Cerebral infarction due to carotid occlusion and carbon monoxide exposure

II. Influence of preganglionic cervical sympathectomy

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SUMMARY Unilateral cerebral infarcts were produced in the rat by ligation of one common carotid artery and subsequent exposure to carbon monoxide. The incidence and extension of brain infarcts was increased in animals with additional ipsilateral cervical preganglionic sympathectomy. Sympathectomy did not affect markedly the respiration and systemic circulation. The effect of sympathectomy was attributed to a cutaneous vasodilation, leading to an extracranial steal phenomenon.

The role of the cervical sympathetic innervation of the cerebral vessels is controversial. It is generally accepted that the influence of the sympathetic innervation on the extracranial vasculature is much more effective than on the intracranial bed. Since the extra- and intracranial vascular beds are connected in parallel, and since flow through the carotid bifurcation is not hampered by ligation of the common carotid artery, our model permits the study of the effects of ipsilateral cervical sympathectomy on the cephalic vasculature.

Materials and methods

The experiments were performed with male rats (Chbb:THOM strain).

Series I

In 60 of 133 animals (300–400 g body weight) the fibres of the cervical sympathetic trunk were divided at the time of the common carotid artery dissection. In the remaining 73 animals the sympathetic chain was allowed to remain intact. The cerebral lesions were studied histologically in the first 29 experimental and 49 control animals. Occurrence of enophthalmos and ptosis were taken as indicators of adequate sympathetic interruption.

Series II

In a separate series of 16 animals the ipsilateral external

carotid artery also was ligated at the time of common carotid artery ligation. Sixteen animals with open external carotid artery served as controls.

Series III

In animals with enophthalmos and ptosis the presence of miosis, the most important sign of sympathetic deficit, was demonstrated as follows: in four animals without dissection of the common carotid artery a preganglionic cervical sympathectomy was performed. After 9 to 50 days the animals were sedated (haloperidol 0.2 mg/kg body weight) and 30 minutes later both eyes were photographed after 60 s of complete darkness. We used an operating microscope and a light flash for photographic purposes. A series of six photographs was taken and the entire sequence was repeated twice. The greatest diameter of the pupil was measured on the prints.

Series IV

In 18 unanaesthetised and unrestrained animals the following parameters were monitored before, during and for 80 minutes after carbon monoxide exposure (3000 ppm in room air, 70 minutes duration): systemic arterial blood pressure, heart rate, respiration rate, and EEG. For the recordings a slip ring assembly was used (for details cf ref 1). In seven of these animals the ipsilateral sympathetic chain had been divided.

Results

Series I

Lethality. After carbon monoxide exposure 27 of 60 animals with Horner's syndrome and six of 73 animals without Horner's syndrome died ($p < 0.001$). The dead animals had massive ipsilateral brain oedema. During carbon monoxide exposure three

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Fig 1 Pattern of infarct distribution in control rats, above (n = 49) and in sympathectomised rats (n = 29), below.

Fig 2 Pattern of infarct distribution in sympathectomised animals without (above) and with (below) additional ligation of the ipsilateral external carotid artery. For abbreviations see ref 1, fig 4.

animals died both in the experimental and in the control group.

Histological findings As shown in fig 1 there was no difference in the pattern of lesions between experimental and control group, but there were highly significant differences in the frequency and extent of infarctions in favour of the control group.

Series II

In this separate series two experimental and two control animals died after carbon monoxide exposure. The regional infarct frequency was reduced in the experimental group (fig 2). In the experimental

group with additional ligation of the ipsilateral external carotid artery the infarcts were significantly more extensive.

Series III

In all animals with enophthalmos and ptosis the mean pupil diameter was smaller on the affected side ($0.001 > p < 0.05$)

Series IV

Figure 3 summarises the course of the parameters recorded in the 18 unrestrained rats. Up to the 50th minute no difference in the circulatory parameters between control and experimental animals

Fig 3 Time course of mean arterial blood pressure (MABP), heart rate, respiratory rate, and of the predominant EEG frequency and amplitude in 7 sympathectomised rats and in 11 control animals during and after an exposure to carbon monoxide.

appeared. After the 50th minute a nearly linear decrease of heart rate was observed in the sympathectomised rats, falling to 1 beat/s at the end of carbon monoxide exposure. Immediately after cessation of carbon monoxide exposure heart rate quickly rose again to the level of the control group. Blood pressure, respiratory rate, EEG amplitudes and frequencies did not differ in the two groups during the exposure or in the recovery period.

Discussion

Our own pathophysiological findings¹ showed that carbon monoxide-induced hypoxia resulted in hypotension of 70 to 80 mm Hg which was the main factor responsible for the development of regional cerebral infarcts. We attribute the greater extent of brain infarcts in sympathectomised animals to an additional fall of the arterial blood pressure distal to the ligation of the common carotid artery. This fall is caused by the marked dilating effect of sympathectomy on the cutaneous vasculature. The resistance of skin arteries to blood flow is maintained in a tonic manner by sympathetic innervation²⁻⁵ in contrast to muscle and brain where the vascular resistance is mainly intrinsically regulated.⁶⁻⁸ Regulation of arterial and venous cutaneous vessels is exerted via sympathetic efferents mainly by alpha-receptors.⁹ Skin vasodilation in animals lacking sweat glands is brought about by reduction of adrenergic constrictor tone.² Our own histological preparations (unpublished data) have shown that rat skin is devoid of sweat glands.

As shown by direct observation of the flow direction in rats,¹ the extracranial cephalic circulation acts like a sink for the intracranial blood flow after common carotid artery ligation. Consequently, sympathectomy enhances this leakage and lowers the arterial blood pressure in the distal common carotid artery. Pressure recordings in the rabbit's ciliary artery after sympathectomy and sympathetic stimulation,^{10 11} and in the dog's carotid sinus after sympathetic stimulation,¹² support this conception.

Since the cutaneous vasculature is mainly supplied by the external carotid artery, we tried to neutralise the effect of sympathectomy by ligating the ipsilateral external carotid artery. There was then a reduction of the extent of infarction. This finding is in keeping with observations of others in dogs,¹³ rabbits^{14 15} and monkeys.¹⁶

There is good evidence that in states of functional anaemia and hypotension a baroreceptor-induced increase of the constrictor tone takes place counteracting the local hypoxic vasodilation.¹⁷ Unilateral preganglionic sympathectomy may have exerted an influence not only by eliminating basal vasoconstrictor

tone, but also by blocking additional baroreceptor-mediated sympathetic tone of skin vessels during exposure to carbon monoxide.

The function of the sinus baroreceptors may have been altered by the sympathectomy. The cerebrovascular response to hypoxia is known to be independent of sinus baroreceptor function.¹⁸ Contrary to the effects of sympathetic stimulation,¹⁹⁻²² sympathectomy increases systemic blood pressure and the sinus response to the lowering of pressure within the sinus.^{23 24} Both responses would improve perfusion by raising blood pressure rather than lowering it.

From recordings in the unanaesthetised and unrestrained rats we know that neither systemic blood pressure nor heart rate is influenced by distal preganglionic sympathectomy, leaving intact the efferent sympathetic cardiac innervation, which originates from the inferior and medial cervical ganglia.²⁵ Direct effects of pCO on medullary centres may be responsible for the bradycardia occurring without further decrease of systemic blood pressure in the sympathectomised rats from the 50th minute of exposure onwards and disappearing immediately thereafter.

Sympathectomy may have exerted effects not only on the extracranial vasculature, but also on the cerebral vessels themselves, since there is an adrenergic innervation of the pial arteries²⁶⁻³² and also of the intracerebral arteries.³³ The postganglionic perikarya are located in the superior cervical ganglia.^{26 30} A constrictor effect of sympathetic stimulation has been demonstrated in several investigations (for example ref 34), in others it was missed or negligible compared with the effect on the extracerebral cephalic vessels.^{35 36} A neurogenically mediated constrictor tone, leading to vasodilation after sympathectomy, has not been identified.³⁷⁻⁴⁰ Possibly the sympathetic effect on brain vessels is modified by pathophysiological conditions. Participation in autoregulation, especially in prevention of superperfusion, and in protection of the blood-brain-barrier have been discussed.⁴¹⁻⁴⁸ Hypocapnia tends to mitigate sympathetic effects;⁴³ slight hypocapnia developed during carbon monoxide exposure in our experiments.¹ All these presumed protective effects cannot explain our findings.

Thus, the dilating effect of the sympathectomy on the skin vessels appeared to predominate in our experiments, representing an extracranial steal from the cerebral circulation.

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