Ischemic Cerebral Edema. A Review

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SUMMARY The genesis of ischemic cerebral edema is multi-factorial and the relative importance of these many factors varies throughout the lesion and with time. The initial event is intracellular edema which may be followed by extracellular edema. This situation precludes any simple treatment, particularly because the favorable alteration of one factor might be detrimental to another.

CEREBRAL EDEMA is by definition a relative increase in the water content of the brain and this may be either in the intracellular or extracellular compartments, or both. There are 2 other causes of brain swelling, vascular congestion and hydrocephalus; these are not due to edema but may be confused with it. The early literature was careful to distinguish between brain swelling (Hirnschwelling) or dry edema and brain edema (Hirnodem) or wet edema, according to the appearance of the cut surface of the brain. It is now possible to explain these differences by a consideration of the possible changes in the 4 intracranial fluid compartments.

Intracranial Fluid Compartments

The 4 intracranial fluid compartments are intravascular, extracellular, intracellular, and the cerebrospinal fluid (CSF). These compartments are separated by barriers which maintain their interior milieu, particularly the blood-brain barrier, which for the purposes of this discussion consists of the endothelial tight junctions and the trans-endothelial resistance to water diffusion. Other properties of the blood-brain barrier, such as active and facilitated transport, will not be considered although these properties play an important part in the passage of osmotically effective molecules, such as sugars. Water is freely diffusible between all these compartments and its movement is entirely passive, following osmotic and hydrostatic pressure gradients. The rate of equilibration depends on the hydraulic conductivity of the various membranes, which is much less for the blood-brain barrier than for other vascular beds. The amount of edema formation depends on the tissue compliance which is a composite of the compliance of all the compartments. The difference in compliance of the extracellular spaces of cortex and white matter is the reason for the usual distribution of extracellular edema between grey and white matter.

Some of these potential pressure gradients are more important than others in the formation of edema. The blood hydrostatic pressure is the source of all intracranial hydrostatic pressures. Alteration of the blood osmotic pressure has been used in treatment. The blood-brain barrier maintains the osmotic balance between blood and brain and its disruption may cause edema. The intra- and extracellular hydrostatic pressures can be considered together as the tissue hydrostatic pressure, although these 2 compartments may alter volume separately under differing osmotic pressures. If the hydrostatic pressure is zero, it is possible to have a shift of water from the extracellular space to the intracellular space, due to membrane failure, without an increase in total brain tissue water.

Although artificial, it is convenient to consider the factors which alter the volume of each of the fluid compartments separately.

1. Intravascular Compartment

Brain swelling due to vascular congestion occurs when cerebral blood vessels are fully dilated by anoxia or hypercapnia, provided that there is adequate input under sufficient pressure to distend small blood vessels and this may require some elevation of the blood pressure. Endothelial cells are relatively resistant to hypoxia and tight junctions are preserved.

2. Extracellular Compartment

Brain swelling due to extracellular edema has been called "vasogenic" edema and corresponds to wet edema, since the cut surface of the brain oozes edema fluid. It can be conveniently divided into edema with an intact blood-brain barrier and edema with a damaged blood-brain barrier.

Edema with an intact brain barrier is an ultrafiltration of plasma and may occur with a moderate or

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slow rise of blood pressure into a disautoregulated vascular bed. Clearly this situation is merely the next stage of vascular congestion. It can be produced easily in experimental animals by a rise in blood pressure and hypercapnia or following the application of pressure to the cortex to produce loss of autoregulation. This is one of the principal mechanisms of edema formation in cerebral tumors, and is the cause of the rapid swelling of the brain which may follow surgical removal of a large intracranial mass, such as a meningioma. If the blood-brain barrier is damaged, the next stage in severity, there is protein extravasation and osmotic extracellular edema in addition to the hydrostatic edema. Hypertensive encephalopathy is a good example. It can be produced experimentally with a rapid rise in blood pressure alone or at lower levels of blood pressure with loss of autoregulation. It can also be induced by trauma, either with pressure or the much studied cold lesion.

This form of edema spreads extensively through the brain, particularly in white matter, by bulk flow along hydrostatic pressure gradients and not by diffusion according to diffusion coefficients. This is known because substances with different diffusion coefficients travel at the same speed and much further than they would by diffusion alone. The edema eventually reaches the CSF, with which it is in contact, so that CSF pressure has some effect on edema resolution. Some edema fluid is also removed by reabsorption into blood vessels.

It is possible to have the blood-brain barrier open to macromolecules without the formation of edema. This occurs with the infusion of hypertonic solutions which are said to shrink the endothelial cells and open the tight junctions. Horseradish peroxidase has been seen on electronmicroscopy in the tight junctions, but the tight junctions are never observed to open and it is likely that the endothelial cells merely become more permeable to macromolecules by increased pinocytosis. Presumably, edema does not develop because the osmotic gradient is not sufficiently altered by the extravasation of protein in the presence of a hyperosmolar vascular compartment, but the relationship between extracellular protein and osmolarity is not linear and there may well be a threshold before significant edema can develop. This dissociation between macromolecule extravasation and edema occurs in stroke and in epileptic seizures.

3. Brain Swelling Due to Intracellular Edema

This has been called "metabolic" or "cytotoxic" edema. It is caused by anything which damages cell metabolism, in particular the sodium pump mechanism, producing a change in the osmotic balance across the cell membrane and intracellular edema. This type of edema corresponds to the dry edematous brain, because the edema is contained in the cells and the cut surface of the brain is, therefore, not unduly wet. It can be produced experimentally with a wide range of poisons such as cyanide and hexachlorophene, by specific sodium pump inhibitors such as ouabain and by direct damage to the cell with trauma, including cold. A combination of intracellular and extracellular edema is produced by reducing the osmotic pressure of the blood with infusions of distilled water or by dialysis.

4. Brain Swelling Due to Hydrocephalus

The CSF hydrostatic pressure is one determinant of the overall cerebral perfusion pressure and it is a measure of the average tissue and venous pressures. It is not as important as it may seem because focal cerebral edema may alter the local perfusion pressure without significant change in the CSF pressure. This phenomenon has even been demonstrated with the generalized edema associated with triethyl tin poisoning and with water intoxication, but edema alone does not reduce blood flow to critical levels without a rise in intracranial pressure.

Effect of Edema on Cerebral Function

Obviously, in metabolic edema function is impaired at the outset since the edema is due to cellular malfunction; but extracellular or vasogenic edema appears to have remarkably little effect on cell function, as shown by electrical activity, until blood flow falls to critical levels. This is shown clinically in patients with benign intracranial hypertension, who may remain quite alert with considerable cerebral edema. Focal cerebral edema may be more serious with the production of a rapidly expanding mass lesion effect and intracranial herniation. In one series cerebral swelling contributed to or caused deterioration or death in 20% of 106 stroke patients.

Effect of Ischemia

It is possible for ischemia to produce all the forms of brain swelling and edema that have been discussed. Firstly, intravascular congestion, which requires an increase in the hydrostatic pressure to capillaries through disautoregulated and, therefore, maximally dilated arteries and arterioles, might occur in stroke if the collateral circulation is very good. It might also occur if an embolus impacts, fragments and moves off leaving a patent vessel to feed the distal disautoregulated vascular bed. Similarly, an ultrafiltrate edema could occur under the same circumstances, but neither of these mechanisms is likely to be very important in most strokes. Ischemic damage to the cell with failure of the sodium pump, together with damage to the blood-brain barrier with protein extravasation, are much more significant mechanisms; that is, a combination of metabolic and vasogenic edema.

Theoretical models of cerebral ischemia are usually based on an idealized situation with obstruction of a main artery causing a central core of infarction and necrosis surrounded by an ischemic zone supplied by collateral circulation. Many experimental models of...
ischemia try to mimic this in the most reproducible way. Unfortunately, such idealized conditions do not happen in practice and in a single infarct all the mechanisms outlined may be operative at the same time and to varying degrees in different parts of the same lesion. Furthermore, the development of an infarct is a rapidly evolving situation with different parts of the lesion developing at different rates, so that the mechanism of edema formation in stroke varies not only throughout the lesion but also with time. This is probably the reason for the widely discrepant experimental and clinical reports of various treatment methods, which is compounded by the varying degrees of ischemia produced and availability of the collateral supply, the species difference in brain volume, including the relative amounts of grey and white matter, and species variation in response to drugs.

Most of the experimental models of cerebral edema are not appropriate for the study of ischemic edema. This applies to triethyl tin and hexachlorophene poisoning, osmotic edema, microembolization, hydrophilic seeds, trauma and pressure from balloons. Cold injury produces a clear, reproducible lesion which mimics ischemic edema pathologically with both intracellular and extracellular fluid accumulation, but the local hemodynamic aspects are very different from a stroke, principally because an infarct is usually protected from the normal systemic pressure. Evaluation of ischemic cerebral edema must, therefore, take cognizance of the rate of development and the duration and depth of ischemia as well as the effect of variations in blood pressure. In addition to these primary factors, there are the effects of the ischemic process on the hydrostatic and osmotic pressures of each fluid compartment and the feedback effect these changes have on the blood flow and intracranial pressure.

Rate of Development, Duration and Depth of Ischemia

Complete ischemia rapidly causes a sequence of events with cessation of electrical activity, failure of the sodium pump, depletion of glucose and increase in lactate. Up to a certain stage this process is potentially reversible but thereafter a stepwise sequence of organelle failure occurs as thresholds for survival are reached and passed. Throughout this time, the blood-brain barrier remains intact and there is virtually no leak of protein.

However, ischemia is usually less than complete, Symon18 has reported blood pressures of between 25–40% normal in the distal vascular bed to a proximal middle cerebral artery occlusion in monkeys and flows down to 25% of normal.18 Some blood flow, therefore, usually exists and the time sequence just outlined may be considerably prolonged or arrested at any stage. The depth of ischemia is very important and may be quite critical. Schibata et al.17 showed no change in the electrolyte or water content of the brain following a middle cerebral artery clip in dogs, but an increase in the ischemic insult by reducing the blood pressure resulted in edema and infarction.

Whether or not the blood-brain barrier opens to macromolecules depends on the blood hydrostatic pressure at capillary level as well as the duration and depth of ischemia. With no pressure and no flow, there is no protein extravasation, partly because the decreasing pressure is zero and partly because of a squeeze on the extracellular space and capillaries by glia swollen with fluid from the extracellular space. This considerably increases the resistance of the blood-brain barrier to the extravasation of macromolecules. It also reduces the spread of extracellular edema,6 as well as reducing perfusion by a squeeze on capillaries.18 With some hydrostatic pressure and sufficient ischemia, the blood-brain barrier opens eventually, but usually after an interval of some hours. The duration for which the barrier remains open is variable and it also depends on the duration and depth of the ischemia.

Klatzo,7 using bilateral carotid occlusion in the gerbil, found the blood-brain barrier open at 24 h after 30 min of occlusion in 50% of animals, whereas if the occlusion was prolonged to 6 h, the barrier was open one h post-occlusion in all animals. Harrison,19 using the same gerbil model, found that the edema was maximal at 8 h, but that the blood-brain barrier did not open until 18–24 h. Although the blood-brain barrier may remain relatively impervious to macromolecules in the early stages of ischemia, there is evidence of increased micropinocytosis in the endothelial cells early in both seizure-induced edema20 and radiation-induced edema21. This may well occur in stroke if the perfusion pressure is adequate. It would account for the early, if less obvious, increase in extracellular edema despite a blood-brain barrier intact against large molecules.

Hossmann22 found that after one h of total ischemia in cats, the extracellular space diminished from 18.9 volumes percent to 8.5 volumes percent, while the total water content and intracranial pressure remained unchanged. This indicated a shift in water from the extracellular to the intracellular space. There was no increase in the water content of the brain because there was no input. Following reperfusion there was a rapid increase in the extracellular fluid and a corresponding rise in intracranial pressure and water content of the brain, the resulting state being a combination of extracellular and intracellular edema.

O’Brien et al.23,24 studied the distribution of water in brains of cats from 4 h to 20 days after occlusion of the middle cerebral artery. In this model the water content reached a maximum at 2 days and also affected the opposite hemisphere (diaschisis). At the same time blood-brain barrier function was studied with 99 m-technetium pertechnetate and 131 iodine labeled albumin. The greatest extravasation did not occur until about 3 to 4 days after infarction and remained high for the duration of the study. Comparison of the extravasation of these tracers to water showed continued high levels of the tracers long after the water level had returned to normal. This is in accord with the clinical experience that edema is maximal between 1 and 3 days after a stroke, whereas the technetium pertechnetate brain scan may not reach
the maximum lesion to background ratio until 7 to 10 days. This is in marked contrast to experimental results using the cold injury model.

It seems clear, therefore, that the sequence of events in cerebral ischemia, so far as edema is concerned, is as follows: firstly there is a shift of water from the extracellular to the intracellular spaces which occurs with even slight ischemia, and some extracellular edema may occur, perhaps associated with increased pinocytosis if the perfusion pressure is adequate. Severe ischemia causes more marked changes with cellular disruption and only later does the blood-brain barrier open to macromolecules and this depends principally on the blood hydrostatic pressure at capillary level. Though why the edema is maximal at 2 days and then improves, not, apparently, following the subsequent break down of the blood-brain barrier, remains unclear. It may be that perfusion pressure is inadequate in the infarcted area and that the osmotic effect is insufficient.

**Treatment**

The treatment of ischemic cerebral edema is based on the various ways in which the fluid content of the different compartments can be modified. In practice, only the vascular compartment hydrostatic and osmotic pressures can be altered directly, but such changes may secondarily affect the other intracranial fluid compartments. The vascular hydrostatic pressure can be changed by alterations in blood pressure or by alterations in vessel caliber. The vascular osmotic pressure can be altered by infusions of hypertonic solutions. The CSF hydrostatic pressure can be lowered by drainage, but this is not relevant to ischemic edema and would probably increase extracellular edema by increasing the hydrostatic pressure gradient. It may also be possible to mitigate the effects of ischemia on membrane barriers, particularly the blood-brain barrier, since there are a number of drugs which alter the properties of membranes, including the barbiturates and steroids.

**Hydrostatic Pressures**

The effect of changes in systemic pressure depend almost entirely on the extent to which this is transmitted to the capillaries. If the major arterial supply to an infarcted region is occluded then the blood supply to the infarct is from the collateral circulation and, at least in the acute stage, the flow will be pressure dependent because the arterioles will be maximally dilated by the anoxic-ischemic stimulus. Symon et al. have shown that the loss of autoregulation is proportional to the degree of ischemia, particularly for falls in blood pressure. They found that autoregulation was partly preserved when the postocclusion flow was greater than 40% of the normal level, but absent when flow was less than 20%. Under these circumstances an increase in pressure causes an increase in flow and this has been shown in patients. Conversely, and perhaps more critical and clinically important, is that a reduction in pressure causes a fall in flow, which could have serious effects.

If the main arterial supply to the infarct is patent or if the collateral supply is exceptionally good, particularly with small lesions, then the situation is rather different. This is because the infarcted area is exposed to systemic pressures and an increase in the blood pressure will tend to open the blood-brain barrier and drive the formation of extracellular edema. These circumstances have been studied extensively in animals with 2 basic types of experimental model.

In cold injury the lesion is exposed to the systemic blood pressure from the start. Klatzo et al. showed that by increasing the blood pressure in cats with the cold injury to 200 mm Hg edema reached the levels in 2 hours that it would normally take 6 hours to achieve in normotensive animals; lowering the blood pressure inhibited edema formation. The other principal experimental model is when arterial clips have been placed on arteries and then removed after varying intervals of time, so that exposure to arterial pressure occurs after infarction. Although in these circumstances a rise in blood pressure may increase the flow, false autoregulation may also occur, that is, a rise in pressure that is not accompanied by a rise in flow in a dissected vascular bed. This is due to an increase in edema caused by the rise in blood pressure which squeezes the capillaries, thereby preventing dilatation and preventing an increase in blood flow. This may occur without comparable rise in intracranial pressure. Grote and Schubert have shown that cold-induced edema can prevent the vasodilatation normally associated with anoxia, and Frei et al. showed that reactive hyperemia only occurs in non-edematous brain. A linear inverse relationship has been found between cerebral blood flow and water content in the brain adjacent to cerebral tumors, showing the effect of focal edema. These observations suggest that it is the local tissue hydrostatic pressure which determines the local perfusion pressure and not the average intracranial pressure.

Fluctuations in blood pressure may be even more harmful as was shown by Matakas et al. in experiments in monkeys. Extracellular edema was induced by balloon compression. Subsequent to release the intracranial pressure rose to a level which depended on the systemic blood pressure. The blood pressure was then increased with norepinephrine, the perfusion pressure increased and the cerebral blood flow increased, but so did the edema and the intracranial pressure. When the effect of the norepinephrine wore off the blood pressure fell, but the intracranial pressure fell proportionally less. For example, a blood pressure change of 100 to 150 mm Hg and back to 100 mm Hg was accompanied by intracranial pressure change of 60 to 90 mm Hg and back only to 80 mm Hg. This effect was repeated with each rise in blood pressure until the intracranial pressure corresponded to the perfusion pressure. The clinical correlation and possible consequences of this
in hypertensive stroke patients with poor blood pressure control are obvious.

A reduction in blood pressure might retard the formation of edema and this has been shown to occur with the cold injury and is likely to occur in patients if a lesion is exposed to systemic arterial pressure, but since flow in disautoregulated vascular beds is pressure dependent, a reduction in pressure could well have a critical effect on cellular metabolism. Astrup et al.34 have shown that evoked responses cease at flow rates below 15–20 ml/100 g/min and disruption of cell membranes and potassium flux occurs at about 6 ml/100 g/min. Since the optimum perfusion pressure requirements are likely to vary considerably in different parts of an infarct and at different stages it is obvious that no general advice can be given about the control of blood pressure, except, perhaps, to avoid extremes — and these would need to be generously interpreted.

**Effect of Alteration in Vessel Caliber**

The principal effect of alteration of CO₂ is on the size of the vascular compartment. Hypercapnia will produce cerebral vaso-congestion in normal brain by dilatation of responsive arteries which could lead to increased extracellular edema. Hypocapnia causes marked vaso-constriction of responsive vessels and this is probably the quickest method of producing an acute and rapid reduction in intracranial pressure. This may prevent intracranial herniation with large infarcts but it is necessarily a short-term procedure.

**Alterations in Blood Osmolarity**

Osmotic agents reduce tissue water content of the normal brain. They only work if the endothelial and cell membranes are intact and, therefore, have a beneficial effect on the edema induced by triethyl tin or in osmotic edema. But they are much less effective in ischemic edema unless there is significant extracellular edema produced by the mass effect of a large infarct. A similar effect is produced by forced diuresis, although some of the agents used, such as furosemide or acetazolamide, also reduce CSF formation35, 36 and this may have a beneficial effect in reducing intracranial pressure and improving edema resolution. There is also some evidence that these agents have an effect on the blood-brain barrier.37

**Possible Effects of Drugs on The Blood-Brain Barrier**

Any discussion of the effects of drugs on blood-brain barrier must consider the effects of free radicals. Free radical peroxidation and there may be less control of the normally well modified effects of flavine and coenzyme Q. These effects may be mitigated by antioxidants. There are 2 basic types, the water soluble, such as ascorbic acid, and the lipid soluble such as the tocopherols and both have a marked quenching effect on free radicals. Steroids probably produce their protective effect by an intercalation with the unsaturated fatty acid tails in the blood-brain barrier membranes. Taken together with antioxidants, therefore, steroids may prevent or stop free radical reactions by quenching the free radicals, chelation of metal complexes, and intercalation and protection of fatty acid chains.

If this is how steroids produce their effect in cerebral edema, it would be surprising if they were effective in ischemic edema because intercalation cannot occur if the membrane is severely damaged. In addition, the speed of events following infarction may overwhelm the possible reparative effects of steroids. The effect of steroids on ischemic edema remains controversial. Numerous experiments have shown reduced mortality in a variety of stroke models in experimental animals but little or no effect on less severe infarcts. This is in accord with clinical experience and is in marked contrast to the dramatic effect of steroids on the edema associated with space occupying lesions and the experimentally induced cold lesion. The edema associated with tumors is principally extracellular and due to loss of autoregulation in the surrounding brain subjected to the pressure of an expanding lesion. This type of edema responds well to steroids, probably because of the relatively slow progression of the lesion which allows the intercalation of steroids into the relatively preserved blood-brain barrier membranes with stabilization and restoration of barrier function. When stroke produces a large focal lesion and mass effect due to massive infarction, steroids may be effective by reducing the pressure induced extracellular edema in surrounding brain, rather than by an effect on the ischemic edema itself. Yamaguchi et al.42 showed that cerebral edema produced by bilateral carotid ligation in rats was not affected by steroids, but that steroids had a beneficial effect on the edema associated with the extravasation of Evans blue dye induced by pressure.

The evidence suggests, therefore, that steroids are effective in vasogenic edema but not in metabolic edema and it is the latter that is the principal problem in the early stages of an infarct.

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