

Cerebrovascular Response to Hypotension in Hypertensive Rats: Effect of Antihypertensive Therapy

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The possibility that antihypertensive therapy in spontaneously hypertensive rats (SHR) will reverse the shift in cerebral autoregulation and improve cerebrovascular performance during sodium-nitroprusside-induced hypotension was tested. Four-month-old SHR and Wistar Kyoto controls (WKY) were tested using four groups. One group each of SHR and WKY received 10 weeks of antihypertensive drug treatment using vasodilators combined with a beta-adrenergic blocker, propranolol. A third and fourth group of SHR and WKY, respectively, received 10 weeks of sham treatment ($n = 15$ rats per group). Systolic pressure was measured weekly by tail cuff occlusion. Antihypertensive drug treatment significantly decreased blood pressure in SHR and WKY over the 10-week treatment period. At the end of 10 weeks, cerebral blood flow (CBF) was measured under control conditions (ketamine anesthesia plus hexamethonium pretreatment) and during SNP-induced hypotension to mean pressure levels of 82–92 mmHg and 54–58 mmHg. CBF was measured with radioactive microspheres and cerebral oxygen consumption (CMR_{O_2}) was calculated as the product of CBF and arterial-sagittal sinus blood oxygen content difference. Antihypertensive therapy did not significantly alter CBF in SHR or WKY, measured under control conditions, compared with sham-treated controls. Decreasing blood pressure to 82–92 mmHg produced a 49% decrease in CBF in sham-treated SHR ($P < 0.05$) but no significant change in CBF in sham- or antihypertensive-treated WKY or antihypertensive-treated SHR. At a mean blood pressure level of 54–58 mmHg, CBF decreased significantly in all SHR and WKY test groups, and decreased significantly more in sham- (69%) than in antihypertensive-treated SHR (49%, $P < 0.05$). These results indicate that long-term antihypertensive therapy may reverse the shift in cerebral autoregulation produced by chronic hypertension. (Key words: Anesthetics, intravenous: ketamine. Anesthetic techniques: hypotension, induced. Blood pressure: hypertension; hypotension. Brain: autoregulation; blood flow; metabolism. Pharmacology: nitroprusside.)

PREVIOUS STUDIES have shown that chronic hypertension produces cerebrovascular changes which inhibit the ability of hypertensives to maintain cerebral blood flow (CBF) and cerebral oxygen consumption (CMR_{O_2}) during hypotension caused by hemorrhage or ganglionic blockade.¹⁻⁴ Recently, we have shown that hyperten-

sive rats are unable to maintain CBF and CMR_{O_2} during sodium nitroprusside- (SNP) induced hypotension.⁵ Lundgren *et al.*⁶ reported in rats that hind-limb vascular hypertrophy becomes apparent within 6 weeks of the onset of hypertension. Similar changes in cerebral vessels may be responsible for the shift in the autoregulatory curve. Lowering the blood pressure in hypertensive rats will reverse hypertension-induced hindlimb vascular changes and improve the maximum capacity for vasodilation in the rat.^{7,8} In these experiments, we have tested the possibility that antihypertensive therapy will reverse cerebrovascular changes in hypertensive rats and improve their ability to maintain CBF and CMR_{O_2} during SNP-induced hypotension.

Methods

ANESTHESIA

In these experiments, we wished to use an anesthetic which produced adequate anesthesia but did not depress CBF or CMR_{O_2} or alter cerebral autoregulation. Idvall *et al.*⁹ reported that ketamine in doses of $1.5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ produced surgical anesthesia in rats and resulted in a small but significant increase in CBF compared with unanesthetized controls. We carried out preliminary experiments to determine whether cerebral autoregulatory mechanisms were maintained in ketamine anesthetized rats. Wistar Kyoto rats (WKY) were used in these tests. Ketamine-anesthetized rats received $1.25 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ketamine, iv, and were ventilated with 20% O_2 and 80% room air. Responses were compared with rats anesthetized with 70% nitrous oxide, and 30% oxygen. CBF and CMR_{O_2} responses were determined according to previously described methods⁵ under control anesthetized conditions and during hemorrhagic-induced hypotension to levels of 80–85 mmHg and 50–55 mmHg. Radioactive microspheres were used to measure CBF; CMR_{O_2} was calculated as the product of CBF and arterial-sagittal sinus blood oxygen content difference. Arterial blood P_{CO_2} was maintained at 35–40 mmHg and body temperature at 37°C. The data, shown in table 1, indicate that cerebral autoregulatory responses were similar between nitrous-oxide- and ketamine-anesthetized rats. CBF, but not CMR_{O_2} , was increased significantly in ketamine- compared with nitrous-oxide-anesthetized rats under control conditions ($P < 0.05$).

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¶ Barry D, Strangaard S, Svendsen U, et al: Adaptive changes in the lower limit of cerebral blood flow auto-regulation in hypertensive rats. *Journal Cerebral Blood Flow and Metabolism* 1:540, 1981.

TABLE 1. Blood Pressure, CBF, and CMR_{O_2} under Control Anesthetized Conditions and during Hemorrhagic-induced Hypotension

Anesthesia	n	Blood Pressure (mmHg)	Cerebral Blood Flow (ml · 100 g ⁻¹ · min ⁻¹)	Cerebral Oxygen Consumption (ml · 100 g ⁻¹ · min ⁻¹)
70% N ₂ O, 30% O ₂	7	141 ± 8	85 ± 5	5.6 ± 0.4
	7	85 ± 2 (-40%)*	75 ± 10 (-11%)	5.1 ± 0.6 (-8%)
	7	52 ± 2 (-63%)*	52 ± 5 (-39%)*	4.5 ± 0.4 (-20%)
Ketamine	11	129 ± 2	119 ± 12	6.5 ± 0.8
	9	81 ± 1 (-37%)*	106 ± 17 (-11%)*	6.5 ± 1.1 (+0.3%)
	8	56 ± 2 (-57%)*	88 ± 12 (-40%)*	5.5 ± 1.1 (-15%)

* $P < 0.05$ compared with control treatment in each group.

Ketamine-anesthetized rats received 1.25 mg · kg⁻¹ · min⁻¹, iv. Percentage change values are shown in parentheses and are reported, compared with control anesthetized conditions. Comparing nitrous-oxide- vs. ketamine-anesthetized rats under control conditions, blood

CBF did not significantly change in nitrous-oxide- or ketamine-anesthetized rats at a pressure of 80–85 mmHg, but decreased significantly at 50–55 mmHg. This is consistent with a lower limit of cerebral autoregulation between 60 and 70 mmHg as reported in humans and other species.^{10,11} CMR_{O_2} was maintained in both ketamine- and nitrous-oxide-anesthetized rats during hemorrhagic-induced hypotension. Ketamine-anesthetized rats appeared more stable throughout the experimental protocol, perhaps due to the inadequacy of 70% nitrous oxide as a complete anesthetic. For these reasons, it was decided to use ketamine anesthesia in experiments testing the cerebral autoregulatory changes which occur in the hypertensive rat following antihypertensive therapy.

ANTIHYPERTENSIVE DRUG TREATMENT

Four-month-old male, spontaneously hypertensive rats (SHR) and Wistar Kyoto control rats (WKY) (Charles Rivers Inc.) were used in these experiments. Systolic blood pressure was measured indirectly one to two times per week using the tail cuff occlusion apparatus of Narco Biosystem. Rats were warmed in a 32°C temperature-controlled oven to allow tail systolic pressure measurement. Preliminary experiments were performed in order to determine the appropriate drug dosage for antihypertensive treatment. Two vasodilator drugs were chosen which may produce their hypotensive action by different mechanisms.¹² Minoxidil (2 mg · kg⁻¹ · day⁻¹) and hydralazine (8 mg · kg⁻¹ · day⁻¹), both vasodilators, produced moderate hypotension, but recovery of blood pressure was noted after several weeks. A combined treatment of 2 mg · kg⁻¹ minoxidil, 8 mg · kg⁻¹ hydralazine, and 8 mg · kg⁻¹ propranolol per day was observed to produce a decrease in blood pressure to the approximate level of that seen in untreated WKY, and was maintained for the 10-week treatment period. The drugs were added to the drinking water with the concentration adjusted to the daily intake of the rat.

pressure and CMR_{O_2} were not significantly different ($P > 0.10$). Changes in blood pressure, CBF, and CMR_{O_2} during hemorrhagic-induced hypotension were not significantly different between the two anesthetic treatment groups ($P > 0.10$).

Four test groups were chosen with 15 rats per group. SHR and WKY received either ten weeks of antihypertensive drug or sham (water) treatment. Initiation of treatment was staggered so that an equal number of rats from each group completed the treatment regimen and could be tested each week.

SURGERY

At the end of the 10-week period of drug or sham treatment, rats from each test group were prepared for microsphere test procedures. Rats were anesthetized with 1.5–2.0% halothane to allow the insertion of a PE-50 tubing catheter into the femoral vein. Once inserted, an iv infusion of 1.25 mg · kg⁻¹ · min⁻¹ ketamine was started and the halothane was discontinued. At least one hour elapsed between the time of terminating the halothane and the start of experimental tests. Rats received a constant iv infusion of 1.25 mg · kg⁻¹ · min⁻¹ ketamine during the surgical and test procedures using a Harvard® infusion/withdrawal pump. A tracheostomy was performed and the rat was ventilated mechanically with 20% oxygen and 80% room air using a Harvard small animal respirator. PE-50 tubing catheters, filled with heparinized isotonic saline, were inserted into both femoral arteries and both femoral veins and into the left ventricle via the right carotid artery. Pressure pulses were monitored to ensure proper placement of the ventricular catheter. Following the completion of this surgery all incisions were closed using wound clips and the rat was positioned in a stereotaxic head holder. The skull was exposed, the bone over the sagittal sinus drilled away, and a 23-gauge needle inserted into the sinus stereotaxically to be used for drawing blood samples. Following the completion of all surgical procedures, the rat was allowed 15 min to stabilize. During this time the arterial P_{CO_2} was adjusted to approximately 35 mmHg. Rectal temperature was monitored using a Yellow Springs Inc.® thermoprobe and body temperature was maintained at 37°C with the aid of overhead

heat lamps. Mean blood pressure was recorded continuously from a femoral artery catheter.

INDUCTION OF HYPOTENSION

In preliminary experiments, a high rate of tachyphylaxis was observed in SHR during SNP-induced hypotension. This is consistent with a previous report.¹³ Hexamethonium ($1 \text{ mg} \cdot \text{kg}^{-1}$) infused slowly iv abolished the development of tachyphylaxis with little change in baseline blood pressure. In these experiments, $1 \text{ mg} \cdot \text{kg}^{-1}$ hexamethonium was infused iv over 5 min in each rat in order to produce a minimal change in blood pressure. Ten minutes later, microsphere tests were started. Each rat received up to three microsphere tests, all of which were completed within 90 min of hexamethonium treatment.

Microsphere tests were performed using a modification of previously described methods.^{5,13} Tests were performed randomly in all four test groups under each of three test conditions: 1) control: no SNP infusion; 2) mid-pressure: SNP was infused to maintain a mean pressure level of 85–90 mmHg for 10 min; and 3) low-pressure: SNP was infused to maintain a pressure level of 55–60 mmHg for 10 min. The SNP infusion rate, mean blood pressure, and heart rate were noted immediately before each microsphere test. SNP was dissolved in isotonic saline at $1 \text{ mg} \cdot \text{ml}^{-1}$ before each test and protected from the light during the infusion. The SNP infusion rate was controlled using a Harvard variable speed infusion pump.

MICROSPHERES

Before each microsphere injection the pressure pulses of the left ventricular catheter were monitored to ensure proper catheter placement. Three separate labeled microspheres were used, cobalt-57, ruthenium-103, and scandium-46 (New England Nuclear). Stock solutions containing 500,000 $15\text{-}\mu\text{m}$ microspheres per milliliter were suspended in isotonic saline with 0.01% Tween-80®. Microsphere samples were vortexed for one minute, a 0.2-ml sample withdrawn, injected into the left ventricle, and flushed in with 0.2 ml saline over a 20-s period. Starting immediately before each injection and continuing 45 s after the end of the microsphere injection, blood was withdrawn from both femoral artery catheters at a rate of $0.4 \text{ ml} \cdot \text{min}^{-1}$ using a 2-channel Harvard infusion/withdrawal pump. Arterial blood-gas measurements were obtained at the end of each microsphere test. Arterial and sagittal sinus blood samples also were taken after each microsphere test for measurement of cerebral arterial-venous blood oxygen content difference. Blood pressure was maintained at each respective pressure level throughout the testing pro-

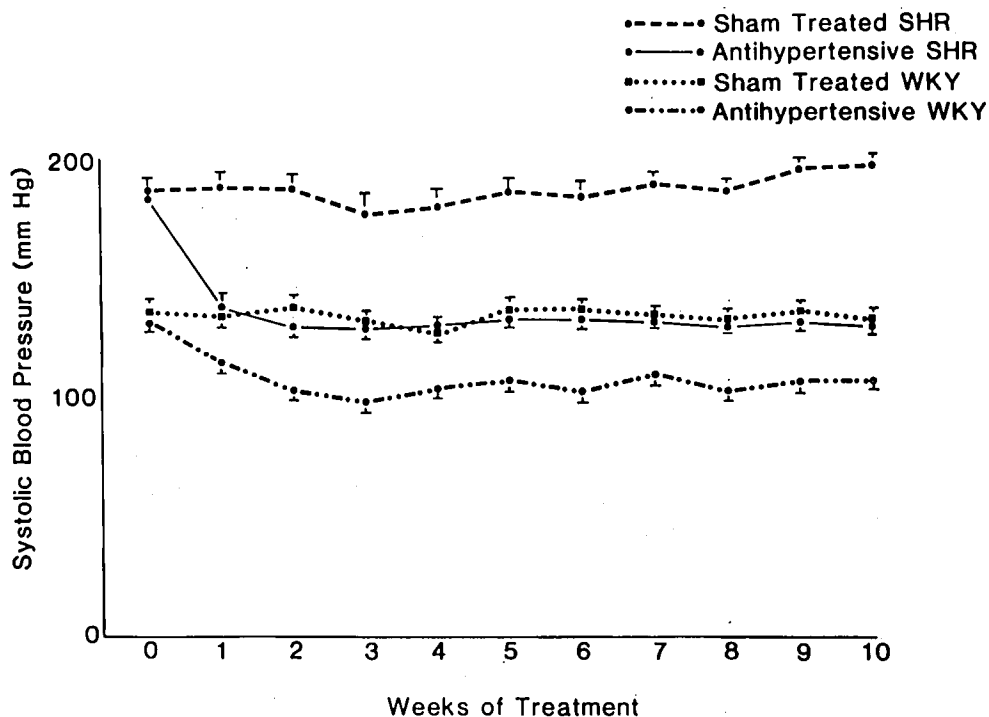
cedure. Blood that was withdrawn during each microsphere test was replaced with rat donor blood. The rat was allowed 15 min to stabilize before the next test procedure. Rats whose blood pressure did not recover to within 10% of control levels during the stabilization period were not continued in the study. At the end of the third or final microsphere test the rat was killed and the brain removed, weighed, and stored in 10% formalin overnight. The following day, the activity of each microsphere label in brain and blood samples was analyzed using a Nuclear Chicago 1035® gamma counter and Nuclear Data 600® multi-channel analyzer. CBF was analyzed according to the methods of Heymann *et al.*¹⁴ using an Interdata® computer. Oxygen content of blood was calculated from measurements of oxyhemoglobin (Instrumentation Laboratory CO-oximeter) and oxygen tension (Instrumentation Laboratory 1303 blood-gas analyzer). CMR_{O_2} was calculated as the product of CBF, corrected for brain weight and cerebral arterial-venous blood-oxygen content difference. Preliminary tests indicated that three repeated control microsphere tests in the same rat produced reproducible measures of CBF and CMR_{O_2} under the same experimental conditions as used here. All data are reported as means \pm SE. Blood pressure, arterial blood gases, CBF, and CMR_{O_2} changes during hypotension were compared within groups using unpaired *t* tests. CBF and CMR_{O_2} responses to graded hypotension were analyzed between test groups using unpaired *t* tests and a treatment by groups analysis of variance. Changes in CBF and CMR_{O_2} during SNP-induced hypotension were compared between each test group using *F* tests for intergroup analysis, as described by Bruning and Kintz.¹⁵

Results

The effect of antihypertensive drug treatment on systolic blood pressure is shown in figure 1. Sham treatment had no significant effect on blood pressure in SHR or WKY over the 10-week treatment period. In SHR, the combined treatment with minoxidil, hydralazine, and propranolol decreased systolic blood pressure to the same level seen in sham-treated WKY by the second week and pressure was maintained at this level for the remainder of the ten week treatment period. Tail systolic pressure also decreased significantly in drug-treated WKY over the 10-week treatment period. At the time of testing, body weights for each of the groups were as follows: sham-treated SHR = $373 \pm 8 \text{ g}$; drug-treated SHR = $377 \pm 9 \text{ g}$; sham-treated WKY = 402 gm ; and drug-treated WKY = $428 \pm 7 \text{ g}$.

Blood-gas, cardiovascular, and cerebrovascular changes under control anesthetized conditions and during SNP-induced hypotension are shown in table 2. Before hexamethonium treatment, mean blood pressure

FIG. 1. Tail systolic blood pressure changes in SHR and WKY during antihypertensive drug (2 mg·kg⁻¹ minoxidil, 8 mg·kg⁻¹ hydralazine, 8 mg·kg⁻¹ propranolol) per day or sham treatment for 10 weeks (n = 15 per group). As determined by analysis of variance, antihypertensive drug treatment decreased blood pressure in SHR and WKY compared to sham treatment over the 10-week treatment period (*P* < 0.01). Blood pressure of drug-treated SHR was not different from sham-treated WKY during the treatment period (*P* > 0.10).



of each of the test groups were as follows: sham-treated SHR = 189 ± 6 mmHg; antihypertensive-treated SHR = 146 ± 5 mmHg; sham-treated WKY = 138 ± 3 mmHg; and antihypertensive treated WKY = 103 ± 3 mmHg. As shown in table 2, hexamethonium treatment produced a modest decrease in blood pressure in each

of the test groups. Antihypertensive drug treatment produced a significant decrease in blood pressure in both SHR and WKY (*P* < 0.01). The percentage decrease in blood pressure was 23% in SHR and 25% in WKY. Blood pressure was decreased to similar mid and low pressure levels in SHR and WKY using SNP infu-

TABLE 2. Cardiovascular, Cerebrovascular, and Arterial Blood-gas Values under Control Anesthetized Conditions and during SNP-induced Hypotension

	BP	HR	P _{CO₂}	P _{O₂}	pH	CBF	AV _{O₂}	CMR _{O₂}	n
Untreated WKY									
Con	120 ± 4	327 ± 14	39 ± 1	135 ± 5	7.37 ± 0.01	134 ± 6	5.2 ± 0.3	6.9 ± 0.3	12
Mid	88 ± 2*	322 ± 20	39 ± 2	142 ± 7	7.37 ± 0.01	125 ± 8	5.8 ± 0.4	6.9 ± 0.5	10
Low	54 ± 2*	324 ± 29	37 ± 2	144 ± 9	7.40 ± 0.01	89 ± 8*	6.9 ± 0.6*	5.8 ± 0.5	10
Treated WKY									
Con	94 ± 6†	297 ± 19	37 ± 1	127 ± 7	7.37 ± 0.02	139 ± 14	4.5 ± 0.4	6.4 ± 0.5	10
Mid	82 ± 2*	280 ± 15	37 ± 1	126 ± 3	7.40 ± 0.01	146 ± 8	5.0 ± 0.2	6.9 ± 0.5	9
Low	55 ± 2*	300 ± 12	35 ± 1	136 ± 4	7.41 ± 0.01	91 ± 4*	6.0 ± 0.3*	5.5 ± 0.4*	11
Untreated SHR									
Con	180 ± 6	384 ± 11	37 ± 1	149 ± 7	7.38 ± 0.01	119 ± 6	5.8 ± 0.4	6.2 ± 0.4	9
Mid	92 ± 2*	378 ± 7	36 ± 1	151 ± 7	7.36 ± 0.01	61 ± 9*	8.1 ± 0.3*	5.7 ± 0.6	10
Low	58 ± 2*	349 ± 11	34 ± 2	145 ± 9	7.38 ± 0.02	37 ± 5*	8.8 ± 0.7*	3.5 ± 0.5*	9
Treated SHR									
Con	139 ± 3†	369 ± 11	36 ± 1	138 ± 4	7.41 ± 0.01	107 ± 12	4.8 ± 0.2	5.1 ± 0.7	8
Mid	91 ± 2*	372 ± 14	36 ± 1	131 ± 6	7.41 ± 0.01	102 ± 13†	5.0 ± 0.4†	5.3 ± 0.8	9
Low	56 ± 4*	354 ± 19	34 ± 1	137 ± 7	7.41 ± 0.01	55 ± 5*†	6.2 ± 0.4*†	3.5 ± 0.3*	10

Values reported as means ± SE.

* *P* < 0.05 compared with control treatment in each group.

† *P* < 0.05 antihypertensive compared with sham-treated rats.

BP = arterial blood pressure (mmHg); HR = heart rate (min⁻¹);

P_{CO₂} = arterial P_{CO₂} (mmHg); P_{O₂} = arterial P_{O₂} (mmHg); pH = arterial pH; CBF = cerebral blood flow (ml · 100 g⁻¹ · min⁻¹); AV_{O₂} = cerebral

arterial-venous O₂ content (ml O₂ · dl⁻¹); CMR_{O₂} = cerebral O₂ consumption (ml · 100 g⁻¹ · min⁻¹).

Con = control blood pressure during 1.25 mg · kg⁻¹ · min⁻¹ ketamine and 1 mg · kg⁻¹ hexamethonium. Blood pressure for Mid and Low range were produced by iv SNP infusion.

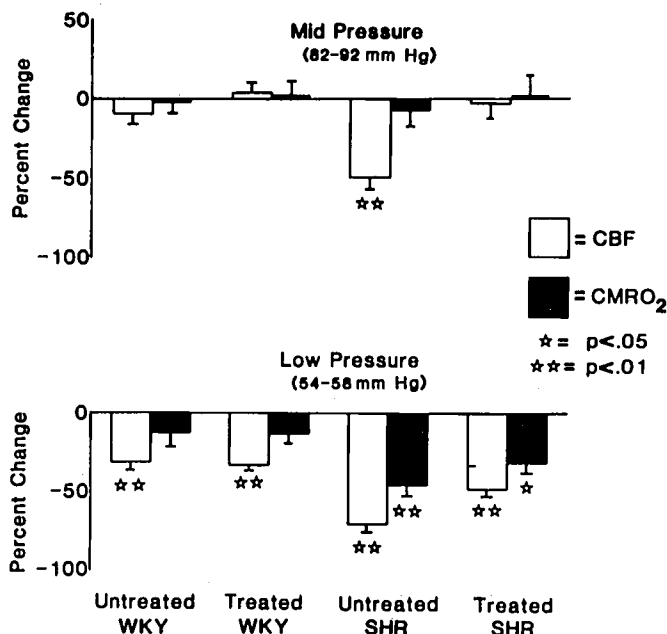


FIG. 2. Change in CBF and CMR_{O_2} in antihypertensive (treated) and sham (untreated) SHR and WKY. Data plotted as per cent change from control values obtained in each group. Mid and low pressures were produced by SNP infusion and are reported in table 1. Significant values indicate change from control values observed in each group. By analysis of variance, decreases in CBF and CMR_{O_2} during SNP-induced hypotension were significantly greater in sham-treated SHR than in antihypertensive-treated SHR or either WKY treatment group. Decreases in CBF and CMR_{O_2} during SNP-induced hypotension were also greater in antihypertensive-treated SHR compared with either WKY test group ($P < 0.05$) but were not different between antihypertensive- and sham-treated WKY ($P > 0.10$).

sion. The SNP infusion rates required for each group were as follows: sham-treated SHR, mid-pressure = $19 \pm 8 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, low-pressure = $43 \pm 13 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$; antihypertensive-treated SHR, mid-pressure = $13 \pm 5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, low-pressure = $15 \pm 5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$; sham-treated WKY, mid-pressure = $8 \pm 3 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, low-pressure = $18 \pm 5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$; antihypertensive-treated WKY, mid-pressure = $4 \pm 3 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, low-pressure = $9 \pm 1 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. As analyzed by analysis of variance, both CBF and CMR_{O_2} varied significantly between SHR and WKY test groups under control anesthetized conditions ($P < 0.01$). Therefore, CBF and CMR_{O_2} changes during SNP-induced hypotension were analyzed as per cent change from control as shown in figure 2. Analysis of variance of these data indicated a significantly greater decrease in CBF and CMR_{O_2} in sham-treated SHR during SNP-induced hypotension compared with antihypertensive-treated SHR and each of the WKY test groups ($P < 0.05$). Decreases in CBF and CMR_{O_2} during SNP-induced hypotension were also significantly greater in antihypertensive-treated SHR compared with either

WKY test group ($P < 0.05$), but were not significantly different between antihypertensive- and sham-treated WKY.

Discussion

It has been reported that chronic hypertension produces a shift in cerebral autoregulation and inhibits the ability of these subjects to maintain CBF and CMR_{O_2} during hypotension induced by hemorrhage or ganglionic blockade.¹⁻³ Further, these changes are magnified by aging.⁴ Recently, we tested the possibility that CBF and CMR_{O_2} could be maintained in SHR during SNP-induced hypotension because of the reported direct vasodilating effect of the drug.⁵ We found instead that CBF and CMR_{O_2} decreased in young and aged SHR but not in WKY during moderate SNP-induced hypotension (65 mmHg). Those results are supported by the current study. During SNP-induced hypotension, the lower limit of cerebral autoregulation was between 55 and 85 mmHg in WKY. This is consistent with the estimates of 60-70 mmHg reported in normal humans by Lassen¹⁰ and Oleson.¹¹ In untreated SHR, the lower limit of autoregulation was above 92 mmHg and CMR_{O_2} was decreased when the blood pressure was lowered to 58 mmHg. This is in agreement with Stranggaard *et al.*¹⁶ who reported a lower limit of autoregulation of 120 mmHg in hypertensive humans and a hypoxic limit of 68 mmHg.

Results presented here indicate that antihypertensive therapy can produce a significant improvement in terms of maintenance of CBF and CMR_{O_2} during hypotensive challenges. While these data suggest the importance of antihypertensive therapy in medical treatment, ultimate evaluations must be based on clinical experience. The model used in these experiments was the genetically hypertensive rat. Cerebral autoregulatory mechanisms appear to be similar in the rat model compared with humans. A shift in cerebral autoregulation occurs in hypertensive rat which is similar to that reported in humans.^{2,4,10} Further, a reversal of hypertension-induced cerebrovascular changes also has been reported in humans following antihypertensive therapy.¹⁷ However, the hypertensive rat, unlike humans, does not develop atherosclerosis during hypertension.¹⁸ This and other possible differences between humans and rats may alter the time course and the overall ability of antihypertensive therapy to improve cerebrovascular function in a clinical setting.

The purpose of these studies was to evaluate the effect of antihypertensive treatment on the ability of SHR to maintain CBF and CMR_{O_2} during SNP-induced hypotension. Ketamine was chosen as the anesthetic because of its ability to maintain adequate anesthesia without depressing CBF or CMR_{O_2} . Preliminary experi-

ments indicated that in normotensive rats, ketamine increased control CBF compared with rats anesthetized with 70% nitrous oxide and 30% oxygen, but that cerebral autoregulatory responses were similar between the two anesthetic regimens. An ability to maintain the surgical preparation for a longer time with consistent blood gases was apparent with ketamine, perhaps due to the inadequacy of nitrous oxide as a complete anesthetic. For these reasons, ketamine was chosen as the anesthetic for these studies. Ketamine has been shown to increase CBF and possibly CMR_{O_2} by some,^{19,20} but not all, investigators.²¹ While Dawson *et al.*¹⁹ reported a small but significant increase in CMR_{O_2} with ketamine, others have found no significant change during ketamine anesthesia.^{20,21} This appears consistent with data reported here as compared with 70% nitrous-oxide- and 30% oxygen-induced anesthesia. However, the maintenance of normal cerebral autoregulatory responses with ketamine suggest that the cerebrovascular changes observed in sham- and drug-treated SHR were primarily due to the chronic hypertensive state and antihypertensive therapy, respectively, and not the effect of the anesthetic.

Hexamethonium is a ganglionic blocker which does not cross the blood-brain barrier.²² It was used in these experiments to inhibit reflex cardiovascular responses which are apparent during SNP-induced hypotension.²³ This was accomplished with minimal changes in baseline blood pressure. Without hexamethonium it was necessary to infuse much larger doses of SNP during the hypotensive period and a high incidence of cardiovascular failure was observed in SHR, probably due to cyanide toxicity.²⁴ It is doubtful that hexamethonium altered cerebral autoregulation in these studies since it has no reported direct effects on cerebral vessels or the central nervous system and has been used in early studies in humans to test cerebral autoregulation.³

It was observed here that antihypertensive-treated SHR and WKY had consistently and significantly lower CMR_{O_2} compared with untreated controls. This may be related to the central beta-adrenergic blocking action of propranolol. It has been shown that under certain conditions, sympathetic stimulation will increase CMR_{O_2} and this effect can be blocked by propranolol pretreatment.²⁵ Not only did propranolol block the effect of sympathetic stimulation but it also produced a moderate decrease in CMR_{O_2} when infused alone (20%).²⁵ This led MacKenzie *et al.*²⁵ to conclude that CMR_{O_2} can be increased by beta-adrenergic mechanisms in the brain and that a basal noradrenergic drive on cerebral metabolism can be blocked by propranolol. If a similar effect occurred in these experiments, it may represent a long-term effect of propranolol on baseline metabolism or a moderation of acute effects produced

by ketamine anesthesia and/or the surgical and experimental procedures.

The finding that antihypertensive drug treatment improves the maintenance of CBF and CMR_{O_2} in SHR during hypotension is consistent with the report of Stranggaard.¹⁷ He found that the lower limit of autoregulation was decreased in hypertensive patients given antihypertensive treatment compared with untreated hypertensive subjects. The shift in cerebral autoregulation to a higher pressure range in the hypertensive subject is accompanied by a structural change in resistance vessels and an increased wall/lumen ratio of cerebral arteries.²⁶⁻²⁸ The improvement in the cerebrovascular response to SNP-induced hypotension after antihypertensive drug treatment may be due to a reversal of cerebral resistance vessel hypertrophy. Warshaw *et al.*²⁹ reported that 23 weeks of antihypertensive drug therapy in SHR lowered the resistance vessel smooth muscle cell content in the arterial vasculature in direct proportion to the reduction in blood pressure. Weiss⁷ showed that 10 weeks of antihypertensive treatment in SHR significantly decreased the resistance observed at maximal dilation in the rat hind-limb, and Lundgren⁸ found that hind-limb vascular resistance changes induced in renal hypertensive rats could be reversed rapidly by reducing the blood pressure. The fact that we did not see a complete reversal of cerebrovascular changes in SHR after 10 weeks of antihypertensive therapy may be due to an inadequate length of treatment or because of structural changes, such as fibri-nohyalin incorporation into vessel walls.³⁰ Such an effect would inhibit the reversal of resistance vessels to a normotensive state.

In conclusion, these results provide evidence that cerebrovascular changes induced by chronic hypertension can be reversed partially by antihypertensive drug treatment. It may be possible to produce a more complete reversal of these cerebrovascular changes by longer drug treatment or by use of different antihypertensive drugs. The ability to improve cerebral autoregulation may be related to the ability of antihypertensive drugs to reverse cerebrovascular hypertrophy produced in the hypertensive subject. If this is true, it is expected that reversal of cerebral autoregulatory changes may be difficult to achieve in aged hypertensive subjects in which structural vascular lesions and arteriolar intimal fibri-nohyalin lesions are more prominent.¹⁸

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