The role of baroreceptors and chemoreceptors in the regulation of the cerebral circulation

I. M. JAMES AND LINDSAY A. MACDONELL
Department of Medicine, Royal Free Hospital, London

(Received 30 May 1975)

Summary
1. Ten experiments, each using two dogs, were performed to evaluate the effect of chemoreceptor and baroreceptor activity on the cerebral circulation.
2. The carotid bifurcation areas were vascularly isolated bilaterally and perfused with arterial blood from a second animal.
3. Bilateral vagotomy interrupted stimuli from the aortic group of receptors.
4. Administration of 5% carbon dioxide to the donor animal resulted in an increase in cerebral (cortical) blood flow in the recipient.
5. A change in the arterial perfusion pressure from the donor resulted in a reciprocal change in the cerebral blood flow of the recipient. These changes were abolished by sectioning the sinus nerves.

Key words: baroreceptors, cerebral circulation, chemoreceptors.

Introduction
Impulses from peripheral baroreceptors and chemoreceptors are known to cause extensive systemic circulatory changes but the way in which the cerebral circulation participates in these integrated responses is largely unknown. Until fairly recently the cerebral vasculature, in contrast with that in other beds, was considered to be less influenced by its motor nerve supply than by local chemical changes, e.g. in $P_{CO_2}$ or pH (Kety, 1964). The baroreceptors, situated principally in the carotid sinus and the aortic arch, and the chemoreceptors, situated principally in the carotid and aortic bodies, are, however, ideally located to monitor changes in blood destined for the brain and are known to respond to the same physical and chemical alterations that are associated with changes in the calibre of cerebral blood vessels. If arterial pressure is lowered, the discharge from the peripheral baroreceptors decreases and vanishes at mean pressures around 40–60 mmHg (Folkow & Neil, 1971). Associated with this fall in pressure, simultaneous vasodilatation of cerebral vessels occurs preventing a fall in cerebral blood flow at least until the pressure has fallen below a mean of 60 mmHg (Harper, 1966). An increase in blood pressure, on the other hand, is associated with an increased rate of baroreceptor discharge and an increased degree of vasoconstriction of cerebral vessels. The net effect of these changes is to ensure constancy of cerebral blood flow and presumably therefore a constancy of oxygen supply to the brain. Both hypercapnia and hypoxia effect an increased rate of discharge from the chemoreceptors (Folkow & Neil, 1971) and both these abnormalities of blood gas tension are associated with vasodilatation of cerebral blood vessels (Kety & Schmidt, 1948).

A number of reports indicate that cerebral blood vessels are innervated in a similar fashion to those in other vascular beds. The most impressive evidence for this is morphological (Dahl & Nelson, 1964; Iwayama, 1970; Iwayama, Furness & Burnstock, 1970; Lavrentieva, Mchedlishvili & Plechkova, 1968) and histochemical (Falck, Nielsen & Owman, 1968; Ohgushi, 1968; Kajikawa, 1969); these studies make it clear that in most species there is an adrenergic pathway originating in the superior cervical ganglion which is constrictor and a dilator pathway, which
may be cholinergic, carried by the cranial nerve VII. Furthermore, the concept that the cerebral circulation is not greatly influenced by changes in vasomotor nerve activity has been challenged (James, Millar & Purves, 1969). Indeed it appears that the vasomotor nerves have an increasingly greater influence on cerebral vessels as blood gas tensions and blood pressure deviate from normal values, and it has been shown that the cerebral vascular response to hypoxia and CO₂ is conspicuously reduced after section of both depressor nerves and both sinus nerves (James, Millar & Purves, 1969). What remains unclear, however, is how far these vascular responses to pressure and blood gas changes depend on intrinsic factors, i.e. changes in local CO₂ or hydrogen ion concentration, and how far they are determined by extrinsic mechanisms, i.e. neurogenic reflexes.

As a result of studies in baboons in which the chemoreceptors and baroreceptors were vascularly isolated, Ponte & Purves (1974) claim that cerebral blood vessels are reflexly controlled and that the peripheral arterial receptors are involved. The effect of the receptors is most conspicuous in the vascular response to hypoxia and, together with intrinsic factors in the cerebral vascular bed, they determine the size of the vascular response to changes in CO₂ and pressure.

The present series of experiments were designed to further investigate this claim.

Methods

Preparation of animals

Ten experiments were carried out, each involving two dogs. The carotid bifurcation regions of one dog (the recipient) were vascularly isolated and perfused with arterial blood from a second dog (the donor). The brain of the first dog was thus being perfused only by its vertebral arteries. The dog, as distinct from man, receives the bulk of its brain blood supply via the vertebral arteries even under physiological conditions.

The procedure for setting up these experiments was as follows.

Isolation of the region of the carotid bifurcation.

The recipient dog was anaesthetized with intravenous sodium pentobarbitone (25 mg/kg body weight). A tracheotomy was performed and the dog was ventilated at a constant rate and depth. The areas of the carotid bifurcation were exposed on both sides. The internal carotid, the external carotid above the junction of the lingual artery and all other branches such as the occipital artery were ligated and tied. Blood was initially shunted from both femoral arteries into the common carotid arteries and then back into the femoral veins via catheters in the lingual arteries. Great care was taken to ensure that the sinus nerves were not damaged during this dissection. To eliminate aortic receptor responses, bilateral vagotomy was performed. The sympathetic supply to the head was also partially interrupted as this portion of the sympathetic runs with the vagus as a single trunk in the dog (Stromberg, 1964). The veins in the area of the carotid body were left undisturbed.

As soon as the remaining surgical procedure necessary for measuring cerebral blood flow had been completed (see below) the donor dog was anaesthetized and tracheotomized as before. This dog was also ventilated at a constant rate and depth throughout the experiment. Both femoral arteries and femoral veins were catheterized. Femoral arterial blood was then shunted from the donor dog into the common carotid arteries of the recipient dog. This blood was returned to the femoral veins of the donor dog via the lingual arteries of the recipient dog. During the switching over of the blood supply to the recipient carotid bifurcation regions from recipient to donor dog, the time that this region was without a blood supply was limited to 30 s.

To prevent clotting of blood in the recipient carotid bifurcation areas, the donor dog was anticoagulated with 25 000 units of heparin. The systemic arterial blood pressure of the recipient dog, and the perfusion pressure of the vascularly isolated carotid bifurcation regions were monitored with Bell and Howell pressure transducers and mean pressure was determined electronically. The final preparation is shown diagrammatically in Fig. 1.

Baroreceptor and chemoreceptor reflexes. The functioning of the carotid baroreceptors was tested by first raising and then lowering the perfusion pressure in the system supplying the vascularly isolated carotid bifurcation area of the recipient dogs. This was done by partially occluding the outflow and inflow catheters respectively by means of a screw clip. A change in the opposite direction of the recipient systemic arterial blood pressure was taken to indicate that the carotid baroreceptors were functioning normally (Heymans & Neil, 1958).

The recipient dogs were then allowed to ventilate
Cerebral circulation reflex control

Donor dog  Recipient dog

Fig. 1. Diagram of the final experimental preparation. Blood circulates from the femoral arteries (F.A.) of the donor dog to the vascularly isolated areas of the carotid bifurcation of the recipient dog and back via the femoral veins (F.V.) to the donor dog. The internal carotid arteries (I.C.A.) on both sides are tied off, as are the external carotid arteries (E.C.A.) above the lingual arteries (L.A.). The sinus nerves on both sides are carefully preserved but the vagi are cut bilaterally. C.C.A. = common carotid artery; P = pressure transducer.

spontaneously and resting respiratory rate was monitored. 5% CO₂ in air was then administered to the donor dog. The resulting increase in respiratory rate and decrease in Pa₄CO₂ of the recipient animal was assumed to demonstrate that this dog's carotid chemoreceptors were functioning normally (Biscoe, Purves & Sampson, 1970).

Cerebral blood flow measurement. Blood flow through the cerebral cortex was measured after the method of Ingvar & Lassen (1962) by intra-arterial injection of ⁸⁵Kr. A catheter was inserted retrogradely from the superior thyroid artery on the right into the brachiocephalic artery. Craniotomy and removal of the dura over the right parietal cortex was carried out in the conventional manner. Radioactivity was measured with a small Geiger counter placed over the right parietal region. The radioactive gas dissolved in sodium chloride solution (150 mmol/l) was injected into the brachiocephalic artery slowly over approximately 1 min so that the radioactivity monitored over the parietal region was constant for at least 45 s. Cerebral cortical blood flow was then estimated by analysis of the first 100 s of the ensuing decay curve as suggested by Lassen (1959).

A small catheter was placed in the superior sagittal sinus in such a way that flow was not impeded but samples of cortical venous blood could be obtained. In the calculation of cerebral metabolism it was assumed that the superior sagittal sinus drains blood only from cortex. There is evidence in the dog to support this assumption (Hegadus & Shackleford, 1965). Oxygen content was measured by the method of Linden, Ledsome & Norman (1965) and glucose by a glucose oxidase method (Trinder, 1969). pH, Pa₂O₃ and Pa₄CO₂ were measured with appropriate radiometer electrodes.

Experimental procedure

Once the preparation was complete, the following experimental procedures were carried out:

(a) 5% CO₂ in air was administered to the donor dog for 15 min (ten dogs).
(b) 5% CO₂ in air was administered to the recipient dog for 15 min (three dogs).
(c) The perfusion pressure to the vascularly isolated carotid bifurcation regions of the recipient dog was increased by adjusting a screw clip on the outflow catheter of the system (ten dogs). Measurements were made as soon as the carotid bifurcation pressure and recipient systemic pressure had reached a steady level.
(d) The perfusion pressure was then decreased by adjusting a screw clip on the inflow catheter of the system (ten dogs). Again measurements were made as soon as pressure changes had reached a steady level. (In three recipient dogs, both sinus nerves were then sectioned. Afferent denervation was thus complete in these animals since both vagi had previously been cut.)
(e) The effect of 5% CO₂ in air administered to the donor dog was investigated in the recipient animals, while they were both artificially and spontaneously ventilated.
(f) The perfusion pressure to the isolated carotid bifurcation region was then altered as before.
(g) The systemic arterial blood pressure of the three recipient dogs was lowered by haemorrhage from a femoral artery while the perfusion pressure to the isolated carotid bifurcation regions was held constant. Cortical blood flow was measured at various systemic arterial pressures.
TABLE 1. Cross-perfusion experiments

Results show effects on recipient dogs of: administration of 5% CO₂ to donor dog; an increase in perfusion pressure to recipient carotid bifurcation areas; a decrease in perfusion pressure to recipient carotid bifurcation areas. Experimental values (EXP) are compared with immediately preceding control values (C). Mean values ± SEM are shown; n = 10 (i.e. twenty dogs used in ten cross-perfusions). * Significantly different from preceding control by paired analysis (P < 0.05). MABP = mean arterial blood pressure of recipient dog; PP = perfusion pressure to recipient carotid bifurcation regions; \( P_{a,\text{CO}_2} \) = arterial carbon dioxide tensions of recipient dog; CMRO₂ = cortical oxygen consumption; CMRG = cortical glucose consumption.

<table>
<thead>
<tr>
<th>Expt.</th>
<th>Cortical blood flow (ml min⁻¹ 100 g⁻¹)</th>
<th>MABP (mmHg)</th>
<th>PP (mmHg)</th>
<th>( P_{a,\text{CO}_2} ) (kPa)</th>
<th>CMRO₂ (mmol min⁻¹ 100 g⁻¹)</th>
<th>CMRG (mmol min⁻¹ 100 g⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>EXP</td>
<td>C</td>
<td>EXP</td>
<td>C</td>
<td>EXP</td>
</tr>
<tr>
<td>Control</td>
<td>66.1 ± 5.0</td>
<td>64.3 ± 6.0</td>
<td>124 ± 10.2</td>
<td>122 ± 11.2</td>
<td>96 ± 9.6</td>
<td>94 ± 10.0</td>
</tr>
<tr>
<td>5% CO₂ to donor dog</td>
<td>67.9 ± 5.0</td>
<td>91.7* ± 7.9</td>
<td>123.5 ± 10.2</td>
<td>122.0 ± 10.1</td>
<td>95.8 ± 9.6</td>
<td>94.0 ± 10.0</td>
</tr>
<tr>
<td>Increased perfusion</td>
<td>76.9 ± 7.9</td>
<td>56.3* ± 5.0</td>
<td>111.3 ± 7.7</td>
<td>104.4* ± 8.4</td>
<td>80.8 ± 8.5</td>
<td>109.0* ± 8.6</td>
</tr>
<tr>
<td>pressure</td>
<td>54.6 ± 5.5</td>
<td>89.9* ± 7.3</td>
<td>106.6 ± 8.4</td>
<td>116.8* ± 9.6</td>
<td>88.2 ± 8.5</td>
<td>69.1* ± 9.6</td>
</tr>
</tbody>
</table>
Results

(a) 5% $CO_2$ to donor dog (Table 1). Administration of 5% $CO_2$ in air to the donor dog caused significant elevation of recipient cortical blood flow, oxygen and glucose consumption.

There was no significant change in either perfusion pressure of the vascularly isolated carotid bifurcation regions or recipient systemic arterial blood pressure.

(b) 5% $CO_2$ to recipient dog. When 5% $CO_2$ in air was administered to three recipient dogs (donor dog breathing air) there was a large fall in cortical blood flow (see Fig. 2). Cortical oxygen and glucose utilization also fell.

(c) Increased perfusion pressure. Increases in perfusion pressure caused on average a fall in mean arterial pressure of some 6%, a fall in cortical blood flow of 27% and a decrease in cortical oxygen consumption of 31%. Cortical glucose uptake also fell on many but not all occasions.

(d) Decreased perfusion pressure. Decreases in perfusion pressure resulted on average in an increase in mean arterial pressure of some 10%, in cortical blood flow of 40%, in cortical oxygen consumption of 45% and in cortical glucose consumption of 42%.

(e) $CO_2$ after section of the sinus nerve. The administration of 5% $CO_2$ in air to the donor dog after sinus nerve section caused no change in cortical blood flow or metabolism in the recipient animals. When the recipient dogs were allowed to ventilate spontaneously after nerve section, administration of 5% $CO_2$ in air to the donor failed to cause hyperventilation or any change in $Pa_{CO_2}$ of the recipient.

(f) Changes in perfusion pressure after section of the sinus nerves. The effects of alterations in the pressure perfusing the isolated carotid bifurcation regions on recipient cortical blood flow were abolished by section of the sinus nerves. No change in cortical blood flow was observed under these conditions when this pressure was either raised or lowered.

(g) Changes in systemic arterial pressure of the recipient animal. When arterial pressure in the recipient dogs was lowered by haemorrhage after section of the sinus nerves an equal percentage fall in cortical blood flow occurred. One response is illustrated in Fig. 3, demonstrating the linear relationship between pressure and flow under these circumstances.

![Graph](image1)

**FIG. 2.** Response of cortical blood flow of recipient dog to:
(a) increasing $Pa_{CO_2}$ in donor dog [two values for each of ten experiments; $P$ for the significance of $r$ is < 0.001 ($n$ = 20)]; (b) increasing $Pa_{CO_2}$ in recipient dog [two values from each of three experiments; $P$ for the significance of $r$ is < 0.001 ($n$ = 6)].

![Graph](image2)

**FIG. 3.** Changes in cerebral blood flow caused by changing the mean arterial blood pressure (MABP), by bleeding, in one dog after bilateral section of sinus nerves and bilateral vagotomy.
Discussion

Changes in cerebral blood flow

Activation of the chemoreceptors by changing the CO₂ content of the blood perfusing the isolated carotid bifurcation region caused moderately large increases in cerebral blood flow. The increase in flow could not be ascribed to recipient CO₂ changes or to blood pressure changes. That the increase must have been mediated via the sinus nerves was shown by the fact that it could no longer be demonstrated once the nerves had been sectioned.

Changes in perfusion pressure at the carotid bifurcation also caused changes in cerebral blood flow. Thus an increase in perfusion pressure caused a slight fall in blood pressure of some 6% and a large fall in flow of 27%. A fall in perfusion pressure on the other hand caused a slight increase in blood pressure of some 10% and a large increase in flow of 40%. These changes could no longer be demonstrated once the nerves had been sectioned. After total afferent denervation a fall in blood pressure caused by haemorrhage was accompanied by a similar percentage fall in flow. In other words a passive pressure flow relationship was found to exist as soon as the nerves were sectioned. Although a fall in blood pressure caused by haemorrhage cannot be strictly equated with a fall in blood pressure due to baroreceptor activity, it would appear that raising sinus pressure with the nerves intact causes a decrease in flow which cannot be adequately explained by the fall in blood pressure alone. Such a striking difference in flow response in both directions makes it more likely that the changes in flow are partly due to changes in cerebral vasomotor tone. Such conclusions would be in agreement with the work of Ponte & Purves (1974).

Changes in metabolism

Gilboe & Betz (1973) showed that in the isolated canine brain oxygen consumption is flow-dependent. Increases in flow caused by increasing perfusion pressure were accompanied by increases in oxygen utilization. In the present experiments, oxygen consumption also increased as flow increased and decreased as flow decreased. It could be argued, however, that the changes in blood flow were secondary in some way to primary changes in cortical metabolism since this would be accompanied by an increase in CO₂ production. That this is unlikely to be the explanation for the flow increase is suggested by the observation that the direct administration of 5% CO₂ to the recipient dog caused a fall in cerebral blood flow. Thus a direct vasodilator response to CO₂ was not obtained in these animals. Although this observation in no way negates the importance of local factors, such as tissue CO₂ under more physiological conditions, it strongly suggests that the vasodilatation seen here must have been due to other factors. Harper, Deshmukh, Rowan & Jennett (1972) suggested that there may be two control mechanisms, a local one affecting intraparenchymal vessels and a neurogenic mechanism affecting extraparenchymal vessels. The relative importance of these systems could vary under different physiological conditions. For example, most of the experiments performed showing neurogenic mechanisms have been performed under some form of anaesthesia. Intrinsic mechanisms affecting intraparenchymal vessels may be more important in the conscious animal. Also, neurogenic mechanisms could be responsible for the crude adjustment of cerebral vasomotor tone whereas intrinsic mechanisms affecting intraparenchymal vessels were responsible for the fine adjustment.

Acknowledgments

We thank Mr Stephen Hall for excellent technical assistance. This study was supported by a grant to I.M.J. from the Medical Research Council.

References


Cerebral circulation reflex control


