Cerebral perfusion and stroke

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Stroke is a heterogeneous syndrome caused by multiple disease mechanisms, but all result in a disruption of cerebral blood flow with subsequent tissue damage. This review covers the mechanisms responsible for regulation of the normal cerebral circulation, and how they are disrupted in disease states. A central concept in treating patients with acute ischaemic stroke is the existence of an ischaemic penumbra of potentially salvageable tissue, and the evidence for its existence in humans is reviewed.

METHODS FOR MEASUREMENT OF CEREBRAL BLOOD FLOW

Various different techniques (table 1) allow measurement of regional cerebral perfusion, although many are only semiquantitative. Such techniques require a tracer or contrast agent and an imaging technique allowing its concentration to be measured. Commonly used techniques include positron emission tomography (PET), single photon emission computed tomography (SPECT), xenon computed tomography (CT) and contrast CT perfusion, and magnetic resonance imaging (MRI) perfusion studies.

Nuclear medicine methods

Nuclear medicine methods use radionuclides as tracers and the tomographic approach in image reconstruction. These can be distinguished on the basis of the physical characteristics of the radionuclides. SPECT uses low energy, photon emitting radionuclides. PET uses coincidence radiation employing positron emitting radio-nuclides which, after annihilation, produce two 511 keV γ rays. PET allows quantification, while with SPECT only semiquantification is possible. Both involve exposure to significant radiation doses. The tracer most commonly used for PET CBF measurements is 15O labelled water. Only PET allows measurement of oxygen utilisation and therefore the oxygen extraction fraction.
Xenon based techniques Stable xenon methods Intravenous xenon methods
MR based techniques Exogenous perfusion Xenon CT
CT based techniques Contrast perfusion imaging Xenon CT
SPECT $^{99m}$TcHMPAO $^{123}$I labelled IMP
Transcranial Duplex ultrasound Ultrasound perfusion Quantification not yet possible
Volume flow (in major arteries) Doppler based techniques Flow in major arteries and not tissue perfusion
Carotid and vertebral ultrasound Non-Doppler based techniques Flow in major arteries and not tissue perfusion
Transcranial Doppler ultrasound Velocity rather than flow measurement

CBF, cerebral blood flow; CT, computed tomography; IMP, inosine 5’-monophosphate; MR, magnetic resonance; SPECT, single photon emission computed tomography; $^{99m}$TcHMPAO, technetium-99m hexamethylpropylene amine oxime.
acetylcholine. It was subsequently found that this “endothelium derived relaxing factor” is nitric oxide (NO), synthesised by endothelial cells from the amino acid L-arginine by the enzyme NO synthase (NOS). There are three isoforms of this enzyme: endothelial NOS (eNOS), neuronal NOS (nNOS), and an inducible NOS (iNOS). Endothelium derived NO plays a crucial role in maintenance of blood vessel calibre and therefore blood flow throughout the vasculature. It is also important in preventing thrombosis through inhibition of platelet adhesion, activation, and aggregation, and in preventing atherosclerosis by inhibition of vascular smooth muscle cell proliferation. Under normal conditions there appears to be a functional balance between the endothelium dependent vasodilator effects of NO and the endothelium derived constrictor substances such as endothelin, thromboxane, and angiotensin II. Extensive animal data in a variety of species have shown that tonic release of NO plays an important role in maintaining resting CBF. More recently the role of NO in maintaining basal CBF has been shown in the human: inhibition of NO by the NO synthase inhibitor N-monomethyl-L-arginine (L-NMMA) resulted in a 30% fall in CBF.

Cerebral autoregulation

CBF remains relatively constant despite moderate variations in perfusion pressure. This phenomenon, described as “cerebral autoregulation,” plays an important protective role against the danger of hypoxia at low perfusion pressure, and the risk of brain oedema at higher arterial pressure. As a rough approximation the lower and upper limits of autoregulation occur at mean arterial pressures of 60 and 150 mm Hg in the normotensive human. Between these limits CBF is relatively but not absolutely constant. Once the limits of autoregulation are reached, CBF increases or decreases passively with increases or reductions in perfusion pressure.

Reductions in CBF below the limit of autoregulation result in brain hypoperfusion. In an attempt to compensate for this, the extraction coefficient of oxygen from the blood increases. Clinical symptoms of functional disruption are not observed until the reduction in CPP exceeds the ability of the increase in oxygen extraction to satisfy the metabolic demands of cerebral tissues. If mean arterial pressure increases above the upper limit of autoregulation, resistance arteries in the brain cannot sustain vasconstriction. An early sign is the appearance of “sausage stringing,” characterised by an alternating pattern of dilated arterial segments with focal regions of constriction. The dilated segments represent regions of passive dilatation, and the constricted segments regions of sustained autoregulation. Further increases in CPP result in dilatation along the entire length of the arterioles, and CBF increases passively. This is accompanied by damage to the cerebrovascular endothelium and disruption of the blood–brain barrier. The latter results in extravasation of plasma proteins through the vessel wall and subsequent oedema. These events are important in acute hypertensive encephalopathy.

The upper and lower limits of autoregulation are not fixed but vary under both physiological stimuli and disease states. Activation of the sympathetic nerves results in upward shift of both the lower and upper limits—a potentially protective response because acute elevations in arterial pressure are usually accompanied by sympathetic activation. The autoregulatory plateau is shifted to higher values in patients with chronic hypertension. This protective response can have deleterious effects if blood pressure is excessively reduced, when symptoms of ischaemia may occur at a relatively higher blood pressure.

Cerebral autoregulation is impaired in various disease states including head injury, ischaemic stroke, and subarachnoid haemorrhage. This may result in an already damaged brain being excessively sensitive to fluctuations in perfusion pressure.

Assessment of cerebral autoregulation in the human

Traditionally, studies in the human have estimated “static” autoregulation. Steady state values of CBF are determined across a range of blood pressures. This is achieved by the use of drugs or shifts in blood volume—for example, using tilt tables or negative pressure. Determination of the full range of autoregulation requires blood pressure to be manipulated across a wide range, and the long time interval between measurements made at different pressures can make interpretation of studies difficult. More recently methods for estimating “dynamic” autoregulation in humans have been developed. These determine the rate of response of CBF or flow velocity after a sudden change in arterial blood pressure. A technique allowing measurement of CBF with very high temporal resolution is required. The only technique that can provide this is transcranial Doppler ultrasound. In the most widely used technique a sudden fall in blood pressure is induced by inflating leg cuffs above venous pressure and then rapidly deflating them. The rate of rise of CBF velocity in the middle cerebral artery is then compared with the rate of rise of blood pressure continuously monitored using a non-invasive device such as a Finapres. Using this technique, autoregulation has been shown to be impaired distal to carotid artery stenosis, following head injury, and in ischaemic stroke. Although the measurement of dynamic autoregulation gives a useful estimate of how the cerebral circulation can compensate for fluctuations in perfusion pressure, it may not necessarily be measuring the same mechanisms that determine static autoregulation.

Physiological mechanisms of autoregulation

The mechanisms responsible for CBF autoregulation in the human are not fully understood. Traditional hypotheses are that neurogenic, myogenic, and metabolic factors play a role. More recently NO has been implicated. Autoregulation is preserved in animals that have undergone sympathetic and parasympathetic denervation, suggesting that neurogenic factors are not of primary importance.

The myogenic hypothesis states that smooth muscle in the resistance arteries responds directly to alterations in perfusion pressure by contracting during increases in pressure, and relaxing during reductions in pressure. This would provide a mechanism whereby responses in cerebral resistance arteries could occur within seconds of an autoregulatory stimulus. In vitro animal experiments support this hypothesis, with constriction of isolated arteries occurring following a rapid increase in intravascular pressure. In vivo experiments have not, in general, provided such strong support. The metabolic hypothesis states that reductions in CBF stimulate the release of vasoactive substances from the brain, which in turn stimulates the dilatation of cerebral resistance arteries. Several candidates for this role have been proposed—including carbon dioxide, hydrogen ions, oxygen, adenosine, potassium, and calcium—but no definite role has been demonstrated for any of these.

Endothelial factors, particularly NO, have been suggested as mediators of cerebral autoregulation. In some animal studies, impaired autoregulation has been reported following inhibition of NO, but others have found no effect. In ENOS knockout mice there was a greater fall in CBF during haemorrhagic hypotension than in wild type mice, consistent with an alteration in the lower limit of autoregulation. In humans the NOS inhibitor L-NMMA resulted in a significant impairment of dynamic autoregulation.
Arterial blood gases, the hypercapnic response, and CBF
CBF is very sensitive to changes in blood CO₂ concentrations, largely mediated by concomitant changes in the pH of brain tissue. Apart from this direct effect of pH on cerebral vessels, secondary mechanisms may mediate vasoactive effects through a pH dependent alteration in the release of other vasoactive factors. Prostaglandins have been suggested as mediators of CO₂ dependent changes in CBF, based on the effects of the inhibitor of cyclo-oxygenase, indomethacin. However, further studies in animals and humans cast doubt on this mechanism in adults, although it does appear to be important in newborn animals.

Studies in rats suggested NO dependence of the hypercapnic response, although this NO production is primarily through nNOS rather than eNOS. However, results in higher species have been less consistent, and studies in primates have shown conflicting results. A complicating factor in animal studies is that anaesthesia may alter cerebrovascular responses. A study in humans showed that inhibition of eNOS by intravenous NG-monomethyl-L-arginine (L-NNMA) did not alter the hypercapnic response.

Reducing arterial PO₂ results in an increase in CBF, whereas an increase in arterial PO₂ above normal values has a much lesser effect. Hypoxia appears to act both through a direct effect on cerebral resistance vessels, and through indirect effects including the release of vasoactive factors such as hydrogen ions, adenosine, and potassium ions. It has also been suggested that pH dependent mechanisms—mainly the production of lactate—participate in hypoxic vasodilatation.

Clinical relevance of the hypercapnic response
The response of CBF to hypercapnia is widely used in humans to estimate cerebral perfusion reserve, most often in patients with carotid stenosis or occlusion. The haemodynamic consequences of a carotid stenosis—for example, during a fall in blood pressure—will depend on distal collateral supply, particularly through the circle of Willis. An estimate of this cerebral perfusion reserve can be obtained by measuring CBF during both normocapnia and hypercapnia (with concentrations of 5–8% CO₂ in air). In the presence of impaired reserve, resistance vessels are already vasodilated, and the capacity to increase CBF further is reduced (fig 1). A wide range of imaging methods has been used to measure the hypercapnic response, including PET, SPECT, MRI, and xenon based techniques. For techniques that do not allow absolute quantification (such as SPECT), side to side differences are calculated; this makes interpretation difficult in bilateral carotid stenosis. Transcranial Doppler monitoring of middle cerebral artery flow velocity has become widely adopted in this context. Its validity is suggested by angiographic studies showing that the diameter of the middle cerebral artery does not change during hypercapnia. Acetazolamide, a carbonic anhydrase inhibitor, can be used as the vasodilator stimulus instead of CO₂.

Prospective studies have shown that a reduced hypercapnic response ipsilateral to a carotid occlusion is associated with an increased risk of stroke or transient ischaemic attacks (TIA). It has been suggested this test may identify a subgroup of patients with carotid occlusion who benefit from extracranial-intracranial bypass, although this hypothesis has yet to be tested. There is some evidence from prospective studies that patients with tight carotid stenosis, as opposed to occlusion, and who have impaired perfusion reserve are at increased risk of stroke, but the association appears less strong than for carotid occlusion.

Local coupling of cerebral blood flow and metabolism
Local CBF is tightly coupled to changes in neuronal metabolism, and this forms the basis of functional brain imaging using BOLD MRI. Over a century ago Roy and Sherrington suggested that “…(the brain) is well fitted to provide for a local variation of the blood supply in accordance with local variations of the functional activity”.

Numerous studies have shown that local increases in neuronal activity result in a local increase in glucose utilisation, accompanied by local increases in CBF. The precise mechanisms linking neuronal activation, metabolism, and flow are not fully understood. Various factors are likely to contribute to this coupling process, including potassium release with neuronal depolarisation, and H⁺ and adenosine release when there is a mismatch between oxygen delivery and utilisation. NO may play a key mediator role, probably through production via nNOS rather than eNOS. In animal models, cerebral vasodilatation associated with simple somatosensory stimulation appears to be mediated by nNOS derived NO. In the human, L-NNMA given intravenously did not alter the local CBF response to learned sequential movements, but, because of its poor blood–brain barrier penetration, it probably only inhibits eNOS.

Cerebral circulation responses to focal ischaemia
Protective responses to a progressive fall in cerebral perfusion pressure
CPP can fall because of systemic arterial hypotension, or severe stenosis in an extracranial or intracranial supplying artery, or a combination of the two. As CPP falls, intracranial resistance vessels dilate to maintain CBF; this results in an increase in CBV. When vasodilatation is maximal, further falls in CPP result in a fall in CBF. Because oxygen delivery to the brain normally greatly exceeds demand, metabolic activity is maintained initially by increasing the OEF from blood. When oxygen extraction becomes maximal, flow is inadequate to meet metabolic demands, cellular metabolism is impaired, and the cerebral metabolic rate of oxygen (CMRO₂) begins to fall. This sequence of events is illustrated in fig 2.

Critical flow thresholds
As cerebral autoregulation is impaired or lost in moderate to severe ischaemia, CBF varies passively with CPP. This relationship has allowed investigators to gradually reduce CBF and assess critical flow thresholds at which certain functions are lost. Experimental studies in primates and cats, and clinical studies in humans during carotid endarterectomy, have shown that spontaneous and evoked electrical activity ceases
when CBF falls below 16–18 ml/100 g/min. This level of ischaemia therefore represents a threshold for loss of neuronal electrical function (that is, electrical failure). It was subsequently shown that there is a lower threshold (10–12 ml/100 g/min) for loss of cellular ion haemostasis (that is, membrane failure). At this lower threshold, K+ is released from and Ca2+ taken up by the cells. Rapid efflux of K+ and uptake of Ca2+ represents a generalised collapse of membrane function and at this point cells also take up Na+ and Cl− with osmotically obligated water. The threshold for infarction appears similar to that for energy failure/loss of membrane haemostasis, but it varies with the duration of the insult.

More recent studies suggest that the pattern of thresholds may be more complex, although the general principle of two major critical flow thresholds (loss of electrical function and then loss of cellular ion haemostasis) still applies. Protein synthesis is inhibited first (at a CBF of about 50 ml/100 g/min), and is completely suppressed below 35 ml/100 g/min. This is above the level at which glucose utilisation and energy metabolism are disrupted. Glucose utilisation transiently increases at flow rates below 35 ml/100 g/min, before it sharply declines below 25 ml/100 g/min. This corresponds to anaerobic glycolysis with the beginning of acidosis and the accumulation of lactate. At flow rates below 26 ml/100 g/min, tissue acidosis becomes pronounced and both phosphocreatine and ATP begin to decline. Anoxic depolarisation, as assessed by recording extracellular potassium and calcium activities, occurs at even lower values (<15 ml/100 g/min) (fig 3).

THE ISCHAEMIC PENUMBRRA

The concept of an ischaemic penumbra is crucial to the treatment of acute stroke. It follows on from the finding of separate thresholds for electrical failure and loss of ion haemostasis. The concept is that following a focal ischaemic insult a penumbral region exists around a core of densely ischaemic and irreversibly damaged tissue. This penumbral region contains electrically inexcitable but viable cells. It is characterised by reduced CBF with relatively preserved or increased CMRO2 and OEF.52 53 Deterioration of CMRO2 from the acute to subacute phase has been shown to be mainly cortical surrounding the ischaemic core, whereas in the baboon, as in the human, predominantly involves the subcortical structures supplied by the perforating arteries. In later studies it was found that the duration of ischaemia, as well as the absolute flow, plays a crucial role in determining the fate of ischaemic tissue. For example, in the macaque monkey, tissue with CBF of around 15 ml/100 g/min could withstand about three hours of occlusion, while tissue with a perfusion of around 5 ml/100 g/min would stand only two hours. This time dependence has crucial significance when considering acute treatment in humans, and implies that treatment will be most successful when it is given as early as possible. A crucial question when assessing the potential for acute stroke therapy is how extensive the ischaemic penumbra is in the human.

Is there an ischaemic penumbra in the human?

PET studies have suggested that there is a significant ischaemic penumbra in humans, and that reversibly ischaemic tissue may persist for much longer than initial experiences in smaller animals suggested. These studies used oxygen-PET and quantitatively measured the main physiological variables involved in tissue ischaemia—namely CBF, CMRO2, OEF, and CBV. Using this technique, a pattern of changes termed “misery perfusion” can be identified. This is characterised by reduced CBF with relatively preserved or even normal CMRO2, thus fitting the concept of penumbra with tissue of reduced perfusion but relatively maintained neuronal function. The hallmark of misery perfusion is an increased OEF, ranging from the normal value of about 30–40% up to a theoretical maximum of 100%, where the tissue extracts all the oxygen supplied by the blood flow reaching it. In the late 1980s and early 1990s several groups applied PET to investigate the pathophysiology of ischaemic stroke. In the acute phase in patients with anterior circulation stroke, misery perfusion was found to affect mainly the cortex, while the capsule–basal ganglia region often showed markedly reduced CMRO2 and only moderately increased OEF. Deterioration of CMRO2 from the acute to subacute...
stage of stroke was reported, and this was interpreted as the transition from ischaemia to necrosis. However, no study directly documented the presence of tissue that was still metabolically active within a region that went on to infarction, as determined by follow up CT or MRI. Baron and colleagues studied 30 patients with first ever middle cerebral artery territory ischaemia within 18 hours of stroke onset and co-registered these early PET scans with late CT scans done to assess final infarct size. Those voxels or regions within the finally infarcted tissue with preserved CMRO$_2$ on acute stage PET were identified. Of the 30 patients, there were eight who survived until the late CT, had follow up PET, had a middle cerebral artery territory infarct of $>16$ mL, and were scanned on late CT scanning, and had technically adequate PET studies. In seven of these, voxels were found which progressed to infarction but initially had CMRO$_2$ values above the threshold for irreversible damage. The tissue identified represented substantial volumes of the final infarct, being a mean of 35% and as high as 52% in one patient. Furthermore “penumbral” tissue was observed in two cases at 16 hours and in another case at 13 hours after stroke onset.

Proving that this is indeed penumbral tissue requires intervention studies in which the penumbra is salvaged by treatment that restores flow. However, the concept is supported by the results of clinical trials showing that thrombolysis improves outcome, and also by more recent MRI studies (see below). Further support is provided by PET studies in the baboon which showed that tissue with acute misery perfusion went on to infarction if the middle cerebral artery was permanently occluded, but escaped infarction if the artery was reopened at six hours. Interestingly, the time window for reperfusion in the baboon was much longer than in previous macaque experiments, and considerably longer than PET studies in the cat. These significant species differences emphasise the importance of undertaking studies in humans.

Can MRI identify an ischaemic penumbra?

Although PET studies give quantitative information on CBF and oxygen metabolism they are not widely available, difficult to do in large numbers of patients, and involve the administration of radioisotopes. The ability to identify potentially salvageable tissue using more widely available techniques has great attraction. There is considerable interest in the potential of MRI to identify an “ischaeamic penumbra,” based on a combination of perfusion and diffusion weighted imaging techniques. Most studies have used exogenous perfusion techniques to measure the perfusion deficit. The most promising technique for identifying ischaemic tissue is diffusion weighted imaging (DWI). Diffusion imaging is dependent on the apparent diffusion coefficient (ADC) of water in tissue. Following ischaemia, ADC values rapidly decline, corresponding to a region of high signal on DWI. This ADC decline is likely to reflect the accumulation of intracellular water, cytotoxic oedema, disruption of high energy metabolism, and loss of ion homeostasis. These ADC changes do not occur uniformly in the ischaemic region, and in experimental stroke models ischaemic tissue with the most severe perfusion deficit has the earliest and most severe fall in ADC. Serial DWI studies in animal models have demonstrated the evolution of ADC changes over time, and shown that mild declines in ADC early after stroke are potentially reversible.

The concept of diffusion–perfusion mismatch has been developed as a possible way of identifying potentially salvageable tissue in the human. The rationale is that tissue that is abnormal on DWI and has low perfusion is destined for infarction. In contrast, tissue that is normal on DWI but has perfusion reduced to penumbral levels may either recover, particularly if flow is restored, or progress to infarction. There is considerable support for this hypothesis. Within six hours of stroke onset approximately 70% of acute patients will have a perfusion volume greater than the diffusion volume, 20% will have equal volumes, and in 10% the perfusion volume will be smaller, representing spontaneous reperfusion. Baird et al studied 13 patients with ischaemic stroke in whom both DWI and perfusion imaging were measured at an initial time point (2 to 53 hours) and at follow up time points (7 to 725 days). Lesion volume increased by 230% when the perfusion volume exceeded the initial DWI volume, but decreased by 47% when perfusion volume was smaller than, or equivalent to the DWI volume. Barber et al reported an increase of 62% in the DWI lesion volume between acute (<24 hours) and subacute (3–5 days) time points, when the perfusion volume was greater than the DWI lesion volume (11 of 17 patients). The remaining six patients in whom the perfusion volume was less than the DWI volume had a stable DWI lesion volume.

Studies in patients receiving thrombolysis provide further evidence that this mismatch does represent reversibly ischaemic tissue. Patients undergoing intravenous thrombolysis, who underwent successful reperfusion, had reduced lesion volume as defined by DWI and later by T2 weighted MRI. Similar results have been found in patients receiving intra-arterial thrombolytic treatment. MRI studies also emphasised the heterogeneity of human stroke. In some patients mismatch is still present many hours after stroke, consistent with the PET studies, while in others there is no mismatch early after stroke. This may partly explain why acute stroke trials have been disappointing and it has led to the suggestion that treatment needs to be tailored to the patient more effectively. Current therapeutic trials are targeting patients with persisting mismatch for treatment with thrombolytic and other agents.

Recent data have suggested that the diffusion–perfusion concept is more complex. Initially it was thought that tissue appearing abnormal on DWI in humans was almost always destined to infarction. Case reports were published showing reversibility of DWI changes, and a more recent series has confirmed that DWI abnormalities may recover, although probably in a minority of patients. Furthermore on repeat scanning at seven days such recovered areas may remain normal, or DWI and T2 abnormalities may reappear. This is consistent with animal studies showing secondary delayed ADC declines after temporary focal occlusion. The clinical significance of these changes is not fully understood, but if they predict a worse clinical outcome they may represent a therapeutic target for post-reperfusion neuroprotective targets. Despite the MR diffusion–perfusion concept being more complicated than initially appreciated, there is considerable evidence that it does allow “penumbral” tissue to be identified. Its clinical use will depend upon current prospective randomised trials showing that it can identify a subgroup of patients who benefit particularly from therapeutic interventions such as thrombolysis.

MRI is much more widely available than PET, but nevertheless few units can offer it to all patients with acute stroke. This has led to attempts to use the more available technology of CT perfusion to identify the extent of reversibly ischaemic tissue. Compared with DWI, non-contrast CT imaging is poor at showing ischaemic tissue in the first few hours. However, with the use of a rapid intravenous injection of iodinated contrast in combination with newer multislice CT scanners, maps can be obtained of CBF, CBV, and MTT, in addition to conventional non-contrast CT images, with acquisition times of less than 10 minutes. CT perfusion measurements have been found to correlate well with stable
xenon-CT estimates. Using this method, an ischaemic cerebral area (penumbra plus irreversibly damaged tissue) has been defined as a CBF reduction of more than 34% compared with the contralateral hemisphere. Within this area, regions with a CBV below a predefined cut off (2.5 ml/100 g) were selected as irreversibly damaged tissue, with the remainder defined as penumbra. In a validation study against MRI in 13 subjects, a highly significant correlation was found between the CT defined irreversibly damaged tissue and the region of MR DWI abnormality. The ischaemic cerebral area correlated strongly with the MR defined MTT defect, but less well with the MRI perfusion defect obtained from CBF maps. The authors suggested that CT perfusion provides a similar degree of information to MRI on penumbral tissue. Other small studies have also shown correlations with MRI estimates, but much more data from larger series are required, ideally including comparisons with PET as well as with MRI. This should both confirm these findings, and show that the CT derived information allows prediction of outcome and selection of a group who may benefit from thrombolytic and other treatments. A further limitation of CT perfusion in comparison with MRI is that slice coverage is limited.

**MECHANISMS OF INFARCTION IN PENUMBRAL TISSUE**

A complex cascade of mechanisms is responsible for the progression of penumbral tissue to infarction. Understanding these processes is crucial for developing potentially effective treatment strategies. Mechanisms determining both flow and the cellular and metabolic consequences of hypoperfusion are important.

Key factors determining outcome are the presence and extent of collateral flow, and the time at which recanalisation occurs. Cerebral autoregulation is disrupted within the ischaemic penumbra, which may make the tissue particularly vulnerable to alterations in blood pressure. Continued embolisation and thrombus propagation may also play a role. Experimental evidence suggests that progressive microvascular obstruction contributes to the progression of ischaemic damage following stroke. Various processes may contribute to the activation of cerebral microvessels following ischaemia, including alterations in integrin–matrix interactions, leucocyte endothelial cell adhesion, blood–brain barrier permeability changes, and microvascular occlusion owing to adhesion of leucocytes, activated platelets, and fibrin deposition.

A complex cascade of cellular and metabolic consequences follows focal ischaemic injury. This is illustrated in fig 4 and has been reviewed in detail elsewhere. Only some of the more important aspects are covered below.

Excitotoxicity appears to play a crucial role. Glutamate release activates postsynaptic N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazole (AMPA) receptors. This results in calcium and sodium influx into cells, leading to cellular oedema and activation of the catabolic processes that destroy cellular integrity. These initial events are amplified by further increases in intracellular calcium through activation of voltage mediated calcium channels. The intracellular calcium increase induces protein kinases and calmodulin regulated enzymes. Glutamate release appears to be a primary process in a cascade of molecular reactions mediated by NO and free radicals. NO generated in neurones and microglia causes cell death by inhibiting mitochondrial functions, including apoptosis, and promoting the formation of free radicals such as the highly toxic peroxynitrite radicals. Knockout mice which lack nNOS develop infarcts of smaller size. Glutamate diffusion from areas with high concentration and more severe ischaemia to less severely ischaemic regions may also lead to progression.
of injury. Cerebrospinal fluid and plasma concentrations of glutamate are higher in patients with progressing ischaemic stroke than in those with non-progressing stroke.74 Peri-infarct depolarisations may play an important role in progression of damage.75 These depolarisations are similar to the phenomena of spreading depression observed after mechanical or chemical injury to normal cortical tissue in animal models. DWI studies of rat stroke models have shown that peri-infarct depolarisations lead to an increase in the size of the ischaemic lesion.76 The underlying mechanism may be an increase in energy demands upon already compromised tissue, or an energy consuming process.77 In normal tissue, this increased energy demand is met by an increase in perfusion, but this is not possible when CBF is reduced. The relevance of peri-infarct depolarisations in human stroke has not been determined, although with DWI monitoring it may be possible to show an imaging correlate.

Inflammation is probably important in extending ischaemic injury. Most inflammatory reactions are mediated by cytokines. These have been implicated in several mechanisms that may potentiate ischaemic brain injury,78 including release of NO from inducible NOS by astrocytes, recruitment, activation, and adhesion to the endothelium of infiltrating leukocytes, the promotion of a local procoagulant state, and the regulation of apoptotic processes.

SUMMARY

Many anatomical and physiological responses ensure that the brain receives adequate blood supply, and protect it against the devastating consequences of cerebral ischaemia. The disruption of these by focal ischaemia can now be investigated by an ever increasing range of methods to estimate perfusion, many of which can be implemented on routine clinical neuroimaging equipment. PET studies in humans have demonstrated reversibly ischaemic penumbral tissue following focal ischaemia; its extent varies markedly between patients but in a subgroup it may persist for hours. It is hoped that imaging techniques will allow patients with salvageable tissue to be identified for specific therapeutic interventions.

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