
Comparative Responses of the Carotid and Vertebral Arterial Systems of Rhesus Monkeys to Betahistine

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SUMMARY A newly developed photoelectric method was used in 5 rhesus monkeys to measure the mean transit time of blood through the carotid and vertebral arteries, together with measurement of the blood flow through the tissues of the fronto-parietal area supplied by the carotid artery and of the cerebellar tonsil supplied by the vertebral artery. Following intravenous administration of betahistine mesylate, a histamine analog, the mean transit times of blood through the 2 arteries were equally shortened by 10%, despite a 20% decrease in the mean arterial blood pressure. The cerebral tissue blood flow was increased by betahistine, from 70.4 to 81.4 ml/100g/min and from 73.2 to 84.0 ml/100g/min, respectively. Since histamine has been reported to produce a decrease in cardiac output, the increase in cerebral blood flow confirmed that betahistine is a selective cerebral vasodilating agent. However, by comparing the hemodynamic data for the two cerebral arterial systems, it can be concluded that the responses of the carotid and vertebral arterial systems to the vasodilating action of betahistine were essentially the same in extent.
difference in response of the carotid and vertebral arterial systems to betahistine in rhesus monkeys. For this comparison, a new photoelectric method for measuring hemodynamic changes developed by us was used. The results were further evaluated from the viewpoint of the hemodynamic changes brought about by betahistine in the cerebral arteries and tissues, and the changes in intracranial pressure, together with certain additional data obtained in previous experiments with cats.

**Methods**

**Experimental Procedures**

Five rhesus monkeys weighing 3.5–6.4 kg were used. All the monkeys were anesthetized with 50 mg/kg body weight of Chloralose and 500 mg/kg body weight of Urethane, and immobilized with Alcuronium Chloride. Tracheal intubation was performed and respiration was controlled with a Harvard Respirator, Model 662. One femoral artery and 1 femoral vein were catheterized to monitor the systemic arterial blood pressure (SABP) and to administer pharmacological agents. A catheter was inserted into the right axillary artery, advanced proximally, and ligated in place with stainless steel threads so that the catheter tip was positioned at the middle of the right subclavian artery between the origins of the common carotid and vertebral arteries. This catheter was used for repeated manual injections of 1 ml saline to produce hemodilution curves in the cerebral tissue supplied by these arteries (fig. 1). For detecting tissue hemodilution curves and recording cerebral blood volume (CBV) in the cortex, a photoelectric method was used. This method was designed to measure the light transmittance of a limited layer of brain between a light source and a detector. It has been described in detail elsewhere with some data supporting its validity. Briefly, the apparatus consists of a 0.7 mm electric lamp implanted in cerebral tissue and a photodiode covered with a 550 nm band pass filter to detect the changes in light transmission through the tissue layer to the surface of the brain. Such an apparatus was fixed air-tightly in 2 regions of the brain; a) the right fronto-parietal cortex, tissue which is supplied by the carotid artery and b) the right cerebellar tonsil, tissue supplied by the vertebral artery (fig. 2). The surgical technique for fixation of the apparatus has also been described. The photodiode outputs from the cerebral and cerebellar surfaces were connected to a polygraph (Rikadenki) and recorded continuously for changes in cerebral blood volume (CBV) together with systemic arterial blood pressure (SABP) and intracranial pressure (ICP). ICP was measured by a strain gauge transducer from a flexible thin-walled polyethylene catheter inserted epidurally and positioned in the vicinity of the fronto-parietal region. The catheter was anchored to the skull with dental cement (Durelon, ESPE, GMBh, West Germany) making an air-tight fitting in the space between the burrhole and photoelectric apparatus. The outputs from the photodiodes were also fed into another polygraph having a higher chart speed.

**Figure 1.** Schematic diagram showing the carotid and vertebral arterial systems of the rhesus monkey. The locations of the catheter for saline injection and the sensors for detecting the corresponding tissue hemodilution curves are indicated.

**Figure 2.** Posterior view of the dorsal part of the cerebellar tonsil after resection of the posterior edge of the occipital bone. The lead-wires to the electric lamp inserted into the tissue can be seen. A plastic cap equipped with a photodiode is placed over the opening.
CONTROL AFTER BETAHISTINE

FIGURE 3. Records showing pressure changes upon injection (top), tissue hemodilution curves from sensor II (middle), and tissue hemodilution curves from sensor I (bottom).

(Rikadenki) to record the expanded hemodilution curves following injections of 1 ml saline into the axillary arterial catheter. The changes in CBV, ICP and SABP, together with the blood transit times through the arteries, were investigated before, during and after intravenous injection of 1-4 mg/kg body weight of betahistine mesylate (2-methylaminoethylpyridine dimethane sulfonate, Eisai Co. Ltd., Tokyo).

Calculations

Two separate values for the mean transit time of blood were calculated from the tissue hemodilution curves: 1) the mean transit time through the artery from the site of injection to the orifice of the tissue, $t_a$, and 2) the mean transit time through the tissue, $t_t$. $t_a$ was obtained from the mean of the differential of the ascending slope of the tissue hemodilution curve, assuming zero-time as the mid-point of injection (fig. 3). $t_t$ was calculated in a similar manner from the ascending and descending slopes of the curve. This calculation method was adopted since the usual area over height method was considered to yield an overestimation of the mean transit time due to indicator dispersion during the long traverse through the artery. The change in CBV was calculated from the continuous record of tissue light transmission before and after intravenous administration of betahistine. From the values of $f_a$ and CBV, the tissue blood flow was calculated using the equation $(CBV \times 60)/t 	imes p)$, where $p$ is the density of the brain tissue (approximately 1.04 g/ml) and the units of flow are ml/100g/min. The responses of the carotid and vertebral arterial systems to betahistine were compared on the basis of 1) the two corresponding values for the tissue flow obtained at the same time, and 2) the c/v ratio. The c/v ratio, i.e. $t_a$ (after)/$t_a$ (control)/$t_v$ (after)/$t_v$ (control), was calculated immediately after, at 1-2 min, at 4-6 min, and at more than 10 min after betahistine administration.

Theoretically, the values of $t_a$ obtained by this method should be subject to error when the indicator begins to leave the tissue before complete entrance of the indicator into the tissue has been effected. However, figure 4 reveals that such error is minimal since the time of the maximum on the tissue hemodilution curve coincides fairly well with the disappearance time on the arterial hemodilution curve recorded simultaneously from the pial artery, which is assumed to represent the orifice of the tissue.

Results

Continuous Recordings

Typical examples of the tissue hemodilution curves obtained in the control state (left) and after intravenous administration of betahistine (right) from the vertebral arterial territory (middle) and carotid arterial territory (bottom) are shown in figure 3. The time and mode of injection are also indicated. The values of $t_a$ and $t_v$ calculated from the curves were reduced after betahistine administration, indicating that the blood velocity through both the carotid and vertebral arteries increased. Continuous recordings of CBV, ICP and SABP before, during, and after betahistine administration are shown in figure 5. In spite of the marked decrease in BP, the parameters CBV(C), CBV(V), and ICP all increased. However, the change in ICP was not coincident with that in CBV, the former increase being rapid and far in advance of that in CBV. The rapid increase in ICP was a mirror image of the decrease in SABP.

Changes in MABP and $f$ Through the Arteries

Betahistine decreased both the systolic and diastolic blood pressure in all 5 animals. The mean value (n = 5) of the mean arterial blood pressure (MABP) was 92.4 ± 15.9 mm Hg in the control state, 75.6 ± 26.0 mm Hg at 1-2 min ($p < 0.05$), 73.6 ± 25.4 mm Hg at 4-6 min, and 72.0 ± 18.7 mm Hg at more than 10 min ($p < 0.05$) after betahistine injection.

The values of $t_a$ were 1.55 ± 0.38 sec in the control state, 1.42 ± 0.38 sec at 1-2 min ($p < 0.05$), 1.43 ± 0.43 sec at 4-6 min, and 1.45 ± 0.50 sec at more than 10 min after betahistine injection. Those of $t_v$ were 1.15 ± 0.32 sec in the control state, 0.93 ± 0.45 sec at 1-2 min, 1.06 ± 0.34 sec at 4-6 min, and 1.07 ± 0.42 sec at more than 10 min. The ratio of $t_a/t_v$ was thus 1.3 in the control state. This figure was in good agreement with the ratio of the lengths of the carotid and vertebral arteries from the site of injection to the respective tissues. The c/v ratio was also found to remain close to unity in spite of the injection of betahistine: 0.93 at 1-2 min, 1.03 at 4-6 min, and 0.97 at more than 10 min.
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Figure 4. Hemodilution curves produced in the cat by saline injection into the carotid artery via a lingual catheter. \( C_t(t) \) denotes the tissue hemodilution curves and \( c_a(t) \) the hemodilution curves in the pial artery supplying blood to the tissue. Note that the ascending slope of \( C_t(t) \) equals the integral of \( c_a(t) \).

Tissue Hemodynamic Changes

The mean transit time of blood through the tissue in the carotid arterial territory, \( T_{tc} \), was 4.4 ± 0.5 sec in the control state and 4.3 ± 0.8 sec after betahistine administration. The mean value of \( T_{tc} \) was 4.3 ± 0.8 sec in the control state and 4.0 ± 0.9 sec after betahistine administration. The change in CBV in the carotid arterial territory was + 0.4 ± 1.3 Vol%, while that in the vertebral arterial territory was + 0.4 ± 0.6 Vol%. Assuming the control CBV to be 5.2 Vol% for the rhesus monkey, the calculated flow in the carotid arterial territory was modified by the administration of betahistine from 70.4 ± 8.5 ml/100g/min to 81.4 ± 33.0 ml/100g/min, and that in the vertebral arterial territory from 73.2 ± 12.5 ml/100g/min to 84.0 ± 21.8 ml/100g/min.

Discussion

Intravenously administered histamine has been reported to produce a decrease in cardiac output. If this is also true for betahistine, then the results obtained by our group and others, such as increased

Figure 5. Continuous recordings of CBV (C), ICP (C), CBV (V), and SABP before, during and after intravenous administration of betahistine. In the case shown, an additional ICP recording was also made from a catheter located in the cisterna magna (ICP(V)).
CBF in spite of a decrease in SABP, can be taken to indicate that the cerebral vessels are more dilated by betahistine than the vessels of other organs. Betahistine is assumed to be a relatively selective cerebral vasodilating agent. Our results indicate that betahistine produces identical hemodynamic changes in both the carotid and vertebral arterial systems.

In our experiments, accelerated blood transit through the cerebral arteries was observed to accompany a decrease in SABP. Figure 6 demonstrates the essential features of an earlier manometric experiment measuring the pressure in an unopened pial artery of cats which may help to clarify the cerebral hemodynamic changes brought about by betahistine. It should be noted that the pial arterial pressure decreased steadily after intravenous administration of betahistine, whereas SABP tended to return to its original value. Nevertheless, the pial blood flow was accelerated and increased. To be compatible with such accelerated flow, an enormous dilatation of the arteries smaller than the pial artery would need to occur, overwhelming the decrease in pial arterial pressure, and hence, the "local" perfusion pressure. Such a hemodynamic change in the cerebral vessels may resemble the CO₂ type increase in flow characterized by a shortened t and increased CBV rather than a papaverine type change with prolonged t and increased CBV (unpublished data). Supposing that a small arterial branch leading from a pial artery supplies blood to a region which is somehow in a pathological condition, then the blood flow through this branch may, depending on the actual responses of the vessel peripheral to the branching site, be decreased, unchanged or even increased on betahistine administration. In order to estimate the changes in blood flow through the pathological region caused by vasodilators, factors related to the vascular responses in the adjacent collateral vessels must also be taken into account.

The rapid rise in ICP observed to precede an increase in CBV or cerebral vasodilation. Any methodological delay related to the CBV change can be discounted since the apparatus follows "real time" changes in the light transmission through the cerebral tissues. A delayed increase in blood flow which lagged behind an SABP change after betahistine administration was observed by Anderson and Kubicek, and they explained the delay using the transit and reaction time differences to the various sites of action considered. Pickering's observation is of interest in this connection, since the headaches felt by the human subjects lagged behind a change in ICP following intravenous administration of histamine. The headaches were assumed by him to be due to cerebral vasodilation. The rapid rise in ICP is not primarily due to a CBV increase in the case of betahistine. It should be noted from figure 5 that the ICP rise is virtually a mirror image of the decrease in SABP, beginning immediately after the commencement of betahistine injection. Histamine is known to alter the permeability of blood vessels, especially capillaries. Such permeability change after betahistine administration might play a role in the rapid fall of SABP and simultaneous rapid rise in ICP which are observed.

Acknowledgment

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References

7. Saga F, Snow JB Jr: Cochlear blood flow in response to
Experimental Regional Cerebral Ischemia in the Middle Cerebral Artery Territory in Primates

Part 3: Effects on Brain Water and Electrolytes in the Late Phase of Acute MCA Stroke

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SUMMARY Experimental regional cerebral ischemia was produced in the middle cerebral artery (MCA) territory in primates (M. mulatta) by macrosphere embolization. Determinations of percentage tissue dry weight and tissue sodium and potassium concentrations were obtained in samples from the ischemic and non-ischemic hemispheres at various times from 12 to 48 hours after the onset of cerebral ischemia.

Samples from the cortex normally supplied by the occluded MCA showed maximal accumulation of edema fluid with fluxes in sodium and potassium in reciprocal directions at 12 hours and similar edematous changes in putamen at 24 hours after embolization. By 48 hours after MCA occlusion and despite the presence of infarction, partial reversal was observed in the redistribution of water and electrolytes in these gray matter structures.

In contrast to cerebral cortex and putamen, the adjacent subcortical white matter showed progressive increases in water content from 12 to 48 hours and definite increases in tissue sodium with decreases in potassium were not observed until 48 hours after MCA occlusion.

This late severe white matter edema associated with cerebral infarction appears to be a major factor responsible for the hemispheric swelling observed at this stage.

CLINICAL and experimental studies have shown that cerebral edema following an acute stroke is at maximum within a few days and eventually subsides in about 3 weeks if the patient or the experimental animal survives the acute phase.1-4

Results obtained by Little et al.5, 6 from morphological studies in brains of squirrel monkeys following surgical clipping of the middle cerebral artery (MCA) have demonstrated a primary and a secondary phase in the evolution of ischemic cerebral edema. The initial phase begins shortly after arterial occlusion, is characterized by mild swelling of the gray and white matter, increases gradually in severity and lasts from 3 to 6 hours. Thereafter, a secondary phase begins and is characterized by massive swelling, especially of the white matter. Rapid increases in severity of this edema reached its peak at 24 hours or longer.8

In a previous communication we demonstrated that hemispheric swelling became apparent in the experimental side as early as 4 to 5 hours after onset of regional cerebral ischemia in the MCA territory in primates.7 Obvious changes in gray matter water content and in tissue sodium and potassium concentrations were detected at this time. However, minimal increases in subcortical white matter water content was found without changes in electrolytes.7

The present study was designed to extend our observations of ischemic brain tissue water content and in tissue sodium and potassium concentrations after much longer periods of MCA occlusion in macaques.

Methods

The left MCA of 10 adult primates (M. mulatta) (3 to 4 kg body weight) was occluded by a method of...
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