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Oxygen Consumption in the Spontaneously Hypertensive Rat (40368)

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The spontaneously hypertensive rat (SH) has been widely utilized as an animal model for the study of physiological functions as they pertain to essential hypertension in man. In a recent report, Wright *et al.* (1) demonstrated a marked decrease in the responsiveness to thermal stress in the SH rat which they, in part, attributed to deficient water mobilization for evaporative cooling. The possibility remained that changes in metabolic heat production, cardiovascular adjustments to heating or other factors which might accompany the development of hypertension could influence thermoregulation of hypertensive animals in hot environments.

The work of Kloetzel *et al.* (2) demonstrating a high percentage of hypertensive individuals in industrial jobs requiring heat exposure has emphasized the need for studies to define stress responses in diseases such as hypertension in which the early symptoms may go undetected or the use of maintenance therapy combined with peer group pressure may encourage normal work and recreational activities. The limits which are described for physical exertion and exposure to environmental factors are nearly always based on data obtained from young, healthy individuals, and it may be reasonable to question their applicability to individuals exhibiting chronic alterations in physiological functions. In the present study, oxygen consumption and rectal temperatures of SH and normotensive rats were determined during exposure to a range of environmental temperatures designed to induce mild cold or heat stress. In an attempt to determine the nature of the observed differences, the effects of beta adrenergic blockage on O_2 uptake in cool and warm environments was examined.

Materials and methods. Male SH rats (blood pressure = 163 ± 7 mm Hg and weight, 341 ± 7 g) of the Okamoto-Aoki strain (3) and parent strain Wistar-Kyoto (WKY) normotensive (bp = 112 ± 5 mm Hg and weight, 447 ± 16 g) rats were examined at 15–20 weeks of age. Animals were housed at 24 ± 1° and 50% relative humidity with a 14 hr light–10-hr dark photoperiod. Water and Purina rat chow were available *ad libitum*.

Oxygen utilization was determined using the open flow system of Ben-Porat *et al.* (4). The animals were studied in 3.0 liter metabolic chambers submerged in a 170 liter waterbath held at ± 0.1° of the desired temperature. Room air was passed through the chamber at approximately 0.6 liter/min and the ambient temperature (Ta) in the chamber monitored with thermometers inserted into the chamber space. Water was absorbed on dryrite which had been incorporated into the inflow and outflow lines and in the chamber floor. Carbon dioxide absorbant (NaOH) was placed in the chamber floor and outflow lines. Air samples of about 1.0 liter were collected in Saran plastic bags at 30-min intervals over a 3.0-hr period for determination of O_2 content with the Beckman E-2 O_2 analyzer. In order to avoid variations in the data associated with the early adjustment of the animal to the chamber environment, only the last three values were averaged and compared. Pairs of SH and WKY animals were placed in the preheated chambers at either 0900 or 1300 hours (Eastern Standard Time) for exposure to a total of 5 ambient temperatures ranging from 21° to 32°. Animals were exposed to a single environmental temperature at each experiment with experiments spaced at 7-day intervals over a 5-week period. In order to minimize acclimatory effects and error related to circadian variations in data, exposure scheduling was randomized as to the sequence of exposure temperatures and was arranged in such a fashion that equal

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numbers of animals in each group were utilized in morning and afternoon determinations. Body temperatures were determined before and at the end of each exposure with YSI thermister probes inserted 5–7 cm into the rectum. Oxygen consumption was calculated per metabolic body weight, ml O_2/min/$kg^{-0.74}$ (5).

Following the determinations in untreated animals, the effect of beta adrenergic blockage on the rectal temperature and O_2 utilization was examined at Ta 21° and 30°. Animals were administered propranolol (Inderal, Ayerst Laboratories; 3.0 mg/kg) by ip injection at 12 hr and immediately prior to placement in the metabolic chamber. Preliminary experiments with animals not used in this study indicated that this dose regimen resulted in an average 18% (74 bpm) drop in heart rate at 2 hr after the second injection.

Two weeks after the termination of the O_2 uptake studies the animals were anesthetized with Secobarbital sodium (Lilly, 0.06 ml/100 g) and blood samples were obtained by heart puncture for TSH, T_3 and T_4 determination by radioimmunoassay (6) of the serum. Animals were then sacrificed by cervical dislocation and the thyroid gland removed into 10% formalin for histological examination.

Results. The oxygen consumption of SH animals as compared to the WKY group was elevated at each temperature examined although the differences were statistically significant ($P < 0.05$) only at temperatures above 25° (Fig. 1). Propranolol had no effect on the O_2 uptake of either the SHR and WKY groups at 21° but resulted in 14% and 12% decreases ($P < .001$) in the normotensive and SH rats, respectively, at 30°. Propranolol did not, however, ameliorate SHR-WKY differences in O_2 consumption at 30°.

The SH rat rectal temperatures obtained at the end of the 3-hr exposure showed a slight (0.4–0.6°) elevation above control values at ambient temperatures above 25° (Fig. 1). The rectal temperature of the SH rats receiving propranolol was increased above the values recorded for untreated SH animals whereas no change was observed for the WKY group at Ta 21°. No effect on rectal temperature was noted in either group following propranolol administration at Ta 30°.

Histological examination of thyroid tissue

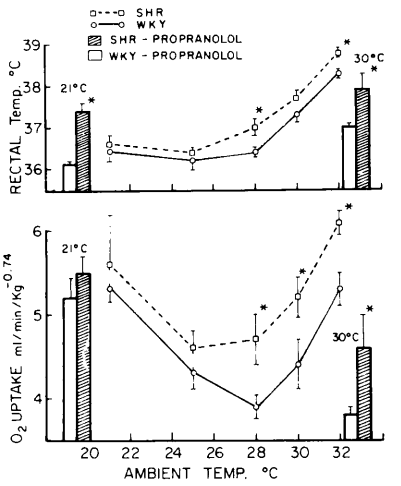

FIG. 1. Oxygen utilization and post exposure rectal temperatures of normotensive and spontaneously hypertensive rats at different ambient temperatures. An asterisk indicates significant differences from control, $P < 0.05$ or greater. Data are presented as the mean ± SE of 10 animals.

revealed no apparent differences between the WKY and SHR groups. In contrast, the serum T_3 levels were elevated ($P < .005$) while T_4 concentrations tended to be lower in the hypertensive animals (Table I). Serum TSH levels were markedly elevated in SH rats, showing a more than 4-fold increase above those recorded for the normotensive controls.

Discussion. A comparison of oxygen utilization of SH and normotensive rats indicates an enhanced metabolic response (15–20%) to higher temperature environments in SH rats (Fig. 1). The corresponding increase in end exposure rectal temperature (0.4–0.6°) in the warm environments suggests that this phenomenon is related to the relative inability of the hypertensive animal to prevent body temperature elevation as compared to normotensive controls. It is not clear, however, as to whether the increase in O_2 utilization represents a major contributing factor to the elevation in rectal temperature observed in the SH rat or a manifestation of the increase in body temperature occurring as a result of defective thermoregulatory function in other heat loss effector systems. Elevation in O_2 uptake seen in the SH rat may result from the direct effect of the higher body temperature on metabolic rate or on the energy requirement for increased respiratory, behavioral

TABLE I. THE SERUM T_3, T_4 AND TSH VALUES OBTAINED FOR NORMOTENSIVE AND HYPERTENSIVE RATS.

Group	Weight (g)	T_3 (ng%)	T_4 (ng%)	TSH (ng%)
WKY	477 ± 16	43.1 ± 2.0	4.6 ± 0.2	19.3 ± 3.0
SHR	341 ± 7	54.2 ± 2.7[a]	3.9 ± 0.2	81.8 ± 4.4[a]

[a] Significant difference ($P < 0.05$ or greater). Data are presented as mean ± SE of 10 animals.

and secretory functions designed to increase heat loss.

The O_2 consumption measurements in WKY and SH rats before and after administration of the beta adrenergic blocking agent propranolol provide information concerning the contribution of circulatory catecholamines (7) and the activity of the sympathetic nervous system (8) to the difference in the metabolic rate between these groups. In both animal groups propranolol exerted a marked anticalorigenic effect at 30° ambient temperature, whereas no effect was observed at 21°. Since the effect of administering propranolol will depend upon the amount of sympathetic tone in the organs or tissues examined (9), our results suggest that at 30° the animals of both experimental groups were in a similar state of thermal stress and increased sympathetic tone which was abolished by administration of propranolol, without affecting body temperature. As compared with normotensive WKY animals, it seems that spontaneously hypertensive rats are hypersensitive to high temperature stress. However, their elevated metabolic rate at high ambient temperature seems not to be related to an increased sympathetic tone. The slight effects of propranolol on O_2 uptake in both groups at 21° indicates a relatively minor adrenergic influence. The mechanism of rectal temperature increase in SH rats which received propranolol at Ta 21° is not certain.

The findings of Kojima and co-workers (10) indicate that thyroid function is reduced in the SH rat, suggesting that oxidation metabolism may also be expected to be reduced in these animals. On the other hand, it has been repeatedly shown that oxygen consumption is elevated in humans demonstrating essential hypertension (11, 13). Our observations on circulating T_3 and T_4 levels and thyroid histology tend to suggest normal or slightly increased thyroidal activity in SH rats. The remarkable elevation noted in hypertensive TSH levels is in agreement with the observations of Kojima *et al.* (7) and indicates a marked abnormality in thyroid function and a relatively refractory response to pituitary stimulation. The observation of elevated O_2 uptake in SH rats only at high ambient temperatures, however, suggests that factors unrelated to the pituitary–thyroid axis may be operant in the SH rat which would result in elevated metabolism, particularly in stress situations. For example, the hyper-responsiveness to adreno-sympathetic adrenergic stimuli in hypertensive rats is well documented (14, 15), and it is possible that stress induced activity in these systems might result in a disproportionate elevation in metabolic rates. In view of the complementary activity of thyroxine to the positive calorigenic effect of epinephrine (16), the nature of the influence of the thyroid in SH animals should be investigated further.

Summary. Oxygen utilization was found to be elevated in SH rats as compared to control animals, and the difference was statistically significant at ambient temperatures above 25°. Corresponding elevations in rectal temperature were noted, and it was concluded that the enhanced metabolic response was related to the relative inability of the hypertensive rat to prevent rectal temperature elevation during heat stress. It was not clear as to whether the increase in O_2 uptake was a causal factor or resulted from body temperature elevation due to defective heat loss by the SH rat. Propranolol induced a significant reduction in oxygen usage of both SHR and WKY groups at Ta 30° but not at 21° indicating an adrenergic influence on metabolic rate during acute heat stress which was absent during cooler exposures. Serum T_4 levels of SH rats were not significantly different from control values whereas T_3 levels were elevated (26%) indicating normal or slightly increased thyroid activity. In comparison, TSH levels were elevated fourfold indicating a markedly abnormal thyroid response to this hormone.

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