma levels of aldosterone and thyroxine and lowered plasma levels of immunoreactive insulin, and their endocrine system develops a much stronger response to a single epinephrine injection than does that of Wistar rats. This is manifested in a still higher aldosterone level, elevated corticosterone and insulin concentrations, and reduced thyroxine content in the plasma.

Key Words: *hereditary arterial hypertension; endocrine system; response to epinephrine*

Although the endocrine system is known to be implicated in the pathogenesis of essential hypertension, the question as to whether the highly varied endocrine changes seen in this condition are primary or secondary remains a subject of debate which, in addition to being of theoretical interest, has direct relevance to medical practice [2]. Important information bearing heavily on this question has come from studies with the genetic models of essential hypertension provided by rats of different strains produced by controlled breeding of animals with particular levels of arterial pressure (AP) [10]. The evidence in hand permits two generalizations to be made. First, genetically hypertensive rat strains vary widely in the characteristics of their endocrine functions. Second, there are also substantial differences between evaluations of altered endocrine functions as possible etiological factors in different strains. For example, impaired steroidogenesis involving boosted production of 18-OH-DOC by the adrenal cortex is regarded as a primary cause of AP elevation (provoked by increased NaCl intake) in the DS strain [12], whereas alterations in adrenal function are viewed as being secondary to the hypertension in the SHR strain, which is currently the most popular animal model of human hypertensive disease [14]. In short, while elevated AP is a feature shared by all animal models of human hypertension, different models show important differences in endocrine characteristics. If essential hypertension is understood to be an inherent or hereditary pathological condition, then its considerable heterogeneity, both genetic and pathophysiological, must be recognized. Consequently, different animal models of hereditary hypertension can furnish information on different mechanisms by which the hypertensive status is established, and each inbred strain in fact reproduces in pure form a particular variety of hypertension.

As previously reported [3,11], we developed a rat strain (called NISAG) characterized by stress-sensitive hypertension that closely mimics the stress-dependent form of human hypertension. In the present study we compared endocrine functions in NISAG rats with those in Wistar rats, with particular reference to the effects of epinephrine, which is a stress hormone and is directly involved in cardiovascular regulation.

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MATERIALS AND METHODS

Adult (aged 5-6 months) male rats of hypertensive NISAG and normotensive Wistar populations were used. Endocrine functions were evaluated both before and on days 3, 7, and 21 after a single epinephrine injection (2 mg/kg body weight subcutaneously) by measuring, immediately after instantaneous decapitation, the plasma concentrations of the following hormones: aldosterone, insulin, thyroxine (T_4), and triiodothyronine (T_3) by the radioimmunoassays and corticosterone by the method of competitive protein binding to labeled ligand. The significance of mean intergroup differences was assessed by Student's *t* test. Each test series consisted of 9-12 rats of either strain.

We found earlier [4] that epinephrine at the 2 mg/kg dose level causes metabolic damage to the myocardium in rats, leading to its focal necrotization (myocardial infarction model) with consequent circulatory disturbances. In the present study, therefore, endocrine responses were in effect being compared in NISAG and Wistar rats with experimental myocardial infarction. As indicated by ECG data, the myocardium of NISAG rats appears to be more prone to damage because the cardiovascular system is initially altered in this strain [6].

RESULTS

Baseline characteristics of endocrine functions. The endocrine status of intact NISAG rats (Table 1) is characterized by significantly elevated aldosterone and T_4 concentrations in the peripheral blood plasma. Such changes in endocrine function can be regarded as one of the pathogenetic mechanisms underlying the hypertensive status in NISAG rats. It has been shown that enhanced mineralcorticoid function, manifested in raised plasma aldosterone, may be a cause of some forms of hypertension in man [1] as well as in experimental animals [13]. This also appears to be true of elevated plasma T_4 [8]. Indeed, hyperthyroidism may be associated with the development of a hypertensive state; thus, an overactive thyroid has also been described in hypertensive LH and Munster rats; moreover, the development of hypertension in these strains can be prevented by thyroidectomy [9].

In line with the general concepts of endocrine shifts in hypertension is also a drop of plasma insulin. In NISAG rats, depressed insulin levels may be linked with the elevated sympathetic tone, which may in turn be responsible for inhibition of insulin secretion via the α-adrenoceptors. Previously, we detected a lowered glucose tolerance in hypertensive rats [5]. This finding, together with that of depressed plasma insulin, suggested that NISAG rats are prone to develop insulin-dependent diabetes mellitus, which agrees well with the clinically observed nonrandom association of hypertension with diabetes mellitus [7]. However, our analysis of the endocrine response to insulin in NISAG rats indicates that although this strain may show a tendency to develop diabetes, the latter is unlikely to be a consequence of insulin deficiency.

Response of the endocrine system to epinephrine. Epinephrine caused more damage to the myocardium of NISAG rats, which appears to explain the significant decreases in AP observed in these rats after epinephrine administration. This situation resembles

TABLE 1. Arterial Pressure (AP) Values and Plasma Hormone Concentrations in Wistar and NISAG Rats

Parameter	Rats	Baseline level	Day after epinephrine injection		
			3rd	7th	21st
AP, mm Hg	Wistar	127±2.0***	119±6.0	126±4.0	119±3.0***
	NISAG	153±2.0	127±5.0***	138±4.0**	142±3.0**
Aldosterone, nmol/liter	Wistar	1.0±0.15***	1.1±0.20***	1.4±0.10**	1.2±0.20
	NISAG	2.0±1.10	7.5±1.30***	3.9±0.80*	0.9±0.06***
Corticosterone, μg/liter	Wistar	42.1±3.4	41.9±4.3	42.2±3.1**	44.3±3.8*
	NISAG	40.5±2.6	46.1±3.4	88.9±12.8**	63.7±7.0**
Insulin, μU/ml	Wistar	29.1±3.0**	38.2±6.9**	28.0±4.7	20.9±2.6
	NISAG	14.5±3.4	61.7±3.8***	37.0±4.3***	40.0±9.3*
T_3, nmol/liter	Wistar	1.6±0.01	1.0±0.30	1.2±0.30	0.8±0.05**
	NISAG	2.2±0.31	1.4±0.20	1.9±0.20	1.1±0.20
T_4, μmol/liter	Wistar	84.1±3.2*	101.1±11.0***	99.0±8.8*	95.4±8.1***
	NISAG	103.5±8.0	46.1±4.8***	66.0±10.1*	55.0±4.6***

Note. *$p<0.05$, **$p<0.01$, ***$p<0.001$ in relation to NISAG rats; *$p<0.05$, **$p<0.01$, ***$p<0.001$ in relation to baseline.

that frequently seen clinically in hypertensive patients after the onset of myocardial infarction. Such AP falls in NISAG rats are probably mainly responsible for the substantial elevations of plasma aldosterone recorded on day 7 and especially on day 3 after epinephrine injection, when its level exceeded the baseline value more than threefold. While the aldosterone concentration on day 21 was even significantly below the baseline level in these rats, their AP had risen to approach baseline by that time. In contrast, normotensive Wistar rats showed no significant changes either in AP or in plasma aldosterone in response to epinephrine (Table 1).

The response of glucocorticoids in NISAG rats appears to have been a late one, being significant only on days 7 and 21, and it was less marked than the response of mineralcorticoids. The mean corticosterone concentration rose in these rats to almost 89 μg/liter, probably as a result of the chronic stress due to focal lesions in the myocardium. Again, no significant change in glucocorticoid function was recorded for Wistar rats on any of the three days.

Nor did Wistar rats develop significant changes in the plasma concentration of T_4, whereas the hypertensive rats had drastically reduced levels of this hormone at all times. Such falls of T_4 may be another factor responsible for the AP drop after epinephrine injection. The T_3 concentration, too, was below baseline in NISAG rats throughout the observation period. The strongly inhibited secretory activity of the thyroid gland in the epinephrine-exposed NISAG rats is most likely due to their state of chronic stress.

The variations of plasma insulin in NISAG rats seem paradoxical. Indeed, although the chronic stress associated with myocardial damage should be expected to result in inhibited function of insulin-producing cells, the opposite was true in our study. Thus, the plasma insulin concentration had risen more than fourfold by day 3 and remained significantly above baseline thereafter, whereas no significant changes in insulin were recorded for Wistar rats. Further research is needed to explain these observations. As a working hypothesis we suggest that the elevation of insulin in NISAG rats was associated with the activation of reparative processes to make up for the destructive consequences of epinephrine injection, whereas no substantial mobilization of the insular apparatus occurred in Wistar rats because their myocardium was less damaged by epinephrine and, hence, the anabolic reactions were less intensive.

The above evaluation of endocrine functions in hypertensive NISAG rats leads to the conclusion that this strain is characterized by intensified mineralcorticoid function, elevated thyroid activity, and reduced plasma insulin concentration as compared to the normotensive Wistar rats. These characteristics of the endocrine system may be linked to the increased susceptibility of NISAG rats to stress — one of their main features — and may contribute to the establishment of their hypertensive status. The more pronounced endocrine responses to epinephrine in NISAG rats are most likely due to the greater damage it causes to their myocardium. The primary causes of the more severe myocardial damage and circulatory disorders and of the intensified endocrine responses in this strain appear to be preexisting changes in the cardiovascular system. However, the possibility that species-specific functional features of the endocrine system per se contribute to the endocrine reactions observed in NISAG rats cannot be ruled out.

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