Editorial Review

Cerebral oxidative metabolism in hypertension

C. John DICKINSON
Wolfson Institute of Preventive Medicine, London, U.K.

1. The evidence is now overwhelming that so-called 'essential' hypertension in man, i.e. high systemic arterial pressure for no apparent cause, is commonly initiated by increased efferent sympathetic activity directed to the cardiovascular system. Eventually structural and other changes take place in the heart, kidneys and blood vessels. These may reinforce, augment and even conceal the initially neurogenic background. The cause of the increased sympathetic activity remains in dispute, but it is probably not psychological in most cases.

2. The brain has a high requirement for energy - twice that of the heart, at rest. In the normotensive adult, the brain's needs are met almost exclusively by the oxidation of glucose. This results in a cerebral respiratory quotient for the brain of approximately unity. The brain can utilize other materials, notably ketones, as it does to a considerable extent in the fetus. It retains this capability in adult life, even though normal adults do not make use of it.

3. In human hypertension the cerebral respiratory quotient falls in proportion to the rise of arterial pressure, indicating the consumption of other fuels in addition to glucose. β-Hydroxybutyrate is certainly one of these, but fatty acids may also be utilized.

4. A similar or greater reduction of cerebral respiratory quotient than in essential hypertension is seen in chronic cerebrovascular disease and in chronic heart failure in man. This raises the possibility that although cerebral blood flow is only slightly reduced in hypertensive patients at rest, the cerebral circulation is potentially under threat. The change in the pattern of oxidative metabolism may be looked upon as an adaptation to the threat. This would fit in with strong epidemiological and pathological evidence linking hypertension with cerebral, especially vertebrobasilar, atheroma.

5. Many of the pathophysiological changes in essential hypertension have parallels in the spontaneous hypertensive rat and its stroke-prone variant. Such rats have an impaired cerebral blood supply. Infarctions are easily produced by arterial occlusions which have little adverse effect on Wistar–Kyoto rats. Spontaneous hypertensive rats and stroke-prone spontaneous hypertensive rats also have reduced cerebral glucose utilization, which mirrors the situation in essential hypertension.

6. The Cushing response - threatened medullary ischaemia activating sympathetic vasomotor efferent nerves - could provide the mechanism by which chronic borderline or intermittent cerebral circulatory inadequacy passed a signal to activate sympathetic efferent nerves, either directly or through altered brain metabolism.

7. Other interpretations are possible, but the evidence of this review suggests that further investigation of cerebral oxidative metabolism in hypertension and in related conditions may shed light on the still elusive aetiology of essential hypertension.

INTRODUCTION

Evidence for increased sympathetic nerve activity in hypertension

Most investigators concur that efferent sympathetic nervous activity is increased in the early stages of essential hypertension, and may play a part in its initiation. In most studies plasma catecholamines are increased [1]. The more reliable turnover studies confirm that peripheral catecholamine release is increased [2], notably from heart and kidneys [3]. Increased spillover of noradrenaline into the internal jugular veins has also been observed. Since ganglion blockade does not reduce this, the noradrenaline presumably derives from brain neurons themselves [3]. Spillover is also significantly increased in the normotensive relatives of essential hypertensive subjects [4].

Direct electrical recordings of efferent sympathetic nerve impulses from nerves to skeletal muscles show that there is truly increased neuro-
genic activity and not just increased responsiveness to a normal level of sympathetic nervous tone [5]. There is abundant evidence that, on average, resting heart rate and cardiac output are both increased in early essential hypertension [6].

The inbred spontaneous hypertensive rat (SHR) is now the main object of study in about a quarter of all original papers published in journals of hypertension. Altered renal function plays an important part in causing hypertension in the SHR [7]. There is also a myriad of other differences from the parent Wistar–Kyoto (WKY) strain [8]. However, since Okamoto et al. [9] first observed it, the SHR has been almost consistently reported to show more sympathetic nervous activity than the WKY rat, e.g. [10].

**Why is efferent sympathetic nerve activity increased?**

The increased efferent sympathetic nervous activity in essential hypertension clearly derives from the brain itself. Many people have assumed that the cause is probably psychological. A frequently quoted example is 'suppressed hostility' in black subjects [11]. A subtle psychological cause of increased sympathetic activity is almost impossible to disprove, but has been made very improbable by formal psychological testing of young people before their blood pressure was known [12].

Although baseline psychological tests of normotensive middle-aged men in the Framingham study suggested that markers of anxiety predicted the later development of hypertension, such subjects would inevitably know of adverse life events in close relatives. This might account for the findings. In any case the relationship was not observed in middle-aged women in the same study [13]. The most substantial evidence so far is from the British Medical Research Council's study in which 12000 subjects filled in a well-validated questionnaire before their blood pressure was known [14]. This study gave no support at all to psychological factors playing any part in the aetiology of sustained hypertension, although no-one would dispute that emotions have profound short-term effects on blood pressure.

If increased sympathetic nerve activity derives from the brain itself, but is not psychological in origin, what is its cause? Much current work has described alterations in cell membrane ion transport, especially of sodium. It is therefore possible that membrane transport changes in the brain might increase sympathetic neural activity, although it appears more likely that the membrane changes are secondary to increased sympathetic nerve activity [15]. Many specific alterations of cerebral function arising in adult life are associated with localized brain pathology, but no specific lesions have yet been identified in the brains of essential hypertensive patients. Because hypertensive patients are predisposed to cerebral arterial disease and strokes, this review examines the possibility that increased sympathetic nervous activity may be the brain's response to a problem in its energy supply.

**SUPPLY OF ENERGY TO THE BRAIN**

**Oxidative metabolism in the brain: uptake and metabolism of substrates**

The whole body at rest consumes about 250 ml/min of oxygen. The normal adult brain consumes about 3.8 ml min\(^{-1}\) 100g\(^{-1}\) of oxygen [16], which for an average weight of brain (1400 g) is 53 ml/min. At rest this is about one-fifth of total oxygen consumption, and twice the oxygen consumption of the heart. The brain is therefore one of the most metabolically active organs of the body, even though it comprises only about 2% of the body weight. The high metabolic rate requires the efficient removal of heat. In all mammalian species tested the temperature of the brain cortex and deep brain sites is higher than that of arterial blood [17]. The hypothesis has even been advanced that the profound inhibition of many heat-producing functions during slow-wave sleep is part of a homeostatic feedback process to keep the brain cool [18]. During rapid-eye-movement sleep, cerebral neuronal activity and metabolic heat production are increased, and there is a rise in brain temperature [19].

The energy stores of the brain are extremely small in relation to its high metabolic rate. Pooled data from several sources suggest that at the maximum observed rate of change, 10–15% of the total amount of oxygen and glucose in the brain is reacting every second. The maximum rate of consumption of ATP is even faster. About 25% of the total ATP of the brain may be metabolized every second [20]. General anaesthetics have profound effects on oxidative metabolism, reducing both glucose uptake and glycolysis by the brain.

Glucose is the main fuel of the brain in adult mammals. The adult brain metabolizes \(\alpha\)-glucose preferentially. It can handle both \(\alpha\)- and \(\beta\)-isomeric forms, with preferential uptake of the \(\beta\)-form; but the abundance of the enzyme mutarotase in brain and the rapid spontaneous mutarotation of glucose-6-phosphate minimize differences in uptake of the epimers. The brain is far less capable of metabolizing other sugars. The penetration of substances from blood into brain can be measured by the 'brain uptake index' (BUI). This is taken to be 100% for (tritiated) water uptake during a single passage after carotid artery injection. Polar compounds have an average BUI of only 2%. Essential brain metabolites are transferred through specific carrier systems. Such metabolites have BUIs ranging from 10 to 60%. The BUI for \(\alpha\)-glucose is 32%; that for \(\gamma\)-glucose uptake is unmeasurable. \(\alpha\)-Glucose uptake is therefore highly specific and carrier-mediated...
The hexose monophosphate pathway is more important in the young animal, whereas the Embden-Meyerhof pathway is mainly used for energy production in the adult brain [22]. Lactate and pyruvate are relatively impermeable compared with glucose, but both substances can be transported across the blood–brain barrier by saturable stereo-specific transport mechanisms. Both lactate and pyruvate can readily be oxidized within brain cells. Lactate has been identified as a particularly important substrate during brain development and in the early postnatal period. In newborn animals, acetoacetate is metabolized by the brain at the same rate as glucose, although in adult animals glucose is metabolized about three times faster than acetoacetate. The difference may reflect the relatively high levels of ketones in the blood at birth, and perhaps the low fetal tissue oxygen tension. Ketones are used until the end of the suckling period. There are important mammalian species differences; for example, although adult rat brain metabolizes ketones effectively, the brain of adult dogs does so very little [23]. If hypoglycaemia is produced by insulin infusion in man, the intravenous infusion of ketones allows lower blood glucose concentrations to be tolerated without the appearance of symptoms or of the hormonal responses associated with severe hypoglycaemia [24]. In general, the higher the concentration of ketone bodies in the plasma, the higher their rate of metabolism by the human brain. The same applies to lactate and pyruvate. Although ketones can substitute up to about 50% of the oxidizable substrate necessary for neuronal function, the presence of quite small amounts of glucose has a disproportionately large facilitating effect on the brain’s ability to catabolize ketones. Cerebral tissues can oxidize several fatty acids, but normally only on a small scale. However, during perfusion of the cat’s brain in the complete absence of glucose, large amounts of protein and lipids are metabolized, although the presence of small amounts of glucose prevents this [25]. The brain is also capable of metabolizing amino acids [26]. Labelled $^{14}$C$\text{O}_2$ can be produced within the brain from $^{14}$C-labelled amino acids, but no amino acid can fully replace glucose as an oxidizable energy-yielding substrate.

All the evidence to be reviewed suggests that the energy needs of the adult brain in situ can be fulfilled completely – and are normally fulfilled completely – by the oxidation of glucose. The rate of oxidation of glucose by brain slices is, weight for weight, faster than that of glucose oxidation by hepatic, cardiac or renal slices. In contrast with many other tissues, the brain does not need insulin to extract and oxidize glucose, although insulin does have small but measurable effects on central nervous system function. Insulin-sensitive glucose uptake appears to be related to specific parts of the brain; for example, in the rat the insulin-sensitive glucose transporter protein GLUT4 and its mRNA is exclusively found in the cerebellum, although GLUT1 and GLUT3 are widely distributed in the brain [27]. GLUT1 is the glucose transporter of the blood–brain barrier, and is mainly located on the abluminal side of brain capillaries [28].

The chemical equation for the complete oxidation of glucose by a blood-perfused organ predicts that glucose consumption and oxygen utilization should be related in the ratio of 1.34, assuming the units

\[
\text{Arteriovenous glucose concentration difference in mg/100 ml}
\]

\[
\text{Arteriovenous oxygen content difference in ml/100 ml}
\]

and assuming that all glucose taken up by the organ is oxidized on site. All investigators have observed higher figures, e.g. 1.67 [16]. It is notable that only some 50% of $^{14}$C-labelled glucose can be recovered in cerebral effluent blood as labelled $\text{CO}_2$ and $\text{HCO}_3^-$. It is therefore likely that glucose carbon equilibrates in the brain with a metabolic carbon pool which, in addition to glucose, includes glutamic, N-acetylaspartic and $\gamma$-aminobutyric acids, glycogen and glutamine. This makes it difficult to determine how much glucose is oxidized in any particular part of the brain, and how much has become part of the metabolic carbon pool.

**Respiratory quotient of brain**

In a living system in a steady state, the respiratory exchange ratio or respiratory quotient (RQ) – $\text{CO}_2$ produced/O$\text{O}_2$ consumed – is mainly determined by the fuels whose oxidation provides energy. In the equation

\[
\text{C}_6\text{H}_{12}\text{O}_6 + 6\text{O}_2 \rightarrow 6\text{CO}_2 + 6\text{H}_2\text{O}
\]

the complete oxidation of glucose produces the same number of molecules of $\text{CO}_2$ as of O$\text{O}_2$ consumed, and the RQ is unity. The oxidation of other substrates produces an RQ less than unity: about 0.71 for fats, and about 0.81 for amino acids. For the whole human body at rest, eating an average Western diet, the RQ is 0.82. On the other hand, in brain suspensions, tissue slices, and in perfused mammalian brains of cat, dog and monkey the RQ of the brain is approximately unity. This suggests that the normal brain principally derives its energy from the oxidation of glucose, even though it is capable of using other substrates.

Single organs, unlike the body as a whole, are not closed systems. To take a simple example: (i) if incoming glucose is dehydrogenated within the brain to pyruvic acid, according to the general equation

\[
\text{C}_6\text{H}_{12}\text{O}_6 + \text{O}_2 \rightarrow 2\text{C}_3\text{H}_4\text{O}_3 + 2\text{H}_2\text{O}
\]

and (ii) the pyruvate leaves the brain without undergoing further change, oxygen would have been consumed within the brain without the evolution of
any CO₂. This would obviously lower the apparent RQ. Despite these theoretical difficulties, all the evidence, from isolated cell systems to the whole normal adult human brain, is compatible with glucose being the brain’s main fuel.

The situation in the mammalian fetus is somewhat different. The fetus is tolerant of hypoxia. L-Lactate can enter the fetal brain readily, and may even be the preferred substrate for energy production after a period of anoxia. There is a gradual shift during development in most animals studied from predominate ketone body utilization by the brain to predominant glucose utilization. The tolerance of the brain to hypoxia, and its capacity for anaerobic metabolism, diminish after birth, although with great variation between different mammalian species.

**Measurement of the cerebral RQ**

Indirect methods have to be used in man to determine the cerebral RQ. These require measurement of the gas contents of blood flowing into and out of the brain. Normally about 56% of CO₂ contained in cerebral venous blood derives from the brain itself. In a steady state, the RQ of a blood-perfused organ can be measured by the ratio

\[
\text{(Jugular venous – arterial) CO}_2 \text{ content difference}
\]

\[
\text{(Arterial – jugular venous) O}_2 \text{ content difference}
\]

This provides an estimate of the intrinsic RQ of brain tissue, although there are a few reservations. Some authors have even envisaged the possibility that the consistent finding of a cerebral RQ very close to unity might be accidental, reflecting only (for example) the partial catabolism of glucose to pyruvic acid, and the conversion of carbohydrate to fat. This seems improbable. There is no good evidence in healthy individuals that the brain produces substantial amounts of pyruvic or lactic acids [29]. Another problem is that in any closed system the relative amounts of fat and carbohydrate oxidized can only be calculated after the protein oxidation rate is known. This is difficult to measure in an isolated organ. Furthermore, the rates of fuel consumption calculated from the apparent RQ are strictly net rates of complete utilization, rather than of oxidation. For example, carbohydrate converted to fat would be measured as carbohydrate utilization, carbohydrate synthesized from amino acids as ‘negative carbohydrate utilization’ and fat synthesized from carbohydrate or amino acids as ‘negative fat utilization’ [30].

Despite all these reservations, the consistent finding of a cerebral RQ of unity is very strong evidence that the adult brain uses glucose predominantly. Gibbs et al. [31] in their classic study of 50 healthy young men reported that the cerebral RQ was 0.99. The standard error was ± 0.01 (my calculation from their data). Between 1942 and 1961 there were 16 studies involving 223 normal subjects in which cerebral RQs were either recorded, or (more usually) could be calculated from the published tables of raw data. This possibility arose as a by-product of Kety’s method for measuring cerebral blood flow. This required collection of blood from an internal jugular vein, as well as from an artery. Values were given in each subject for arterial and jugular venous oxygen and carbon dioxide contents. A meta-analysis of these papers [32] confirms that the normal cerebral RQ is very close to unity, at least at or above 0.98. Criticisms are often levelled against meta-analysis. They are certainly justified when different analytical methods are used. Fortunately all the necessary blood gas measurements in the reports reviewed were made using the Van Slyke-Neill technique, and most authors had been trained in Kety’s laboratory.

After the 1950s, new methods for measuring cerebral blood flow by the uptake of radioactive inert gases (krypton and xenon) came into use. It was no longer necessary to collect or to analyse internal jugular venous blood. Cerebral RQs could no longer be derived from raw data tables. Even modern methods such as positron emission tomography (PET) do not provide the necessary information. Because of their rapid diffusibility, ketones (for example) cannot easily be studied, even though PET can accurately localize and measure glucose uptake [33]. Measuring glucose and oxygen consumption simultaneously in the same subject by PET is a tedious procedure. At the time of writing this has not yet been done in human hypertension.

**BLOOD SUPPLY OF THE BRAIN**

**Cerebral blood flow in normotension and hypertension**

The brain’s capacity for autoregulation is well established in man and in many other animals. Discrete stimulation of specific brain regions can alter cerebral blood flow; but cerebral blood flow seems normally to be regulated by the rate of metabolism in nervous tissue, which itself reflects the total amount of interneural traffic [34]. This applies to individual regions as well as to the brain as a whole. The correspondence, whatever its cause, must play an important part in autoregulation of overall cerebral blood flow. In the early stages of sleep total cerebral blood flow is normal, although cortical blood flow is slightly diminished. There is a patchy reduction of glucose metabolism, which particularly affects the thalamic nuclei. In deep sleep cerebral blood flow falls substantially [35], but in rapid-eye-movement sleep it may be increased [36].

Modern techniques for measuring total and regional cerebral blood flows by inhaled inert gases and by SPECT (single-photon emission computed tomography) require much less instrumentation and disturbance to the subjects than Kety’s original
nitrous oxide technique. The classic observation that cerebral flow blood at rest was the same in hypertensive and normotensive individuals now needs revision. Cerebral blood flow has more recently been reported to be significantly less than normal in essential hypertension [37, 38] and much less than normal in severe hypertension [39]. The reason for the difference from the old observations is almost certainly that the invasive instrumentation needed for the old nitrous oxide technique had increased the anxiety of the subjects, elevated their blood pressure and raised their cerebral blood flow above that in a true resting state.

Cerebral autoregulation is so powerful that despite wide variations of systemic arterial pressure in hypertensive as well as normal people there may be no measurable change in cerebral blood flow. Even in severe hypertension cerebral autoregulation is efficient [40]. During moderate therapeutic blood pressure reduction in essential hypertensive patients, total cerebral blood flow may remain normal. In some cases this could be due to the drug dilating the cerebral arterioles to exactly the same extent as in other organs. In other cases the intrinsic autoregulatory capacity of the cerebral circulation could be entirely responsible. Whatever the reason, substantial blood pressure reductions are surprisingly well tolerated, and may spare some vulnerable parts of the cerebral vasculature from high-pressure damage. Nonetheless, some patients treated with hypertensive drugs have focal areas of definite cerebral hypoperfusion, even though they show no measurable changes in neural function [41]. Some drugs seem to predispose to greater disturbance of cognitive function than others, even though cerebral blood flow may not be different [42].

It is generally assumed that the cerebral circulation in essential hypertension is no different from that in other vascular beds, in which increased resistance of its arterioles matches the increased resistance of arterioles in other parts of the body. This assumption runs contrary to previous necropsy studies of large cerebral arteries in essential hypertensive patients [43]. In another pathological study relative lack of medial hypertrophy of intracerebral arterioles was notable [44], suggesting that proximal arterial narrowing may have reduced the transmural pressure in smaller downstream vessels. Proximal large artery atheroma may also explain why the cerebral vasculature in essential hypertension dilates less with inhalation of CO₂ [45] and constricts less than in normotensive people [46].

Despite the near normality of total cerebral blood flow in hypertension, there may be localized and perhaps intermittent borderline ischaemia, leading to a change in energy production in the brain. It has already been reported that the jugular venous blood lactate concentration is slightly increased in benign and considerably increased in malignant hypertension [47]. Such evidence of cerebral anaerobic glycolysis supports the concept that the brain's blood supply may be inadequate. Further investigation of cerebral metabolism in essential hypertension is needed. Observations should be made at rest and if possible during sleep [6].

**Cerebral circulation and metabolism in the SHR**

The SHR, and especially its 'stroke-prone' derivative (SHRSP), provide remarkable parallels to man. Despite the brain of the SHR being some 10% smaller than the brain of the WKY rat [48], with larger cerebral ventricles and appreciably fewer neurons per brain structure [49], the brain's blood supply is precarious. A comparison of SHR with essential hypertension reveals similar abnormalities in cerebral vascular resistance, oxidative metabolism and vulnerability to ischaemia. Cerebral autoregulation is well preserved in SHR, but the brain is not thereby preserved from ischaemic damage. Carotid artery ligation in SHR or SHRSP produces a higher incidence, or greater extent, of ischaemic damage than in WKY, with much higher levels of internal jugular venous blood lactate [50–53]. Glucose utilization (measured by the 2-deoxyglucose method) has been reported to be reduced in both SHR [54] and SHRSP [55], even though cerebral blood flow in SHR is 'fairly similar' to that in WKY animals [54]. Cerebral mitochondria in SHRSP show submicroscopic signs of damage [56]. There have been no values published yet for the cerebral RQ in SHR. The technical difficulties would be formidable. When bilateral vertebral artery ligation was combined with moderate hypotension induced by controlled haemorrhage (blood pressure lowered to 50 mmHg in WKY and to 80 mmHg in SHR), cerebellar blood flow and ATP concentrations were much diminished in SHR. Under these conditions the cerebellar blood flow was 9.4 in SHR compared with 24.2 ml min⁻¹ 100 g⁻¹ brain in WKY [57]. Lactate and lactate/pyruvate ratios were increased in SHR.

One possibility was that there might be some gross anatomical variants of the cerebral blood supply of SHR to account for the differences from WKY. In 1982 (C. J. Dickinson, unpublished work) the aortas of six SHRs were injected with contrast material, but radiologically it appeared that the gross anatomies of the major cerebral arteries and their branches were the same as in WKY rats. There must be a generalized reduction of the calibre of small arteries and arterioles in the SHR. This might be related to oscillations in arteriolar calibre. In cats, regular fluctuations of brain tissue oxygen tension occur with a cycle length of about 10 s, presumably corresponding to cyclical opening and shutting of many adjacent cerebral capillaries [58]. Similar small-scale oscillations of cerebral arteriolar calibre have been seen in WKY rats; but they are much greater in SHR, and are almost continuous in
SHRSP [59]. Neither SHR nor SHRSP suffer from the stenotic or occlusive cerebral atheroma seen so commonly in human hypertension. SHR has in common with essential hypertension a precarious cerebral arterial supply [60].

Treatment of SHR with angiotensin-converting enzyme inhibitors gives some protection to the brain against ischaemic damage from cerebral arterial ligation, probably by relaxation of excessive arteriolar constrictor tone. Medial hypertrophy of cerebral arterioles on one side of the brain can be prevented by ligation of the common carotid artery on that side [61]. The obvious and universally accepted conclusion from these and other experiments is that the rise of pressure in itself results in the structural arteriolar changes in the SHR. However, the obvious and universally accepted interpretation may be incomplete. Just because the rise of pressure in itself is clearly a cause of cerebral arteriolar constriction, the converse is not necessarily ruled out. A significant cause of the cerebral circulatory inadequacy of SHR and SHRSP is genetic rather than due simply to the rise in blood pressure [62], as are some of the metabolic differences [63].

**ENERGY METABOLISM OF THE BRAIN UNDER ABNORMAL CONDITIONS**

Energy metabolism in long-term impairment of the blood supply of the brain

When for any reason cerebral blood flow falls, there is an initial increase in glucose consumption and in anaerobic catabolism of glucose. With more severe ischaemia, glucose metabolism declines. After acute cerebral ischaemia in man, blood flow is relatively more reduced than oxygen consumption, and oxygen consumption is more reduced than glucose consumption. This must indicate substantial anaerobic glycolysis, which is confirmed by an increase in cerebral lactate production [64]. After severe and prolonged brain anoxia, cerebral glucose consumption may be only 75% of normal in conscious patients with permanent brain damage, and as low as 50% of normal in patients in a vegetative state [65].

Although PET studies do not suggest that in the absence of hypertension and manifest cerebrovascular disease there is any substantial reduction in cerebral metabolic rates of glucose and oxygen with increasing age [66], elderly senile patients with symptomatic cerebrovascular disease have not only reduced cerebral blood flow, but the glucose oxidation rate has been noted to be 40% less than in the young, and oxygen consumption 22% less [67]. This must reflect the oxidation of substances other than glucose. Patients who have suffered unilateral cerebral infarction have reduced cerebral glucose metabolism in the damaged regions, but also in some contralateral and more remote regions as well, possibly because of disturbances of the neural network by retrograde neuronal degeneration. It is not known for certain what fuel(s) other than glucose the brain uses in these situations. Reduced oxidative metabolism has been demonstrated in most conditions with impaired mental function, together with a reduction in total cerebral blood flow [67]. Energy-providing metabolism, particularly of carbohydrates, is reduced in patients with cerebrovascular disease and chronic mental disorders [68]. In patients with overt cerebrovascular disease, cerebral RQs of 0.90 [69], 0.88 [70] and even as low as 0.79 [71] have been recorded.

So far there have been no animal studies of cerebral RQ in conditions in which there has been a long-standing reduction of energy supply, either by reduction in blood flow or by hypoglycaemia. However, in rats subjected to a short episode of global cerebral ischaemia, impaired oxidative metabolism of glucose is seen in many areas, may persist for several days, and is associated with morphological changes in brain mitochondria. Glycolysis may be impaired for more than 24 h. Cerebral lactate concentration may remain elevated for up to 7 days after the acute ischaemic episode [72]. Fetal sheep (at 0.75 gestation) made hypoxaemic for 8 h maintained cerebral oxidative metabolism well but lactate efflux increased after several hours. The fetal brain is clearly capable, at least partially, of switching energy production to anaerobic metabolism of glucose [73].

**Cerebral oxidative metabolism in human hypertension**

There have been 13 studies on 151 patients with essential hypertension in whom it was possible to calculate cerebral RQs [32]. All were published before 1956. Many were control values taken before some physiological manoeuvre or before the administration of some drug. Cerebral RQ varied inversely with blood pressure, a fall which could not be accounted for by the fall in RQ with ageing. It is thus difficult to escape the conclusion that other fuels substitute in part for glucose in the essential hypertensive brain. The more severe the hypertensive condition, the more use there is of these other fuels. An RQ of 0.91 would be compatible, for example, with about 30% of the total energy needs of the brain being met by fat, or 80% being met by β-hydroxybutyric acid. (The exclusive oxidation of β-hydroxybutyric acid gives an RQ of 0.89 [74]). In regions especially vulnerable to ischaemia (in particular the junction zone between anterior and middle cerebral artery territories), the local glucose metabolic rate has been found to be reduced [75]. Further work is needed to discover what fuels provide energy to the hypertensive brain, but the fuels are likely to include fatty acids as well as ketones. In a most interesting study of 14 patients with arteriosclerosis, Gottstein et al. [70] were able...
to raise the cerebral RQ from 0.88 to 0.99 in patients with cerebrovascular disease by the intravenous infusion of glucose. They suggested that in vascular disease of the brain the cerebral metabolism of non-carbohydrates is increased 'as a consequence of disturbed permeation or utilization of glucose'. A similar disturbance appears to be present in essential hypertension, which might be regarded as a step in the progression towards overt cerebrovascular disease (see below). In malignant hypertension, cerebral venous lactate and lactate/pyruvate ratios are significantly increased when compared with non-malignant hypertension and normotension [76]. This suggests chronic circulatory inadequacy. There is a dearth of observations of RQ or oxidative metabolism in secondary forms of hypertension, but it is interesting that an RQ reduced to about the same extent as in essential hypertension has been observed in a small series of patients with aortic coarctation, with hypertension in the upper part of the body: RQ = 0.90 [77].

Borderline or intermittent cerebral ischaemia in hypertension might perhaps explain cortical thinning (so-called leukoaraiosis) in some cases of hypertension without notable mental or neurological defects [78]. It may be relevant that similar changes have been noted in the brain of the SHR. In young adult SHR, compared with WKY control rats, the cerebral ventricles are enlarged. Glucose metabolism is reduced in several areas, and there are appreciably fewer neurons per brain structure [49].

Hypertension, symptomatic cerebrovascular disease and heart failure all show long- as well as short-term changes in cerebral oxidative metabolism. All these disadvantageous conditions are likely, intermittently, to involve impaired removal of heat from the brain. It is therefore tempting to speculate that perhaps there could be local generation of so-called 'heat shock proteins'. These are well known to have a protective role for tissues under adverse conditions [83]. It is unclear whether any part of their protective role involves changes in oxidative metabolism, but such adaptations could obviously give some protection against ischaemic injury.

It is also interesting to speculate to what extent states of shock (i.e. life-threatening reductions of cardiac output) give the brain an embarrassing surplus of heat. There is some evidence that a rise of brain temperature increases sympathetic activity. In the dog, the cerebrospinal fluid (CSF) pressure and the systemic arterial pressure have been observed consistently to rise when brain temperature is increased [84]. Such a mechanism might help to protect the brain against ischaemic injury. A rise of brain temperature caused by a falling cerebral blood flow would counteract a fall in cerebral perfusion pressure by increasing sympathetic nervous tone. This mechanism could in the long term augment the Cushing response (see below).

ASSOCIATION OF CEREBRAL ARTERIAL PATHOLOGY AND ESSENTIAL HYPERTENSION

The close association between hypertension and atheroma of the larger cerebral arteries was recognized as long ago as 1917 [85]. The evidence for a uniquely close association has steadily increased since then. In 1960, Dickinson and Thomson [43] reported the results of a perfusion study of the internal carotid and vertebral arteries in a series of human cadavers. This showed close correlation between vertebral artery fluid-carrying capacity and ante-mortem blood pressure (determined independently from the hospital notes). The correlation was less for the internal carotids, less still for the renal, and almost non-existent for the femoral arteries. This correlation has been confirmed since in 21 pathological studies [6].

Current opinion is virtually unanimous that the relationship can be adequately explained by hypertension selectively causing or aggravating cerebral atheroma. Experimentally, renal artery clip hypertension increases atheroma in the Macaque monkey [86] (though mainly in the aorta and coronary arteries). Aortic constriction in the monkey increases the extent and severity of atheroma in the larger cerebral arteries [87]. The complementary additional possibility is that atheroma might cause hypertension. In their extensive pathological studies, Davis and Klainer [88, 89] found that the association

Cerebral heat dissipation in disease

The damaged brain is very sensitive to heat, and small differences in local metabolic heat production can have profound effects on recovery from ischaemia. Increased temperature aggravates and reduced temperature ameliorates tissue damage [79]. If cerebral metabolic rate remains the same, reduction of cerebral blood flow necessarily raises the brain's temperature. This has been observed and measured in neonates with cerebral hypoperfusion resulting from congenital heart lesions [80]. It seems inevitable that a similar elevation of brain temperature is likely to occur in severely hypertensive states in the adult. In congestive heart failure, for example, cerebral blood flow is usually slightly below normal [81]. One of the generally accepted benefits of the use of angiotensin-converting enzyme inhibitors in heart failure is that the threshold of cerebral autoregulation is shifted in such a way that cerebral blood flow is reasonably well maintained in situations in which some reduction would otherwise be inevitable [82]. There have been no comparative measurements of brain temperature during slow-wave sleep in essential hypertensive and normal individuals. If cerebral metabolic rate remains the same but blood flow is slightly lower, brain temperature should be higher in hypertensive people.

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between coronary artery atheroma and hypertension was variable. It may have resulted from a unifying underlying cause, which might have been 'atheroma in general' affecting the 'blood supply to kidneys or brain'.

Jannetta et al. [90] noted a relationship between essential hypertension and possible extrinsic pressure on the (left) ventrolateral medulla by a looping artery in the posterior cranial fossa. This idea has received some radiological and pathological support, but also strong criticism. It was reported that surgical repositioning of a looping artery can reduce the blood pressure of a substantial number of patients with essential hypertension [90]. However, as yet no control observations about the operation have been published, and judgment must be suspended at the present time.

**COULD CEREBRAL ARTERIAL DISEASE CAUSE CHRONIC HYPERTENSION?**

It is difficult to model in animals the gradual throttling of large cerebral arteries that atheroma can bring about in man. Anastomoses open up quickly after major cerebral artery ligations. Complicating influences from the carotid sinus also have to be eliminated. Early animal models of chronically increased cerebrovascular resistance causing chronic hypertension have been listed and reviewed elsewhere (see p. 113 of [6], pp. 12–17 of [91], and [92, 93]). In man, although the alteration in cerebral oxidative metabolism might result from hypertension, it seems more likely that the metabolic changes and the elevation of blood pressure might both result from primary cerebral arterial disease. As already mentioned, cerebral blood flow is now known to be significantly impaired in the hypertensive individual. The same applies in heart failure. There are many similarities in pathophysiology between heart failure and essential hypertension [6]. It is therefore worth remarking that the cerebral RQ in heart failure in man has been noted to be considerably less than normal (0.87 [94]), as in essential hypertension.

All these arguments are speculative, although they provide a plausible and economical explanation for the otherwise unexplained increased central neurogenic activity in essential hypertension. However, it is also possible that an alteration in cerebral metabolism is the primary change, which increases sympathetic nervous activity. This then raises the blood pressure and causes selective atheromatous disease in the larger cerebral arteries.

One major difficulty in accepting a primary role for arterial disease in causing hypertension in man is that cerebrovascular disease often co-exists with normal blood pressure. In some cases this could be due to complicating arteriosclerotic heart disease keeping blood pressure down. In others it could be due to relative sparing of the hind-brain circulation.

In our necropsy studies [43, 95], arterial disease of the vertebral and basilar arteries was consistently associated with hypertension in life, except when heart disease was present.

Another difficulty is that lowering of blood pressure undoubtedly protects against strokes. As already mentioned, cerebral autoregulation is powerful. Furthermore, cerebral infarction is commonly due to thrombo-embolic vascular occlusion rather than to a general reduction of cerebral blood flow. Epidemiological studies of the effects of hypotensive therapy on cerebral atheroma have not been carried out for long enough to know whether there is any evidence of permanent reduction in blood pressure. In rats, the lower limit of cerebral autoregulation – and hence structural cerebrovascular resistance – can be reduced by long-term hypotensive therapy [96]. The results in essential hypertensive patients have been disappointing so far [45]. Perhaps long-term hypotensive therapy needs to be combined with chronic reduction of plasma cholesterol.

**Effects of acute restriction of the cerebral circulation on brain metabolism and systemic arterial pressure**

Although many previous authors had reported that restriction of the cerebral arterial blood supply increased heart rate, force of heartbeat and blood pressure, Harvey Cushing [97] was the first to recognize the quantitative relationship between impaired arterial perfusion of the brain and the resultant rise in blood pressure. In anaesthetized dogs he observed that when applied CSF pressure approached systemic arterial pressure, the latter rose so that cerebral perfusion was always maintained. He tracked down the origin of what is now called the 'Cushing response' to the brain stem. Even lower pontine section failed to destroy the response. Most people, from Cushing onwards, have regarded the response as simply a last ditch protection of the brain when its supply of blood has almost ceased. This view underrates the normal function of the response, although Guyton [98] has pointed out that in the short term the Cushing response has the highest gain of any of the known blood pressure stabilizing systems. A recent review [99] has emphasized the crucial effects of general anaesthesia. This greatly increases the brain's tolerance for ischaemia, and raises the threshold of the response. In conscious dogs, mean arterial pressure cannot be kept below 50–55 mmHg for more than about 30 s – either by increased carotid sinus pressure [100] or by electrical stimulation of the carotid sinus nerves [101], even when other known baroreceptors are denervated. It appears that some other central nervous detector – most plausibly the Cushing response – comes into play. In unanaesthetized fetal sheep *in utero* the Cushing response to increased intracranial pressure is exquisitely sensitive and
The physiological basis for the Cushing response remains controversial. Cushing himself believed it to be due to ischaemia of the brain stem, but others have suggested that increased CSF pressure produces a mechanical distortion of the brain stem, which excites pressor centres there [103]. There are some objections to this view [104]. The response is very closely related to the applied intracranial pressure, once this starts to approach systemic arterial pressure. By analogy with the systemic arterial baroreceptors or with the sino-atrial venous stretch/baroreceptors, any sensor responding to the pressure difference between arterial pressure and CSF pressure should alter its discharge rate and thus affect efferent sympathetic nerve activity almost instantaneously. Changes in CSF pressure or in medullary blood flow exert slower effects, as has been repeatedly observed in dogs [105]. These effects seem best explained by a local metabolic or chemical change.

So-called 'benign intracranial hypertension' (pseudotumor cerebri) is a clinical syndrome in which there is raised intracranial pressure without obvious cause, but which need not be associated with any rise in systemic arterial pressure. This has sometimes been taken to negate a physiological role for the Cushing response, but it should not do so. Cerebral blood flow may be normal [106] or even increased [107] in this condition, so no cerebral ischaemic stimulus would be expected.

Obviously a reduced cerebral blood flow, whether brought about by proximal obstruction of large arteries or by raised intracranial pressure, will lower tissue $P_{O_2}$ and raise local $P_{CO_2}$. It will also raise $H^+$ activity (lower pH) because of the generation of lactic acid by anaerobic glycolysis. Any or all of these factors could be the stimulus. Sun and Reis [108] at present favour hypoxia alone as the principal stimulus. They have convincing evidence that pacemaker neurons in the rostral ventrolateral medulla in rats increase their firing rate when local $P_{O_2}$ falls or when cyanide is given. On the other hand, cerebral arterial hypoxaemia of a mild degree is not a strong pressor stimulus, whereas a rise in local $P_{CO_2}$ can be. A rise in carbon dioxide tension may augment the pressor response to local reduction of $P_{O_2}$ [109] at the same time as supplying a strong stimulus to ventilation. Although carbon dioxide inhalation and chronic ventilatory failure, raising arterial $P_{CO_2}$, do not normally change blood pressure much, the direct peripheral vasodilatation is offset by sympathetic neurogenic vasoconstriction. In the presence of adrenergic neuron blockade, $CO_2$ inhalation is profoundly depressor. The depressor effect of adrenergic neuron-blocking agents is enhanced by a rise in ambient $P_{CO_2}$ [110].

Another possibility is that a signal might come from a temperature change. If metabolic rate remains the same while blood flow falls, the temperature of the brain will rise. This might affect the discharge rate of sympathetic efferent neurons, although there is little direct information about this. Many hypothalamic and hind-brain neurons are thermosensitive, and the majority increase their discharge rate as temperature rises [111], although in most regions a relatively smaller number of cells is found whose discharge is provoked or increased by cold. Whether these cells are independent operators or are under tonic inhibition by heat-sensitive neurons is not known. The exact nature of the chemical, metabolic or thermal stimulus is less important than its inevitable relationship to the state of oxidative metabolism in the chemosensitive areas. The areas responsible have not been precisely delineated, but certainly are predominantly, and perhaps exclusively, in the medulla. Cushing [97] showed this nearly a century ago by his ablation experiments in dogs. Although the hypothalamus is well known to be the main blood temperature sensor, there is no good evidence that it plays any significant part in the Cushing response.

Can long-term increased cerebrovascular resistance raise systemic arterial pressure?

The question remains open as to whether low-grade constriction or partial obstruction of the cerebral arterial circulation could produce a long-term blood pressure elevation. There is strong evidence that it can. Cerebral arterial disease certainly appears able to change the pattern of oxidative metabolism in the brain in a way that resembles the situation in cerebrovascular disease and heart failure. The stage may be set for a vicious circle moving slowly over many years. Borderline or intermittent cerebral ischaemia alters oxidative metabolism and raises blood pressure via the Cushing response; hypertension then increases cerebral atheroma, which in due course further threatens the blood supply of the brain. This plausibly explains many epidemiological observations which are reviewed elsewhere [6]. It also explains why hypertension should have such a close and consistent relation to cerebral, especially vertebro-basilar, atheroma.

CONCLUSIONS

Essential hypertension is well known to be partly genetically determined, and partly environmental. From identical twin and other studies, the contributions of each factor have been estimated to be roughly the same, i.e. 40–60% for each. Even in those individuals with a strong genetic predisposition to hypertension the blood pressure may remain normal and unchanged throughout adult life if the environment is favourable. To explain the difference in oxidative brain metabolism between normal and hypertensive people we need to consider what might
be the nature of the genetic and environmental factors concerned. Since oxidative metabolism takes place within mitochondria, since mitochondria contain DNA, and since several inherited neurological diseases are known to be transmitted through mitochondrial rather than nuclear DNA [112], it would be superficially plausible to attribute the cerebral metabolic abnormalities in essential hypertension to some genetic fault developing in neuronal mitochondria. However, since spermatozoa contain virtually no mitochondria, the inheritance of mitochondrial disorders has to take place exclusively through the female line. There is no evidence for this in human hypertension, and no hypertensino-genic genes have been reported to be 'X-linked'. Thus, although a functional defect in cerebral mitochondria may well underlie essential hypertension, such a defect would have to be acquired rather than inherited.

A plausible explanation for the clinical and epidemiological findings is that cerebral arterial disease (atheroma and thrombo-embolic vascular occlusion) at least in some cases might come first. This allows or causes the brain to use fuels other than glucose for a substantial part of its energy needs. Certainly ketones are used, probably fatty acids also. Either as a result, or as an associated phenomenon, the Cushing response is activated during periods of rest and sleep. The response limits the nocturnal fall of blood pressure by increasing sympathetic vasomotor activity, until the brain stem's blood supply is once again secure. This obviously raises the lower limit or trough of blood pressure which the brain will tolerate. In modern hypertensive jargon this would limit 'dipping' – the fall of night-time blood pressure to a level well below the lowest levels observed during the day. The rise of blood pressure over long periods of time would accelerate the deposition of proximal cerebral artery atheroma, and account for the well-known tendency of blood pressure to rise slowly over decades at a rate which depends on its initial absolute level. It would also cause 'structural reinforcement' in arterioles, heart and kidneys by which hypertension could be sustained without any necessity for increased sympathetic neural activity [113].

The evidence is now strong that in essential hypertension in man, and in the spontaneous inbred hypertensive rat, the cerebral circulation is in some sense under threat. In both cases the brain appears to have altered the way in which it derives its energy. Whether this is a cause or a consequence of the hypertension remains to be determined.

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REFERENCES

Hypertensive brain metabolism


