7 INJURY AND CELL FUNCTION

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7.1 Introduction

This chapter reviews the mechanisms by which primary impact acceleration forces applied to the neuraxis cause damage to the cranial contents and the cellular basis by which secondary insults, particularly ischemia, exacerbate primary damage to produce the composite clinical picture usually seen.

There are now data available from in vitro and in vivo models and from human studies that allow conclusions to be drawn about the effects of trauma upon neuronal and astrocytic function. Trauma has effects on cell membranes, ion channels of axons and neurons and astrocytes, and also on whole brain systems affecting substrate delivery, blood flow, brain metabolism and neurological function. Although many aspects of the pathophysiology of neurotrauma remain poorly understood, the enormous advances made over recent years have provided promising new avenues for therapy which will be clinically tested over the next few years.

7.2 Biomechanical characteristics of neurotrauma

The manner in which kinetic energy is applied to the cranium during injury is extremely variable. At one extreme, the helmeted head of a restrained aircraft pilot may decelerate from a velocity of several hundred miles per hour to zero over tenths of a second during a crash. The cranium may never contact a solid object, yet the brain is irreversibly damaged. Such pure deceleration injury maximally damages axons and most frequently occurs as a result of motor vehicle accidents, where it is always complicated by an additional impact component. At the opposite end of the spectrum are those unusual injuries in which the stationary head (e.g. of a machine operator) is slowly crushed by slow-moving machinery. Such injuries classically produce massive fractures, extra-axial hematomas and contusions, yet these patients usually do not lose consciousness, because axonal injury is absent and the reticular activating system and projection fibers are not disturbed by shear forces.

Thibault and Gennarelli, and coworkers, have used the ‘Penn 1’ and ‘Penn 2’ primate impact acceleration injury model to characterize the relationship between the magnitude of acceleration/deceleration force, the time duration over which it is applied, and the consequences for the intracranial contents (Figure 7.1; Gennarelli, Thibault and Adams, 1985). A brief, high-intensity decelerational force, as seen when the head strikes a solid floor at the end of a standing fall, will tear parasagittal bridging veins, causing an acute subdural hematoma. When the deceleration force is of higher magnitude and longer in duration, as in vehicle...
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accidents, diffuse axonal injury is caused. When both the magnitude and the duration of the decelerational force is less, transient unconsciousness, 'concussion', is caused but few structural effects are seen when the brain is examined either ultrastructurally or by light microscopy (Chapters 2 and 3).

7.2.1 BRAIN MOVEMENT DURING IMPACT

Studies performed more than 20 years ago using various biomechanical modeling techniques, demonstrated that the brain moves within the cranial cavity in response to decelerational forces (Holbourne, 1943; Gurdjian, Lissner and Hodgson, 1966). The ‘gelatin-like’ brain reverberates and swirls within the cranial cavity for many milliseconds after impact in response to lines of force (Kuijpers, Claessens and Sauren, 1995; Ommaya et al., 1966; Peerless and Rewcastle, 1967). The brain is anchored within the cranial cavity only by the parasagittal bridging veins, parasinusoidal granulations, cranial nerves and tentorium. Movement of the lobes of the brain forward towards the anterior cranial basal structures, particularly the sphenoidal ridges, concentrates force at the bases of the frontal lobes and the tips of the temporal lobes (Figure 7.2; Gurdjian, Lissner and Hodgson, 1966). Surface contusions are thus very much more frequent at these sites than elsewhere (Chapters 2 and 3). It is generally held that shearing forces transmitted through the brain stem and the reticular activating system are responsible for immediate loss of consciousness, although there is evidence in the human brain that shearing force also concentrates in the deep white matter structures such as the corona radiata, explaining the frequent finding of parasagittal ‘gliding contusions’ (Stritch, 1956; Chapter 3).

7.2.2 FOCAL INJURY

Focal brain injuries are usually associated with a breach of the cranial coverings, such as a compound depressed fracture. By definition, they produce focal cortical contusions with or without associated intracerebral hematoma formation (Figure 7.3). Such injuries may occur in association with a more significant diffuse injury of the type described above, e.g. when the rapidly decelerating cranium strikes a sharp pointed surface within a motor vehicle, but in most instances they are the result of the stationary cranium being struck by moving objects with relatively small mass such as sticks, baseball bats or golf clubs. Usually, impacts of this type do not cause prolonged unconsciousness but they may cause permanent focal
neurological deficit due to the immediate effects of the penetrating/focal injury, or even death due to the delayed consequences of cerebral contusion or intracranial hematoma (see below and Chapter 19).

7.2.3 PENETRATING INJURY

Penetrating injuries may be caused by missiles or projectiles, which have low mass but strike the cranium with high or very high velocity, or by stab wounds, in which sharp objects moving at low velocity are driven into the cranial cavity. Stab wounds damage vascular structures, cranial nerves and white matter fiber tracts. When the wounding instrument remains imbedded within the skull and brain the prognosis is remarkably good with appropriate management, but if the weapon is levered free by the assailant, the resulting arc of blade movement within the brain may be devastating (Du Trevou and Van Dellen, 1992). Angiography is usually needed to exclude vascular injury.

7.2.4 MISSILE INJURIES

Missile injuries and their effects on the brain are highly variable and unpredictable. Cranial wounding by high-velocity military firearms (> 2000 m/s) is almost always fatal because the kinetic energy transmitted to the cranium is enormous. When a bullet traverses the intracranial contents, its effects are twofold: a pressure wave reverberates through the brain, transmitting extremely high pressure as the bullet enters followed by low pressure of equal magnitude behind the missile’s path. These pressure waves occur in proportion to the velocity of the projectile, and largely determine survival. The second consequence of missile injuries is direct vascular and neural disruption which results from the tearing effects of the bullet itself and in-driven skull fragments. These effects are similar to other forms of contusion, although the magnitude of vascular damage and consequent hematoma formation may be much greater. Patients in persistent deep coma, (Glasgow Coma Scale 3–5) after bullet injury of high or low velocity have a 90–95% likelihood of a bad outcome (death or severe disability) unless an associated extra-axial hematoma can be removed (Graham et al., 1990). Although cranial gunshot wounds and their management are not a primary focus of this book, most aspects of their pathophysiology and management are common to blunt or closed cranial injury. (For an excellent review, the reader is referred to Chapters 60 and 61 in Narayan, Willberger and Povlishock, 1996.)

The two factors common to all types of severe cranial inquiry are:

- **the transmission of kinetic energy through the brain which passes as pressure waves of varying magnitude and duration** (Figure 7.2);
- **direct impact damage to small and large vascular structures and neurons close to the cortical surface.**

From Figure 7.1 it may be seen that the magnitude of shearing force needed to transiently impair neurological function is many times less than the magnitude of shear force needed to disrupt axons. It has been estimated that the magnitude of shear that is required to damage the pial vasculature may be five times greater than that needed to damage axons (Gennarelli, Thibault and Adams, 1985; Hayashi et al., 1980). Although this gradation of force suggests that vascular structures should be damaged less frequently than axons and membranes, this may not be the case, because focal forces, as seen in cerebral contusion are often concentrated within the first few millimeters of the cortex under the pia, especially at the frontal and temporal tips, thus producing damage to the microvasculature and distribution arterioles in the majority of patients who sustain moderate and severe brain trauma (Figure 7.3).

7.3 Biomechanical effects and age

At both extremes of the age spectrum, the brain is more vulnerable to vascular damage in response to shearing forces. In the premature neonate, for example, relative absence of myelination and reduced astrocyte maturity are probably responsible for the high incidence of periventricular white matter hemorrhage resulting from the shearing forces sustained during birth trauma.

In the elderly, brain atrophy may result in reduced neuronal and astrocyte density with poorer support of vascular structures, such that progressive pericontusional hemorrhage and edema are greatly facilitated.

The section below will review the effects of these different patterns of biomechanical forces upon the hierarchy of structures in the neuraxis.

7.3.1 CELL MEMBRANES AND ION CHANNELS

Neurons and their dendritic processes represent an enormous membrane surface area. Although dendritic spines, synapses, gap junctions and myelinated axons constitute specialized regions within the neuronal membrane, ion channels are by far the most frequent structures embedded in neuronal membranes. To date over 15 varieties of neuronal ion channels have been identified. The most common of these, voltage gated channels, are closely linked functionally with the sodium/potassium ATPase
pump (Sachs, 1991; Schwartz and Kandell, 1991; Siegelbaum and Koester, 1991). Many types of ion channel are linked to the specific agonist-gated receptors, and others are linked within the cell with second messenger systems, such as adenylate cyclase and G proteins (for review see Siegelbaum and Koester, 1991).

Although the surface area and complexity of 'bimolecular leaflet' membrane may be less for astrocytes, there is now clear evidence that astrocytes are excitable, possess ion channels, and may be depolarized, though to a much lesser extent than neurons (Bowman et al., 1992; Kimelberg and Nordenberg, 1989; Orkand, Nicholls and Kuffler, 1966). Astrocytic membranes also constitute an important component of the blood–brain barrier and there is now extensive evidence to show that this barrier function is disturbed transiently by mechanical trauma (see below).

The effects of traumatic mechanical shearing upon neuronal membranes is not well understood. Bimolecular leaflet membranes themselves appear to be 'stretchy' and relatively resistant to deformation and movement, even at high shear rates, and indeed some degree of motility and elasticity occurs normally with arterial pulse pressure waves and with extremes of sagittal plane neck movement which stretches the spinal cord and medulla several centimeters.

Recent studies using patch clamp techniques and in vitro tissue culture of neurons growing on deformable surfaces have shown that ion channel function may be radically altered by mechanical deformation at certain shear magnitudes and rates (Bowman et al., 1992; Sachs, 1991; Tavalin, Ellis and Satin, 1995).

Specific classes of 'mechanotransducing' ion channels have been identified using patch clamp techniques in both neurons and glia (Bowman et al., 1992; Sachs, 1991). Some of these ion channels remain 'leaky' for several hours after mechanical deformation (Tavalin, Ellis and Satin, 1995). We speculate that the majority of voltage-sensitive and agonist-gated ion channels are also sensitive to transient mechanical deformation by shearing forces. Recent in vitro experiments have shown that monolayer neuron and astrocyte cultures growing on a flexible plastic membrane, which are rapidly deformed by a brief air jet impulse, undergo rapid calcium entry and subsequent neuronal death, with efflux of lactate and potassium into the culture medium (Tavalin, Ellis and Satin, 1995).

Data from in vivo trauma models such as fluid percussion injury and contusional impact models have shown massive rapid transient efflux of potassium into the extracellular fluid (ECF), associated with a fall in sodium content in ECF (Bullock et al., 1995; Di et al., 1996b; Katayama et al., 1990; Nilsson et al., 1993). These changes may be explained by rapid alterations in the 'pump leak' relationship that exists between voltage-dependent ion channels and the sodium–potassium-dependent ATPase pump, and the opening of agonist-gated channels.

We speculate that the structural complexity and allosteric relationships that characterize agonist-dependent ion channels and their receptors means that they may be even more sensitive to mechanical deformation with consequent increased 'leakiness'. Astrocytes are known to function as potassium uptake buffers, having the capacity to rapidly take up potassium from the extracellular space (Bullock et al., 1991, 1994; Kimelberg and Nordenberg, 1989; Newman, 1986). However, this results in rapid astrocyte swelling, sometimes to enormous proportions. Such astrocyte swelling is the ultrastructural hallmark of both acute cerebral ischemia (see below) and focal cerebral contusion. It is almost always seen in animal trauma models and in humans after trauma (Figure 7.4; Bullock et al., 1991; Schroeder et al., 1994).

Figure 7.4 Electron micrograph made from human gray matter taken from the periphery of a resected contusion in a patient with increased intracranial pressure after severe head injury (magnification ×1500). Note the microvessels (V) with narrowed lumen and an entrapped red cell. The asterisks denote massively swollen astrocytic cytoplasm, above due to swelling of the astrocyte 'end feet' processes abutting on a blood vessel and below surrounding the astrocyte nucleus.
7.3.2 EFFECT OF SHEAR FORCES ON SYNAPSES AND SYNAPTIC FUNCTION

Direct investigation of synaptic function is difficult immediately after trauma. Recent microdialysis studies have investigated the time course of changes in neurotransmitters within the extracellular space after fluid percussion injury and brief transient surges in release of excitatory amino acids and acetylcholine have been demonstrated (Figure 7.5). Moreover, a three- to fourfold surge in extracellular potassium was also demonstrated, using the same techniques (Katayama et al., 1990; Newman, 1986). About one-third of this potassium release could be blocked using Tetrodotoxin, suggesting that two-thirds of the potassium release was occurring through agonist-operated channels. Recent studies from our laboratory have similarly shown that blockade of voltage-operated ion channels prior to traumatic brain injury (TBI) failed to ameliorate the negative neurological and behavioral effects of the trauma, and produced only a modest effect on K+ flux in the ECF, suggesting that agonist-operated ion channels are more important after TBI in mediating ionic events (Di et al., 1996b).

There are now data available from microdialysis studies in patients who have sustained severe head injury and in patients with ischemic events superimposed upon their primary trauma, which show that ECF excitatory amino acids (EAAs) rise to levels 50–60 times higher than normal values when a secondary ischemic event occurs superimposed on the trauma (Bullock et al., 1995; Zauner et al., 1996a). Excitatory neurotransmitters released from damaged cells and neurite processes may be responsible for these increases, and EAAs may also come from the intravascular compartment. This conclusion is supported by the finding that levels of structural amino acids in these patients were also raised and appeared to fluctuate in parallel with EAAs (Di et al., 1996a).

The behavioral changes that persist up to weeks or months after TBI, even in animals without any evidence of structural damage, have been taken as evidence to support functional changes at the synaptic level or in relation to second messenger systems (see below). Recent neurochemical studies have shown evidence of synaptic alterations and G-protein coupling relationships in the cell membrane that manifest as prolonged increased in protein synthesis in response to muscarinic cholinergic receptor activation and certain categories of catecholaminergic receptors (Delahunty et al., 1995; Miyazaki et al., 1992; Prasad et al., 1994).

These changes may translate into effects on long-term potentiation in the hippocampus which have been demonstrated in the absence of structural changes after trauma and may be an important mechanism underlying the traumatic effects on learning and memory.

7.3.3 EFFECT OF SHEAR INJURY UPON AXONS

About 50 years ago, neuropathological studies first demonstrated accumulation of axoplasmic retraction ‘balls’ at sites of axonal discontinuity (Strich, 1956; Peerless and Rewcastle, 1967).

These were chiefly found on large myelinated fibers in patients who were unconscious from the time of injury and subsequently died. These ‘retraction balls’ were found in high density in white matter tracts in about 25% of severely head-injured patients (Adams, Doyle and Ford, 1989).

Recent ultrastructural studies have shown, surprisingly, that the development of retraction balls is a gradual process requiring more than 12 hours in lower mammals such as rodents and around 24 hours in humans to become fully developed (Povlishock, 1992). This raises the intriguing possibility that diffuse axonal injury may be amenable to therapeutic intervention. In accordance with these findings, Blumbergs et al. have recently shown that a number of patients who showed the features of diffuse axonal injury (DAI) on examination of the brain at postmortem were actually lucid and conscious during part of their clinical course (Chapter 3). This suggests that neurons and axons that subsequently show the changes of diffuse axonal injury may function after impact prior to degeneration, or that other, less affected, axon tracts

![Figure 7.5](image)

**Figure 7.5** The rapid and transient increase in potassium release and extracellular glutamate, as detected by microdialysis after fluid percussion injury in the rat. (Source: reproduced from Katayama et al., 1990, with permission.)
do not progress to DAI. Povlishock et al. have recently shown that retraction balls and axonal degeneration are particularly common at the points where axons must deviate around small vessels within white matter, suggesting that the axons may be fixed at these points (Povlishock, 1992).

Carefully sequenced ultrastructural examinations beginning a few minutes after diffuse cerebral impact have now demonstrated a fascinating sequence of events that incriminates primarily the microtubular intra-axonal cytoplasmic system (Pettus et al., 1994). Adjacent to nodes of Ranvier, the outer myelin layer and axoplasmic membrane is first seen to balloon and distend, compatible with the hypothesis that ion flux through conformationally distorted ion channels may be occurring. Subsequently, normal axonal transport ceases because the intracytoplasmic microtubular system begins to collapse and concatenate upon itself like ‘a deck of cards collapsing’ (Pettus and Povlishock, 1995). The factors that cause this cytoskeletal collapse are not fully understood. However, this process is thought to result in axoplasmic stasis at the site of these changes with subsequent accumulation of axoplasm proximally to form the reactive axonal swellings previously termed retraction balls (Grady et al., 1993).

These changes have far-reaching consequences for neuronal function. Interruption of the axon causes proximal Wallerian degeneration of the affected neuron. Distally, the axon degenerates, fragments and disappears, resulting in deafferentation of the affected neuronal fields. The functional consequences of this process may include seizures because of lack of inhibitory effects, spasticity, intellectual decline and unmodulated behavior patterns. When this is widespread, and Wallerian degeneration destroys many neurons, the whole brain becomes atrophic, with ventriculomegaly and, in the worst cases, a persistent vegetative state (Adams et al., 1989; McLellan et al., 1986).

7.3.4 ANIMAL MODELS AND THERAPEUTIC IMPLICATIONS

Until recently, it has been difficult to produce diffuse axonal injury in rodent models because of the biomechanical characteristics of the rodent cranium and brain, and most animal studies have been performed using cats and mini-pigs. The Marmarou weight-drop model, in which a 500 g weight is dropped through 2 m on to the unrestrained ‘helmeted’ cranium of an anesthetized rodent has produced diffuse axonal injury in relatively high density (Marmarou et al., 1994). This model, therefore, offers the possibility of testing therapeutic hypotheses relatively cheaply in large numbers of animals.

7.3.5 EFFECTS OF SHEAR FORCE UPON MICROVASCULATURE

The cerebral microvasculature is more resistant to shear damage than axons. In the majority of significant head injuries, however, focal concentrations of force develop at the tips of the frontal and temporal poles that are sufficient to disrupt these pial vessels causing a focal contusion. In other words, focal injury is superimposed on diffuse injury (Kuijpers, Claessens and Sauren, 1995).

Recent ultrastructural studies in both head-injured humans and in appropriate animal models have demonstrated major anatomical changes in the injured microvasculature. These changes include the following (Bullock et al., 1994; Bullock et al., 1991):

- swelling of perivascular astrocytic ‘end feet’ such that apparent narrowing and distortion of the vascular lumen is frequently seen (Figure 7.4);
- increased endothelial microvacuolation and micro-pseudopodial activity, suggesting increased trans-endothelial flux of intravascular components such as water, ions or protein-rich fluid;
- perivascular hemorrhage and transvascular diapedesis of red cells – these hemorrhages may coalesce to form a frank intracerebral hematoma or hemorrhagic contusion;
- increased intravascular leukocyte adherence – this process has been observed in both trauma and ischemia, and may be caused by cytokine activation due to free radical release in response to shearing injury in the endothelial cell walls.

Frank vascular disruption has been seen surprisingly infrequently in human pericontusional biopsy material, suggesting that small vessels ‘stretch and leak’ much more frequently than they ‘tear or burst’. These microvascular changes have profound functional consequences, chiefly reduction of local cerebral blood flow (CBF) and development of vasogenic and cytotoxic edema, with increased intracranial pressure (ICP) (Schroeder et al., 1994; see below).

7.4 Major vascular damage secondary to shear injury

Acute subdural hematoma complicates about 20% of severe head injuries and carries the worst outcome of any of the subgroups of severe head injury patients. This complication is almost always caused by rupture of any of three types of surface vessel.

7.4.1 RUPTURE OF BRIDGING VEINS

Biomechanical studies with the ‘Penn 1’ and ‘Penn 2’ models have shown that reproducible acute subdural hematomas can occur as a result of rupturing of the
parasagittal bridging veins when the cranium is rapidly decelerated with a relatively low magnitude of shear force applied (Gennarelli, Thibault and Adams, 1985). Such circumstances are clinically produced by a fall from standing height on to a solid surface such as a floor. Boxing injuries, particularly rotational accelerations of the head, also classically produce these injuries. Avulsion of parasagittal and Sylvian bridging veins is usually accompanied by a degree of diffuse axonal injury and polar contusion (Adams, Doyle and Ford, 1989; Chapter 3). What remains unclear, however, is the mechanism by which low-pressure venous bleeding can accumulate to form a hematoma of sufficient size to compress the brain. We speculate that episodes of coughing, straining, or vomiting may ‘pump out’ sufficient blood to progressively tamponade the brain as clotting occurs. However, such subdurs also occur in patients unconscious from the time of injury, who have none of these episodes. That the blood vessels are attached to the sagittal sinus, which is held open rather than compressed by the hematomas, may be important.

7.4.2 SUBDURAL HEMATOMAS OF ARTERIAL ORIGIN

When polar contusions are extensive, they may burst through the pia to accumulate in the subdural space. This results in the classical ‘burst lobe’ injury charac-
terized by subdural hematoma, polar contusion, intracerebral hematoma and hemispheric swelling.

7.4.3 COALESCEENCE AND RUPTURE OF PARENCHYMAL SMALL VESSELS BLEEDING FROM A CONTUSION

This frequently occurs when a coagulation defect develops as a result of consumption of clotting factors or anticoagulant therapy (Bullock et al., 1990a). Such subdurals are usually associated with sizable intraparenchymal clots.

7.5 Metabolic consequences of TBI

Because the brain is dependent upon aerobic metabolism for substrate delivery (oxygen and glucose), and because of the frequent impairment of oxygenation and perfusion that occurs following severe head injury, metabolic derangement is an extremely frequent and important consequence of TBI. Metabolic changes may be global, involving the whole brain, or focal, developing in the region of intracerebral and subdural hematomas and contusions. Evidence demonstrating metabolic derangement after TBI has come from several sources, including:

- animal studies using the 2-deoxyglucose technique to measure glucose metabolism in global models such as fluid percussion injury and focal models such as contusion and subdural hematoma;
- positron emission tomography studies using fluorodeoxyglucose in humans;
- measurement of jugular/arterial differences of oxygen and lactate to yield global measures of oxygen consumption and lactate production in humans (AVD02 and CMRO2);
- measurements of whole brain lactate, ATP and other metabolites using MR spectroscopy in animal models;
- measurement of extracellular fluid lactate, glucose and oxygen content by microdialysis and oxygen electrodes in humans.

Data from these studies allow the following synthesis to be constructed regarding the metabolic consequences of TBI.

Immediately following impact, the shearing forces applied to neuronal tissues result in massive ion fluxes across neuronal membranes, widespread loss of resting membrane potential and release of neurotransmitters into the extracellular space. Within minutes of these events, the brain attempts to restore ionic homeostasis by reuptake of neurotransmitters and ion pumping. These processes are intensely energy-dependent and result in an abrupt increase in glucose utilization. Studies with the fluid percussion model in rats have shown that this increase in glucose metabolism, to facilitate ATP generation, is brief and maximally localized to those parts of the brain that are maximally deformed by the shearing forces (Kawamata et al., 1995). Evidence suggests that ionic pumping, and glutamate surges in astrocytes both preferentially activate anaerobic glycolysis, thus producing lactate, especially in astrocytes (Pellerin and Magistretti, 1994). This depletes ECF glucose. When focal lesions such as subdural hematoma, focal infarction or cerebral contusion are present, then glucose use increases for a longer period in the ‘penumbral’ border zone around the densely ischemic core of these lesions (Kuroda and Bullock, 1992; Sutton et al., 1994). This increase may persist for two to four hours in the rat, and 5–7 days, in humans (Kuroda et al., 1992; Bergsneider et al., 1996). In both animal models and humans, glucose use is depressed when measured days after the injury, and remains so for weeks after impact, which is consistent with the reduced metabolic needs of the comatose brain (Yoshino et al., 1991).

In humans, recent PET studies have shown that these increases in glucose are maximal in the penumbral zone of contusions and in the hemisphere underlying hematomas when this brain is viable (Bergsneider et al., 1996; Figure 7.7). Such tissues are often adjacent to ‘low-density’ cytotoxic edema areas on CT scan. Studies performed with PET at later time points have shown uniformly decreased metabolism, both for glucose and oxygen in humans, for 1–4 weeks after impact.

7.5.1 LACTATE

Numerous studies in animals and humans have shown that TBI is characterized by increased brain lactate production, which normalizes gradually after the first few days in those humans who survive, but remains at levels five to ten times normal in those who die (Crockard and Taylor, 1972; Inao et al., 1988). Measurements have been made in extracellular fluid, CSF and whole brain using different techniques but the results are consistent (Kawamata et al., 1995; Zauner et al., 1996b; Figure 7.8).

Recent microdialysis studies have demonstrated that extracellular fluid glucose declines to extremely low levels – sometimes zero – when lactate is increasing (Myseros et al., 1995; Zauner et al., 1996b; Figure 7.8).

Marmarou et al. originally postulated that these data could be explained best by a shift to anaerobic metabolism within cerebral tissue such that the glycolytic pathway would consume glucose and generate lactate while the Krebs cycle and mitochondrial NADPH phosphorylation had ceased to occur (Inao et al., 1988), otherwise lactate would be consumed. Such situations generally occur in circumstances of restricted
oxygen delivery to tissues. Although the oxygen tension at which aerobic Krebs cycle metabolism ceases to occur in human cerebral tissue is not well known, it is probable that this develops only when brain oxygen tension levels fall below about 20 mmHg (Zauner et al., 1996b). Marmarou and others have shown in animal experiments that trauma incapacitates mitochondrial phosphorylation, thus causing a shift towards anaerobic metabolism (Inao et al., 1988). Recently, however, an interesting link between increased ECF glutamate and increased anaerobic glycolysis has been shown in astrocytes, such

*Figure 7.7* Increased focal glucose use in humans and two animal models after neurotrauma. (a) CT scan and (b) fluorodeoxyglucose-11 PET study in a patient with frontal contusions 4 days after injury. Note the dark areas of increased glucose use adjacent to the contusions, and markedly reduced glucose use in the contused cortex (light areas on PET study). (c) Increased glucose use and decreased regional cerebral blood flow in a rat model of focal cerebral contusion immediately after trauma. Glucose use was around 150 mol/g/min and CBF was as low as 5 ml/100 g/min in hippocampus and contusion periphery (Sutton et al., 1994). (d) Decreased glucose use and slightly decreased cerebral blood flow 24 hours after injury in the same rat contusion model as shown in (c). (Source: Reproduced by courtesy of Dr David Hovda, UCLA Brain Injury Research Center.)
that astrocytes consume glucose and produce large amounts of lactate, which may be used as a preferential energy substrate by neurons. Pellerin and Magistretti hypothesize that this allows astrocytes to preferentially pump ions and maintain ion homeostasis when glutamate is high, as in neuroexcitation (Pellerin and Magistretti, 1994). This would explain many of the above findings in neurotrauma.

Recently we have studied severely head-injured patients with an oxygen-sensitive microelectrode.

Figure 7.8 Multiparameter monitoring in two patients with severe head injury. (a) Patient died 38 hours after establishment of monitoring. Note that blood flow in the region of the multiparameter monitor was 15 ml/100 g/min 5 hours after injury. Note that dialysate lactate increases to levels three times normal. Brain oxygen concomitantly decreases from the threshold level of around 20 mmHg, and brain glucose steadily declines (normal dialysate glucose 800 mmol/l). (b) Patient with massive brain injury progresses rapidly from uncontrollable ICP to brain death. Note that blood flow measured at time zero is 9.3 ml/100 g/min and brain oxygen declines rapidly to anaerobic levels, indicating cessation of blood flow. Cerebral lactate climbs to massively increased levels (5000 mmol/l). Brain glucose is close to zero throughout the monitoring period.
implanted in the brain, capable of measuring brain oxygenation, CO2 generation, pH and temperature in parallel with extracellular fluid lactate and glucose levels measured by microdialysis (Zauner et al., 1996b). These studies have confirmed the finding that lactate generation is increased in about 65% of measurements, even in the presence of adequate cerebral blood flow and brain oxygen levels, thus confirming the hypothesis that lactate may be a normal metabolite during neuroexcitation (Doppenberg et al., 1996; Figure 7.9).

It remains to be determined whether high levels of ECF lactate are intrinsically harmful to the injured brain. However marked cerebral acidosis may exacerbate calcium-mediated damage to intracellular enzyme systems and may also interfere with ion channel function (King, McLaurin and Knowles, 1994; Siesjö, 1992(a)). High tissue lactate levels could foster a decline in brain pH, as has been shown in numerous post-traumatic studies, both in animal models and in our recent human studies.

7.5.2 FLOW–METABOLISM UNCOUPLING AFTER TRAUMA

Several studies have shown that cerebral blood flow may be markedly reduced within the first few hours after severe brain injury in both humans and animal models (Bouma, Muizelaar and Stringer, 1992; Obrist et al., 1984). In zones of focal cerebral contusion and beneath intracranial hematomas, flow may fall to levels close to the thresholds for ischemic brain damage (Kuroda and Bullock, 1992; Schroeder et al., 1994; Jones et al., 1981). When there is a concomitant increase in glucose metabolism, then cerebral tissue is placed at an increased risk of damage to intracellular structures dependent upon continuous oxygen delivery, such as mitochondrial and various enzyme systems. These include, in particular, the enzyme systems that break down free radicals, thus leading to delayed damage in the hours that follow, especially during the reperfusion phase (Kontos, 1985; Siesjö, 1992a, b, Schroeder et al., 1994b).

Therefore, we hypothesize that the most severely damaged tissue, that which sustains the greatest magnitude of shearing injury, will be unable to restore ionic homeostasis in spite of maximally increasing glycolytic activity. If tissue blood flow is reduced during this time of maximal metabolic need, tissue glucose and oxygen levels will fall to subthreshold levels. Tissue swelling will be exacerbated and ischemic necrosis will occur. The vulnerability of brain regions to ischemia varies; hence the process is not uniform. CBF may be further reduced at the tissue level by such processes as astrocytic swelling (Figure 7.10), and generally by low blood pressure, high ICP (itself generated by cytotoxic swelling) or intracranial hematomas causing distortion. Probably the effects of all these insults may be cumulative and occur to a varying extent in the majority of patients with severe head injury.

![Diagram](image-url)
Figure 7.10 Hypothetical scheme to depict post-traumatic and postischemic events, with opening of ion channels and uptake of potassium by astrocytes, which jeopardizes the microcirculation.
Implications for therapy

If this hypothesis is true, it would explain the relative success of therapies such as metabolic suppression using barbiturates or hypothermia, or raising cerebral perfusion and CBF by the use of pressors. Diuretics and rheological agents, such as mannitol, may help to improve tissue perfusion during these crucial early periods (Muizelaar et al., 1983). Ion channel blockade using agents directed at both voltage-dependent and agonist-operated channels may be important avenues for future therapy, as may be the use of hemoglobin substitutes, which augment the oxygen carrying capacity of the microcirculation to damaged tissue (Di et al., 1996a; Figure 7.8).

BIOCHEMICAL CONSEQUENCES OF IMPACT INJURY

In addition to its effect on ion channels and membranes, which are described above, traumatic shearing forces also have profound effects upon intracellular biochemical events and also membrane and cytoplasmic second messenger systems.

Second messenger systems and neurotrauma

‘Second messengers’ are large molecules, situated usually within the neuronal membrane or adjacent to its inner surface within the cytoplasm, which have the capability of modulating or amplifying external signals brought to the cell via neurotransmitters and mediators, such as glutamate (metabotropic receptor), adenosine, steroids and acetylcholine (Figure 7.11). A number of recent studies have shown that second messenger systems, probably because of their large molecular size and the complexity of their stearic interactions, are vulnerable to the shear forces of neurotrauma. In some circumstances, second messenger systems may be amplified (up to 200-fold or more) while other types of second messengers are downregulated or deactivated by neurotrauma (Delahunty et al., 1995; Kuroda, Dewar and Bullock, 1993). It is thought that such systems may play an important role in complex neurological processes such as encoding of memory and so these changes in second messenger systems could constitute a mechanism for the behavioral and memory changes that are seen in both animals and humans after neurotrauma (Bortolotto et al., 1994). In the fluid percussion model, no anatomical changes are seen in the presence of these long-lasting neurobehavioral deficits (Prasad et al., 1994; Miyazaki et al., 1992).

Intracellular mechanisms

THE ROLE OF CALCIUM

Several studies have now demonstrated rapid and massive intracellular increase in free calcium ions within minutes after trauma (Fineman et al., 1993; Nilsson et al., 1993; Kawamata et al., 1995). This is similar to the situation following severe acute ischemia, in which calcium increases about tenfold within seconds of the onset of severe ischemia (Siesjö, 1992a).
In both these clinical situations, calcium is thought to enter cells through many different channels which may be opened by several mechanisms, including:

- voltage-dependent channel opening, induced by mechanical deformation of membrane and ion channels, as described;
- agonist-dependent channel opening, mediated by neurotransmitter substances released in excess into extracellular fluid (see below).

Intracellular vesicular calcium may be released into the cytosol by exocytosis induced by shear trauma or cytoskeletal disruption.

The specific T-, L- and N-type calcium channels, which are voltage-dependent, may also be activated by trauma, ischemia and other intracellular events. These channels are of interest because calcium antagonists – e.g. nimodipine, which blocks L channels, and the omega conotoxins, which block N channels – are undergoing clinical evaluation (Chapter 18). Calcium may be particularly important in mediating the delayed ischemic neuronal death that may be superimposed upon the effects of primary trauma in the majority of severely head-injured patients (see below; Figure 7.10).

Recently, the dihydropyridine calcium antagonist nimodipine has shown a significant beneficial effect in two clinical trials specifically focused upon head-injured patients with subarachnoid hemorrhage (Harders et al., 1996; European Study Group on Nimodipine in Severe Head Injury, 1994). This effect is probably mediated via these neuroprotective effects rather than by restoration of blood flow alone.

### 7.6.2 THE ROLE OF FREE RADICAL GENERATION

Free radicals are highly reactive ionic molecules bearing an unpaired electron in their outer electron shell, which confers extremely high chemical reactivity. These compounds are the normal byproduct of oxidative metabolism within mitochondria, and they fulfill important physiological roles within various tissues, such as polymorphonuclear-leukocyte-mediated destruction of bacteria (Kontos, 1985; Siesjö, 1992b). Because these highly charged molecular species may react with various structures within the cell membranes, proteins and the genome, potent enzyme systems exist within all cells to break them down. Intracellular calcium inactivates some of these mechanisms, such as peroxidase and xanthine oxidase (Kontos, 1985). It is speculated that free radicals are generated especially in circumstances of posts ischemic reperfusion when the tissue is replete with oxygen (from which most free radicals are derived) and after ischemic events when the protective enzymes may be inactivated. Free radical generation is also favored by the presence of free ferrous iron, which acts as a catalyst to the Haber–Weiss reaction depicted below (Siesjö, 1992b):

\[
\begin{align*}
\text{Hydroxyl radicals (OH)} & : \\
\text{Generation of hydroxyl radicals} & \rightarrow \text{OH} \\
\text{O}_2 + \text{Fe}^{3+} & \rightarrow \text{O}_2 + \text{Fe}^{2+} \\
\text{H}_2\text{O}_2 + \text{Fe}^{2+} & \rightarrow \text{OH}^- + \text{OH} + \text{Fe}^{3+} \\
\text{OH}^- + \text{H}_2\text{O}_2 & \rightarrow \text{OH}^- + \text{OH} + \text{H}_2\text{O} \\
\end{align*}
\]

Free radical may be found in traumatized brain within a few hours of injury as repair mechanisms cleave iron from hemoglobin in breaking down red cells, which is an extremely frequent sequel of severe brain injury. To date, however, there is no technique for demonstrating the existence of free radical species in the human brain after trauma, although studies using a number of indirect techniques have shown an increase in free radical activity following trauma and ischemia in various animal models (Siesjö, 1992a, b; Hall and Braughler, 1989). There is evidence to suggest that free-radical-mediated damage may be particularly marked within the endothelium of cerebral capillaries after trauma, and it is likely that the large neuroprotective molecules directed against the free radical mechanism (Tirilazad (amino steroid) and polyethylene-glycol-conjugated superoxide dismutase (PEG-SOD)) do not penetrate extensively into brain tissue. This may in part explain their failure to benefit patients in clinical trials (Chapter 18).

### 7.6.3 THE ROLE OF HYDROGEN IONS

Although hydrogen ions in the extracellular space are powerful cerebral vasodilators, high concentrations of hydrogen ions within cells appear to be harmful because they alter the function of intracellular enzymes (Siesjö, 1992a). An interesting feedback system exists whereby low pH causes conformational changes in the NMDA ion channel, thus preventing further ingress of sodium and calcium and egress of potassium during cellular acidosis.

### 7.6.4 POLYAMINES

The polyamines spermine, spermidine, putrescine and cadaverine are metabolic breakdown products of purine catabolism within the cell. They accumulate in toxic concentrations within cells following both trauma and ischemia because the breakdown enzymes for their destruction are inactivated, probably by calcium-mediated mechanisms within the cell. The presence of high concentrations of these substances within cells is cytotoxic both in tissue culture and \textit{in vivo}. 
7.6.5 EFFECT OF NEUROTRAUMA ON PROTEIN SYNTHESIS AND GENE SIGNALING

Recently, molecular techniques such as northern and Western blotting, in situ hybridization and immunohistochemistry have allowed the effects of neurotrauma upon protein synthesis and gene expression to be explored. Understanding for these processes is, however, far from complete. In general, early after impact, protein synthesis is suppressed for a few hours but at about 5–6 hours gene expression begins to occur and in those neurons and astrocytes that are destined to survive impact, and which are capable of manifesting a regenerative response, a phase of intense protein synthesis occurs that lasts for many days. There is now intense interest focused upon the idea that identification of potentially harmful intrinsic mediators that are produced by neurons or astrocytes early after injury could allow ‘blocking drugs’ to be devised, which could then be potentially therapeutic. Among the earliest substances produced in large amounts during this early post-traumatic period are the vasodilator neurotransmitter nitric oxide (NO), which may be directly toxic to neurons in excessive amounts (Dawson, 1994). Nitrate oxide synthase, the enzyme responsible for its production, is induced shortly after injury. Blockade of the enzyme has now been shown to be neuroprotective after brain injury (Mesenge et al., 1996).

7.6.6 GENE REGULATION IN THE NORMAL NEURON

Because neurons do not reproduce, the vast majority of their genetic material remains repressed by operon genes and regulator proteins. Only those genes concerned with structural protein synthesis function at a low level, and those concerned with neurotransmitter synthesis and maintenance of energy metabolism continue to be highly active during normal neuronal life. There is evidence that, during embryonal development, enormous numbers of redundant neurons develop in the central nervous system (CNS), and only those that make active functioning synaptic connections with their target organs persist into the adult form of the CNS. The process responsible for this ‘die-back phenomenon’ among redundant neurons has been shown to be ‘apoptosis’ or programmed cell death – which is under genetic control and now appears demonstrable using molecular biological techniques (see below).

7.6.7 IMMEDIATE EARLY GENE EXPRESSION – ‘STRESS GENES’ AFTER TRAUMA

Recently, the heat shock protein HSP70 has been identified, and its gene has become easily identifiable by both Western blotting and in situ hybridization. HSP70 begins to be synthesized and its gene becomes activated about 6 hours after sublethal, stressful events such as transient cerebral ischemia and neurotrauma (Massa, Swanson and Sharp, 1996). Its synthesis maximizes at about 48–72 hours in rodents and then declines. Other genes with the same temporal and mechanistic characteristics have also been identified – these include c-fos, c-jun and the heme oxygenase gene, the last of which has particular importance after subarachnoid and intracerebral hemorrhage because heme oxygenase is the enzyme responsible for breaking down hemoglobin into free iron and biliverdin, and iron may catalyze free radical production (Rehcrona, Hauge and Siesjö, 1989; Siesjö, 1992a). The third of the immediate early (IE) triad is the glucose transporter gene, which is activated massively in neurons that usually do not go on to die after a stressful event. It is uncertain whether these neurons will continue to function normally during the time these IE genes are expressed. Thus the concept emerges that these genes are a marker of populations of neurons that may be vulnerable to subsequent second insults that may occur during the period when these IE genes are regulated. Alternatively, they may be a manifestation of protective mechanisms whereby the neurons are protecting themselves against a transient, but potentially lethal, stress. Some studies have suggested that IE gene expression may be protective and, therefore, if these genes could be expressed by a gene manipulation therapeutic technique, this may be neuroprotective (Figure 7.12). There is speculation that calcium entry may be the ‘trigger’ for this IE gene expression and, thus, that it may be ion-channel-dependent (Marsa et al., 1996).

7.6.8 APOPTOSIS AND NEUROTRAUMA

In non-neural tissues and in neoplasia, death of ‘redundant’ cells without any inflammatory response, has long been recognized by pathologists, and its histological features are well known. Recently, new in situ and molecular techniques (e.g. TUNEL staining, and blotting for the c-myc gene) have suggested that this form of delayed, genetically programmed cell death also occurs in neurons after brain ischemia and trauma (Islam et al., 1995; Rink et al., 1994). Its importance, its potential for therapy and its relationship to ‘delayed neuronal death’ (see below) remain to be elucidated.

7.6.9 SECONDARY ISCHEMIC NEUROLOGICAL DAMAGE

The incidence of ischemic brain damage seen at postmortem in severely head-injured patients who die is extremely high, with estimates ranging between
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During life, most of these patients do not manifest the long periods of low cerebral perfusion pressure (e.g. < 30 mmHg for 30 min or more) that are known to be necessary for the generation of ischemic damage. Likewise, in animal models of impact-type head injuries such as fluid percussion, weight drop and contusional impact, widespread ischemic damage is not seen other than around the periphery of focal contusions. Thus, there is a fundamental paradox and the high incidence of ischemic brain damage is not easily explained. This concept of delayed secondary neurological damage after head injury is also supported by the ‘lucid interval’ statistics. Between 30% and 40% of severely head-injured patients who die will, at some time, have demonstrated a period of lucidity sufficient to obey commands or speak (Adams, Doyle and Ford, 1989; Graham, 1995). This implies that primary impact events were not sufficiently severe to damage the brain beyond the capacity for function, therefore emphasizing the importance of secondary damage (Reilly et al., 1975; Chapter 4). The genesis of these types of secondary brain damage after severe head injury has become the focus of major research endeavors in those academic centers that care for head-injury patients. This is because primary impact damage of the diffuse axonal injury type has hitherto been considered not to be amenable to any form of postevent treatment. Indeed, to date, no laboratory study has yet shown that the development of ‘retraction balls’ can be delayed or retarded by therapy. Those processes that are set in train at the time of the primary impact but then may be magnified in subsequent days to exacerbate brain damage are therefore of great interest. The observation that about 70% of severely head-injured patients manifest high intracranial pressure during their clinical course is the intensive care unit accords with this concept (Becker et al., 1977).

7.6.10 THE GENESIS OF ISCHEMIC BRAIN DAMAGE AFTER SEVERE HUMAN HEAD INJURY

Until recently, numerous studies using various cerebral blood flow measurement techniques had failed to demonstrate levels of blood flow sufficiently low to cause ischemic neuronal damage. However, tomographic regional blood flow measurements early after severe injury have now clearly demonstrated flow levels < 18 ml/100 g/min – sufficient to generate neuronal ischemic necrosis in about 34% of severely injured patients (Bouma, Muizelaar and Stringer, 1992; Schroeder et al., 1994; Schroeder, Muizelaar and Kuta, 1994). These were predominantly patients with fixed dilated pupils, acute subdural hematoma or early acute brain swelling (Chapter 5). Other studies using these same techniques have revealed profound regional flow reductions around intraparenchymal lesions such as contusions and intracerebral hematomas where blood flow is about 18 ml/100 g/min (Schroeder et al., 1994; Schroeder, Muizelaar and Kuta, 1994; Zauner et al., 1996a). This is in accordance with the uniform neuropathological observation in humans that pyknotic neuronal degeneration and astrocytic swelling is seen in the tissues surrounding focal contusions (Adams, Doyle and Ford, 1989; Figure 7.4; Chapter 5).

7.6.11 MECHANISM BY WHICH REDUCED CEREBRAL BLOOD FLOW CAUSES TISSUE DAMAGE

The landmark studies by Symon’s group and Jones et al. have demonstrated a time-dependent hierarchy of neuronal events in response to progressive reduction of CBF (Astrup, Siesjö and Symon, 1981; Branston et al., 1974; Jones et al., 1981; Figure 7.13). In the healthy, normally autoregulating brain, cortical flow reduction down to levels around 20 ml/100 g/min may be tolerated without functional consequences, although the EEG may begin to slow and the subject may develop anxiety and drowsiness. Abruptly, at around 20 ml/100 g/min, consciousness is lost and the brain loses the capacity to make neurotransmitter substances so that coma ensues (Branston et al., 1974; Siesjö,
When flow falls below 18 ml/100 g/min, ionic homeostasis becomes jeopardized because the energy-dependent Na/K-ATPase pump system, which maintains ionic gradient across the cell wall, cannot function. At this level, neurons move to anaerobic metabolism and lactate begins to be generated in large amounts. When flow falls further to levels around 10 ml/100 g/min, membrane integrity is lost, massive calcium influx begins and the biochemical cascade of neuronal destruction becomes irreversible (see below). The ultrastructural hallmarks of this process are mitochondrial swelling and perineuronal astrocytic process vacuolation, followed by swelling of the Golgi apparatus and intracellular cytoplasmic vesicles. Eventually, nuclear definition is lost (karyorrhexis; Graham, 1985; for review see Siesjö, 1992a, b). Many of these postischemic events are synergistic with the loss of ionic homeostasis seen after trauma.

7.6.12 INFARCTION VERSUS SELECTIVE NEURONAL LOSS

When flow is profoundly reduced (i.e. less than 5–10 ml/100 g/min) within the distribution of one cerebral end artery for more than 60–90 minutes, infarction ensues. That is, there is immediate necrosis of all cell types within a zone of the brain (Symon, Pasztor and Branston, 1974). However, when the flow reduction is less marked (e.g. to levels around 15–18 ml/100 g/min) and when this persists for periods of more than about 30 minutes, then selective neuronal loss may occur (DeGirolami, Crowell and Marcoux, 1984; Pulsinelli, Brierley and Plum, 1982). Neuronal types that are the most vulnerable within the mammalian brain are:

- hippocampal neurons of the molecular layer, CA1 and CA3 sectors;
- cerebellar granular cells;
- cortical neurons, particularly the larger cells, in areas such as the cuneate visual cortex.

This may occur when flow is globally reduced throughout the whole brain for various periods of time. Within the context of head injury, this type of neuronal loss is especially important in patients with raised intracranial pressure, where cerebral perfusion pressure may be marginal (around 30–40 mmHg) for many hours, or even days. In such patients, recent studies have demonstrated an extremely high frequency of ischemic neuronal loss especially in the hippocampus (Graham, 1985; Chapter 3). Such bilateral hippocampal loss and cerebellar damage may explain the high frequency of memory disorders and coordination difficulty seen in the majority of severely head-injured survivors. This concept also accords with the almost universal finding of marked cerebral atrophy in those patients who survive severe head injuries.

7.6.13 DELAYED NEURONAL DEATH

First described by Kirino et al. about 15 years ago, delayed death of large neurons, especially in hippocampal CA1 and CA3 sectors, 5–10 days after an ischemic insult, has been clearly shown in rodent models, and probably in humans, after cardiac arrest episodes (Kirino, 1982; Kirino, Yamure and Sano, 1984). When histology is studied 24–48 hours after ischemia, no abnormality is seen in these rodent global ischemia models, and gross behavior is also normal initially. This suggests a sublethal insult that later amplifies to cause cell death. High levels of glutamate have been implicated in these phenomena, and glutamate antagonists prevent the delayed cell death. ‘Apoptosis’ may be an alternate explanation for this phenomenon.

7.6.14 ‘DOUBLE INSULT’ MODELS AND SYNERGISTIC DAMAGE MECHANISMS AFTER NEUROTRAUMA

Jenkins et al. have shown that a mild global ischemic insult insufficient to cause neuronal death alone, when combined with mild trauma (fluid percussion injury (FPI) insufficient to cause neuronal death or major behavioral sequela), causes massive hippocampal neuronal necrosis (Jenkins et al., 1989). This occurs when trauma and ischemia occur up to 24 hours apart. When the ischemia occurred more than 7 days after FPI, however, neuronal necrosis did not occur. This synergistic damage phenomenon could also be abolished by treatment with scopolamine, a muscarinic cholinergic antagonist, and phencyclidine, a glutamate antagonist.

Figure 7.13 The relationship between cerebral blood flow and tissue infarction, modified from Jones et al. 1981 – data obtained from studies in awake primates. Note that after 30 minutes of severe ischemia, reversible neuronal changes have occurred but recovery is possible. However, when the ischemic period is prolonged to 2–3 hours, irreversible infarction takes place. In head-injured humans there is probably a ‘left shift’ of this curve.
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(Jenkins et al., 1988). Both these phenomena are of considerable clinical importance and although not fully understood both are amenable to drug therapy.

7.7 Brain swelling and cellular events after neurotrauma

Brain swelling occurs in almost all patients with severe brain injury, and to a lesser extent in 5–10% of those with moderate injuries (Miller et al., 1981; Marmarou, 1994; Chapters 3 and 4). This high incidence is a major reason for neurointensive care management for these patients, and this is a major reason why aggressive surgical management of mass lesions improves outcome. The causes of brain swelling after severe head injury are multifactorial and poorly understood (Figure 7.14). The widespread misconception that the increase in brain volume that occurs after neurotrauma is due to vasogenic edema which should be treated with corticosteroids is still responsible for the unnecessary deaths of head-injury patients; despite the lack of evidence supporting the use of corticosteroids in numerous clinical trials (Chapter 18). These misconceptions were fueled by laboratory studies using models, such as the cold injury model, that do not mimic the edema pattern of head injury but rather that of meningiomas and gliomas (Long, 1984).

There is now compelling evidence from animal models such as weight-drop injury and fluid percussion that, immediately after impact, extracellular fluid volume may increase briefly for less than 30 minutes and that this may be associated with a transient opening of the blood–brain barrier to medium-molecular-weight markers – 50–70 kDa (Ito et al., 1996). Some authorities feel that this brief blood–brain barrier opening develops because of the hypertensive surge associated with impact, particularly in fluid percussion injury. There is, of course, no data for these early postinjury events in humans. More likely, there is a net shift of small ions, chiefly Na/K and Cl, together with obligated water, from the intravascular compartment to the extracellular fluid. This occurs down a concentration gradient, because ions have begun to shift into neurons and astrocytes that are grossly swollen (Figure 7.4). Recent MRI diffusion-weighted imaging studies show that, after about 1 hour, the extracellular space rapidly shrinks as water moves into cells because of the ionic shifts already referred to above (Ito et al., 1996). Diffusion-weighted imaging techniques will show a reduction in the diffusion index consistent with constrainment of water molecules within cells: this situation is exacerbated by superimposed ischemia (Ito et al., 1996).

At the worst end of the spectrum brain tissue that is most severely injured is unable to restore ionic homeostasis because insufficient glucose can be delivered to the tissue via the microcirculation and a ‘vicious cycle’ may be set up whereby the microcirculation is squeezed by astrocyte ‘end feet’ that swell because of potassium uptake. This tissue appears dark because of cytotoxic edema on the CT scan, and there is ‘loss of gray–white definition’ or ‘the ground-glass appearance’ on the CT scan (Chapter 9). Under these circumstances, intracranial pressure rises to further jeopardize global brain perfusion and cause death. This same sequence of events occurs within the ‘penumbra’ of focally contused tissue round localized contusions (Schroeder et al., 1994).

There is now clear evidence that the majority of early brain edema, both global and focal, is cytotoxic rather than vasogenic. In humans studied with both

Figure 7.14 Massive intraoperative brain swelling following removal of an acute subdural hematoma.
gadolinium-enhanced MRI and pertechnetate-enhanced SPECT scans, vasogenic edema with opening of the blood–brain barrier is only seen at later time points around contusions, and not at all in patients with diffuse non-focal injuries (Bullock et al., 1990; Lang et al., 1991; Todd and Graham, 1990). Vasogenic edema probably becomes important around focal contusions on the second through the 10th–15th day.

Brain engorgement studies using MRI- and CT-based techniques to estimate cerebral blood volume have shown that blood volume is uniformly reduced initially after acute brain injury, although many patients will demonstrate a phase of hyperemic CBF, with increased flow values demonstrable from the second through the seventh day after injury, most strongly seen after removal of intracranial hematomas (Chapter 5; Fatouros et al., 1985).

Marmarou et al. have recently used mathematical modeling techniques to estimate that the vascular component of brain swelling after severe brain injury probably represents about 25% of the overall increased in brain bulk, with the remainder being due predominantly to cytotoxic edema (Marmarou et al., 1993). Clearly, however, all three of these components of swelling may occur in the same patient, and they may fluctuate in magnitude within the same patient at different times after severe brain injury (Figure 7.15).

We hypothesize that the ‘erectile brain swelling’ seen in severely injured patients, chiefly after removal of acute subdural hematoma, is caused primarily by redistribution within the swollen brain tissue, primarily due to cytotoxic edema (Figure 7.14). However, postischemic reperfusion is obviously an important component of this rapid-onset brain swelling, and indeed this can often be seen with the naked eye, as small blood vessels over the pia dilate and reperfuse after the subdural has been removed. Blood flow studies have confirmed this (Chapter 5).

7.7.1 RESOLUTION OF BRAIN SWELLING

Kimelberg and others have hypothesized that astrocytes function as a ‘syncytium’ or ‘wick’ to conduct potassium away from neurons, particularly in injured brain, and thereby aid in the establishment of ionic homeostasis (Kimelberg and Norenberg, 1989). Thus there is a net loss of potassium from injured tissue into the microvasculature which begins hours after onset. In mildly affected tissue, astrocyte swelling will begin to resolve after about 1–2 hours. In our own human ultrastructural studies, astrocytes around contusions appear to be shrinking by about the fifth day after injury (Bullock et al., 1991). Clearly, when the microcirculation is competent and CBF remains above about 20 ml/100 g/min, recovery of brain swelling will be much more rapid, and it is unlikely to occur at all when blood flow in the microcirculation is below these ‘threshold’ levels.

7.7.2 IMPLICATIONS FOR THERAPY

Mannitol may exert its tremendously beneficial effects in head-injured patients by opposing ionic flux into damaged tissue by keeping the intravascular space hyperosmolar (Nath and Galbraith, 1986).

Clearly, however, its rheological effects are also extremely important, and mannitol has been shown to reduce cerebral blood volume, through vasoconstriction, and it also increases CBF (Muizelaar et al., 1983). A number of therapeutic strategies that block ion channels are currently in clinical trials, and the effect of measures that reduce the metabolic demand of the damaged tissue, such as barbiturates and hypothermia, are being evaluated (Chapters 18, 19).

7.8 Conclusion

Mortality rates for severe brain injury have fallen about 10% per decade over the last 25 years, yet during this period no single drug therapy has been
shown to be effective in clinical trials. This reduction in mortality rates has been achieved by improvements in prehospital care, early diagnosis, removal of intracranial hematoma and better neurointensive care therapy. Each of these measures acts by optimizing the conditions for substrate delivery (oxygen and glucose) to the injured brain, and their importance cannot be overemphasized. The focus for the next decade in head injury care, therefore, needs to be twofold:

- to disseminate knowledge regarding the principles of optimal care that have been worked out over the last 25 years, so that all head-injured patients may benefit;
- to translate the enormous advances in pharmacological therapy for brain damage, and monitoring and detection of brain damage, from the laboratory into the clinical arena.

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7.10 References


- to disseminate knowledge regarding the principles of optimal care that have been worked out over the last 25 years, so that all head-injured patients may benefit;
- to translate the enormous advances in pharmacological therapy for brain damage, and monitoring and detection of brain damage, from the laboratory into the clinical arena.