ACTA PHYSIOLOGICA SCANDINAVICA
SUPPLEMENTUM 350

On the relation between blood pressure and blood flow in the canine brain with particular regard to the mechanism responsible for cerebral blood flow autoregulation

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GÖTEBORG 1970

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ACTA PHYSIOLOGICA SCANDINAVICA

SUPPLEMENTUM 350

FROM THE DEPARTMENTS OF CLINICAL PHYSIOLOGY I AND II, UNIVERSITY OF GÖTEBORG, SWEDEN

On the relation between blood pressure and blood flow in the canine brain with particular regard to the mechanism responsible for cerebral blood flow autoregulation

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This thesis is based on the following papers, which are published in this supplement.

I. On the relation between blood pressure and blood flow in the cerebral cortex of dogs. By Barbro Ekström-Jodal, Egil Häggendal and Nils Johan Nilsson 29–42.

II. The cerebral venous oxygen saturation during rapid changes in the arterial blood pressure. An oximetric study in dogs. By Barbro Ekström-Jodal, Egil Häggendal and Nils Johan Nilsson 43–50.

III. Effect of increased venous pressure on cerebral blood flow in dogs. By Barbro Ekström-Jodal 51–61.

These papers will be referred to in the text by the given Roman numerals.

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INTRODUCTION

Autoregulation of blood flow, in the restricted sense that there is a tendency to keep the flow constant in spite of variations in perfusion pressure, is a characteristic feature of the pressure-flow relation in the brain, as well as in skeletal muscle, kidney, intestine, liver and myocardium, as discussed at the symposium on autoregulation of blood flow in 1963 (Johnson 1964 a). The first evidence of such a regulation was presented in 1902 by Bayliss, who studied the effects of changes in the arterial blood pressure on the volume of the hind limbs of dogs, cats and rabbits. He found signs of an active regulation of blood flow in response to changes of the arterial blood pressure, acting in the direction to keep the flow constant. This regulation, also observed in the kidney and intestine, was independent of nervous influence.

The mechanism by which the response is effectuated is, however, still a matter of debate. Several different theories have been discussed, as reviewed by Johnson (1964 b), but the following three have been most emphasized.

In view of the contraction observed in other muscles in response to stretch, Bayliss postulated that the muscular coat of arteries reacts in a similar way to rises in the intravascular pressure. He also suggested that there would exist a certain tone already in response to the normal blood pressure, a lowering of the pressure implying a diminished stimulus, thus leading to dilatation. This hypothesis forms the basis for the *myogenic theory*, which has been extensively described by Folkow (1964). It implies the existence of a basal tone, resulting from vasomotion. An increased transmural pressure potentiating vasomotion would lead to a rise in vascular resistance and vice versa. The precapillary resistance vessels are considered to be the site of the changes in resistance, and the important consequence would be the prevention of oedema formation, when the arterial blood pressure is raised.

The *metabolic theory* for flow autoregulation (Berne 1964) implies in principle that, primarily, the flow passively follows changes in the perfusion pressure, leading to an altered chemical situation in the tissue. Secondarily, this change in concentration of the metabolites induces changes of the calibre of the resistance vessels, which act to keep the flow constant. Much interest has been focused on oxygen and on different products of metabolism such as carbon dioxide and lactic acid as being the possible trigger of the reaction, but so far no single substance has been shown to be responsible. Autoregulation according to this theory is thus a flow-dependent

phenomenon, and the teleological view that it is designed to guarantee the chemical homeostasis of the tissue seems natural.

The *tissue pressure theory* does not include any active smooth muscle response in the vessel walls but ascribes autoregulation to purely mechanical events. Thus, when the arterial blood pressure is raised, there is an increase in the outward filtration of fluid owing to the changed pre- to postcapillary pressure ratio. Provided the organ is enclosed in a capsule that is stiff enough, an increase in the tissue pressure will be produced. The low-pressure vessels with little rigidity in the wall, *i.e.* the veins, should be the section of the vasculature most sensitive to such a pressure increase, tending to collapse and thereby raise the postcapillary resistance. The reverse course of events would take place, when the arterial blood pressure is lowered, resulting in a pressure-flow relation, characteristic for flow autoregulation.

Concerning the regulation of the cerebral blood flow, there have been wide differences in opinions from time to time. Already in 1783 Alexander Monro the younger, as quoted by Bayliss and Hill (1895), presented the view that the quantity of blood within the skull must be almost invariable, considering the brain substance, enclosed in the rigid skull, as practically incompressible. This view did not seem to allow for the dilatation of the pial vessels later observed by Donders (1851) in combination with asphyxia, but it was vividly supported by Bayliss and Hill (1895), who especially criticized the report by Roy and Sherrington (1890). The latter authors recognized two factors of importance in the regulation of the cerebral blood flow. Firstly, changes in the arterial blood pressure were found to effect an alteration of the blood flow in the same direction, and, secondly, some intrinsic control, probably independent of nervous influence, was suggested. This suggestion was partly based on observations, made during asphyxia, of an expansion of the brain, which could not be ascribed to blood pressure changes. Bayliss and Hill, repeating these experiments, could not find evidence for any active regulation of cerebral blood flow and concluded, that under physiological conditions the blood flow passively follows the arterial and venous blood pressures. This view, further extended by Hill (1896) became dominant during the following decades and was upheld despite the later discovery by Bayliss (1902) of an active vascular response to blood pressure changes in other vascular areas.

The first systematic study of the effect on the cerebral vessels of blood pressure changes *per se*, in which clear signs of an autoregulatory response were found, was presented by Fog (1934), using the pial window technique of Forbes (1928). Irrespective of how the arterial blood pressure changes were achieved (arterial bleeding or stimulation of the vagus or depressor nerves; aortic compression or stimulation of the sympathetic nerves) the response to a pressure increase was vasoconstriction and to a pressure decrease, vasodilatation. In this work and later (1937 and 1938) Fog suggested that variations in the endovascular pressure induce the changes observed in the diameter of the pial vessels.

The existence of flow autoregulation in response to changes of the arterial blood

pressure in the cerebral circulation has later been confirmed in a number of studies using different techniques (Forbes, Nason and Wortman 1937, Carlyle and Grayson 1955, Rapela and Green 1964, Hirsch and Körner 1964, Harper 1965, Häggendal and Johansson 1965, Bozzao *et al.* 1968; for reviews see also Lassen 1959 and 1964). Moreover autoregulation has been shown to occur in response to increased intracranial pressure (Noell and Schneider 1948, Rapela and Green 1964, Shulman and Verdier 1967, Häggendal *et al.* 1970 a). Other investigators have reported a passive pressure-flow relation in isolated brains (Geiger and Magnes 1947, Sagawa and Guyton 1961). The discrepancy of results may be attributable to the method used, as cerebral autoregulation appears to be a vulnerable phenomenon, easily damaged by for instance traumatic preparation procedures (Fog 1934, Rapela and Green 1964).

The tissue pressure hypothesis at first seems to be a quite possible explanation for blood flow autoregulation in the brain with its very rigid enclosure. It is, however, probably excluded by the fact, that autoregulation takes place to the same extent, where the perfusion pressure is reduced by intracranial pressure increases, as when the arterial blood pressure is lowered.

In discussing the other two mechanisms mentioned above a commonly held opinion has been that both are actually engaged (*e.g.* Lassen 1959 and 1964, see also Harper and Häggendal 1968), but some facts concerning the general regulation of cerebral blood flow seem to have favoured the concept of a mechanism governed by metabolic factors. Thus, it is well-known from numerous reports, that the cerebral blood vessels react readily to changes in the arterial blood-gas tensions, so that hypoxia and hypercapnia induce vasodilatation, and hypocapnia vasoconstriction; for a review see Lassen (1959). Changes in the tensions of oxygen or carbon dioxide in the tissue have been considered likely to provide the sensitive mechanism required for the flow autoregulation to the extent observed in the brain (Rapela and Green 1964; see also Lassen 1964 and Harper 1965).

The myogenic theory, discussed by Forbes, Nason and Wortman (1937) and Fog (1938) as a quite possible explanation of the reactions found, has received some support in more recent years. Häggendal and Johansson (1965) reported findings that appeared inconsistent with the metabolic theory but explainable in terms of the myogenic theory. A preliminary study of the influence of changes in the transmural pressure, as opposed to changes in the perfusion pressure, on the cerebrovascular resistance was presented at the International CBF Symposium 1969 by Ekström-Jodal *et al.*, suggestive of a non-metabolic, probably myogenic mechanism. At the same symposium there was also presented a study by Held, Gottstein and Niedermayer (1969) showing an autoregulatory response on a lower flow level, when there was a pulsatile as compared to a non-pulsatile flow with the same mean pressure. This was interpreted as indicating a myogenic mechanism.

For a recent review of autoregulation of cerebral blood flow the reader is referred to Häggendal, Nilsson and Norbäck (1970).

AIM OF THE PRESENT STUDY

The main purpose of the present investigation was to study the mechanism responsible for the autoregulation of cerebral blood flow. This includes a study to define the pressure-flow relation in normotension, *i.e.* within the so called autoregulatory pressure range, in conditions with normal and increased blood flow, and in hypotension, where autoregulation was exhausted, as well as the time requirements for the completion of the autoregulatory response. It also concerns the reaction of the cerebral blood vessels to changes in the arterial carbon dioxide tension in states with such a low blood pressure that autoregulation is exhausted; the capacity to autoregulation in the face of different degrees of arterial hypoxia; and reactive hyperemia (I and II). Moreover an attempt to differentiate effects of changes in the distending, *i.e.* transmural pressure, from those of changes in the perfusion pressure has been performed (III).

METHODOLOGICAL CONSIDERATIONS

General procedure

Unselected mongrel dogs, anaesthetized with pentobarbital, were used. The animals were artificially ventilated, and changes in the blood gas situation were achieved by administration of different gas mixtures. The arterial blood pressure was changed by bleeding or reinfusion of blood. Measurements of cerebral blood flow were not performed until 15 minutes after changes of ventilation and until 5 minutes after changes of blood pressure in order to assure a "steady state".

Measurement of cerebral blood flow

For the study of such a vulnerable process as the autoregulation of blood flow in the brain a leading principle in the choice of methods must be that as little trauma as possible is inflicted. In this respect the radioactive gas elimination technique of Lassen *et al.* (1963) has definite advantages. No direct interference with the brain tissue is involved, because the elimination of intraarterially injected radioactive krypton (Kr^{85}) is recorded through the intact skull with a scintillation detector. Another advantage with this method, in experiments where numerous flow measurements are desired, is that it includes no blood loss. In this study the injections were made via a catheter into the intact left vertebral artery close to the base of the skull, leading to a high concentration of the indicator in the brain with little extracerebral "contamination". The catheter, left in an unwedged position, hardly interferes with the blood supply of the brain. Norbäck (1966), using the same technique, reported that the difference between the blood pressure measured in the aorta and at the tip of the catheter in the vertebral artery was only 10 mm Hg.

The elimination curve obtained was resolved into two main components, considered representative of the two major types of tissue in the brain, *i.e.* grey and white matter (Lassen *et al.* 1963). Experimental evidence for the correctness of this assumption was presented by Häggendal, Nilsson and Norbäck (1965), and the reader is referred to this study for details of the curve analysis. A third, slow component was often recognized, probably due to such factors as administration of small amounts of indicator to extracerebral tissue and to recirculation. By the use of a careful collimation the background activity registered in the curves could be kept low and did not significantly affect the solution of the curves. Flow correspond-

ing to the different components can be calculated with the equation for an exponential clearance function, if the elimination rate of the indicator from the tissue and the partition coefficient of the indicator between tissue and blood are known. The value of the partition coefficient for Krypton is influenced by changes in the hematocrit of the blood (Lassen *et al.* 1963, Glass and Harper 1962, Ingvar and Lassen 1962) but as only minor differences between the measurements were encountered no corrections were considered necessary and the value of 0.95 for cerebral grey matter was used throughout the study. The flow in the grey matter, *i.e.* the flow calculated from the fast component of the clearance curve, is given in the results. One reason for this is that cerebral venous blood, required for the calculation of the cerebral metabolic rate of oxygen, can most conveniently be sampled in dogs from the superior sagittal sinus, which has been found to drain predominantly cerebral grey matter (see below). Furthermore, the component representative of grey matter is less influenced by possible errors in drawing the third slow component in the γ curve (Häggendal, Nilsson and Norbäck 1965). Using the same method of flow determination and curve analysis as was used in this study, Häggendal (1965) studied the error of the method in subsequent measurements, which was found to be around 10% of the mean value.

Analysis of blood from the superior sagittal sinus

Cerebral venous blood was withdrawn via a needle bored through the skull bone down into the sinus. In combination with practically every measurement of cerebral blood flow simultaneous samples were taken from the sinus and a femoral artery for the determination of oxygen saturation and capacity, pH and carbon dioxide tension; the metabolic rate of oxygen in the grey matter could then be calculated. In the oximetric studies (II) the oxygen saturation of blood from the superior sagittal sinus was continuously followed during rapid changes in the arterial blood pressure, changes in the oxygen saturation being taken as a relative measure of changes in the blood flow. In these procedures, of course it is of critical importance that the sagittal sinus blood is representative of venous blood from the grey matter. A substantial contribution of extracerebral blood could be expected to change the results, and in studies of cortical metabolism Gleichmann *et al.* (1962) used the blood from the superior sagittal sinus as representative of cortical venous blood only after elimination of the diploic veins. However, earlier results from this laboratory by Häggendal, Nilsson and Norbäck (1965) with registration of the β curve from sagittal sinus blood did not indicate any important extracerebral contribution and Häggendal and Norbäck (1966) did not find any changes in the venous oxygen saturation, when blood was withdrawn with varying rates, which is in accordance with the findings in the present study (II). However, care was taken to draw the samples relatively slowly (about 5 ml/min) in order to avoid a possible error from this source.

The contribution of blood from white matter to the superior sagittal sinus is small enough to be almost negligible (Häggendal, Nilsson and Norbäck 1965). Moreover a contribution of a certain amount of blood from white matter should probably not invalidate the results as the relation between both flow and oxygen consumption in grey and white matter is about 5 to 1 (Homburger *et al.* 1946, Häggendal, Nilsson and Norbäck 1965, Gleichmann *et al.* 1962), giving the same arterio-venous oxygen difference for the two tissues. This relation between cerebral blood flow and oxygen consumption in grey and white matter seems to remain constant during the different conditions studied. Thus, flow in white matter is autoregulated in the same pressure range as flow in grey matter (Bozzao *et al.* 1968, James, Millar and Purves 1969). The latter authors found a similar percentual increase of flow in white as in grey matter when the arterial oxygen tension was lowered from normal to around 40 mm Hg and also when the arterial carbon dioxide tension was changed within the range from around 25 to 65 mm Hg.

For the oximetric studies it is of major interest that the cerebral oxygen consumption is constant during each registration. Available information indicates that this is the case. Thus, no changes in oxygen uptake were found by Hirsch *et al.* (1955) in combination with blood flow reductions down to around 50% of the normal value. Häggendal and Norbäck (1966) demonstrated a maintained oxygen uptake in hypotension, even when this was so pronounced that the cerebral blood flow was reduced. Moreover the cerebral metabolic rate of oxygen is unaffected by wide variations in the arterial carbon dioxide tension, as indicated by the studies of Kety and Schmidt (1948) and of James, Millar and Purves (1969).

PART I

ASPECTS ON THE PRESSURE-FLOW RELATION IN THE BRAIN

Description of the pressure-flow relation (I and II)

Within a wide pressure range a tendency to maintain constant flow values was demonstrated in animals with normal cerebral blood flow (Fig. 1), as well as when a primary vasodilatation had been induced (Fig. 1, I). In fact the flow was kept almost perfectly constant. Considering the errors inborn in the method for flow measurement it is difficult, on the one hand, to exclude that some decline in flow accompanied the pressure reduction, but on the other hand an error of the method should give a scatter of the flow values and not a consistent overestimation of the values at lower arterial blood pressures compared to those at the higher pressures. The constancy of oxygen uptake usually found and exemplified in Table I for the animals illustrated in Fig. 1, also contradicts a systematic error of the flow method

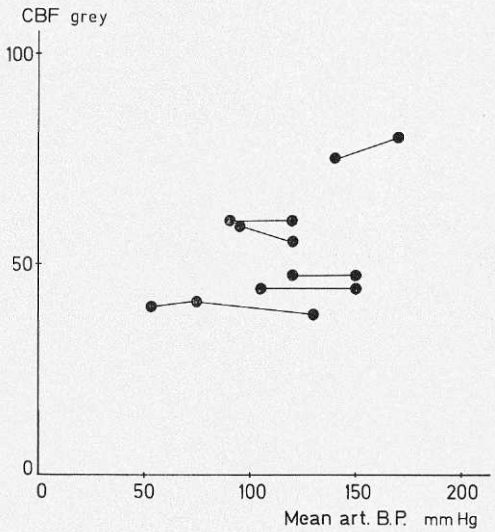

Fig. 1. Relation between mean arterial blood pressure and cerebral blood flow in grey matter (CBF_{grey}, ml/100 gmin) in six dogs. Constant or almost constant flow is demonstrated for each animal within the pressure range studied.

Table I. Data obtained from the experiments presented in Fig. 1.

Abbreviations:

P_{aCO_2} = Arterial carbon dioxide tension.
S_{aO_2} = Arterial oxygen saturation.
Mean art. B.P. = Mean arterial blood pressure.
CBF_{grey} = Calculated blood flow in cerebral grey matter.
CMR_{O_2} = Cerebral metabolic rate of oxygen calculated from CBF_{grey} and the arterio-venous oxygen difference.

P_{aCO_2} mm Hg	S_{aO_2} %	Mean art. B.P. mm Hg	CBF_{grey} ml/100 gmin	CMR_{O_2} ml/100 gmin
33	93	120	55	5.3
32	90	95	59	5.8
22	98	150	44	6.2
24	97	105	44	6.2
33	92	130	38	3.6
31	89	75	41	3.9
29	93	53	40	4.1
46	91	150	47	6.0
46	85	120	47	5.8
42	82	120	60	5.7
40	81	90	60	5.6
36	92	170	80	5.0
39	92	140	75	4.4

as responsible for the apparent constancy of flow. In the literature there are several reports of this remarkable effectivity of flow regulation observed with different techniques. Among others Carlyle and Grayson (1955) found a constant flow down to an arterial blood pressure value as low as about 30 mm Hg using a calorimetric method with blood flow recorders implanted in the brain; Rapela and Green (1964), measuring venous outflow from the confluence of the sagittal, straight and lateral sinuses with both lateral sinuses occluded, also found constant flow values down to very low blood pressures; Harper (1965), using the radioactive gas elimination technique with β registration from the exposed cortex, came to the same result in principle, although finding flow constancy within a more narrow pressure range. Dealing with this mechanism, susceptible to derangement, it seems reasonable to pay more attention to positive than to negative evidence in respect even to an absolute constancy of flow, since impairment of autoregulation might possibly not

be an all-or-none phenomenon but rather a more less pronounced attenuation of the mechanism, as indicated by studies on the effect of artificial perfusion on the response (Rapela and Green 1964). Furthermore, in the present study, the perfect readjustment to the original venous oxygen saturation found in the oximetric study (II), when the arterial blood pressure was changed within the autoregulatory range supports the view that the autoregulatory mechanism in the brain is capable of maintaining constancy of flow.

The pressure-flow relation in hypotension has not been extensively studied so far. However, Harper (1965) demonstrated a linear relationship in hypotension. Also in hypercapnia (Harper 1965) and hypoxia (Häggendal and Johansson 1965) linear relationships have been presented. On the other hand Fog (1934) and Forbes, Nason and Wortman (1937) reported contractions of the directly observed pial arteries in response to marked blood pressure reductions. Furthermore, Rapela and Green (1964) found a pressure-flow relation in hypercapnia indicating a passive vascular bed, *i.e.* curvilinear with the convexity towards the pressure axis. The above-mentioned linearity implicates an ability of the vessel wall to react to some extent to pressure changes and/or metabolic factors.

In the present work the study of the pressure-flow relation in hypotension below the autoregulatory range (I) was facilitated by induction of a primary flow increase by hypercapnia or papaverine infusion before reducing the arterial blood pressure in small steps. A curvilinear relation was found with the convexity towards the pressure axis. No difference in the relation was observed whether hypercapnia or papaverine was used. This appearance of the relation does not, however, exclude an ability of an active response of some kind being retained in hypotension, although not strong enough completely to counteract the effect of the pressure changes on the elastic vessel walls. In hypoxia, profound enough to impair autoregulation, metabolic factors, resulting from the hypoxia, might give rise to a vasodilatation, when the pressure is reduced (see below). On the other hand the normal auroregulation in this case might be only impaired, not abolished, which would also modify the response (*cf. p.* 19).

Time relations in the autoregulatory response (II)

When the arterial blood pressure was changed within the autoregulatory pressure range by rapid withdrawal or infusion of blood, the cerebral venous oxygen saturation, continuously analysed oximetrically, was found first to change in the same direction as the pressure, but then to return gradually towards the basal level (Fig. 1, II). The time for this response to be complete, *i.e.* from the pressure increase or decrease to the point where the control level of oxygen saturation was reestablished, was about 45 and 40 seconds, respectively. These figures are in accordance with or somewhat shorter than those reported in other studies (for references see paper II.)

Reactive hyperemia (I)

This term denotes an increased cerebral blood flow in normotension, combined with a passive pressure-flow relation, elicited by a period of reduced perfusion pressure. The phenomenon has been observed both when the reduction of the perfusion pressure has been accomplished by a rise in the intracranial pressure (Noell and Schneider 1948, Häggendal *et al.* 1969 and 1970 b) and after periods of pronounced arterial hypotension (Freeman and Ingvar 1968). Usually the period of hypotension preceding the reactive hyperemia has been combined with a substantial flow reduction. In some of the reported cases, however, no flow reduction had been observed (Häggendal *et al.* 1970 b), which is interesting with regard to the mechanism behind the phenomenon. In an attempt to a further evaluation of the role of hypoxia for the appearance of reactive hyperemia, the flow reaction to arterial blood pressure increases after a period of hypotension with reduction of flow was studied in animals, where a primary vasodilatation had been induced by hypercapnia or papaverine infusion. In spite of the fact that the blood flow had not been reduced to values below normal and that the venous oxygen tension had not been lower than about 40 mm Hg a marked flow increase was encountered (Fig. 7, I), which gradually subsided. These results confirm those obtained by Häggendal *et al.* (1970 b) and indicate that tissue hypoxia is not a prerequisite for reactive hyperemia. Nor does carbon dioxide accumulated in the tissue during the hypotension seem likely to uphold such a long-lasting vasodilatation. It might be of interest to compare this derangement of the normal pressure-flow relation to the "luxury perfusion syndrome". This term was recently introduced by Lassen (1966) and denotes a state characterized by "an over-abundant cerebral blood flow relative to the metabolic needs of the brain tissue". With normal arterial oxygen saturation "bright-red venous blood" would be the cardinal feature of the syndrome. In cases, where the high oxygen saturation in the venous blood is the result of the flow increase ordinarily seen when the normal autoregulation is impaired, the two terms, reactive hyperemia and luxury perfusion, are synonymous, as far as the blood pressure and the arterial oxygen content are high enough. However, it is clear that the combination of high flow values and "red veins" is compatible with a normal pressure-flow relation, *e.g.* in hypercapnia. On the other hand a deranged pressure-flow relation may be associated with dark venous blood in hypotension and/or pronounced hypoxia.

The pressure-flow relation in arterial hypoxia (I)

In combination with an extreme arterial hypoxia Häggendal and Johansson (1965) found signs of an abolished autoregulation. In the present study, however, it was possible to demonstrate a well functioning regulation in some cases even when the arterial oxygen saturation was reduced down to 40 per cent and a certain degree of flow increase had occurred. From a consideration of the general relation between

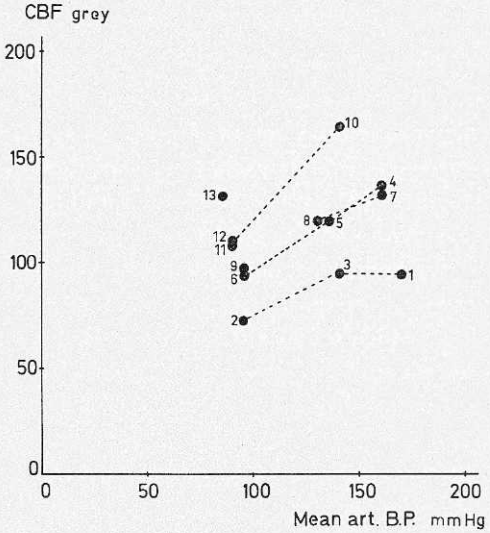

Fig. 2. Relation between mean arterial blood pressure and cerebral blood flow in grey matter (CBF_{grey}, ml/100 gmin) in one animal at different values of arterial oxygen saturation. The numbers mark the chronological order of the measurements and refer to the numbers in Table II. Measurements performed at about the same arterial oxygen saturation are connected by broken lines. An imperfect autoregulation is illustrated in hypoxia. In hypotension below the autoregulatory range there is a vascular dilatation in response to decreasing arterial oxygen saturation down to a certain limit (no. 11). With maintained low arterial oxygen saturation and blood pressure a further vasodilatation beyond this limit is induced by intravenous administration of glucose (no. 13).

arterial oxygen saturation and cerebral blood flow (see Fig. 2, I) it seems improbable that a complete abolishment of autoregulation could take place at a higher oxygen saturation than where the steep increase in blood flow begins, because such an abolishment would be expected to cause a comparatively large flow increase. The vasodilatation encountered in pronounced hypoxia is probably related to tissue hypoxia (Noell and Schneider 1944, Häggendal, Nilsson and Norbäck 1966), and in this range of arterial oxygen saturation optimal conditions for metabolic blood flow autoregulation should be provided. In Fig. 2 and Table II the results are presented from an experiment where some points may be of interest in this connection. Autoregulation in this animal was impaired, but not completely abolished at an arterial oxygen saturation of about 55 per cent (nos. 4, 5, 6). At an arterial pressure, where the blood flow in the normoxic situation was reduced due to low blood pressure, the flow was higher in hypoxia. When the measurements were repeated after about 45 minutes (nos. 7, 8) no signs of reactive hyperemia were found. With increasing arterial hypoxia a further vasodilatation was encountered in normotension (no. 10). In hypotension there was a flow increase when the arterial oxygen saturation was lowered from 57 to 46 per cent (nos. 6, 11), and there seemed to be a tendency to

Table II. Data obtained from the experiment presented in Fig. 2.
The numbers refer to those in the figure.

Abbreviations:

$P_{a_{O_2}}$ = Arterial oxygen tension.
$P_{v_{O_2}}$ = Venous oxygen tension in blood from the superior sagittal sinus.
CVR = Cerebrovascular resistance calculated from mean arterial blood pressure and CBF_{grey}.
For the remaining abbreviations see legend to Table I.

No.	$P_{a_{CO_2}}$ mm Hg	$S_{a_{O_2}}$ %	$P_{a_{O_2}}$ mm Hg	$P_{v_{O_2}}$ mm Hg	Mean art. B.P. mm Hg	CBF_{grey} ml/100 gmin	CVR mm Hg / ml/100 gmin	CMR_{O_2} ml/100 gmin
1	36	92	73	45	170	94	1.81	5.8
2	35	93	84	36	95	73	1.30	6.6
3	39	92	87	49	140	95	1.47	5.5
4	39	54	37	27	160	137	1.17	6.3
5	41	57	38	27	135	120	1.13	6.7
6	41	57	38	24	95	94	1.01	6.2
7	44	51	36	26	160	132	1.21	6.9
8	42	51	36	24	130	120	1.08	7.0
9	38	58	40	24	95	97	0.98	6.9
10	46	36	31	23	140	165	0.85	6.1
11	41	46	37	22	90	108	0.83	6.6
12	41	38	33	18	90	110	0.82	5.0
13	42	36	33	20	85	132	0.64	5.4

keep the venous oxygen tension constant (22–24 mm Hg, nos. 6, 8–11) over a wide blood pressure range when the arterial oxygen saturation was varied between 57 and 36 per cent. Decreasing the arterial oxygen saturation in hypotension from 46 to 38 per cent did not induce any further vasodilatation and the venous oxygen tension and the oxygen uptake decreased, indicating an inability to respond to arterial hypoxia, while the cerebrovascular resistance was still fairly high. This finding would be in line with earlier observations that maximal vasodilatation does not seem to take place even at very pronounced arterial hypoxia if the arterial carbon dioxide tension is not simultaneously increased (Häggendal and Johansson 1965). Against the background of a theory of hydrogen ions as the factor by which hypoxia acts on the vessels (Skinhøj 1966, Betz and Kozak 1967, Lassen 1968) a hypothetical explanation for the limited vasodilatatory response could be an insufficient supply of substrate required for the increasing anaerobic metabolism. Evidence of an interference with glycolysis in the brain due to substrate depletion in hypoxia was discussed by Cohen (1966). An indication that this might be a limiting factor for hypoxic vasodilatation is the flow increase encountered in hypotension after administration of glucose (no. 13), when no further dilatation had occurred with decreasing arterial oxygen saturation (nos. 11–12). In this animal 40 ml of a 10 per cent solution of glucose were given, which did not appreciably alter the oxygen capacity of the blood.

Reaction of the cerebral vessels to changes in the arterial carbon dioxide tension in hypotension (I)

Different results have been reported in the comparatively few studies published concerning the ability of the cerebral blood vessels to dilate in response to an increase of the arterial carbon dioxide tension, when autoregulation is exhausted. Thus Harper (1965) reported lack of response in hypotension. On the other hand Häggendal and Johansson (1965) studying the situation when autoregulation was impaired by extreme hypoxia found a scattering of the pressure-flow relation, that could be attributed to differences in the arterial carbon dioxide tension, and Häggendal *et al.* (1969 and 1970a) also demonstrated a reactivity to carbon dioxide, when the perfusion pressure was lowered beyond the autoregulatory range by induced increase in the intracranial pressure. The investigation of this reaction in hypotension meets with some difficulties in that the ensuing flow changes can be expected to be relatively small and the passive-elastic properties of the vessel wall imply changes in the vascular dimensions as a result of even small pressure changes.

In Fig. 6, I, a reaction to carbon dioxide in hypotension below the autoregulatory range is illustrated in terms of cerebral vascular resistance. There is a tendency to vasodilatation with increasing arterial carbon dioxide tension. With the oximetric technique a similar reaction was noticed during severe hypotension, *i.e.* higher cerebral venous oxygen saturation with higher concentration of carbon dioxide in the inspired air.

Discussion

The compatibility of these results with the metabolic theory for the autoregulation of blood flow will be discussed. It is obvious that a metabolic mechanism, being basically flow-dependent, cannot keep the flow absolutely constant; some change is necessary to evoke a stimulus. Since the regulation, as discussed above, is practically perfect, it follows that an extremely sensitive mechanism would be required. The metabolic factors most discussed as eliciting the reaction have been oxygen, acting directly or via some metabolite resulting from tissue hypoxia, carbon dioxide and the hydrogen ion concentration in the tissue (Rapela and Green 1964, Lassen 1964). The latter factor has attracted further attention recently in view of the theory stating that changes in the hydrogen ion concentration may be the common link for the influence on the vessels by both oxygen and carbon dioxide (Skinhøj 1966, Betz and Kozak 1967, Zwetnow, Kjällquist and Siesjö 1968, Severinghaus 1968, Lassen 1968). In fact none of these factors seems likely to be able to establish a very sensitive regulation.

Thus, the reaction of the vessels in response to changes in the arterial oxygen saturation is quite small around the physiological values, and there is no marked vasodilatation until the arterial hypoxia has become pronounced (Fig. 2, I) (Häggendal and Johansson 1965). The constrictive effect of an elevation of the arterial oxygen tension is practically negligible (Lambertsen 1961, Reivich 1964). Further-

more, the presence of autoregulation at supernormal flow levels seems almost conclusively to rule out hypoxia as the regulatory factor.

Concerning carbon dioxide the effect on vascular resistance by changes in its arterial tension is pronounced also around the normal value. There is, however, evidence against carbon dioxide being a primarily important factor. As discussed by Harper (Harper and Häggendal 1968) an increase in the hydrogen ion concentration in the extracellular fluid corresponding to a change in the arterial carbon dioxide tension from 40 to about 70 mm Hg would be required to reduce the vascular resistance to the extent observed, when the arterial blood pressure is lowered within the autoregulatory range.

In addition, when the lower limit for autoregulation is reached in hypotension, the metabolic theory implies that the vessels are maximally dilated due to the regulatory factors. The fact that the response to both carbon dioxide and oxygen is retained below the autoregulatory pressure range adds to the improbability of either being the main autoregulatory agent.

A vasodilatatory influence of hypoxia in combination with a flow reduction secondary to a fall in blood pressure could be expected to be especially pronounced in severe hypoxia, since here vasodilatation in response to a small decrease in oxygen availability is known to be very marked in normotension. It might even be so large as to create a fairly effective autoregulatory response. Such a regulation might be discussed in the case illustrated in Fig. 2, where there are signs of an imperfect autoregulation. Whether the autoregulatory tendency noted in the hypoxic state is a result of a hypoxic influence modifying a passive pressure-flow relation or is an expression of an impairment of the ordinary mechanism in the higher pressure range is not possible to judge. In the hypotensive state, however, a metabolic influence would seem to be responsible for the cerebrovascular dilatation.

The relatively long time period required for flow adjustment has been assumed to favour a metabolic theory, since a myogenic mechanism might be expected to induce a faster response (Harper 1966). In vitro studies on the reaction of vascular smooth muscle to quick stretch have shown, however, that the response may require about 60 seconds to become fully developed (Sparks 1964), thereby differing from other smooth muscle, *e.g.* in the urinary bladder, which exhibits a much faster response.

In regard to the mechanism responsible for the reactive hyperemia it should be pointed out that in paper I the main problem studied was whether it was possible to induce the phenomenon under conditions where metabolic factors could reasonably be excluded. No more detailed analysis of the duration and degree of hypotension was performed. It seems likely that metabolic factors might contribute to the induction and maintenance of reactive hyperemia in some circumstances but they are not a prerequisite for the appearance of the phenomenon. It may be discussed whether the reactive hyperemia demonstrated in paper I is of the same origin as the transitory passive flow response occurring in combination with pressure rises in the autoregulatory range as demonstrated in paper II using the oximetric technique.

PART II

EFFECT OF INCREASED VENOUS PRESSURE ON THE CEREBRAL BLOOD FLOW

An autoregulatory mechanism depending on vascular smooth muscle response secondary to changes in the chemical environment, should be effective, when the perfusion pressure, and thus flow, is altered, irrespective of how this change is achieved. A myogenic mechanism, on the other hand, would in principle be independent of the perfusion pressure and respond to changes in the transmural pressure. Such considerations have been the background for an experimental approach, previously used in different vascular beds, employing increases in the venous pressure, while the level of the arterial blood pressure is controlled, preferably so that the venous and arterial blood pressures are raised to the same extent (see Folkow 1962). In this situation the perfusion pressure is maintained constant, while the transmural pressure is raised. In a passive vascular bed this would lead to an increased flow due to distension of the elastic vessel wall, while in an actively responding vascular bed, governed by metabolic factors, there would be a tendency to keep flow constant. If the response were due to stretch of the smooth muscles, a contraction would ensue, which, if powerful enough, would cause a flow reduction. This latter kind of response has been found in skeletal muscle and intestine (Folkow 1949, Folkow and Öberg 1961, Johnson 1959 and 1964 c).

The brain cannot be directly subjected to this otherwise convenient procedure ol differentiating the effects of the two mechanisms, as it is enclosed in the rigid skulf and any change in the venous pressure consequently will lead to a change in the tissue pressure altering the transmural pressure in proportion. In the present study this difficulty was overcome by the removal of large parts of the skull and dura over both hemispheres, thereby providing conditions for expansion of the tissue. The venous pressure was raised by inflation of a balloon attached to a catheter and placed in the right atrium of the heart. No special measures were taken to maintain the arterial blood pressure during the increase in venous pressure, since any additional surgical trauma was considered undesirable. The inflation of the balloon tended to cause a moderate decrease of the arterial blood pressure, presumably due to a reduction of the cardiac output. Such a decrease of the arterial pressure would curtail the possibility of revealing differences in the cerebrovascular response, as the

accompanying decrease in transmural pressure would counteract the increase induced by the venous pressure rise. This difficulty was avoided by using a reference value for each animal (see paper III).

In Fig. 2, III, was demonstrated a difference in the percentual changes of the cerebrovascular resistance if the perfusion pressure was reduced by venous pressure increase or by arterial pressure decrease. A reduced perfusion pressure induced by elevation of the venous pressure was accompanied by either unaltered or increased cerebrovascular resistance, while arterial pressure reductions were accompanied by proportionate lowering of the resistance. When the arterial blood pressure was reduced by bleeding with the venous pressure maintained high and constant, there was autoregulation on a lower flow level than with normal venous pressure (Fig. 1, III).

Discussion

These results indicate a mechanism triggered by changes in the transmural pressure to be responsible for the cerebral blood flow autoregulation. No attempts to block possible nervous influence were made, but available information from other vascular beds, where the response was shown to be independent of nervous factors, make it unlikely that such an influence would be important in the case of the brain. Furthermore, the adrenergic innervation of the intracerebral vessels is sparse (Carlsson, Falck and Hillarp 1962). On the basis of earlier studies it has been concluded that the nervous supply to the brain vessels is hardly of any functional significance (Sokoloff 1959). Although interest in this problem is now growing (Rapela, Green and Denison 1967, Langfitt and Kassell 1968, Mchedlishvili 1969, James, Millar and Purves 1969) there is no evidence to suggest that nervous vasomotor control should be of decisive importance for autoregulation in the brain.

The myogenic hypothesis then remains to be considered. This theory, described in detail by Folkow in 1964, has recently been reviewed by Mellander and Johansson (1968). In short, parallels have been drawn to the function of the smooth muscles of the ureter and intestine, which show spontaneous rhythmic contractions, the frequency of which increases in response to stretch (Bozler 1948, Bülbring 1955). Evidence of vascular smooth muscle automaticity has been revealed by electrophysiological studies, beginning with the report of Funaki (1958), who recorded action potentials with microelectrodes in the muscle cells of the small vessels in the frog tongue. Furthermore, rhythmic activity has been demonstrated in small pre- and postcapillary vessels, studied microscopically *in situ* in the bats wing (Nicoll and Webb 1955, Wiedeman 1957 and 1966). This vasomotion, has been suggested to create the "basal tone" remaining in most vascular areas after elimination of all known extrinsic regulatory influence.

The observation that the basal tone is least pronounced in those vascular circuits, which show inefficient or no autoregulation (Folkow 1962) might suggest that autoregulation in response to changes in the transmural pressure is effectuated by the

same mechanism; direct studies on small precapillary vessels have shown that vasomotion does become potentiated in response to an increase in the transmural pressure (Nicoll and Webb 1955, Wiedeman 1966), although the extent to which this increase in vasomotion can account for flow constancy has not been exactly established. Such a mechanism would, however, explain one contradiction in the original theory, namely that if the stimulus were distension, it would seem to be abolished, if the resistance to flow were upheld by a continuous contraction of the smooth muscle cells. With the concept of a changed frequency of contractions when the pressure is altered, a perfect constancy of flow, although still remarkable, implies no real contradiction. Observations like those reported in paper I of well functioning autoregulation at high flow levels, and of reactivity to oxygen and carbon dioxide in hypotension might possibly be explained in terms of a differentiated response to different stimuli in separate parts of the precapillary resistance section. Some experimental evidence of such a response exists. Thus, studies in skeletal muscle during exercise have indicated that metabolic factors are comparatively more important than the transmural pressure as determiners of the tone of the resistance vessels and vice versa concerning the precapillary sphincter region (Lundvall, Mellander and Sparks 1967).

GENERAL SUMMARY AND CONCLUSIONS

Different aspects on the pressure-flow relation in the brain have been studied and discussed with regard to the mechanism responsible for cerebral blood flow autoregulation.

Evidence of an ability of the autoregulatory mechanism to establish a perfect flow constancy in response to arterial blood pressure changes at normal and high flow levels was presented.

The pressure-flow relation in hypotension below the autoregulatory pressure range in conditions with a primarily induced vasodilatation was found to be curvilinear with the convexity towards the pressure axis.

A cerebrovascular reaction to changes in the arterial tensions of both carbon dioxide and oxygen was demonstrated in hypotension, which indicates a possibility of this apparently passive pressure-flow relation being modified by metabolic factors.

With rapid changes of the arterial blood pressure there was initially a change of flow in terms of a change in the cerebral venous oxygen saturation in the same direction. After that, within the autoregulatory pressure range, the flow gradually returned to the control level, this response being completed in about 40 seconds from the beginning of the alteration of the pressure.

Reactive hyperemia could be elicited after a period of hypotension without signs of tissue hypoxia, and it was suggested that this might be a prolongation of the normal transitory flow increase following pressure rises within the normotensive pressure range.

During arterial hypoxia autoregulation was effective even when a hypoxic vasodilatation had occurred. In extreme arterial hypoxia an impairment of the autoregulatory function was noted; the pressure-flow relation, however, was not "purely" passive. In hypotension below the autoregulatory pressure range a vasodilatation was encountered with decreasing arterial oxygen saturation, which might establish an important regulation, when the normal autoregulation is impaired.

On account of the results obtained metabolic factors were considered unlikely to be responsible for the normal autoregulation of cerebral blood flow. This was further stressed by the results from the following group of experiments. Here studies on the vascular response to increases of the venous pressure compared to the response to arterial blood pressure reductions were performed after removal of the skull coverings in an attempt to separate the effect on flow by changes in the perfusion pressure from

those by changes in the transmural pressure. A mechanism most likely of myogenic nature stimulated by changes in the transmural pressure was demonstrated to be responsible for the normal cerebral blood flow autoregulation.

In view of the increasing availability of methods to study regional cerebral blood flow and metabolism applicable to diseased states a detailed knowledge of the normal pressure-flow relation and the reaction of the blood vessels to different influences in different pressure ranges is important. The present work might increase the possibilities for a sound clinical approach to the study of problems concerning cerebral blood flow.

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