INFLUENCE OF VAGAL INPUT ON CEREBRAL BLOOD FLOW IN MONKEYS AND DOGS AFTER EXPERIMENTAL CEREBRAL VASOSPASM

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Abstract. Cerebral blood flow (CBF) was a response to experimental subarachnoid haemorrhage (SAH) in four monkeys and three dogs. Decrease in CBF was observed in the white and gray matter and in the flow measured within the internal carotid artery as the result of SAH. Bilateral vagotomy enhanced CBF in the gray matter and blood flow in the internal carotid artery to values exceeding the control ones. Results suggest the existence of a receptor susceptible to subarachnoid haemorrhage and connected with vagal nuclei.

INTRODUCTION

Investigations on the influence of the cholinergic system on cerebral arteries have a history of more than half a century. At present it is supposed that the influence of the cholinergic system on smooth muscles is not limited solely to the effect of mediator activity in the vasomotor nerve endings, but that it also modifies the activity of adrenergic nerve endings forming the perivascular plexus by the axoaxonal interactions (10, 11). There are, however, descriptions of vasodilatation occurring in the vascular wall changed by inflammation due to the axon reflex not involving the central nervous system (31). It seems that the vasospasm in subarachnoid haemorrhage (SAH) shows certain features of this pa-
thology (6). Therefore, the authors' purpose was to investigate the influence of the cholinergic system on the regulation of cerebral blood flow in conditions of SAH.

**MATERIAL AND METHODS**

Four green monkeys Macacca Mullatta of either sex and three male dogs were fastened and then induced with ketamine (10 mg/kg i.v.) and atropine (0.05 mg/kg i.v.). The animals were intubated, paralyzed with d-tubocurarine (0.5 mg/kg i.v.) and placed on positive pressure ventilation to maintain constant PaCO₂. Anesthesia was maintained with a mixture of 70% N₂O and 30% O₂. Systemic blood pressure from the femoral artery (Statham strain gauge) and end-tidal CO₂ (infrared capnograph, Godart) were recorded on a polygraph (Medipan). To prevent brain edema, all animals received dexamethazone 0.7 mg/kg of body weight i.v. The head of the animal was placed in a stereotaxic apparatus and fronto-parieto-temporal craniectomy was performed. In one experiment petrosalcraniectomy was performed extradurally with a middle cranial fossa approach. The greater petrosal nerve was sectioned near its hiatus. The subarachnoid hemorrhage was produced in the following way: the animal was placed in a prone position. 22 gauge spinal needle was inserted through the atlantooccipital membrane into the cisterna magna. Through the needle, 4 ml of CSF was withdrawn and 4 ml of autologous arterial blood was injected at a rate of 1 ml/min. The common carotid arteries and vagus nerves were exposed bilaterally and the external carotid arteries were ligated in 7 animals to eliminate the extracranial circulation. Blood flow in the left carotid artery was measured with Doppler's electromanometer (UDP-10, Sonpan) and continuously recorded. In four animals, the left internal carotid artery was cannulated (external carotid arteries were ligated) and regional (fronto-parietal region) blood flow was studied with intraarterial ¹³³Xe injection method (see details 20). A bolus of ¹³³Xe in physiological saline (0.2 - 0.8 ml and activity approx. 40 μCi) was introduced. CBF was calculated from two components derived from the double-exponential analysis of the ¹³³Xe clearance curves (32). After selective vagotomy (in one animal) the central end the right vagus nerves were placed on a pair of silver electrodes connected to a constant current stimulator (Cobrabid). Stimulus parameters were 10 Hz and 1 Hz of 0.5 ms pulse duration and 0.5 - 5 mA current strength. Acid base balance parameters and PaO₂ were measured in arterial blood with an automatic blood analyzer (Corning).
RESULTS

In the course of the experiments the respiratory parameters and the acid-base balance of the animals were maintained at the normal level. pH was $7.38 \pm 0.03$ SD, $\text{PaCO}_2 = 42.0 \pm 4.1$ SD mmHg, $[\text{HCO}_3^-] = 24.7 \pm 1.6$ SD mmol/l, $\text{PaO}_2 = 140 \pm 23$ SD mmHg. The results of CBF, ICAF, mean arterial blood pressure measurements and heart rate are shown in Tables I-III.

It is noteworthy in Table I that vagotomy enhances cerebral blood flow in the gray matter, CBFw remaining unchanged.

Calculations of cerebral blood flow as mean changes of CBFg and ICAF indicate that, as the result of SAH, this flow is reduced to $54.5 \pm 3.7$ ml/100 g/min, that is $13.3\%$. Vagotomy leads to an increase in blood flow to $112.0 \pm 48.5$ ml/100 g/min, that is $105.5\%$ as compared with the state in SAH.

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<th>Table I</th>
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<td>Results of values CBFg, CBFw, ICAF, MABP, HR in control animals, after subarachnoid haemorrhage (SAH) and vagotomy</td>
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<tr>
<td>CBFg ml/100</td>
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<tr>
<td>Control</td>
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<td>SAH</td>
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<td>Vagotomy</td>
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CBFg, cerebral blood flow in grey matter; CBFw, in white matter; ICAF — internal carotid artery flow; MABP, mean arterial blood pressure calculated as systolic pressure $+$ $2$ diastolic pressure; HR, heart rate; SAH — subarachnoid haemorrhage.

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<th>Table II</th>
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<td>Influence of electrical stimulation (1 Hz and 10 Hz) on ICAF, MABP and HR. Control state after SAH and vagotomy</td>
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<tr>
<td>Abbreviations as in Fig. 1</td>
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<tr>
<td>ICAF %</td>
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<td>Control after SAH and vagotomy</td>
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<tr>
<td>Stim 1 Hz</td>
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<td>Stim 10 Hz</td>
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Results of parameters CBFg, CBFw, MABP and HR in control animals, after SAH, petrosalectomy and vagotomy. Abbreviations as in Fig. 1

<table>
<thead>
<tr>
<th></th>
<th>CBFg ml/100</th>
<th>CBFw g/min</th>
<th>MABP mmHg</th>
<th>HR min⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>66.5</td>
<td>44.6</td>
<td>90</td>
<td>92</td>
</tr>
<tr>
<td>SAH</td>
<td>55.4</td>
<td>21.9</td>
<td>90</td>
<td>80</td>
</tr>
<tr>
<td>Petrosalectomy</td>
<td>110.9</td>
<td>24.0</td>
<td>85</td>
<td>76</td>
</tr>
<tr>
<td>Vagotomy</td>
<td>168.0</td>
<td>13.9</td>
<td>107</td>
<td>90</td>
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Stimulation of the vagus with 10 Hz and 1 Hz frequency caused a diminution of cerebral flow (Table II).

Petrosalectomy resulted after SAH in an enhanced blood flow in the gray matter (Table III). Subsequent vagotomy caused a further increase in CBFg.

DISCUSSION

Although the significant reduction in regional CBF accompanying subarachnoid haemorrhage has been described by numerous authors (19, 21, 22), the cause of diminished brain perfusion is still subject to discussion. Some authors consider vasospasm of the cerebral arteries to be the main cause of CBF decrease (2, 8, 16, 25), whereas others find no correlation between reduced CBF and vasculat contraction in the course of SAH (13, 18, 30, 33, 37). It was also noted (4) that the vasospasm is of biphasic character. According to some authors, in the first phase lasting practically from the moment of extravasation for about one hour, serotonin from the haemolysed blood platelets is responsible for the state of the vessels (1, 3, 9, 26, 36). Others consider as a cause of the vasospasm the rise of catecholamine level (15, 24). The hypothalamus has also been believed to play a role in the occurrence of acute vasospasm, on the basis of the fact that the extract of this brain region introduced into the subarachnoid space produces a contraction of the cerebral arteries (34). In the second phase of vasospasm, lasting six or seven days, a different mechanism of the spasm is suspected, since the inflammatory-proliferative picture of the walls of intracranial vessels has been described, with accompanying myonecrotic changes (6, 12, 35).

In the present experiments a diminution of cerebral flow was observed (in the white and gray matter) 30 min after SAH, that is, in the first phase of the vasospasm. It does not seem probable that the develop-
ing brain oedema (17) could be responsible for the decrease. It should be noted that our animals were treated with steroids to prevent oedema and subjected to extensive temporo-parieto-frontal craniectomy to prevent the rise of intracranial pressure (Table I, Fig. 1). It is supposed that changes in ICAF are well correlated with cerebral blood flow (27-29). CBF decrease is observed in response to SAH in the half-hour period fasting from the moment of the appearance of bleeding (haemorrhage). This time is too short to allow the explanation of the reduction of CAF by the vasoconstricting influence of the metabolism of CNS tissues on the cerebral vessels (17). To explain the observed vasospasm we tentatively postulate the existence of the neurogenic and/or neurosecretive pathogenesis of this spasm.

After ipsilateral vagotomy an increase of CBF and ICAF, previously depressed due to subarachnoid haemorrhage, was usually observed. This increase concerned only the cortical flow (CBFg), whereas the flow in the brain's white matter (CBFw) remained constantly depressed (Table I). It is worth to note that vagotomy does not cause any appreciable change of the normal cerebral blood flow in the rabbit (Ryba and Głowicki, unpublished data).
Investigations on the role of the vagus nerve in the regulation of the lumen of cerebral vessels were started by Forbes and Wolff (14). Only later experiments (5, 7), however, point to the vagus nerves as an essential link in neurogenic vasodilatation of the intracranial arteries. According to the above quoted authors, bilateral dilatation of the cerebral arteries in response to faradic stimulation of the proximal segment of the vagus nerve is possible only when the integrity of the greater petrosal nerve is preserved. Petrosalectomy abolished ipsilaterally this effect. In these experiments the effect obtained was exactly opposite: bilateral vagotomy caused an increase in the cerebral blood flow reduced by vasospasm in the course of subarachnoid haemorrhage. Thus, the question arises whether this difference may be evoked by the state of the vessels of our animals (vasospasm), and on the other hand, what is the answer of the intracranial arteries to proximal stimulation of the vagus nerve after producing subarachnoid haemorrhage.

As shown by the results, the stimulation of the vagus nerve in the described experiments causes a diminution of blood flow in the internal carotid artery and the stimulation frequency does not affect the direction of the flow changes (Table II and Fig. 1). Thus, it is not the observation described as vagal depressor reflex (23), to consist of the arterial pressure fall and reduction of the frequency of heart rate in response to stimulation of the vagus nerve with an electric stimulus of frequency below 10 Hz. As already mentioned, the vasomotor influence of the vagus nerve on the intracranial vessels was observed only when the continuity of the greater petrosal nerve was intact. On the other hand, the responses of the cerebral vessels to vagotomy and to vagus nerve stimulation described here may have been caused by vasospasm in the course of subarachnoid haemorrhage. These circumstances prompted us to perform petrosalectomy in animals with SAH, and subsequently observe the blood flow in response to vagotomy (Table III). As it is seen, petrosalectomy does not prevent the increase of CBF in response to the later performed vagotomy. It seems, therefore, that the role of the vagus nerves in the regulation of cerebral blood flow in pathologic states of the type of vasospasm in the course of SAH is different than that described up to date in physiological states. Secondly, vagotomy enhances cortical blood flow, while in the white matter it remains constantly depressed in the above described states. This indicates the possibility of neuroregulation of the cortical flow in the course of subarachnoid haemorrhage. It is also possible that there exists a SAH receptor responsible for the vasospasm, which is directly connected with vagus nerve nuclei.
REFERENCES


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