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Review

Brain injury: the pathophysiology of the first hours. 'Talk and Die revisited'

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Summary In the 25 years since the 'Talk and Die' paper there have been substantial advances in the management of patients with severe closed head injury. This paper discusses developments in understanding of primary and secondary injury. Current management focuses on preventing secondary brain injury. That this has been successful is illustrated by a fall in mortality in recent decades. Evidence based guidelines have set standards of management but they do not take into account variations between individuals, between regions of the brain and variations with time from injury. Various monitoring techniques such as transcranial doppler, jugular venous oxygen saturation and ICP waveform analysis attempt to set individual therapeutic endpoints and to target therapy appropriately. Primary injury is no longer seen as a single irreversible event occurring at the time of impact, but rather as a process initiated by the impact and evolving over subsequent hours and days. Experimental studies have identified agents which reduce the evolution of brain injury and improve outcome. An experimental model of brain injury developed by the Adelaide Head Injury Group identifies diffuse axonal injury as a target for therapeutic manipulation. Magnesium has been shown in other studies to improve outcome after diffuse brain injury. This has now been linked with upregulation of beta amyloid precursor protein. Although this and several other experimental therapies have shown great promise, they have not so far produced benefit in large clinical studies. Avoiding secondary insults will remain the goal of management for the foreseeable future. Halting the evolution of the primary injury remains a highly sought after goal. Although elusive so far, it is likely to be the next major advance in clinical care. © 2001 Harcourt Publishers Ltd

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INTRODUCTION

The 1975 paper 'Patients with Head Injury who Talk and Die'[1] illustrated quite dramatically the distinction between primary injury, sustained at the moment of impact and secondary injury due to events which have their effects later. In 1975 primary impact injury was generally considered to be instantaneous and irreversible.

However, since then it has become clear that the effects of the impact are not all instantaneous. In fact a substantial component of cell death resulting from the primary brain injury may begin hours later (Fig. 1). Furthermore and most importantly these continuing effects of the impact are not all irreversible. It is possible in experimental models to halt the progression of the primary injury itself.

Thus brain injury is now seen as a process beginning with an impact rather than a single event which may then be followed by secondary complications. The injury also initiates processes which may lead, if properly understood, to repair and regeneration.

The injury process may be considered in four overlapping phases:[2]

1. Primary injury
2. Evolution of the primary injury
3. Secondary or additional injury
4. Recovery.

This review will describe some current insights into the early events after head injury, illustrated by research undertaken by the Adelaide Head Injury Group, a multidisciplinary group comprising departments of the University of Adelaide, Royal Adelaide Hospital and Institute of Medical and Veterinary Science. The Group encompasses research interests within each of the four phases of brain injury; the Road Accident Research Unit into the interface between mechanical force and brain injury; and clinical neuropsychologists into the relation between injury patterns and outcome.

Two main lines of research into the early phase of injury have been undertaken:

1. Clinical studies which aim to identify the nature of the injury through bedside monitoring
2. Laboratory studies into the primary injury and its evolution.

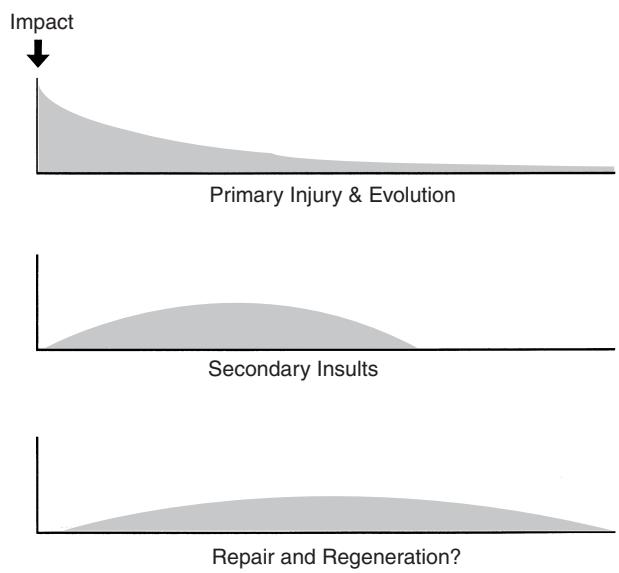

Fig. 1 A current model of the effects of impact on the brain envisages three overlapping and interrelated processes.

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MEASURING CLINICAL INJURY

Thus far the mandate for clinicians is to avoid and treat secondary injury. In general this approach has been effective. Mortality of severe head injury has fallen from about 36% in 1987[3] to 20–24% in a survey of head injury studies reported in 1997.[4] This improvement in outcome can be reasonably attributed to better primary care and reduction of secondary injury. How much further can this be taken?

Evidence based guidelines are derived from statistical analyses of large numbers of patients and offer general treatment end-points. They do not allow for the well-known variation in injury patterns within different regions of the brain, between individuals and with time. For example, the advice to maintain cerebral perfusion pressure (CPP) at 70 mmHg is based on good statistical evidence.[5] However, this may not be appropriate for all patients at all times.

Individual treatment goals have been sought by using:

- Transcranial doppler (TCD)
- Jugular venous oxygen measurement
- Intracranial pressure (ICP) wave form analysis
- Near infra-red spectroscopy.

TRANSCRANIAL DOPPLER

TCD measures systolic, diastolic and mean middle cerebral artery (MCA) flow velocities and a derived value, the pulsatility index (PI).

Changes in the PI can be used to identify the threshold of autoregulation or break point in individual patients. This break point may change with time.[7] Thus the 'correct' CPP might change. For example, at some time and in some patients the perfusion pressure recommended in the 'Guideline' of 70 mmHg might be too low, risking ischaemia, or else too high, risking the complications of hyperperfusion and inotropic therapy used to achieve this level.

MCA flow velocity was measured in an animal model through a temporal bone window in states of intact and impaired autoregulation.[8] In this model, CBF could be measured continuously. Systolic flow velocity closely followed CBF as CPP was reduced below the breakpoint. However diastolic flow velocity fell and pulse amplitude increased before there was any fall in CBF. The increase in pulse amplitude before fall in CBF was reflected by a rise in the PI. These changes clearly indicated the final stages of autoregulatory reserve and the rise in PI gave forewarning of a fall in cerebral perfusion. The CPP level at which these changes occurred depended on the state of autoregulation.

JUGULAR VENOUS OXYGEN MEASUREMENT

In clinical studies, jugular venous oxygen saturation (JVO_2) was measured from a catheter in the jugular bulb. This gives a continuous but indirect measure of CBF. As CBF falls below tissue requirements, O_2 extraction increases and JVO_2 falls.

Even a single episode of sustained low JVO_2 can indicate significant ischaemia and is associated with a worse outcome.[9]

As in the animal experiments in which CBF could be measured directly, a rise in PI anticipated a fall in cerebral perfusion as indicated in patients by a fall in JVO_2. Thus continuous TCD measurements gave early warning of falling perfusion and offered the opportunity for pre-emptive treatment.[10]

INTRACRANIAL PRESSURE WAVE FORM ANALYSIS

Compliance is a measure of brain tightness and is derived from the slope of the volume pressure curve (Fig. 2). An increase in compliance may warn of impending increase in ICP and fall in CPP.

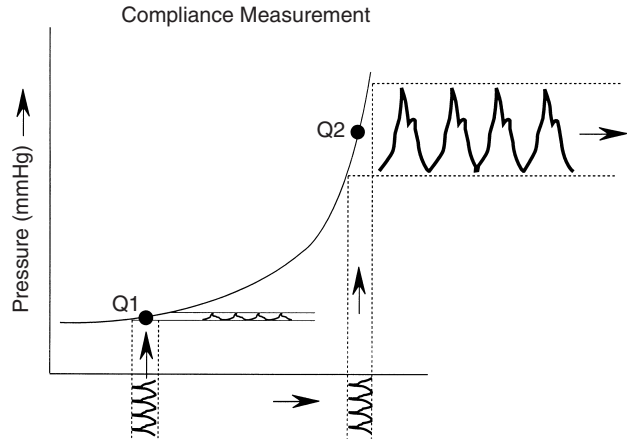

Fig. 2 Compliance and the volume–pressure curve. At point Q1 on the initial part of the volume–pressure curve, the arterial pulse wave (input signal) produces a low amplitude ICP wave (output signal). On the steep part of the ICP curve (Q2), an arterial pulse wave of the same amplitude produces a much higher amplitude ICP wave.

Compliance has usually been measured by injecting a small volume of fluid into the cranium and recording the associated pressure change.[11,12] In fact, pulsations of the cerebrovascular bed provide a regular physiological index of compliance.

Low on the volume–pressure curve, the arterial pulse translates into a low amplitude ICP pulse wave. Higher on the curve, when the brain is tight, the same arterial pulse translates into a high amplitude pulse wave – a familiar clinical observation.

By frequency analysis of the input signal (the arterial pulse wave), and of the output signal (the ICP wave), it is possible to derive compliance and other characteristics of the intracranial compartment.[13–16]

In an animal model ICP was raised by three different methods: hypoxia, hypercarbia and cisternal fluid injection. Increase in ICP due to vascular mechanisms, that is increase in CBV, increased low frequency transmission whereas increase in extravascular fluid resulted in a uniform increase in frequency transmission.[17] In clinical application, identifying the dominant cause for an increase in ICP may allow the most appropriate therapy to be selected – perhaps hyperventilation for hyperaemia and osmotherapy for increased extravascular fluid.

After recording the frequency and causes of episodes of jugular venous desaturation in the Intensive Care Unit (ICU), changes were introduced to the protocol which took into account JVO_2 and TCD data and actively maintained CPP.[18,19] There was a significant fall in the number of episodes of jugular venous desaturation.

Thus a combination of TCD and JVO_2 measurements may make it possible to tailor therapeutic endpoints to individual patients. ICP wave form analysis, if further refined, may point to the most appropriate early treatment for brain swelling.

However, it must be remembered that these monitoring methods are global and do not detect regional variations.

The region around brain contusions illustrates the fallacy of treating a brain injury as a single pathology.

Studies in Glasgow with JD Miller in 1975 demonstrated that blood flow in pericontusional oedema is dependent on local tissue factors. Blood flow in the pericontusion area:

- May not increase with perfusion pressure
- Was independent of global CBF
- Needed to be measured directly to assess therapy.[20]

The distinct flow and metabolic changes around contusions can now be shown by SPECT, microdialysis and tissue electrodes.[21–24]

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Even so, there is little that can be done with the information at present.

UNDERSTANDING THE PRIMARY INJURY

A major goal of current research is to find therapy directed specifically to diffuse brain injury. Diffuse injury produced by inertial acceleration/deceleration stress is most commonly seen after high speed motor vehicle accidents or falls.

All tissue components are affected – neurons, neuronal processes, transmitter mechanisms, glial cells and blood vessels (Fig. 3).

For nerve cells, the immediate effects of mechanical deformation are twofold:

1. Physical disruption of the cell membrane and the cytoskeleton
2. Increased membrane permeability resulting in major ionic fluxes in and out of the cell.[2]

Ca^{++} influx is a prime cause of the damaging cascades of intracellular changes that lead to cell death.[25–27] At least three mechanisms lead to an influx of Ca^{++}:

1. Mechanical transient disruption of the cell membrane permeability
2. Opening of postsynaptic Ca^{++} channels. Glutamate, the excitatory amino acid is localised presynaptically. Glutamate receptors are the principal postsynaptic excitatory receptors and are present through the brain. Other Ca^{++} channels may open in response to trauma or ischaemia
3. Depletion of Mg^{++}. Mg^{++} limits Ca^{++} influx through the NMDA glutamate receptors.

Ionic changes themselves affect the three major cellular components causing swelling of neurons due to influx of Ca^{++} and Na^{++}, swelling of glia which take up the increase in extracellular K^{++} and constriction of the microcirculation by the swollen glia.

The effects of Ca^{++} influx include:

- Activation of enzymes (calpains) which break down cytoskeletal proteins
- Uptake of Ca^{++} by mitochondria leading to the breakdown of mitochondrial energy production[27]
- Production of free radicals and lipid peroxidation.

If these cascades can be halted early, cell mechanisms may be able to redistribute the excess Ca^{++} and restore homeostasis.

One of the most readily identifiable results of mechanical distortion of the brain is axonal injury (AI). There is mounting evidence that Ca^{++} influx is the initiating step in axonal injury.[28]

Diffuse axonal injury (DAI) is probably invariably present in fatal head injury and is the most important cause of traumatic coma in the absence of a mass lesion.[29] Blumbergs and others have found DAI in mild diffuse injury and most recently reported it to be widespread in patients with fatal gunshot wounds.[30,31] Regional AI is found adjacent to penetrating injuries, infarcts and contusions.

AI was initially recognised by Strich[32] and Cajal[33] using silver stains. Silver stains are transported by slow axoplasmic transport and do not show up at the point of injury until about 15 h after injury.

Beta amyloid precursor protein (βAPP) is a protein transported by fast axoplasmic transport. βAPP can be seen by immunohistochemistry at points of AI 1.75 h after injury[34] (Fig. 4).

In 1975 DAI was considered to be immediate, permanent and irreversible. It is now clear that immediate shearing or disconnection of the axon, 'primary axotomy', is only seen in the most severe injuries or in localised areas. Probably most axotomy occurs after 12 to 24 h at focal points of maximum shear injury.[35,36]

The events between initial injury and secondary axotomy are clearly of great importance. Minor injury may lead to transient reversible ionic fluxes and malalignment of microtubules and neurofilaments.

In more severe injury, axonal swellings develop due to aggregation of mitochondria swollen by Ca^{++} uptake and microtubular dissolution due to Ca^{++} activation of calpains. These events occurring over hours, lead to focal disruption of fast axoplasm transport and finally to disruption of the axon (Fig. 5).

The Adelaide Head Injury Group has developed an impact-acceleration model of traumatic brain injury (TBI) in sheep.[37] The freely moving head of an anaesthetised sheep is struck laterally with an explosive device producing both impact contusions and diffuse injury, replicating many of the morphological features of human traumatic brain injury.

The model is being studied in a number of ways. The relationships between force, acceleration and deceleration and brain

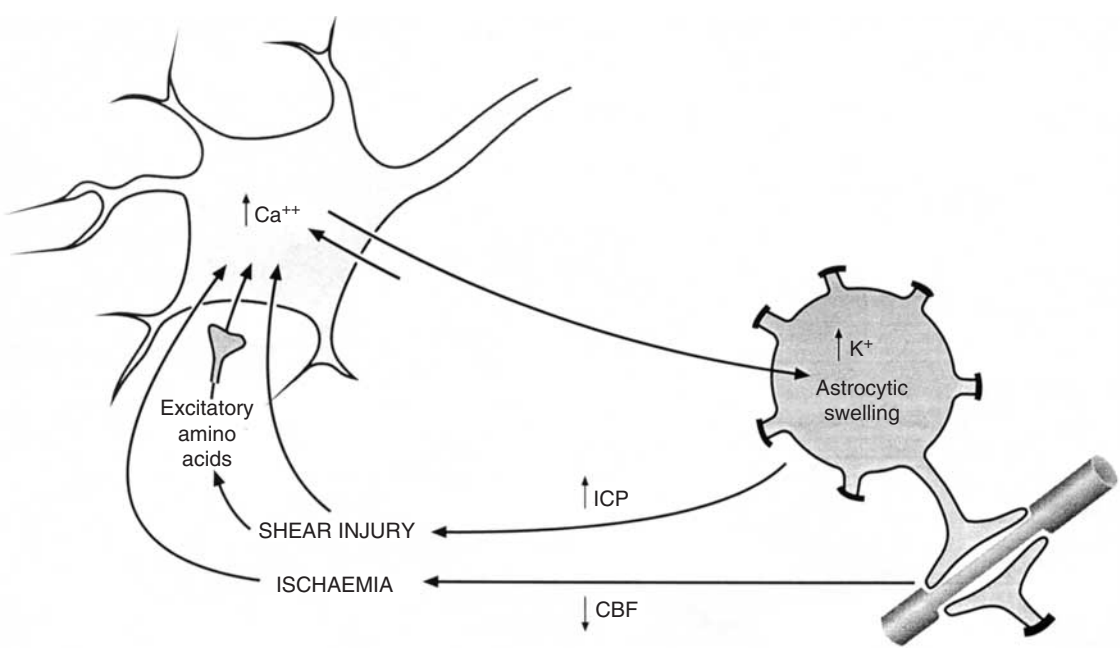

Fig. 3 All brain tissue components, neuroglia, neurons and blood vessels are affected by diffuse injury, and the effects are interconnected.

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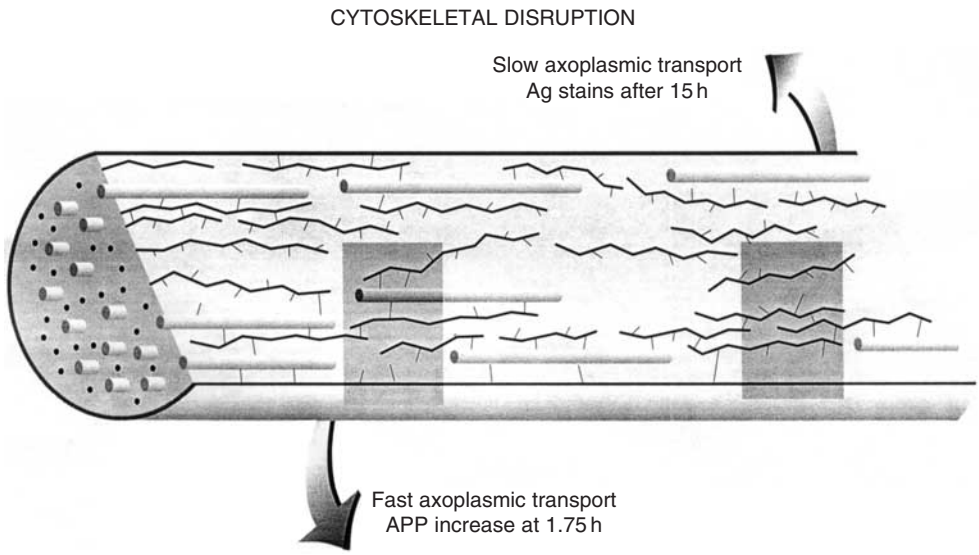

Fig. 4 Standard histological stains for axonal injury identify cytoskeletal disruption. Ag stains are transported by slow axoplasmic transport. Consequently evidence of axonal injury is not shown until approximately 15 h after injury. APP staining which depends on fast axoplasmic transport is positive 1.75 h after injury.

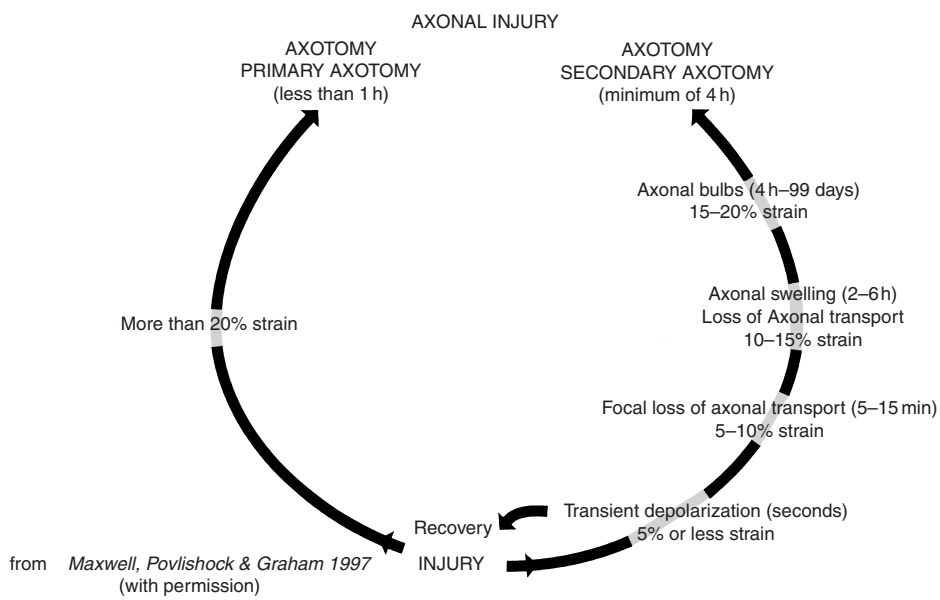

Fig. 5 The major factor determining the pathway to axotomy is the severity of the initial injury. Experimentally a strain of more than 20% results in primary axotomy. With lesser strains the pathway to secondary axotomy is stepwise. Whether axotomy occurs will depend on the interplay of many factors both extrinsic and intrinsic. Experimentally secondary axotomy can be prevented by blocking the cytodestructive pathways at various points.

injury patterns are being determined by attaching an array of accelerometers to the skull. This study parallels an analysis of forces and pathology being conducted in human vehicular accidents.

The brain injury itself is studied morphologically and by techniques of cellular biology such as immunohistochemistry and in situ hybridisation.[38,39]

Several other studies have indicated that injury leads to the expression of a wide range of genes, some of which are destructive while others may be involved in attempts to repair.

Studies of the brain injury in this sheep model aim:

- To identify changes in key proteins
- Identify gene upregulation
- To test potential therapies.

In this model AI can be shown by immunohistochemistry for βAPP by 60 min from injury.[37] It was found that the increase in βAPP was not confined to the axon but also occurred in the neuron cell body.

This suggested that the increase in βAPP represented not only accumulation of pre-existing βAPP due to blockage of fast axoplasmic transport, but also an increase in production of βAPP by switching on or 'upregulation' of the mRNA for βAPP.[40–44]

Indeed, mRNA for βAPP can be detected within 30 min of injury, that is earlier than βAPP. It can therefore be used as a very early marker of AI. The same pattern of mRNA upregulation has been found in human head injury.[40]

In this same model there is widespread evidence of dendritic injury indicated by loss of microtubule associated protein (MAP-2).[45] Dendritic injury occurred within histologically normal cortex remote from the impact. Once again excessive influx of Ca^{++} and activation of Ca^{++} dependent proteases are most likely responsible for this cytoskeletal disruption within dendrites.

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EXPERIMENTAL NEUROPROTECTION

Axonal and dendritic injury are identifiable end results of injury cascades and may be used to test the effects of potential neuroprotective agents.

Mg^{++} has a wide range of functions including blocking Ca^{++} entry into cells via the NMDA receptors.[46,47] Several studies have shown improvement in a number of indices including cognitive function in rats treated after brain injury with Mg^{++}.

Studies in the sheep model have shown an increase in the upregulation of mRNA βAPP following a single IV dose of $MgSO_4$ given 30 min after impact. These studies indicated for the first time that the neuroprotective effects of Mg^{++} may be linked to the upregulation of βAPP.

Other steps in the injury cascades are being targeted. In a further study in progress, Ca^{++} influx into mitochondria, an early step in axonal injury, is being blocked by cyclosporin A. Blocking Ca^{++} entry into mitochondria by cyclosporin A has been shown in other studies to preserve cytoskeletal structures.[48]

CLINICAL STUDIES

Since the 'Talk and Die' paper 25 years ago, the complexity of primary injury and the events leading to delayed cell death are better understood.

However, clinical trials of several single agents which have shown promise in the laboratory have been disappointing (Table 1). It has been suggested that the complexity of injury may make it necessary to administer combinations of neuroprotective agents which will act at several steps in the autodestructive secondary injury cascades. Each cascade may have its own critical window for treatment so that sequential or concurrent combinations of therapeutic agents may be necessary[49] (Table 2).

For example:

- Blocking Ca^{++} entry may only be effective during an early and relatively narrow window
- 0^2 free radical production occurs further along the injury chain and may have a wider window for treatment
- Cyclosporin A given 30 min after TBI reduces the degree of DAI in rats[48,50]
- A single IV bolus of Mg^{++} salts given up to 12 h after TBI injury has been shown to improve neurological recovery in rats
- Hypothermia after TBI reduces AI by decreasing calpain mediated proteolysis of the cytoskeleton.[28] Hypothermia may have a role in many stages and therefore a wide window for effect.

Table 1 Therapeutic agents which have undergone clinical trial

Agent	Target
Aminosteroids (Tirilizad) Steroids Indomethacin	Lipid peroxidation
Superoxide dismutase (PEG-SOD)	Free radicals
Ca^{++} channel antagonists (Nimodipine)	Ca^{++} damage
Glutamate antagonists (Selfotel)	Neurotransmitters
Hypothermia Barbiturates	Energy failure

Table 2 Theoretical therapeutic windows for neuroprotective treatment

Ca^{++} toxicity	–	early?
Free radicals	–	later
Mg^{++}	–	to 12 hours
Hypothermia	–	hours to days
Barbiturates	–	hours to days

One of the challenges for the researcher is to separate 'good' from 'bad' responses to injury. Thus, βAPP is a normal component of neurons and there is evidence for a role in repair and regeneration. Is upregulation of βAPP beneficial?

Studies from the Adelaide Head Injury Group have, for example, suggested that the beneficial effects of Mg^{++} may be linked to the upregulation of APP mRNA.

On the other hand it has been recently reported that patients with head injury and the APOE genotype, specifically the apolipoprotein ε4 allele, are more than twice as likely to have a poor outcome at 6 months, more likely to have plaque-like deposits of amyloid β-protein and have 10 times the risk of Alzheimer's disease.[51]

Does the build up of βAPP in neuron cell bodies noted in these studies have a more sinister significance – at least in some people?

CONCLUSION

Avoiding secondary insults will remain the major goal in management, but it is likely that the next significant advances in treating head injury will come through cellular biology – with therapy directed at specific intracellular targets and perhaps promotion of genes which lead to repair and regeneration.

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