Sympathetic and Metabolic Correlates of Hypoxic Moderation of Spontaneous Hypertension in the Rat (42964)

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Abstract. **Exposure to hypobaric hypoxia (H; simulated altitude = 3658 m) was initiated in 5-week-old, male spontaneously hypertensive (SHR) and Wistar-Kyoto (WKy) normotensive rats while normoxic controls (N) for both groups were maintained under laboratory conditions. Significant attenuation of systolic arterial blood pressure was evident in SHR-H relative to SHR-N (125 ± 6 vs 145 ± 5 mm Hg; $P < 0.05$) but not in WKy-H relative to WKy-N (WKy-H, 116 ± 2 vs WKy-N, 117 ± 5 mm Hg). Hypoxia significantly decreased metabolic efficiency in both normotensive and hypertensive rats, although being both more severe and accompanied by significantly impaired growth rate in SHR-H. Urinary excretion of norepinephrine in the SHR was elevated relative to WKy, irrespective of altitude treatment, while hypoxia elicited similar increases in urinary excretion of norepinephrine in both SHR and WKy. Myocardial and adrenal contents of norepinephrine were significantly reduced following 3 days of simulated altitude exposure in both strains of rats. Tissue contents of norepinephrine in hypoxic rats returned to normoxic levels by 21 days of simulated altitude. Both urine and tissue indices provided consistent indirect evidence that changes in sympathetic neuronal activity in response to hypoxia were similar in normotensive and hypertensive rats. These findings suggest that prior reports of reduced α-adrenergic responsiveness in vasculature from hypoxia-exposed SHR reflect a postsynaptic event that is regulated independently of norepinephrine release from sympathetic nerve terminals** [P.S.E.B.M. 1989, Vol 192]

A recent international workshop (1) has drawn attention to the involvement of peripheral arterial chemoreceptors in systemic hypertension. Previous studies from our laboratories (2, 3) have documented the ability of hypoxia to mitigate the development of hypertension, a finding which may be due to hypoxic stimulation of peripheral chemoreceptors. Additionally, we have characterized this phenomenon in the spontaneously hypertensive rat (SHR) as being both age-dependent and related to a general metabolic adaptation to hypoxia that includes reductions in responsiveness in aortic rings (4).

The general characterization of the SHR as a hypersympathetic (5) and hypermetabolic (6) animal is well established. Adding to this the importance placed on the sympathetic nervous system in the development and maintenance of hypertension (7) suggests that reduced sympathetic activity (the result of both sympathetic neuronal release and tissue response) could play a major role in hypoxic moderation of spontaneous hypertension. However, numerous pieces of evidence are available that support the conclusion that sympathetic neuronal release is increased when normotensive rats are exposed to a hypoxic environment (8, 9). If generalized to SHR, these findings lead to the assumption that decreased α-adrenergic responsiveness in hypoxic SHR could reflect a desensitization (down-regulation) process resulting from increased neuronal activity. A problem for this interpretation comes from the finding of an absence of reduced α-adrenergic responsiveness in normotensive rats exposed to hypoxia (4).

It is impossible to resolve this problematic interpretation given the lack of information regarding sympathetic neuronal activity induced by hypoxia in SHR. Information to date regarding sympathetic neuronal activation in the hypoxic SHR remains fragmentary. One report suggested that hypoxia-induced changes in catecholamine metabolism were a component of the

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antihypertensive properties of hypoxia in SHR (10). However, significant differences between chronically treated hypoxic and normoxic SHR did not exist in myocardium or vas deferens; only in data from adrenal glands were statistically significant findings evident. Hence, this study did not provide compelling evidence for alterations in sympathetic neuronal activation in the hypoxic SHR relative to normoxic SHR nor did it allow comparisons between hypoxic SHR and hypoxic WKy.

In this study, we have further characterized the metabolic and catecholaminergic dynamics in SHR exposed to hypoxia during the development of hypertension. Normotensive Wistar-Kyoto rats were simultaneously exposed to hypoxia allowing an interstrain comparison of indices of sympathetic neuronal release with hypoxic exposure. Our present findings indicate that sympathetic neuronal release of norepinephrine is increased equivalently in SHR and the normotensive WKy by hypoxia. Therefore, it is clear that very different tissue responsivity in hypoxic SHR and WKy occurs in the presence of similar increases in sympathetic neuronal activity.

Materials and Methods

Thirty spontaneously hypertensive (SHR) and 30 normotensive Wistar-Kyoto (WKy) male 4-week-old rats were purchased from Charles River Laboratories, Inc. (Okamoto-Aoki strain). After arrival, the rats were maintained at a room temperature of 24.5 ± 1.5°C with a 12-hr light:12-hr dark cycle. After a 4-day acclimatization, baseline (Day −1) measurements of body weight and systolic blood pressure (tail cuff technique with photoelectric detector and gentle heating) were obtained, and rats of the same strain were randomly paired and placed in 30 stainless steel metabolic cages. Approximately 10 separate blood pressure traces were obtained per "blood pressure measurement" with three consecutive measurements within 15 mm Hg used as an objective discriminator of true blood pressure. Blood pressure was determined as a mean value from the three consecutive measures. In certain instances, lack of cooperation by a rat did not allow blood pressure determinations; data were not excluded arbitrarily. Twenty-four hours later, simulated altitude treatment (hypoxia) was initiated in half the rats. Fifteen cages (seven pairs of SHR; eight pairs of WKy) were placed in an altitude chamber and exposed to hypobaric hypoxia (H; simulated altitude = 3658 m). The remaining 15 cages (8 pairs of SHR and 7 pairs of WKy) were maintained under normoxic conditions (N; laboratory altitude = 1520 m) in a nearby room with otherwise similar living conditions. The hypobaric chamber used was a large facility with an antechamber capable of being independently compressed and decompressed, thereby eliminating interruptions in hypoxic exposure within the main chamber which housed the rats.

Measures of food intake (24-hr consumption of Purina powdered rat chow), body weight, and urine collections were obtained on Days 1, 2, 3, 9, and 19 of the experiment. Urine was collected in 0.5 ml of 4 *N* HCl, frozen, and later analyzed for norepinephrine and creatinine content. Additional body weight and systolic blood pressure measurements were obtained on Days 5, 12, and 20 of the experiment. Metabolic efficiency calculations were derived on the basis of body weight gain divided by caloric intake (food consumption × 3.67 kcal/g) × 1000 (11).

On Day 4 (after 3 days of simulated altitude), one rat from every cage was decapitated without anesthesia to assess acute adaptations to hypoxia. The adrenal glands and heart were removed rapidly, placed on dry ice, and stored at −80°C until analyzed for neurochemical content. Blood was collected in heparinized tubes from the cervical wound, centrifugated, and the plasma frozen until creatinine concentrations could be determined. On Day 21 of the experiment, the remaining 30 rats were decapitated, and their tissues and plasma were processed in a manner identical to those on Day 4. Limited access to the hypoxic rats made it impossible to alternate the decapitation procedure between hypoxic and normoxic rats on an individual basis. However, to minimize the likelihood of systematic bias associated with the time of day that rats were decapitated, half of the designated normoxic rats were sacrificed prior to decapitation of hypoxic rats and the remaining normoxic rats were decapitated after all hypoxic rats were processed.

Concentrations of creatinine in the urine and plasma were measured colorimetrically (kit no. 555; Sigma Chemical Co., St. Louis, MO). Concentrations of norepinephrine in the urine (0.5-ml samples) were measured by high-pressure liquid chromatography with electrochemical detection (3 μm, C18 column; detector voltage = 0.7 V). The extraction (cation exchange plus alumina adsorption; approximately 65% recovery) and isocratic chromatographic techniques employed with minor modifications (0.8 ml/min; 0.1 *M* monochloroacetic acid-based mobile phase with 300 mg/liter of sodium octyl sulfate as an ion-pairing agent, 7% acetonitrile, pH = 3.0) have been described in detail elsewhere (LCEC Application note no. 15; Bioanalytical Systems Inc., West Lafayette, IN). Urinary norepinephrine excretion was normalized on the basis of creatinine concentration obtained from the same urine samples as used for norepinephrine determinations. The heart and adrenals were homogenized in 4 ml of 0.1 *M* perchloric acid, spun in a refrigerated centrifuge, filtered through a 0.2-μm filter, and analyzed by high-pressure liquid chromatography in a similar manner as were urinary catecholamines.

Analysis of variance (ANOVA) was used for the primary evaluation of the data; a repeated measures design was employed when multiple measures were taken from the same animal. When significance ($P < 0.05$) was found, the LSD (Fischer's protected LSD) (12) was used for comparison between individual means. Correlation analysis was performed by linear regression.

Results

Analysis of systolic blood pressure measurements revealed a significant interaction between altitude treatment and strain of rat over time (repeated measures ANOVA; $P < 0.05$). Statistically significant reductions in the blood pressures of hypoxia-treated rats, irrespective of strain, were noted as early as the first week of altitude treatment (two-way ANOVA, Day 5, Fig. 1). However, an interactive influence of hypoxia with strain of rat was not noted until Day 20. Further analysis revealed a significant difference between SHR-H and SHR-N ($P < 0.01$, LSD, Day 20) that was not evident between WKy-H and WKy-N.

As with blood pressure, a significant three-way interaction was noted in the body weight measurements between strain of rat, altitude treatment, and time of exposure (repeated measures ANOVA, $P < 0.01$). This finding reflects impaired growth rate in SHR-H that was not evident in WKy-H (Fig. 2). Food consumption was generally greater in SHR relative to WKy but was reduced after acute hypoxic exposure irrespective of strain of rat (repeated measures ANOVA, Day 1 through Day 3; $P < 0.01$, Table I); no interactive effect between strain and altitude treatment was noted ($P > 0.5$). The impressive reduction in growth rate of SHR-H relative to WKy-H without a corresponding reduc-

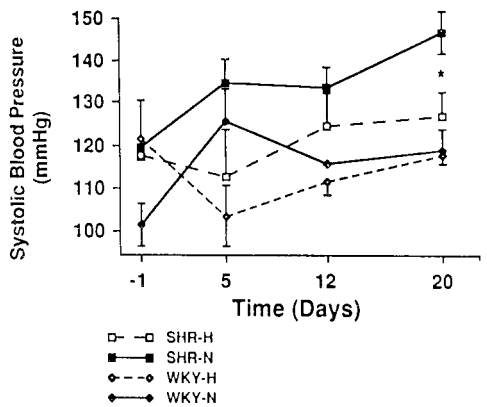

Figure 1. Systolic blood pressure in spontaneously hypertensive and normotensive (WKy) rats exposed either to normoxic or hypoxic treatments. Values represented are mean ± SE. Asterisk indicates a significant difference (LSD, $P < 0.01$) between SHR-N and SHR-H after 20 days of altitude treatment. Significance was also noted between SHR-N and WKy-N at this time. Number of individual values represented by means is greater than 7 except for: SHR-H ($n = 4$, Day −1; $n = 6$, Day 5), SHR-N ($n = 5$, Day −1), WKy-H ($n = 6$, Day −1), and WKy-N ($n = 4$, Day −1). No significant differences were evident prior to initiation of altitude treatments.

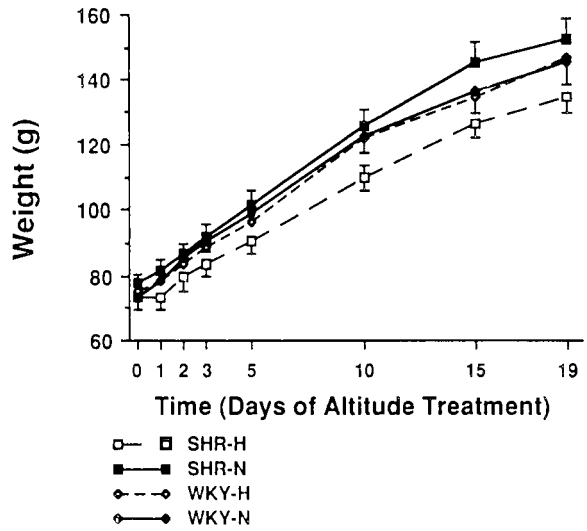

Figure 2. Body weight in spontaneously hypertensive and normotensive (WKy) rats exposed either to normoxic or hypoxic treatments. Values represented are mean ± SE. Repeated measures of ANOVA revealed a significant three-way interaction (time-strain of rat-altitude treatment) indicating an impaired growth rate in SHR-H that was not evident in WKy-H. Paired comparisons (LSD) between SHR-N and SHR-H were significant ($P < 0.05$) on Days 10, 15, and 19.

Table I. Food Consumption (g/100 g of body wt) with Acute and Chronic Altitude Treatment in Hypertensive and Normotensive Rats

	Days of altitude treatment				
	1	2	3	9	19
SHR-H	13.4 ± 0.5 (6)	13.2 ± 0.7 (6)	13.9 ± 0.6 (4)	11.5 ± 0.8 (5)	10.9 ± 0.9 (3)
SHR-N	14.6 ± 0.5 (6)	14.4 ± 0.6 (6)	13.5 ± 0.3 (6)	11.4 ± 0.2 (6)	—
WKy-H	11.5 ± 0.5 (8)	11.2 ± 0.4 (7)	11.9 ± 0.3 (8)	11.4 ± 0.2 (8)	11.8 ± 0.4 (6)
WKy-N	13.5 ± 0.3 (6)	12.9 ± 0.2 (7)	12.2 ± 0.4 (7)	11.8 ± 0.4 (7)	13.2 ± 0.4 (7)
ANOVA					
(Str)	$P < 0.01$	$P < 0.01$	$P = 0.01$	$P > 0.9$	—
(Alt)	$P < 0.01$	$P < 0.01$	$P > 0.9$	$P > 0.5$	($P < 0.05$)

Note. Values presented represent mean ± SE with the number of measurements in parentheses. ANOVA (Str), two-way analysis of variance (strain effect). Alt, two-way analysis of variance (altitude effect). No interactions between strain of rat and altitude treatment were detected with the two-way ANOVA ($P > 0.3$). Major food spillage in the maturing SHR limited accurate assessment of food consumption on Day 19. The significant effect of altitude indicated on Day 19 is the result of comparing WKy-N with WKy-H.

tion in food consumption, is reflected in a markedly impaired metabolic efficiency in SHR-H during the initial days of altitude exposure (Fig. 3, two-way ANOVA, $P < 0.05$).

Urinary excretion of norepinephrine varied as a function of both strain and altitude treatment (Table II). Altitude-induced elevations were most prominent during the first week of exposure but returned to baseline by Day 19 of treatment. Elevations in norepinephrine excretion were consistently noted in SHR relative to WKy and were statistically significant at three of the five time points measured. At no time was there any suggestion of an interaction between altitude treatment and strain of rat (two-way ANOVA, $P > 0.24$). Plasma creatinine concentration was elevated in all hypoxic rats on Day 21 (two-way ANOVA, altitude effect, $P < 0.01$, Table III). A significant interaction between altitude treatment and strain of rat was suggested at the same time point (two-way ANOVA, strain-altitude; $P = 0.06$; LSD, SHR-N versus SHR-H, $P < 0.01$; LSD, WKy-N versus WKy-H, $P > 0.7$).

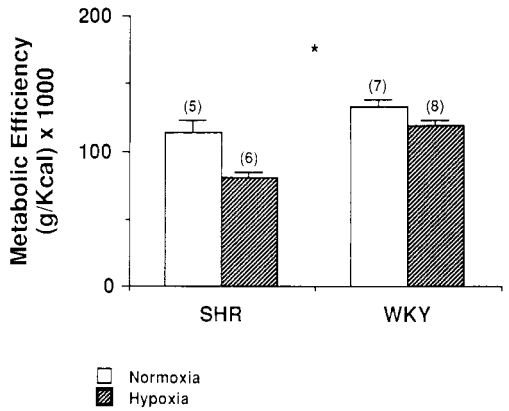

Figure 3. Average metabolic efficiency in spontaneously hypertensive and normotensive (WKy) rats exposed either to normoxic or hypoxic treatments for 3 days. Values represented are mean ± SE. Values in parentheses represent the number of rats per mean value. Asterisk indicates a significant interaction between strain and altitude treatment (two-way ANOVA, $P < 0.05$). Comparison of individual means (LSD) indicated that metabolic efficiency was reduced in SHR-H relative to all other groups and reduced in WKy-H relative to WKy-N.

Major reductions in myocardial norepinephrine content (Fig. 4; data normalized on a myocardial weight basis) were noted with acute exposure to simulated altitude (two-way ANOVA, Day 4, $P < 0.01$) with no indication of a strain-altitude interaction ($P > 0.6$). Total ventricular weight was increased in SHRs when compared with WKy rats (two-way ANOVA; $P < 0.01$) and increased in hypoxic rats relative to normoxic rats on Day 4 ($P < 0.05$); however, no interaction between altitude treatment and strain of rat was evident ($P > 0.5$). Total ventricular content of norepinephrine was found to be increased in SHR relative to WKy (two-

Table II. Urinary Excretion of Norepinephrine (ng/mg of Creatinine) with Acute and Chronic Altitude Treatment in Hypertensive and Normotensive Rats

	Days of altitude treatment				
	1	2	3	9	19
SHR-H	146 ± 12 (6)	143 ± 6 (6)	126 ± 8 (6)	171 ± 19 (6)	114 ± 10 (6)
SHR-N	125 ± 20 (6)	103 ± 9 (6)	113 ± 10 (6)	152 ± 9 (6)	111 ± 10 (4)
WKy-H	98 ± 10 (8)	107 ± 7 (6)	118 ± 8 (5)	120 ± 7 (6)	97 ± 12 (6)
WKy-N	80 ± 8 (5)	84 ± 4 (6)	86 ± 10 (6)	104 ± 2 (6)	106 ± 7 (6)
ANOVA					
(Str)	$P < 0.01$	$P < 0.01$	$P = 0.06$	$P < 0.01$	$P = 0.30$
(Alt)	$P = 0.16$	$P < 0.01$	$P = 0.02$	$P = 0.12$	$P = 0.78$

Note. Values presented represent mean ± SE with the number of measurements in parentheses. ANOVA (Str), two-way analysis of variance (strain effect). Alt, two-way analysis of variance (altitude effect). No interactions between strain of rat and altitude treatment were detected with the two-way ANOVA ($P > 0.24$).

Table III. Plasma Creatinine Concentration (μg/ml) and Total Ventricular Weight (mg) with Acute and Chronic Altitude Treatment in Hypertensive and Normotensive Rats

	Day 4		Day 21	
	Creatinine (μg/ml)	Ventricular weight (mg)	Creatinine (μg/ml)	Ventricular weight (mg)
SHR-H	5.6 ± 0.7 (7)	414 ± 8 (7)	5.0 ± 0.2 (7)	580 ± 28 (7)
SHR-N	4.2 ± 0.5 (8)	388 ± 12 (8)	3.5 ± 0.3 (8)	609 ± 20 (8)
LSD	—	$P = 0.05$	$P < 0.01$	—
WKy-H	4.6 ± 0.4 (8)	377 ± 7 (8)	4.0 ± 0.3 (7)	576 ± 10 (8)
WKy-N	4.4 ± 0.2 (7)	362 ± 9 (7)	3.5 ± 0.3 (7)	552 ± 20 (7)
LSD	—	NS	NS	—

Note. Values presented represent mean ± SE with the number of measurements in parentheses. LSD, Fischer's protected least significant difference. —, test was not appropriate; NS, not significant.

way ANOVA, data not reported, $P < 0.01$) and decreased in hypoxic rats relative to normoxic rats on Day 4 ($P < 0.01$). No significant differences in myocardial data (Fig. 4 and Table III) were evident on Day 21, however.

Acute reductions in adrenal norepinephrine content (Fig. 5) were also noted in hypoxic rats (two-way ANOVA, Day 4, $P < 0.05$) with no evidence of altitude-strain interaction ($P > 0.8$). As with the myocardium, hypoxia-induced changes in norepinephrine content in adrenal glands disappeared by Day 21. A marked elevation in adrenal norepinephrine content ($P < 0.01$) was noted in SHR when compared with WKy at both time points at which it was measured. Differences in epinephrine content of adrenal glands (Fig. 6) were noted in chronic exposure samples (Day 21, 2-way ANOVA, $P < 0.01$). This finding reflected a decrement in epinephrine content in SHR-H relative to SHR-N (LSD, $P < 0.01$) that was not evident between WKy-H and WKy-N (LSD, $P > 0.7$). Epinephrine content in adrenals of rats exposed to chronic hypoxia was found to correlate significantly with plasma creatinine concentration ($r = -0.41$, $P < 0.05$).

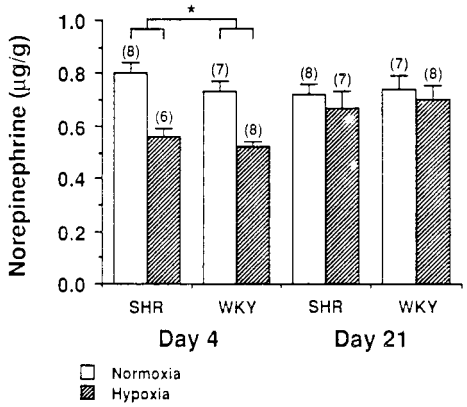

Figure 4. Myocardial norepinephrine content in spontaneously hypertensive and normotensive (WKy) rats exposed either to normoxic or hypoxic treatments. Values represented are mean ± SE and are normalized on a wet tissue weight basis. Values in parentheses represent the number of rats per mean value. Asterisk indicates a significant effect of altitude treatment ($P < 0.01$) with no indication of interaction between strain of rat and altitude treatment ($P = 0.6$, two-way ANOVA).

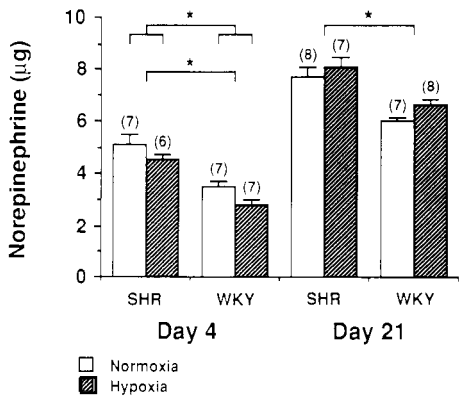

Figure 5. Norepinephrine content in adrenal glands of spontaneously hypertensive and normotensive (Wistar-Kyoto) rats exposed either to normoxic or hypoxic treatments. Values represented are mean ± SE and represent the total content of two glands. Values in parentheses represent the number of rats per mean value. Asterisks (Day 4) indicate significant differences due to both strain of rat and altitude treatment ($P < 0.05$) without interaction between main effects ($P = 0.8$; two-way ANOVA). Asterisk (Day 21) indicates a significant difference due to strain of rat ($P < 0.01$) without an influence of altitude ($P > 0.08$, two-way ANOVA).

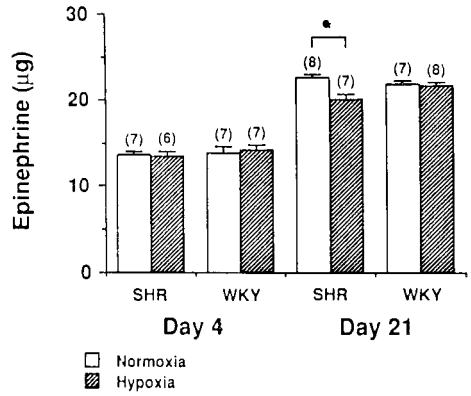

Figure 6. Epinephrine content in adrenal glands of spontaneously hypertensive and normotensive (Wistar-Kyoto) rats exposed either to normoxic or hypoxic treatments. Values represented are mean ± SE and represent the total content of two glands. Values in parentheses represent the number of rats per mean value. Asterisk (Day 21) indicates a significant difference between SHR-N and SHR-H (LSD, $P < 0.01$).

Discussion

Hypoxia mitigated the development of spontaneous hypertension in a manner consistent with previous findings from our laboratory (3). Furthermore, the comparability of blood pressures in SHR-H and WKy-N suggest that mitigation of the hypertension was nearly complete. These findings confirm previous reports that attenuation of hypertension is nearly complete when altitude exposure is initiated in 4- to 5-week-old SHR (3, 10).

We have previously noted differential effects of hypoxia on the growth rate of SHR and WKy (3) which were evident again in this study. This result reflects, in part, a large decrease in resting oxygen consumption that the SHR, but not the WKy, undergoes when exposed to a simulated altitude of 3658 m (3). Others have provided evidence of a close relationship between basal oxygen consumption and growth rate in growing rats (13, 14). We previously hypothesized that the SHR, being hypermetabolic, would have a lowered threshold at which physiologic adaptations to hypoxia would be required (3). Significant correlations between reductions in oxygen consumption and in blood pressure have prompted the suggestion of a relationship between the attenuation of metabolic rate, the attenuation of growth rate and the reduction in blood pressure in the hypoxic SHR.

Evidence of hypoxia-induced attenuation of meta-

bolic efficiency was evident in both strains of rats during the early phase of acclimatization to hypoxia; however, a significant interaction indicated that the decrement was most severe in SHR-H. The transient anorexic influence of hypoxia does not provide an adequate explanation for the loss of metabolic efficiency in SHR-H since hypoxia caused similar decrements in food consumption in WKy. Nor is it likely that a difference in oxygen consumption in SHR-H relative to WKy-H can explain this interaction during early hypoxic exposure (3). The mechanism underlying the impaired growth rate and decreased metabolic efficiency in hypoxic SHR is not known. However, impaired energy utilization has been noted previously in the hypoxic rat (16). These authors demonstrated that fecal weights are greater in hypoxic rats in spite of reduced food intake.

Previous studies from our laboratories have suggested that the mitigation of hypertension in SHR-H is associated with a reduction in responsiveness of aortic rings to α-adrenergic stimulation (4). Although this finding has been associated with the mitigation of the hypertensive state, the possibility exists that a reduction in adrenergic responsiveness is also associated with a reduction in oxygen consumption and growth rate. The importance of norepinephrine as a general metabolic agent (15) supports this line of reasoning. The possibility that reduced adrenergic responsiveness is prominent in the gastrointestinal tract as well as the aorta of SHR-H seems plausible. This influence would be expected to increase gastric motility, promote malabsorption (17), and thereby impair metabolic efficiency.

The increased urinary excretion of norepinephrine (NE-U) in SHR of this study provides confirmation of previous indications that the SHR is in a hypersympathetic state (5). In addition, the present study included two other indirect measures of sympathetic neuronal response to hypoxia, viz. myocardial NE content (NE-M), and adrenal NE content (NE-A). Reductions in both NE-M and NE-A were found only after 4 days of hypoxia in both SHR and WKy. The reduction in NE-M is consistent with a previous finding in hypoxic rats (8). Reductions in tissue content of NE are typically interpreted as an indication of increased release of norepinephrine (8); however, it is not clear that the small change in NE-A would be physiologically relevant. Nonetheless, all of the measures taken in the present study are consistent in providing evidence of enhanced activity of sympathetic nerves and enhanced norepinephrine release, both in SHR relative to WKy and in the early response to hypoxia.

The increase in NE-U and reduction in NE-M and NE-A caused by acute hypoxic exposure in both SHR and WKy demonstrate that the SHR, like other animals exposed to hypoxia, show a generalized increase in sympathetic neuronal release (8, 9). The present study found no evidence of any interaction between strain of rat and hypoxia for measures of NE-U, providing support for the hypothesis that changes in sympathetic neuronal release induced by hypoxia did not differ between SHR and WKy.

Chronic measures of NE-M, NE-A, and NE-U indicated that sympathetic neuronal activity underwent adaptation by Day 21. It is noteworthy that these adaptations were similar in both WKy and SHR. Similar adaptations in catecholaminergic metabolism with chronic hypoxic treatments have been previously noted (9).

The similarity of catecholaminergic responses to hypoxia in WKy and SHR stands in contradistinction to the sustained reduction in α-adrenergic responsiveness of aortic rings from SHR-H, which does not occur in rings from WKy-H (4). Since increased sympathetic neuronal release appears to be a general response to hypoxia shared by SHR and WKy rats, while attenuated responsivity of aortic rings to hypoxia is unique to SHR, it cannot be argued that diminished ring responses reflect a generalized desensitization or "down-regulation" of α-adrenoceptors due to increased NE concentration at the receptor site.

Since it is only vessel ring responses to NE agonists, and not general sympathetic neuronal responses which are unique adaptations to hypoxia in SHR, it follows that it is this unique tissue responsivity that intervenes to protect against the development of hypertension in hypoxic SHR.

The results of this study substantiate previous findings regarding both the hypersympathetic status of the SHR and the generalized increase in sympathetic neuronal release induced in rats by hypoxia. The importance of this study is that it provides consistent evidence that hypoxia-induced changes in indices of sympathetic neuronal release are similar in SHR and WKy. Therefore, previous findings from our laboratories of hypoxia-induced reductions in α-adrenergic responsiveness of SHR but not WKy (4) cannot be coupled to sympathetic neuronal release.

The reduced response of aortic rings to adrenergic stimulation in SHR occurs within a few days after the initiation of hypoxia and persists for at least several months beyond the initiation of the exposure to hypoxia (4). Other laboratories have similarly reported tissue responses to hypoxemia in SHR which appear to be inconsistent with increased sympathetic neuronal release of NE (i.e., decreased heart rate, decreased metabolic rate) (19). Moreover, the elevated peripheral resistance found in young SHR is exquisitely sensitive to acute reductions in pO_2 (20). These findings are in agreement in supporting the hypothesis that tissue responses usually associated with sympathetic neuronal NE release are reduced quickly in SHR upon exposure to hypoxia and that this reduction persists indefinitely. It is unfortunate that these latter findings (19, 20) included no concomitant measures of sympathetic neuronal release of NE. Hypoxia-induced changes in tissue

responsiveness to α-adrenergic stimulation are unique to the SHR since similar changes are either much smaller or absent in hypoxic WKy (4, 19, 20). Since changes in sympathetic neuronal NE release during hypoxia do not seem to differ between hypoxic SHR and WKy, they appear not to be directly involved in the "attenuated hypersympathetic state" that occurs in hypoxic SHR.

It seems likely that reduced α-adrenergic responsiveness is a component of the reduction in systemic blood pressure associated with hypoxia in the SHR (3, 4). Numerous recent reports have suggested that hypoxia exerts its antihypertensive properties via direct influences on the carotid body chemoreceptors (1). If hypoxia-induced decreases in α-adrenergic responsiveness are mediated via a neural or neuroendocrine reflex initiated at the chemoreceptors, the present results make it unlikely that norepinephrine is the messenger. Thus, the hypoxic SHR appears to provide a model whereby tissue responses are modulated at the receptor or postreceptor level rather than through changes in neurotransmitter release.

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