Temporal Variations in Hemodynamic Effects of Immobilization Stress in Normotensive, Stress-Susceptible, and Spontaneously Hypertensive Rats

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Using the catheter technique, temporal variations in arterial pressure and heart rate were examined before, during, and after a 60-minute immobilization-induced stress in normotensive, spontaneously hypertensive, and stress-susceptible awake rats. Stress-susceptible rats developed a hypertensive response to the stress more rapidly than did either normotensive or spontaneously hypertensive animals.

Key Words: *arterial hypertension; animal models; heredity; stress*

Although the pathogenesis of hypertension has been studied inadequately, experimental and clinical findings suggest a number of possible mechanisms underlying arterial pressure (AP) elevation, including alterations in cell membranes, impairment of the renin-angiotensin-aldosterone system, changes in baroreceptor function, and dysfunction of the central mechanisms by which hemodynamics is regulated. Clearly, hypertension can be brought about by various mechanisms. Mild hypertension involves a generally moderate or (in some cases) slight AP elevation but is frequently complicated by hypertensive crises, especially in stressful situations, whereas hypertensive vascular disease is characterized by a high AP and the involvement of various organs with rare hypertensive crises.

In view of this, it seemed useful to compare hemodynamic responses to stress in normotensive rats, spontaneously hypertensive (SH) rats (those with hereditarily determined high AP), and in stress-susceptible rats of a new strain with an inherited predisposition to stress-induced hypertension. The latter strain has been the subject of several recent studies [2,5,6], whose authors believe that it can serve as a better animal model of human hypertension than the SH (Okamoto-Aoki) strain, since an essential component of this model is stress, i.e., exposure to environmental influences. However, the findings from the above-mentioned studies are rather difficult to interpret because AP was measured indirectly using a sphygmographic procedure that itself elicits a substantial change in AP [2] and also because ether anesthesia, which can modify cardiovascular functions, was used [1]. In the present study, hemodynamic parameters were compared using catheters in nonanesthetized normotensive (Wistar), SH, and stress-susceptible rats before, during, and after a short-term immobilization stress.

MATERIALS AND METHODS

Male rats aged 3 to 4 months were used. SH rats were obtained from Prof. Yu. V. Postnov's Laboratory of the Cardiology Research Center and stress-

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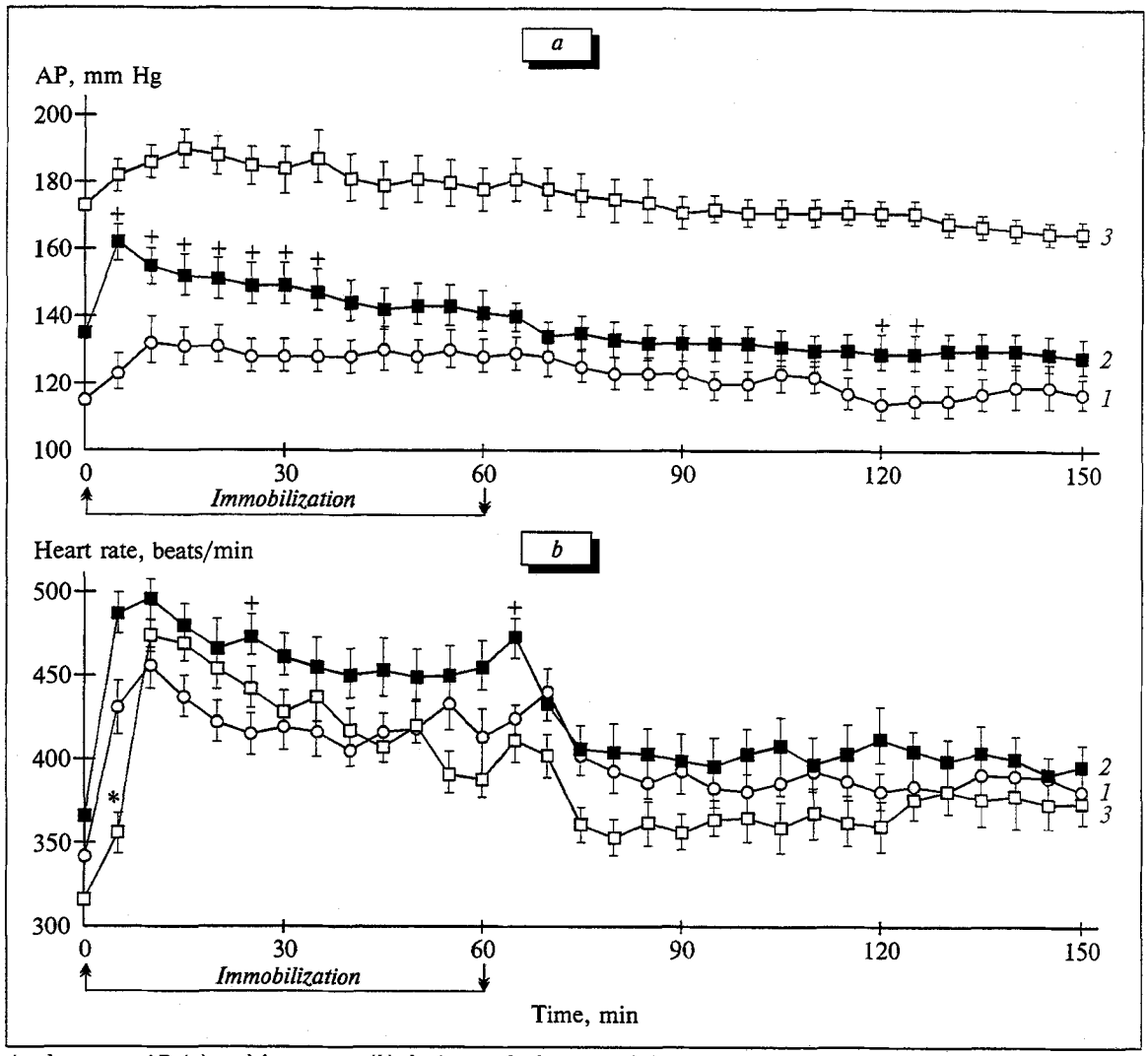

Fig. 1. Variations in the mean AP (*a*) and heart rate (*b*) during and after immobilization in three groups of rats. *1*) normotensive Wistar rats; *2*) stress–susceptible rats; *3*) SH rats. $p<0.05$: $^{+}$in comparison with normotensive rats; *in comparison with SH rats. The mean AP in SH rats was significantly higher at all points ($p<0.05$) than in Wistar or stress–susceptible rats. Arrows mark the start and end of immobilization.

susceptible rats (those with an inherited predisposition to stress-induced arterial hypertension), from the Institute of Cytology and Genetics, Siberian Division of the Russian Academy of Sciences. Normotensive Wistar rats served as controls.

Under Nembutal anesthesia (40 mg/kg intraperitoneally), a catheter was implanted into the abdominal aorta of each rat via the right femoral artery to record AP. The peripheral end of the catheter was passed under the skin and fixed in place in the interscapular region. AP and heart rate were recorded on the following day in awake rats with electric manometers using a computerized multichannel system designed at the North-Western Correspondence Polytechnical Institute, St. Petersburg.

Each rat was placed in a plastic cage and immobilized for 60 min in the prone position by fastening all four limbs to the cage walls. AP and heart rate were measured in the caged rats during 60 min before immobilization (under conditions of free behavior), throughout the 60-min immobilization period, and during the subsequent 90 min. AP and heart rate values were averaged every 5 min. The significance of intergroup differences in these two hemodynamic parameters was estimated by Student's test in Bonferroni's modification [8].

RESULTS

As shown in Table 1, the baseline AP in the stress-susceptible rats was significantly higher (by 15%) than in the normotensive controls and significantly lower than in the SH rats, whereas the baseline heart rate in the stress-susceptible rats was significantly higher than in the SH animals.

TABLE 1. Baseline (before Immobilization) AP Values and Heart Rates and Times of Their Peak Values (during Immobilization) in Awake Wistar, Stress–Susceptible, and SH Rats ($M \pm m$)

Parameter	Rats		
	Wistar (n=7)	stress-susceptible (n=8)	SH (n=8)
Heart rate, beats/min	342±18.7	366±11.9	316±12.0**
Time taken to reach highest heart rate, min	9.3±1.3	6.9±0.94	12.1±1.3**
Mean AP, mm Hg	115±3.1	135±4.2*	173±2.3*,**
Time taken to reach highest AP, min	11.4±2.37	5.6±0.64	18.1±4.0**

Note. $p<0.05$: *in comparison with normotensive (Wistar) rats; **in comparison with stress–susceptible rats.

The immobilization stress led to similar heart rate changes in the rats of all groups (a sharp rise succeeded by a gradual decline toward the end of the immobilization period), except that the SH rats showed a slower increase in the heart rate than the other two groups (Fig. 1) - by 13% at minute 5 as compared to 25% and 43% in the Wistar and stress-susceptible rats, respectively. The variations in AP followed a similar pattern (Fig. 1), although the initial high pressor response (a 20% rise in AP) in the stress-susceptible rats was followed by a more pronounced fall than in the other two strains; also, the AP in these rats, but not in the normotensive controls, tended to return toward baseline during the postimmobilization period.

Comparative analysis showed that the stress-susceptible rats developed more rapid changes in AP and heart rate in the first few minutes of immobilization than did the SH or Wistar rats, i.e., that they are more responsive to stress. This greater responsiveness may also account for the higher baseline AP in these rats in comparison with the other two strains.

The results of direct AP measurements in this study do not allow us to state with certainty that stress-susceptible rats are a suitable animal model of human hypertension, because AP levels in these rats during the postimmobilization period did not differ significantly from those in normotensive controls. In other words, the group of stress-susceptible rats lacked the major attribute of arterial hypertension, namely, a sustained excess of AP over its level in the normotensive group [7]. In terms of cardiac and AP responses, they resemble patients with mild hypertension in whom the disease is still just forming; in such patients, too, the AP response to stress is characterized by a rapid rise and rapid return toward normal. (Interestingly, animals with this type of hyperreactivity were produced by crossing normotensive and SH rats [4].)

It is, of course, difficult to associate findings from an animal study with specific clinical pictures seen in human disease. Nevertheless, the results of the present study reaffirm the important role of stress as a factor triggering the development of arterial hypertension.

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