Cerebral Vasomotor Reactivity in Normotensive and Spontaneously Hypertensive Rats

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SUMMARY Intravenously injected metaraminol induced a larger blood pressure increase in spontaneously hypertensive rats (SHR) than in normotensive controls (NR) when the pressure was raised from the same starting level. Cerebral blood flow (CBF) response in NR was either perfect autoregulation, partial autoregulation or "break-through." When present, the autoregulatory response was very rapid, i.e. the flow returned to the initial value within 10-15 sec. All SHR showed an initial prompt vasoconstrictor response which was followed after 30-40 sec by a gradual flow increase. The blood pressure elevation was highest in SHR when hypertension was induced by compression of the aorta, which supports the hypothesis that the enhanced response is, at least in part, a consequence of an increased vessel wall to lumen ratio. The characteristic CBF pattern observed in SHR after a metaraminol-induced rise in blood pressure was not seen when the blood pressure was increased by aortic compression, which suggests an effect of the drug separate from its pressor effect.

During maximum vasodilatation the cerebrovascular resistance (CVR) was considerably higher in SHR than in NR. Assuming an equivalent vessel density in the 2 groups, our results suggest that structural changes in resistance vessels in SHR encroach on the lumen.

CEREBRAL arterial vessels of spontaneously hypertensive rats (SHR) have an increased vessel wall to lumen ratio compared to normotensive controls (NR). Morphometric studies have not decisively answered the question whether the internal radius is decreased as the blood flow varies with the fourth power of the radius even a slight lumen reduction would considerably decrease the cerebral blood flow (CBF) during maximum vasodilatation and lead to enhanced cerebrovascular resistance (CVR). An increased resistance at complete relaxation of the vascular smooth muscles has been found in SHR in other vascular beds.

A decreased internal radius and increased vessel wall to lumen ratio could help explain the fact that SHR are less likely to develop blood-brain barrier (BBB) dysfunction at abrupt blood pressure increase than NR.

Earlier studies have concerned the reaction of cerebral vessels to changes in perfusion pressure in the rat, but the methods used have not allowed a study of rapid or transient responses. A recently developed venous outflow method now makes it possible to record rapid changes in CBF in the rat. The aim of the present study was to compare the responses in NR and SHR after an abrupt blood pressure increase induced by metaraminol or compression of the thoracic aorta and to study CBF and CVR during maximal vasodilatation at different levels of perfusion pressure.

Material and Methods

Five SHR and 5 NR (local Wistar rats) were used to study hemodynamic responses to an abrupt increase in blood pressure induced by metaraminol. The rats were 4-months-old except for 2 SHR which were 1-year-old. Anesthesia was induced with halothane, the rats were tracheotomized and immobilized with tubocurarine chloride and thereafter mechanically ventilated with a gas mixture containing N2O:O2 in the volume proportions 3:1 with 0.6-0.8 percent halothane added. Cannulae were inserted in a femoral vein (for administration of drugs and blood) and both femoral arteries (for electromanometric recording of mean arterial pressure, MAP, and for sampling arterial blood for blood gas determinations). Halothane was then temporarily withdrawn until a stable blood pressure recording had been obtained. Thereafter, halothane was again added. The main dorsal cerebral venous outflow vessel, the retroglenoid vein, was cannulated on the left side close to its exit from the skull and the blood diverted through a closed extracorporeal circuit with a drop recording device. The blood was returned to the central venous circulation via a catheter in the external jugular vein. The contralateral retroglenoid vein was occluded to minimize extracerebral contamination. For details of the procedure, see Nilsson and Siesjö. Via a needle in the cisterna magna connected to a closed manometer system, the intracisternal pressure (ICP) was measured and the perfusion pressure was calculated as MAP-ICP. After the operative procedures were completed halothane was withdrawn and MAP was lowered to 110-120 mm Hg by bleeding to achieve the same initial pressure in SHR and NR. Repeated blood gas determinations were made to ensure a stable baseline with PACO2 35-42 mm Hg and Pao2 greater than 100 mm Hg. Body temperature was kept close to 37°C by means of intermittent external heating. The photoelectric drop signal, MAP and ICP were continuously recorded with a polygraph. Approximately 30 min after withdrawal of halothane an abrupt blood pressure increase was induced by intravenous metaraminol (0.4 mg • kg⁻¹). Thirty minutes after the blood pressure had returned to approximately initial levels, a second dose of metaraminol was given. Finally, bicuculline, which induces maximal cerebral vasodilatation in combination with an abrupt increase in MAP, was given i.v. (1.2 mg • kg⁻¹). The volume
of venous outflow was converted to CBF in ml • 100 g⁻¹ • min⁻¹ as earlier described.\textsuperscript{12, 13}

In order to compare pressure and flow responses to pharmacologically and mechanically induced acute hypertension, the blood pressure was raised by compression of the thoracic aorta in 4 additional rats (2 SHR and 2 NR).

In a second series 4 SHR and 4 NR (Kyoto Wistar) were used to study CBF during maximum vasodilatation at different levels of perfusion pressure. The rats were approximately 4-months old. The animals were anesthetized and operated on as above but no extracorporeal circuit was established. The retroglenoid vein catheter was used for blood sampling (oxygen content determination) and for recording of the cerebral venous pressure. CBF and CVR were calculated from the arteriovenous difference of oxygen (AVDO₂) assuming a constant cerebral metabolic rate. This assumption seems justified since it was shown in an earlier report that the cerebral metabolic rate of oxygen is constant when the pressure is reduced by bleeding at the levels of perfusion pressure used in the present study.\textsuperscript{13} CVR was expressed in peripheral resistance units per 100 g tissue, PRU₅₀ = perfusion pressure in mm Hg over CBF in ml • 100 g⁻¹ • min⁻¹.

Cerebral vasodilatation was induced by 10 percent CO₂ and AVDO₂ determined at various levels of perfusion pressure starting at high levels and lowering the blood pressure by bleeding down to a perfusion pressure of 50 mm Hg.

Results

Hemodynamic Responses to Metaraminol

The basic MAP levels were 120–130 mm Hg in NR and 170–190 mm Hg in SHR. Starting from approximately the same level, i.e. 110–125 mm Hg, the pressure response to metaraminol was more pronounced in SHR than in NR (maximal MAP 220–255 and 180–210 mm Hg respectively). The pressure increase observed within 5 sec after the pressure started to rise was not significantly different (55–100 mm Hg in SHR and 60–100 mm Hg in NR). Whereas no further increase was seen in NR (except for one rat that showed a rise of 10 mm Hg during 70 sec) the pressure continued to rise in all SHR reaching maximum levels 35–80 sec after the injection of metaraminol. After a transitory flow increase lasting 5–10 sec, which was seen in all rats except for one SHR, the flow response varied and 4 patterns were noticed:

A. CBF promptly returned to the initial CBF level (within 10 sec). The pattern is illustrated in figure 1 and was seen in 2 NR with a moderate increase in MAP (60 and 65 mm Hg) and maximum MAP 180 and 190 mm Hg respectively.

B. A vasoconstrictor response was seen but the CBF remained on a higher level than the initial one, presumably indicating that not all vessels autoregulated (one NR in which MAP rose 80 mm Hg).

C. In 2 NR, with an increase in MAP of 90 and 100 mm Hg, there was no constrictory response. CBF increased and remained high until the MAP decreased, i.e. a "breakthrough" of autoregulation\textsuperscript{14} had occurred (fig. 2).

D. The fourth pattern, which was seen in all 5 SHR studied, was an initial prompt vasoconstrictory response resulting in a return of CBF close to the initial value within 5–10 sec. However, after 30–40 sec a successive increase of CBF took place, indicating that the vessels could not withstand the very high perfusion pressure (fig. 3).
In spontaneously hypertensive rats an initial prompt vasoconstriction is seen but approximately 30 sec after the pressure increase the vessels start to yield resulting in a gradual flow increase.

Thus the flow response varied considerably after the first metaraminol administration. In contrast, the second injection 30 min after the pressure had returned to initial levels, resulted in a uniform response and CBF increased in all NR and SHR. Except in one rat, which showed an almost fourfold increase in CBF, the flow in hypertensive "breakthrough" increased 2-2.5 times and did not reach the very high levels obtained after administration of bicuculline which induces a diffuse cerebral vasodilatation in combination with an abrupt MAP increase (cf Meldrum and Nilsson12).

**Hemodynamic Responses to Compression of Thoracic Aorta**

In this hypertension model the elevation of MAP was greatest in SHR. (MAP increased to 220–225 m Hg in SHR compared to 180–185 mm Hg in NR from a starting level of approximately 90 mm Hg in all rats.) However, the CBF response was uniform and both NR and SHR showed an immediate and lasting CBF increase. When the blood pressure had normalized at the starting level after a hypertensive episode with "breakthrough," it usually took about 10 min before the CBF had returned to the initial level. There was no difference between the rats made hypertensive by compression of the aorta or by i.v. injection of metaraminol.

**CVR during Maximum Vasodilatation**

*Bicuculline.* CVR was higher in SHR than in NR at all perfusion pressures studied (180–50 mm Hg). In both groups CVR was slightly higher than the values recorded during hypercapnic vasodilatation presented below. Thus, at high perfusion pressures (160–180 mm Hg), CVR was 0.3 in NR and 0.6 in SHR. The value for NR was also somewhat higher than earlier reported12 and it is likely that the prior manipulation of the rats with repeated hypertensive episodes had changed the vessel reactivity to some extent.

**Hypercapnia.** The basic MAP was 115–130 mm Hg in NR and 160, 160, 180 and 185 in the 4 SHR. PaCO₂ was repeatedly checked in all rats and varied between 84 and 109 mm Hg with no systematic difference between SHR and NR. CVR was higher in SHR at all levels of perfusion pressure studied (see fig. 4). While CVR did not differ much within the NR group there was a considerable spread of values in the SHR group. At the perfusion pressure of 100 mm Hg CVR was 0.20 in NR and 0.51 in SHR (range 0.35–0.70). As could be expected the highest resistance was found in the 2 most hypertensive SHR (MAP 180 and 185 mm Hg). In these 2 rats the proportional difference in resistance compared to NR was larger at high perfusion pressures which might indicate a certain stiffness of the vessels.

**Discussion**

The greater MAP response to i.v. metaraminol in SHR than in NR is in agreement with earlier studies on the effect of vasoactive drugs.4–7 The fact that an enhanced response was obtained when the pressure was raised by compression of the thoracic aorta supports the hypothesis that it is, at least in part, a consequence of an increased vessel wall to lumen ratio in SHR leading to a more marked reduction of the lumen for the same degree of shortening of the smooth muscle cell.4 The flow responses in NR indicated that the upper limit of cerebral autoregulation was reached in some but not all NR. Hernandez et al.11 reported that the upper limit of autoregulation in the rat is about 160 mm Hg when the blood pressure is increased by metaraminol. Our results suggest that a higher blood pressure can be tolerated at least during a short-lasting drug-induced hypertensive episode. It should be stressed that our study was not primarily concerned with the limits of autoregulation in the 2 groups but with the vascular response to large and rapid pressure changes. The uniformity of response after the second injection of metaraminol, i.e. the occurrence of "break-through" in all rats, suggests that

![Figure 3](http://stroke.ahajournals.org/)

**Figure 3.** Cerebrovascular resistance (CVR) at various perfusion pressures in spontaneously hypertensive rats (SHR) and normotensive rats (NR) during cerebral vasodilatation induced by hypercapnia.
repeated hypertensive episodes may be more harmful to the brain than isolated episodes.

The time-course of the autoregulatory response has been much debated. It is probably influenced by such factors as the initial tone of the resistance vessels and how the pressure increase is induced. Our results show that when the pressure is increased by a vasoactive drug in the rat the autoregulatory response can be very prompt, i.e., the flow returned to the initial value within 10-15 sec.

The present observation that the increase in CBF during hypertensive "break-through" is not so pronounced as when hypertension is combined with a generalized vasodilatation induced by e.g., bicuculline or hypercapnia, is in accordance with earlier studies demonstrating that CBF is heterogenous in acute hypertension.16-17

In spite of the very high MAP induced by metaraminol in SHR (220-255 mm Hg) the cerebral vessels reacted with prompt vasoconstriction which, however, was followed after 30-40 sec by a gradual flow increase (fig. 3). As this characteristic response was not seen when the pressure was raised by compression of the thoracic aorta a pharmacological effect of metaraminol might be responsible for the enhanced but transitory capacity of cerebral vessels in SHR to constrict at very high levels of MAP.

Metaraminol releases norepinephrine and it is known that norepinephrine can have profound effects on CBF and CMRO₂ when the BBB is disturbed.18 Like catecholamines, metaraminol does not significantly pass an intact BBB. However, one possible explanation to the "delayed break-through" in SHR could be that the pressure increase had resulted in areas of BBB dysfunction in spite of a constant CBF and that the gradual increase in CBF was metabolically induced by an intracerebral release of norepinephrine. If so, CMRO₂ would be increased at the time of flow increase but according to our preliminary observations, that is probably not the case.

The wall to lumen ratio is increased in arterial vessels of SHR down to a vessel diameter of 20μm.2, 3 Assuming the same vessel density and no primary difference in CO₂ response, the higher CVR in SHR than in NR during vasodilatation would indicate that structural changes in resistance vessels encroach on the lumen. The values obtained would correspond to an approximate 15 percent decrease of the internal radius. It has been argued that a decrease in number of vessels in the tissue may contribute to the rise in total peripheral resistance in hypertension.19 Hutchins and Darnell10 studied the diameter of the vessels in vivo in the cremaster muscle of young SHR (5-6 weeks) and reported that the number of small arterioles was decreased by 50 percent. No study regarding the vessel density in the brain of SHR has so far been reported. Therefore, we cannot at present exclude the possibility that a difference in vessel density could, to some degree, contribute to the increased resistance.

Earlier studies have not indicated any primary difference in reactivity to CO₂ in hypertensive man21 or in SHR.22 The fact that we decreased blood pressure by bleeding could have increased the sympathetic discharge. It has been suggested that an increased sympathetic activity, by decreasing the lumen of the internal carotid artery and the larger pial arteries, can lead to a decrease in CBF even if intracerebral vessels are maximally dilated.23-24 In the presence of structural changes in cerebral vessels of SHR, a sympathetically vasocostriction could be expected to have a larger influence on the lumen of SHR than NR and could thus, theoretically, be responsible for the increase in resistance. Phentolamine (8 mg/kg) was therefore infused in some SHR during hypercapnia after lowering of the blood pressure by bleeding but no increase in CBF was observed. Thus, it is not likely that an increased sympathetic tone was responsible for the difference in resistance observed in the present study. The most plausible explanation for the lower flow in SHR during hypercapnia seems to be a structural limitation due to a reduced internal radius. The similar results obtained when cerebral vasodilatation was induced by bicuculline are in agreement with this interpretation.

The increased resistance and limitation of maximal CBF in SHR are likely to be of importance in areas with low perfusion pressure and during conditions with enhanced metabolic need. In addition to the decreased capacity to autoregulate at low pressure levels demonstrated in SHR in agreement with earlier studies in hypertensive man,28 the reduced flow at maximal dilatation at any blood pressure level might be responsible for the increase in vulnerability in SHR to, e.g., bilateral ligation of the common carotid artery.27-30

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