

21 NEUROPROTECTION IN HEAD INJURY

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21.1 Introduction

The concept of 'neuroprotection' can be traced to the use of cold by ancient Greek physicians to treat injuries and stroke – which they believed were related to excess body heat (Hoff, 1986). Modern application was allied to the development of major cardiac and vascular surgery in the 1950s (Cooley, Mahaffey and De Bakey, 1955) and in the 1960s neurosurgeons cooled patients during intracranial vascular surgery (Drake *et al.*, 1964). Profound hypothermia for head injury was described by Lazorthes and Campan in 1958; systemic complications limited its benefit and it lost favor, but interest in moderate hypothermia has returned recently.

In the last decade, the impressive reductions in the extent of brain damage that can be obtained experimentally from a variety of methods of neuroprotective treatment have raised high expectations of clinical benefit in stroke and head injury. Nevertheless, at the time of writing these hopes remain unfulfilled and a succession of trials have failed to show consistent significant improvement in outcomes. Although this has led to some skepticism, the results so far may reflect only the inadequacies of the agents concerned – at least in the dosages and regimens employed and in the patient populations treated. The prospects of benefit from neuroprotection remain under intensive investigation.

The original concept of neuroprotection depended upon the initiation of treatment before the onset of the event leading to brain damage and the methods employed aimed to minimize the intensity of insult or its immediate effects upon the brain. This reflected the experience of investigators, who found that the methods then available often failed to work, and could even be harmful, when started after the insult. More recently, the concept of neuroprotection has been extended to include treatment started after the onset of an insult (Figure 21.1). This change reflects new understanding of the mechanisms of brain damage and the development of an immense range

of specifically targeted, powerful, neuropharmacological treatments (Table 21.1).

Much research has been focused on the treatment of cerebral ischemia but the findings, and interventions employed, are likely also to be relevant in the management of head injury. This reflects three factors:

- the increasing clinical awareness of the importance of ischemic damage, due to secondary insults, in worsening outcome after head injury;
- the evidence that trauma heightens the vulnerability of the brain to ischemia;
- the convergence of the concepts of the cellular and molecular mechanisms of progressive ischemic and traumatic brain damage.

21.1.1 SECONDARY INSULTS

It has become clear that hardly ever is it appropriate in clinical practice to consider any severe head injury as a single event. Instead, it is common for patients to survive the initial injury but then suffer additional damage as a result of delayed complications. These have been highlighted clinically as 'secondary insults' (Miller and Becker, 1982) and neuropathological evidence of their occurrence, in the form of ischemic damage, is still common in fatal cases (Graham *et al.*, 1989). The abundant evidence that these insults significantly worsen outcome has been dealt with in depth in previous chapters (e.g. Chapters 4, 5, 7 and 8). *There is therefore ample opportunity for treatment started after the head injury to act as a 'pre-treatment' for subsequent secondary insults.*

21.1.2 THE ADDITIVE EFFECTS OF ISCHEMIA AND TRAUMA

The experimental work of Jenkins and colleagues (1989) established the heightened vulnerability to ischemic brain damage following an experimental head injury. They found that a brief ischemic insult,

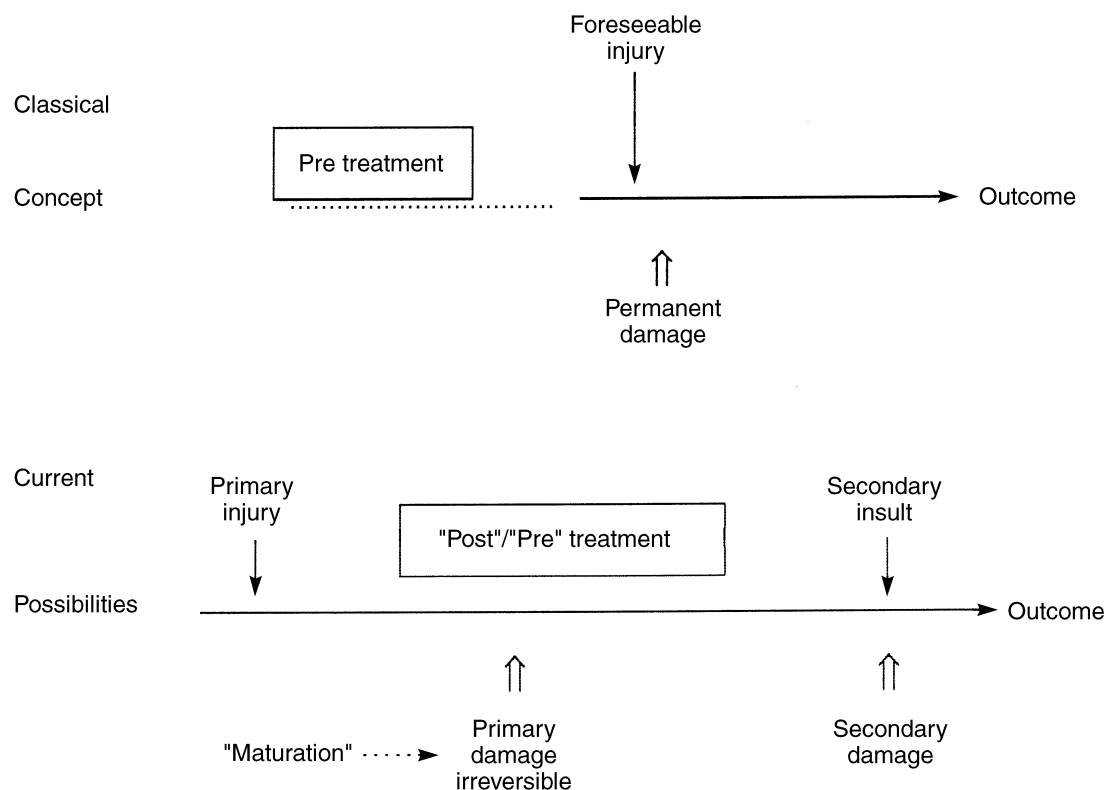


Figure 21.1 The concept of neuroprotection.

too short by itself to cause damage, produced structural changes when preceded by a mild traumatic injury. The mechanisms involved may include a loss of cerebrovascular reactivity (Lewelt, Jenkins and Miller, 1980) and disturbances of cerebral function, metabolism, and ionic and neurotransmitter homeostasis (Katayama *et al.*, 1990).

21.1.3 PROGRESSION OF DAMAGE: 'CASCADES'

Events thought previously to be completed and irreversible within moments of injury are now under-

stood to lead to persisting damage only as a consequence of processes of 'maturation', with time-scales ranging from minutes to hours and even days (Siesjö, 1992a, b; Povlishock, 1992). Although complex, these processes are open to amelioration by a wide range of interventions.

In this chapter we consider the main classes of proposed neuroprotective treatments, their actions and the clinical experience of their use. However, this is a rapidly developing and changing field and the evidence, and our conclusions, are likely to be superseded even by the time of publication.

21.2 From preclinical research to clinical benefit

The intense focus on the discovery and development of neuroprotective agents is reflected in descriptions of a host of potential agents in a vast literature. Readers are referred to articles by Faden and Salzman (1992), McIntosh (1993) and Cohadon (1994) for reviews. *It is clear that only a few of the agents effective experimentally can ever be investigated under clinical circumstances. It is important that these are well chosen, on the basis of as complete as possible a portfolio of preclinical investigations (Table 21.2).* These should include studies in a relevant range of models, under carefully defined experimental

Table 21.1 Main targets and methods of neuroprotection

Mechanism	Neuroprotective method
Energy failure	Hypothermia Barbiturates
Cell swelling	Diuretics
Acidosis	THAM
Free radicals	Superoxide dismutase
Lipid peroxidation	Steroids, amino steroids Indomethacin
Calcium damage	Calcium antagonists
Neurotransmitter	Antagonists to glutamate, etc.

Table 21.2 Translation of neuroprotection to patients: information needed from preclinical investigations

-
- Mechanistic rationale for benefit and S/E
 - Evidence of efficacy: robustness > magnitude
 - Knowledge of limits to potency and S/E time, dosage
 - Regimens – pharmacokinetics
 - Surrogate effect at desired dose
-

conditions, using rigorous measures of outcome and establishing clear dosing parameters. *The initial clinical studies need to be equally thorough to establish the appropriate doses in patients (Table 21.3). Failure to meet these requirements may account for much of the lack of success in phase 3 studies so far. It is becoming clear that the challenge is not so much to achieve benefit experimentally but to combine efficacy with an acceptable margin of safety from adverse side effects in patients.*

21.3 Treatments undergoing clinical evaluation

Two main avenues can be discerned. In the first the focus is on improving metabolism and microenvironment; methods include hypothermia and barbiturates to minimize the effects of energy failure, THAM to correct acidosis and mannitol to counteract brain swelling and edema. In the second the approaches are pharmacological: glucocorticoids to suppress inflammation, superoxide dismutase and new amino steroids to antagonize free radicals and lipid peroxidation, indomethacin to minimize lipid degradation, calcium antagonists to limit either the movement of calcium or the intracellular effects of increased calcium, and antagonists to glutamate excitotoxicity and other forms of neurotransmitter-induced damage.

Some agents may have several potentially beneficial effects, and in some approaches a package or 'cocktail' of agents is employed in the hope of an additive effect. Neuroprotective treatments are used along with strategies designed to optimize the 'milieu intérieur', e.g.

Table 21.3 Translation of neuroprotection to patients: aims of initial clinical program

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- Dose related tolerability
 - Volunteers, patients
 - Loading, maintenance
 - Pharmacokinetics, pharmacodynamics
 - Factors in variability
 - Experience of regimen chosen for efficacy
 - Knowledge of S/E: nature, incidence, duration, management
 - Effect upon some 'marker'?
 - Interactions with conventional treatments
-

enhancement of cerebral perfusion, avoidance of hyperglycemia, hypothermia and the use of hyperventilation, drainage of CSF and diuretics to counteract or prevent raised intracranial pressure.

21.3.1 HYPOTHERMIA

(a) Rationale and activity

Hypothermia decreases cerebral blood flow by approximately 5.2% per degree of reduction in body temperature. Cerebral metabolic rate for oxygen (CMRO₂) and the arterio-jugular-venous oxygen difference (AVDO₂) fall after the institution of moderate hypothermia. This reflects a reduction in energy requirements and hence less energy loss in injured brain; stabilization of cell membranes (Ginsberg *et al.*, 1992) and reduction of neurotransmitter turnover may also contribute to the benefit seen in models of ischemia (Busto *et al.*, 1989). Clifton *et al.* (1993) showed, in an acute percussion head model in the rat, improvement in behavioral outcome and tissue preservation when hypothermia was used during and after an insult, but the effect was lost when cooling was withheld for 30 minutes or longer (Clifton *et al.*, 1991). Hypothermia reduced brain damage in a model of focal injury from compression (Pomeranz *et al.*, 1993).

Hypothermia has been associated with several complications, including cardiovascular instability (mainly arrhythmias) coagulopathies, hypokalemia and an increased risk of infection. Prolonged treatment has resulted in coagulopathy and necrosis. These complications have been particularly associated with profound hypothermia (below 30°C) and are considered to be less frequent at moderate hypothermia (32–33°C).

(b) Clinical status

Several series have reported on relatively small numbers of patients treated with hypothermia and compared with control subjects (Table 21.4). Shiozaki and colleagues studied subjects selected because they had persisting raised intracranial pressure, despite all conventional therapy, and aimed for a temperature of 34°C sustained for 2 days (Shiozaki *et al.*, 1993). Compared with controls, after initiating hypothermia the patients had a lower average intracranial pressure, a higher cerebral perfusion pressure and a higher rate of independent outcome. They drew attention to complications during rewarming from hypothermia, including shock and raised intracranial pressure.

Marion *et al.* (1993) and Clifton *et al.* (1993) used moderate hypothermia of 32–33°C, sustained for 24 or 48 hours. Clifton *et al.* noted no difference in intra-

Table 21.4 Randomized comparisons of normothermia and hypothermia in the management of severe head injury

	<i>Marion et al., 1993</i>		<i>Shiozaki et al., 1993</i>		<i>Clifton et al., 1993</i>	
	<i>Control</i>	<i>Hypothermia</i>	<i>Control</i>	<i>Hypothermia</i>	<i>Control</i>	<i>Hypothermia</i>
Total patients	20	20	17	16	22	23
Dead	2	0	14	8	} 14	} 11
Vegetative	3	2	1	1		
Severe disability	7	6	1	1		
Moderate disability	4	7	0	1	} 8	} 12
Good recovery	4	5	1	5		

cranial pressure in hypothermic and control groups but a tendency for blood pressure and cerebral perfusion to decline in the former. Marion *et al.*, in contrast, observed a reduction in intracranial pressure but did not provide data on cerebral perfusion pressure. Each of these studies also showed a trend to an increased rate of independent outcome in patients treated with hypothermia compared with the controls. The foregoing results pointed to the need for a definitive, randomized study with a sufficient large number of patients and this trial is under way in several North American centers.

21.3.2 THAM

(a) Rationale and activity

Increased lactate and acidosis in the CSF have been recognized in clinical investigations for many years (Kurze, Tranquada and Benneact, 1966; Gordon, 1971), and in experimental head injury models (Unterberg *et al.*, 1988). They have now been confirmed in brain tissue in animals by neurochemical methods (Prasad *et al.*, 1994) and by magnetic resonance techniques in animals (McIntosh *et al.*, 1987) and in man (Oluoch-Olunya *et al.*, 1996). This has stimulated studies of alkalinizing agents such as THAM; (tromethamine; (hydroxy-methyl) amino methane). Studies in cats treated with THAM after fluid percussion injury showed an improved energy state and less edema at 8 hours (Yoshida, Corwin and Marmarou, 1990), a lower ICP and increased survival (Rosner and Becker, 1984). Benefit was also seen in models of local brain injury (Akioka *et al.*, 1976; Gaab *et al.*, 1980). Side effects of

THAM result from the production of bicarbonate, causing an osmotic diuresis but also requiring hyperventilation.

(b) Clinical studies

Wolf *et al.* (1993) studied 49 patients with a severe head injury. Three experimental groups were required because of the need to combine THAM treatment with hyperventilation to eliminate CO₂. Tromethamine was given for 5 days. Although intracranial pressure was better controlled in the patients who received THAM, there was no evidence of benefit on outcome (Table 21.5). An important result of the study was the poorer outcome in the patients treated by hyperventilation alone (Muizelaar *et al.*, 1993). This provided strong additional evidence for the dangers of hyperventilation. Indeed, the authors believed that an effect of THAM was to counteract the ischemia produced by marked hypocapnia in the group treated by hyperventilation alone. *Although there is some continuing support for using THAM and hyperventilation selectively, to assist 'control' of intracranial pressure, it cannot be recommended for routine use.*

21.3.3 MANNITOL

(a) Rationale and activity

Mannitol is widely used in neurosurgery to treat raised intracranial pressure, to decrease brain bulk during intracranial operations and to treat cerebral ischemia. It has been shown to improve cerebral blood flow in a primate model of head injury (Johnston and Harper,

Table 21.5 Randomized comparison of outcome of treatment of severe head injury with tromethamine (THAM), hyperventilation and control cases (Source: from Muizelaar *et al.*, 1993)

	<i>Control</i>		<i>Hyperventilation</i>		<i>THAM + hyperventilation</i>	
	Total	Dead/Veg/Severe	Total	Dead/Veg/Severe	Total	Dead/Veg/Severe
	41	26	36	28	36	23

1973). A 20% mannitol solution, given as a bolus dose, has been shown to reduce raised ICP for up to 60 minutes in a rabbit model of cryogenic brain injury (Zornow, Oh and Schelle, 1990). In an animal model of brain retraction injury, mannitol was shown to increase cerebral blood flow under the area of the brain retractor but did not increase electrical activity. Mannitol was thought to be more neuroprotective when given in small, frequent doses, rather than by continuous infusion (Andrews, Bringas and Muto, 1993). In the injured brain or spinal cord the effect of mannitol on cerebral blood flow has been related to compensatory cerebral vasoconstriction in response to blood viscosity (Muizelaar *et al.*, 1983). Other neuroprotective effects of mannitol have been related to improvement in the microcirculation and the amelioration of cerebral edema (Tanaka and Tomonaga, 1987).

Mannitol given in high doses induces hypernatremia, decreases hematocrit and increases osmolality (Andrews, Bringas and Muto, 1993). It may also cause acute renal failure. The pathogenesis of this is not yet established but may be associated with renal vasoconstriction produced by high concentrations of mannitol (Dorman, Sondheimer and Cadnapaphornchai, 1990). Other detrimental effects of mannitol include hypotension, acidosis and hyperkalemia (Chapters 17 and 18).

(b) Clinical status

Schwartz and colleagues (1984) showed that the use of mannitol to treat raised ICP in severely head-injured patients led to a better CPP than the use of barbiturates. Smith and colleagues (1986) randomized 80 patients to treatment with mannitol empirically (0.25 g/kg 2-hourly and 0.75 g/kg after any neurological deterioration) or as guided by an ICP of more than 25 mmHg. Favorable outcomes occurred in 48% and 54% (i.e. not significantly different). Attempts are now being made to identify the cause of intracranial hypertension and to match the treatment with the cause. Patients in whom raised ICP is thought to be caused by increased brain water due to focal edema related to a focal space-occupying lesion, contusion or hematoma may best respond to osmotherapy (Miller, Piper and Dearden, 1993). This is in accord with the finding of Mendelow *et al.* (1985) that mannitol increases blood flow in the most damaged hemisphere in patients with a focal injury.

21.3.4 BARBITURATES

(a) Rationale and activity

The main mechanism by which barbiturates are neuroprotective has not been established (Moskopp *et al.*, 1991). Effects include a decrease in cerebral metabolic rate, to a more profound extent than the

accompanying reductions in cerebral flow, as a reflection of a decrease in functional activity of the brain (Nordstrom and Siesjö, 1978). Cerebral blood volume falls, intracranial pressure is reduced and edema is less. Other possibilities include a scavenging of oxygen free radicals (Flamm *et al.*, 1977) and a stabilizing of cell membranes (Demopoulos *et al.*, 1977). Some reports indicate that, when given before production of either focal or diffuse cerebral ischemia or hypoxia, barbiturates reduce subsequent damage (Michenfelder, Milde and Sundt, 1976), but later reports disagree (Steen, Milde and Michenfelder, 1989). When treatment is delayed until after the insult, the effects can be deleterious (Spetzler and Hadley, 1989). Clinically, barbiturate administration has beneficial effects in cerebrovascular surgery (Sundt, Piepgras and Ebersold, 1982) but not in cardiac surgery (Scheller, 1992), nor after cardiac arrest.

The main complication of the use of barbiturates is arterial hypotension which occurs in up to 58% of patients (Schalen, Messeter and Nordstrom, 1992). The decline in blood pressure may be greater than the reduction in ICP, so that CPP actually falls, especially in patients with hypovolemia or cardiac disease. Other delayed complications include hypokalemia, hypernatremia and increased risk of infection. Liver and renal dysfunction and cardiac failure have also been reported (Oda *et al.*, 1992; Schalen, Messeter and Nordstrom, 1992).

(b) Clinical status

Several studies show that the administration of barbiturates in doses sufficient to cause burst suppression of the EEG reduces raised intracranial pressure in head-injured patients (Marshall, Smith and Shapiro, 1979; Bricolo and Glick, 1981; Rea and Rockswold, 1983). This effect is seen even in patients with severe rises refractory to other treatments (Eisenberg *et al.*, 1988) and is best seen in patients with preserved cerebral metabolic activity and cerebrovascular reactivity to carbon dioxide (Nordstrom *et al.*, 1988). Unfortunately, this immediate effect on intracranial pressure has not translated into consistent evidence of improved outcome, even though a variety of trial designs have been employed.

Schwartz and colleagues (1984) allocated 59 patients with severe head injury and raised intracranial pressure to treatment first either with barbiturate or with mannitol and allowed 'crossover' when the first method was judged unsuccessful. *Barbiturate treatment was not more successful than mannitol as a first intervention. The group treated initially with barbiturate had a lower cerebral perfusion pressure and a trend to a poorer outcome.* Eisenberg *et al.* (1988), in a multicenter study, randomized patients with refrac-

tory intracranial pressure to barbiturates or 'conventional' treatment. Although barbiturates were significantly more successful in reducing intracranial pressure, this was not reflected in an overall improvement in outcome. One possibility raised by these studies was that treatment had begun too late, after severe brain damage had been sustained. Therefore, it was thought more fruitful to commence early treatment as a routine, in an effort to prevent the development or progression of damage. *Ward et al. (1985) studied patients with a severe head injury and compared the outcome of patients prophylactically treated with barbiturates with randomized controls and found no benefit.* An overview of data from major randomized studies does not show evidence to support a marked benefit of barbiturates (Table 21.6). *Barbiturate treatment, therefore, does not have a place in the routine management of severe head injury, although it can improve physiological values, especially ICP, in the acute stage. Similar effects can be obtained by other new hypnotic agents, for example propofol, that have shorter durations of action and are more convenient to use.*

21.3.5 CORTICOSTEROIDS

The publication of the second National Acute Spinal Cord Injury Study (NASCIS II) renewed interest in the neuroprotective pharmacology of glucocorticoids. The trial showed a significant improvement in neurological recovery in those patients treated with high-dose methylprednisolone within 8 hours of their spinal cord injury (SCI; Bracken *et al.*, 1990). An interesting observation was the need both for high intravenous dosage (30 mg/kg), and for early treatment, i.e. less than 8 hours postinjury.

(a) Rationale and actions

Methylprednisolone is thought to be an inhibitor of lipid peroxidation and of lipid hydrolysis (arachidonic

acid release; Hall, 1992). It is also thought to have a number of other effects, including the maintenance of normal tissue blood flow, maintenance of aerobic energy metabolism and reversal of intracellular calcium accumulation. The neuroprotective activity of methylprednisolone is independent of its glucocorticoid activity. A single, large intravenous dose enhanced early neurological recovery after head injury in a rodent model (Hall, 1985). Prednisolone when given in equal dose with methylprednisolone was equally efficacious but half as potent in the same rodent model. It is thought that both these glucocorticoids are equally efficacious as lipid antioxidants

(b) Clinical status

A number of studies have demonstrated the failure of high-dose dexamethasone to influence ICP or outcome in patients with severe TBI. Thus, a study from Richmond, Virginia, showed that high-dose methylprednisolone (40 mg 6-hourly) did not decrease ICP in patients with severe head injury. There was a high incidence of gastric hemorrhage (50%) and hyperglycemia (85%; Gudeman, Miller and Becker, 1979). *An overview of major published studies does not suggest efficacy, even with the use of dexamethasone treatment up to 96 mg/d (Todd and Teasdale, 1989; Table 21.7).* Nevertheless steroids are still used in many neurosurgical centers in the USA and Germany (Ghajar *et al.*, 1995) and a few in the UK (Malta and Menon, 1996), despite the lack of proven efficacy. A recent overview has suggested that the question is still not definitively answered (Roberts, Anderson and Rowan, 1996).

21.3.6 FREE RADICAL SCAVENGERS AND INHIBITORS OF LIPID PEROXIDATION – PEG-SOD

(a) Rationale and activity

Oxygen-radical-mediated lipid peroxidation is thought to be an important factor in post-traumatic neuronal degeneration (Hall, 1989; Siesjö, Agardh and Bergtsson, 1989) The arachidonic acid cascade metabolites contribute to ischemia of the gray matter and

Table 21.6 Overview of outcome in major randomized trials of barbiturates in severe head injury

	Protocol			
	'Conventional' first		'Barbiturate' first	
	Total	Dead	Total	Dead
Schwartz <i>et al.</i> , 1984	31	14	28	170
Ward, 1985	26	13	27	14
Yano, 1986	60	37	68	40
Eisenberg <i>et al.</i> , 1988	36	19	37	23
Totals	153	83	160	94
Mortality	54%		59%	

Table 21.7 Overview of main randomized 'high'-dose steroids in head injury (Source: data from Faupel, 1986; Cooper, 1978; Saul, 1981; Braakman *et al.*, 1983; Dearden, 1986; Gianotta, 1987; Gaab, 1992)

	Controls	Treated
Total (n)	399	482
Dead/vegetative (%)	40	40
Severe disability (%)	10	12
Moderate/good recovery (%)	51	48

stimulate production of oxygen free radicals. Oxygen free radicals have been implicated in the pathogenesis of microvascular damage (Kontos and Povlishock, 1986) brain edema, cerebral ischemia and spinal cord trauma (Kontos and Povlishock, 1986). These highly reactive free radicals cause peroxidation of membrane phospholipids and oxidation of cellular protein and nucleic acid, and can attack both neuronal membranes as well as the cerebral vasculature (McIntosh, 1993). Free radical scavengers such as super oxide dismutase (SOD) reduce mechanically induced injury of brain cells (McKinney *et al.*, 1996) and reduce infarction in experimental focal reperfusion ischemia, but have a narrow therapeutic dose range (Liu, Beckman and Freeman, 1989). Studies in experimental brain injury show reduced microvascular damage (Wei *et al.*, 1981) and reduced blood-brain barrier opening in cerebral edema (Chan, Longar and Fishman, 1987; Schettini, Lippman and Walsh, 1989). SOD has a very short biological half-life, which limits its clinical utility, but conjugation with polyethylene glycol (PEG) extends the half-life of SOD to approximately 5 days.

(b) Clinical status

A phase 2 trial using polyethylene-glycol-conjugated super oxide dismutase (PEG-SOD) was reported to show both safety and improved outcome in head-injured patients (Muizelaar *et al.*, 1993). No complications were noted in the group using PEG-SOD and unfavorable outcome (dead, vegetative or severe disability) was reduced by one-fifth (Table 21.8). This initial pilot study prompted the conduct of further large trials to seek definitive evidence. Young *et al.* (1996) reported on patients allocated to control or a single administration of either 10 000 U/kg or 20 000 U/kg of PEG-SOD. A total of 463 patients were studied and the groups were well balanced for major prognostic factors. The primary comparison was the

outcome of patients at 3 months after injury, separating favorable (moderate/good) *versus* unfavorable (dead/vegetative/severe). Patients treated with PEG-SOD had a higher proportion of favorable outcomes than controls and the difference was most marked in the 10 000 U/kg group. However, outcome was not significantly different at 6 months (Table 21.8). This study indicated that no additional benefit was likely to be obtained from the higher dosage of PEG-SOD and that a further study was needed, powered to detect a more realistic difference than had been suggested by the pilot study. This further study, involving more than 1000 patients, has been completed and did not show a significant effect upon outcome (Muizelaar, 1996, personal communication).

21.3.7 INHIBITORS OF LIPID PEROXIDATION

(a) Rationale and activity

The 21 amino steroids were introduced as a new class of lipid peroxidation inhibitors, lacking glucocorticoid effects. Of these, tirilazad mesylate (U-74006F) is the most studied. It is a potent inhibitor of iron-catalyzed lipid peroxidation in brain homogenates, decreases iron-induced damage to cultured cortical neurons and inhibits peroxidation in systems that contain neither membranes or iron (Hall *et al.*, 1989). *Unfortunately, these effects are of uncertain relevance because tirilazad does not cross the cerebral endothelium to enter the brain. Any beneficial effects are, therefore, likely to be related to a reduction of microvascular damage.* The effects of tirilazad in experimental ischemia have been variable: both benefit (Park and Hall, 1994; Perkins *et al.*, 1991; Xue, Silvka and Buchan, 1992) and lack of efficacy (Hellstrom *et al.*, 1994; Karlsson *et al.*, 1994) have been reported and the inconsistencies are not simply a reflection of discrepancies in protocol or the choice of focal or global insult or transient rather

Table 21.8 Overview of comparison of effect of PEG-SOD 10 000 U/kg and placebo on outcome at 3 months after severe head injury (Source: Muizelaar, 1996, personal communication)

Protocol No.	% Favorable outcome*		Treatment difference (%)		p value
	Placebo	10 000 U/kg	Absolute	Relative	
007 Phase 2	45.8 (n = 24)	60.0 (n = 25)	14.2	31.0	0.32
005 Phase 3	46.3 (n = 162)	55.7 (n = 149)	9.4	20.3	0.11
006 Phase 3	47.0 (n = 487)	48.9 (n = 483)	1.8	3.9	0.61
007/005/006 Integrated summary	46.8 (n = 673)	50.8 (n = 657)	4.0	8.6	0.15

* Good recovery and moderate disability outcomes combined

than permanent ischemia. Tirilazad was reported to improve early neurological recovery and survival after experimental head injury (Hall *et al.*, 1988; McIntosh *et al.*, 1992; Dumlich *et al.*, 1990), to reduce post-traumatic hydroxyl radical formation and to attenuate traumatically induced opening of the BBB (Mathew *et al.*, 1996).

(b) Clinical status

Two large Phase 2 studies utilizing tirilazad mesylate in patients with head injuries have been performed, one in the United States and Canada, involving 1198 patients, the other in Europe and Australia, involving 1132 patients (Marshall and Marshall, 1996). The results of the latter are awaited, but the North American study was stopped prematurely because of concern by the monitoring committee about an excess mortality in patients treated with tirilazad. This may reflect imbalance in the severity of the groups. *It is, nevertheless, unlikely that this compound will enter routine clinical use in head injuries.* The second generation of 21 amino steroids couple the function of the tirilazad with the 2-methyl amino chroman ring structure of Vitamin E. They have a greater anti-oxidant and free radical scavenging activity and exert a more potent protective action than tirilazad (Hall, 1993).

21.3.8 MODULATORS OF ARACHIDONIC ACID METABOLISM – INDOMETHACIN

(a) Rationale and actions

Calcium-activated proteases and lipases attack cell membranes, degrading phospholipids and arachidonic acid into thromboxanes, prostaglandins and leukotrienes (Leslie and Watkins, 1985). The arachidonic acid cascade has been implicated as a pathophysiological factor in models of experimental cerebral edema, cerebral ischemia, cerebral vasospasm and spinal cord trauma (Awad *et al.*, 1983; Fukumori *et al.*, 1983; Hallenbeck, Jacobs and Faden, 1983). Cyclooxygenase inhibitors, e.g. ibuprofen and indomethacin, improved cerebral metabolism and blood flow in rats following a cortical cryogenic lesion and improved neurological function after a weight-drop brain injury in mice (Pappius and Wolfe, 1983; Hall, 1988).

(b) Clinical status

There has been recent interest in the effects of indomethacin in human head injury and its effects on intracranial pressure, cerebral blood flow and cerebral metabolism. *Indomethacin, given as a bolus injection*

of 30 mg followed by 30 mg an hour has been shown to reduce ICP below 20 mmHg for several hours (Biestro et al., 1995). Cerebral blood flow decreased and there was a fall in rectal temperature (Jensen et al., 1991; Cold et al., 1990). However, evidence that this improves outcome is lacking.

21.3.9 CALCIUM CHANNEL ANTAGONISTS

(a) Rationale and activity

The initial agents available for clinical use were introduced with the aim of reducing calcium overload from all sources but were particularly active on voltage-operated 'L' channels. Typified by the dihydropyridine nimodipine, their vascular effects were considered to be preferential for cerebral vessels. Their actions included increases in cerebral blood flow, and prevention or reversal of experimental vasospasm but also hypotension at higher doses. The balance between such vascular effects and benefits due to reduction in neuronal calcium rises remains unclear. Nevertheless, nimodipine treatment significantly and reasonably consistently reduced damage in both focal (Mohammed *et al.*, 1985; Hadley *et al.*, 1989) and global ischemia (Steen *et al.*, 1985), including reperfusion models. Calcium antagonists have improved outcome in models of traumatic and hemorrhagic damage (Sinar *et al.*, 1988). Clinically, nimodipine has an undoubted benefit in the pretreatment of delayed ischemia after spontaneous subarachnoid hemorrhage (Pickard *et al.*, 1989; Robinson and Teasdale, 1990). It does not have a major effect on ischemic stroke and given intravenously can cause hypotension in such patients (Wahlgren *et al.*, 1994), but a meta-analysis has suggested a possible benefit if treatment is commenced within 12 hours of onset of stroke (Mohr *et al.*, 1994). Compton *et al.* (1990) observed reductions in cerebral blood flow velocity in head-injured patients treated with nimodipine and considered that this reflected a relief of vasospasm.

A new range of 'N' calcium-channel blockers, derived from spider venoms, block neurotransmission and are effective in ischemia, even when treatment is started some hours after an insult. Hypotension is a side effect but one compound (SNX111; Omega Conotoxin) is being evaluated for safety and tolerability in severe head injuries.

(b) Clinical status

In the first two substantial randomized trials of nimodipine in head injury, severely injured patients, selected by their inability to obey commands, received 1–2 mg/h intravenously for 7 days (Table 21.9). In the first, HIT I trial (Bailey *et al.*, 1991), 351 patients in

Table 21.9 Effect of nimodipine on outcome of severe head injury

	HIT I		HIT II	
	Placebo	Nimodipine	Placebo	Nimodipine
Total patients	75	176	429	423
Dead	50	49	98	90
Vegetative	2	8	19	16
Severe disability	37	25	51	57
Moderate disability	33	31	98	101
Good recovery	53	62	148	144
Missing		1	15	18
Unfavorable (D/V/S)	89 (51%)	82 (47%)	168 (41%)	160 (40%)
Favorable	86 (49%)	93 (53%)	246 (59%)	245 (60%)

whom treatment was commenced within 24 hours of injury were analyzed. Unfavorable outcome (dead, vegetative, severe disability), occurred in 51% of control patients and 47% of treated patients. This trend to an 8% relative decrease in unfavorable outcome was not statistically significant but prompted a second study, HIT II (European Study Group on Nimodipine and Severe Head Injury, 1994). A total of 819 patients were treated within 12 hours of becoming unable to obey commands and within 24 hours of injury. Overall, the difference in outcome was small: **40.6% unfavorable in the placebo group and 39.5% unfavorable in nimodipine treated patients. Various subgroups were analyzed and in the group considered by the investigators to show CT scan evidence of traumatic subarachnoid hemorrhage, unfavorable outcome was reduced from 56% in placebo patients to 45% in treated subjects.** The CT interpretation by the investigators was not always borne out by a Review Committee, but where the latter considered subarachnoid to be present there was a similar reduction in unfavorable outcome, from 60% to 52%. The importance of traumatic subarachnoid hemorrhage had not been appreciated when the HIT I study was started (Kakarieka, Braakman and Schakel, 1994). Since then correlations have been established between

a large amount of blood on the CT scan, a high blood-flow velocity assessed by ultrasound, focal reductions in blood flow and CT evidence of focal infarction. Therefore, the data in the HIT I study were analyzed retrospectively, after a review of the CT scans to select those with subarachnoid hemorrhage. This showed that 69% of patients with subarachnoid hemorrhage given placebo had a poor outcome and 77% of patients given nimodipine had a poor outcome (Murray, Teasdale and Schmitz, 1996).

These findings prompted a new trial, carried out in 21 German neurosurgical centers (Harders *et al.*, 1996). The study included severe, moderate and even mildly injured patients and subjects were selected primarily on the basis of the investigators' opinion that the CT scan showed a traumatic subarachnoid hemorrhage – which was not supported by the Review Committee in 21% of cases. Nimodipine was given intravenously for 7–10 days and thereafter orally for 21 days. **Unfavorable outcome occurred in 46% of the placebo group and 25% of the nimodipine group. High transcranial Doppler velocity was less frequently seen in nimodipine-treated patients. Hypotension was more frequent in the nimodipine-treated patients, but this did not adversely effect their outcome (Table 21.10). Thus there is a plausible rationale for the use of nimodipine in**

Table 21.10 Outcome for patients classified by presence or absence of SAH on CT scan

Treatment group	HIT I*		HIT II*		German Study Group†	
	Placebo	Nimodipine	Placebo	Nimodipine	Placebo	Nimodipine
Total	133	124	414	405	61	60
Not SAH	97	89	269	282		
Poor outcome	40 (41%)	34 (38%)	81 (30%)	96 (34%)		
SAH	36	35	145	123		
Poor outcome	25 (69%)	26 (74%)	87 (60%)	64 (52%)	28 (46%)	15 (25%)

* Review group assessment on CT scan

† Investigator's assessment of CT scan

traumatic subarachnoid hemorrhage, even when it is borne in mind that its benefits in spontaneous subarachnoid hemorrhage do not appear to be as a result of reduction of angiographic vasospasm (Pickard et al., 1989).

The debate at the moment is whether the existing clinical evidence is sufficiently definitive for nimodipine to be adopted as a routine in traumatic SAH or whether, given the disparities in evidence from the three studies and the lack of complete consistency in the findings, there should be a further large prospective randomized study. The extensive experience already gained with nimodipine in neurosurgery indicates that, although its efficacy is not overwhelming, this is balanced by a considerably better safety and tolerability profile than several other pharmacological approaches. It should be possible, therefore, to conduct a 'mega trial' of nimodipine much more easily (and cheaply) than for certain other potentially more powerful proposed interventions.

21.3.10 NEUROTRANSMITTER ANTAGONISTS

(a) Introduction

The recognition of the role of agonist-gated channels in allowing calcium entry has focused intense research on the role of neurotransmitters in the progression of ischemic and traumatic brain damage. The principal interest has focused on the role of glutamate. Currently, the clinical value of glutamate-receptor antagonists is the most important issue in neuroprotection research.

Glutamate is localized presynaptically and released in a calcium-dependent fashion on electrical stimulation. Glutamate receptors are the main mediators of synaptic excitation of the central nervous system. They are involved in many important physiological processes, including sensory information handling, learning and memory. At least four distinct glutamate receptor subtypes are recognized. Most interest is focused on the N-methyl-D-aspartate 'NMDA' receptor, which is coupled to a sodium-calcium channel. The NMDA receptor is modulated by glycine and polyamine coantagonists, which facilitate opening of the ion channel. This also requires membrane depolarization, in order to overcome a voltage-dependent block by magnesium ions. Glutamate levels are normally tightly controlled and there are important uptake mechanisms into presynaptic terminals and into glia. Other ionophore-coupled glutamate receptors, such as 2-amino-3 hydroxy-5 methyl isoxazole-4 propionic acid (AMPA) and kainate (KA), are more important in sodium and potassium exchange but are also important targets for neuroprotective drugs. The metabotropic glutamate receptor is linked to phospho-

lipase C and activation leads to an increase in intracellular calcium.

High concentrations of glutamate have been known for some years to be neurotoxic (Rothman and Olney, 1986; Olney *et al.*, 1978, 1989). In experimental models of cerebral ischemia and trauma, and in human trauma and stroke there are immediate increases in extracellular concentrations of glutamate and aspartate at levels of blood flow that are associated with membrane failure and the development of neuronal damage (Zauner and Bullock 1995; Bullock *et al.*, 1996). In models of primary diffuse head injury the elevation in glutamate is transient (Katayama *et al.*, 1990) but it is more long-lasting in models of subdural hematoma in which there is associated focal cortical ischemic damage underlying the hematoma (Miller *et al.*, 1990; Chen *et al.*, 1992). These observations in animals are now being replicated in studies in patients with severe head injury (Bullock 1995) and stroke, using microdialysis (Bullock *et al.*, 1996). The results show that high levels of glutamate occur in regions of focal cerebral damage, in association with cerebral blood flow below the 'threshold' value of 20 ml/100 g/min, in particular in association with raised intracranial pressure.

Much of the evidence for the importance of glutamate in producing brain damage, and the stimulus to clinical applications, has come from the wealth of evidence that administration of glutamate antagonists, in particular against the NMDA receptor, are markedly efficient in reducing the amount of damage produced experimentally (McCulloch, 1995; McCulloch *et al.*, 1991; Myseros and Bullock, 1995). This is most clearly seen for NMDA antagonists in models of permanent focal ischemia (Bullock 1990) where the evidence is overwhelmingly consistent. *There is an emerging view that NMDA antagonists are not so consistently effective in models of diffuse ischemia (Buchan and Pulsinelli, 1991; Pulsinelli, Sarokin and Buchan, 1993), where antagonists of AMPA and other receptors may have more potential benefits. In focal ischemia, benefit has been consistently found with pretreatment and, in many studies, benefit has been also obtained from post-treatment.*

Pretreatment with an NMDA antagonist has reduced behavioral effects in a model of diffuse injury. In the model of subdural hematoma, pretreatment reduces the extent of ischemic damage in the cortex (Chen *et al.*, 1991) and, perhaps as a reflection of this, lowers intracranial pressure (Kuroda *et al.*, 1991). The lack of efficacy of NMDA antagonists in conditions of extremely dense ischemia may reflect the over-riding prime importance of non-receptor-mediated calcium overload when there is severe energy failure. In these circumstances, other antagonists, e.g. AMPA, may be more beneficial.

Blockade of an important excitatory neurotransmission mechanism can be expected to have side effects to offset against potential benefit and the effects of the blockade of NMDA receptors were foreseen by the effects of phencyclidine (PCP). This non-competitive NMDA-channel antagonist was used in psychiatric research as a model of schizophrenia but rapidly achieved 'street' notoriety as a drug of abuse ('angel dust'). There are also similarities with the effects of ketamine, a low-affinity NMDA-channel blocker widely used for 'dissociative' anesthesia. Psychoactive effects of more recent NMDA receptors antagonists in conscious subjects occur in a dose-dependent way (Muir and Lees, 1995) and include light-headedness, dizziness, paresthesia, disinhibition, nystagmus, paranoid ideation, hallucinations and catatonia. NMDA antagonists also have beneficial sedative, analgesic and possibly anticonvulsant effects.

The behavioral effects of NMDA antagonists can be controlled by administration of benzodiazepines but other studies have raised concern about the possibility that, in themselves, NMDA antagonists may be neurotoxic. The area at risk is the limbic system, which is maximally activated by their administration. This is disclosed histologically by the appearance of vacuoles in neurones in the lingulate cortex, reported by Olney, Labruyere and Price, 1989. The precise importance and relevance of this 'Olney' effect is still under review. The vacuoles are transient and more prominent in rodents than in primates but do occur at dosages that may be similar to those likely to be required for clinical benefit.

Cardiovascular effects are of particular importance in subjects with brain damage. Experimentally, the

effects of NMDA antagonists are influenced by anesthesia, which changes a dose-dependent elevation to a hypotensive effect. There is some evidence for a similar pattern with high doses in human subjects.

The complexity of glutamate receptors, in particular the NMDA receptor, is reflected in the large number of modulatory sites amenable to pharmacological intervention (Choi, 1990; Figure 21.2). The possibilities include reduction of presynaptic release of glutamate by 'sodium channel blockers', postsynaptic antagonism at the NMDA receptor by either a high- or low-affinity non-competitive antagonist, competitive receptor-site antagonists, and glycine- and polyamine-site modulators. *The differing properties of the different classes may influence their utility. For example the more rapid brain penetration of non-competitive NMDA-receptor antagonists offers a better pharmacokinetic profile than the much less lipid-soluble competitive agents.* Examples of each class of antagonist have been applied to subjects with severe head injury to assess safety and tolerability, and in some cases these have been followed by efficacy trials (Table 21.11). At the time of writing, information is available only from abstracts and presentations at meetings and definitive reports are awaited.

The safety and tolerability studies have employed increasing dosages and duration of administration in order to seek evidence of safety and tolerability in regimens appropriate to achieve neuroprotective effects. The first study of an NMDA site competitive antagonist concerned the high-affinity, non-competitive antagonist GCS 19755 (Selfotel). The agent was given in increasing doses, 1–6 mg/kg on 82 successive days. There were no important adverse experiences

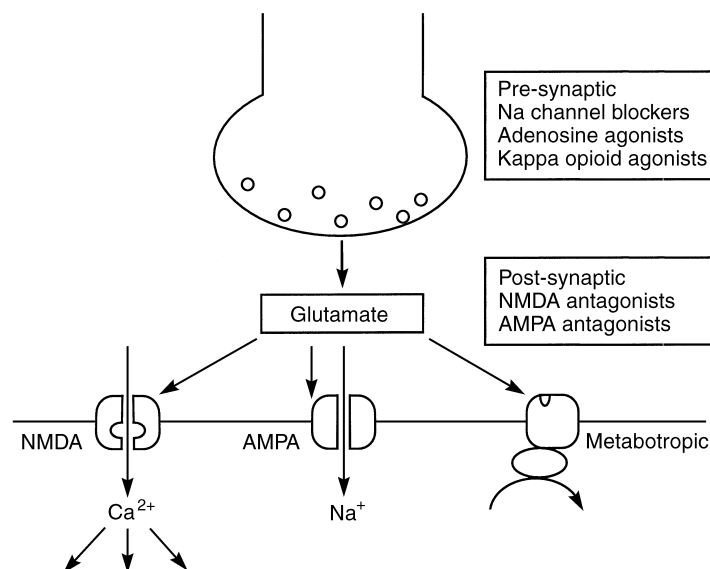


Figure 21.2 Schematic of excitatory amino acid pathways and potential sites for pharmacological intervention.

Table 21.11 Glutamate antagonists potentially clinically applied to head injury

Class	Drugs	Company	Comments
Presynaptic release inhibition	619C89	Wellcome/Glaxo	Phase 2 study halted because of company strategy
Na ⁺ channel block	Enadoline	Parke Davis	Phase 2 in progress
Postsynaptic competitive	Riluzole	Rhône-Poulenc Rorer	Reported to benefit ALS No experience in head injury
	CGS 19755 Selfotel	CIBA-GEIGY	Phase 2 × 2 completed Phase 3 halted by safety committee
	d-CPP-ene EAA 49	Sandoz	Phase 2 completed Phase 3 in progress in Europe
Non-competitive – high-affinity	Aptiganel H (Cerestat)	Cambridge Neuroscience Boehringer	Phase 2 completed Phase 3 in progress in North America and Europe
Polyamine-site	SL820715 Eliprodil	Synthelabo	Phase 2/3 study completed
	CP101-606	Pfizer	Phase 2 completed
Glycine-site	ACEA 1021	CIBA-GEIGY/Cocensys	Phase 2 in Progress
	?	Lubeluzole	Janssen
?	Dexanabinol HV-211	Pharmos	Phase 2 in progress in Israel

that might have been related to the drug in dosages up to 3 mg/kg (Stewart *et al.*, 1997a). At high doses, reductions in blood pressure were observed and intracranial pressure also declined in some patients but this was not significantly related to drug dosage (Stewart *et al.*, 1997b) and in some cases cerebral perfusion pressure fell. In a further phase 2 study dosages of 3 mg/kg or 5 mg/kg were compared to placebo in a randomized blind manner. The preliminary findings supported the initiation of two randomized prospective studies aimed to determine the efficacy of 5 days treatment with 5 mg/kg daily for severe head injuries. These were conducted in North America and in a cooperative group of European/Australasian centers. The studies were stopped in December 1995 because of a concern in the safety monitoring committee about an excess of adverse events in patients in these trials and in parallel trials of patients with stroke. The data that led to this action are not available at the time of writing. The safety of a second high-affinity non-competitive antagonist (CPP-ene, SZEA494) was studied in a double-blind dose escalation study with administration of up to 7 days after injury. Dosages were titrated to achieve a final target serum concentration known to be neuroprotective in experimental circumstances. Preliminary observations in this study indicated an acceptable safety profile and a Phase 3 efficacy study has been initiated in Europe.

Although the non-competitive ion-channel antagonist originally responsible for much of the enthusiasm for glutamate blockade, Dizocilpine MK801, was not pursued clinically, a similar non-competitive antagonist, aptiganel HCL, CNS1102 Cerestat (McBurney *et al.*, 1992), which is effective in focal ischemia (Mineamoto *et al.*, 1993), has been studied in dose escalation protocols in head injury. In the first open study, administration of increasing doses showed reductions of intracranial pressure, increases in blood pressure and a net increase in cerebral perfusion pressure (Wagstaff *et al.*, 1995). In a subsequent study the duration of administration was increased to 3 days, with an acceptable safety and tolerability at a plasma concentration well above the level known to be neuroprotective in animals. A study in a combined group of North American and European centers, aimed at determining efficacy, is currently in progress.

Eliprodil (SL820715) is a synthetic antagonist of the polyamine site on the NMDA receptor and has preclinical neuroprotective efficacy (Gotti *et al.*, 1988). Eliprodil in normal volunteers is associated with dose-dependent prolongations of the QT interval but appears to have less psychological effects, at least in the dosages employed, than either competitive or non-competitive antagonists. Trials of eliprodil have been conducted in selected groups of head-injured patients in Europe and the results are awaited at the time of writing.

The binding of glycine to the glutamate receptors is required for NMDA-channel activation and endogenous concentrations of glycine are sufficiently high for the site to be fully saturated under normal conditions. Partial agonists such as ACEA 10201 reduce damage in ischemic models and are under study for safety and tolerability in head-injured patients. Two agents initially considered to reduce presynaptic release of glutamate commenced safety and tolerability studies in severely injured patients. Studies with 619C89 were halted as a result of policy changes following the merger of Wellcome and Glaxo. Studies with enadoline continue and this agent is now considered to have effects in blocking abnormal sodium currents, representing a distinctly different approach to neuroprotective treatment. Riluzole, which has shown benefit in patients with amyotrophic lateral sclerosis, is considered to be a sodium-channel blocker and to inhibit glutamate release, and is under consideration for studies in head injury. Lubeluzole inhibits glutamate-induced brain damage but is thought to act at an intracellular level through a nitric oxide mechanism and application to head injury will depend upon the results of efficacy studies in patients with stroke.

21.3.11 FUTURE

Other strategies of neuroprotection under consideration for clinical evaluation, on the basis of experimental studies, include an antagonist of bradykinin to reduce blood-brain-barrier damage, agents that limit white cell adhesion to endothelial receptors and hence reduce inflammation, agents that inhibit neuronal nitric oxide production without blocking vascular dilatation, adenosine analogs that reduce transmitter release, inhibitors of calcium-activated enzymes, agonists of the GABA receptor (e.g. chloromethiazole), as well as neurotrophins and growth factors. 'On the horizon' are approaches that interfere with gene expression after injury, for example by encouraging production of protective proteins or blocking so-called 'death genes' that are involved in either necrotic or apoptotic cell death.

21.4 Conclusion

The high incidence of ischemic damage in fatal head injuries, a third of whom have spoken after injury, and the frequent occurrence of secondary insults despite the best medical and surgical treatment point to the great potential for pharmacological treatment to improve outcome after head injury. The agents that are now entering early clinical studies are the fruits of intensive experimental and clinical investigation over the last two decades. Irrespective of the results of the current studies, much remains to be learned and new

approaches can already be foreseen. Realization of these opportunities will involve answering a number of questions and facing a number of challenges.

Many mechanisms have been identified that may contribute to the initiation or progression of brain damage after head injury and ischemia (Siesjö *et al.*, 1992). Which of these are truly important in clinical circumstances? Is it appropriate to envisage a sequence – initial events being dominated by ionic and neurotransmitter events, followed by membrane degradation through free radical mechanisms, and thereafter balances between inflammatory and reparative processes, such as necrotic and apoptotic cell death, determined by gene responses and growth and survival factor production? This view would indicate that a sequential program of neuroprotective treatment is appropriate. The alternative view is that many processes are occurring concurrently, in which case 'cocktails' may be most efficacious.

More attention may need to be paid to distinctive mechanisms in different types of injury, dictating the appropriate choice of treatment. For example, it is likely that it is only in patients with traumatic subarachnoid hemorrhage that calcium-antagonist treatment may be appropriate at present. Patients with a focal injury such as contusion or hematoma, with marked space-occupying effect, increased intracranial pressure and reduced perfusion, may be most appropriate candidates for glutamate-antagonist treatment, whereas this is unlikely to benefit those with uncomplicated diffuse primary injury. The unraveling of the potentially complex series of combinations will depend upon imaginative interactions between clinical and experimental investigators, aimed at identifying indices of the different mechanisms of damage in patients, along with therapeutic trials of sufficient size to determine differential effects in preselected subgroups of injuries.

There are major conceptual and practical issues in applying neuroprotective drug treatment. Ideally, treatment is best commenced as soon as possible after the injury but this is increasingly difficult to achieve in investigative trials. In part this reflects uncertainties about procedures for consent for research in emergency circumstances – relating to differing regulatory attitudes rather than fundamental ethical problems. Is there a time window beyond which it is not appropriate either to initiate or to continue treatment? There is an indication from the study of methyl prednisolone in spinal-cord injury that treatment initiated after 8 hours had an adverse effect, but this is not necessarily relevant to head injury, in which there is much evidence that secondary insults can occur for days after injury.

The translation of the exciting preclinical findings into benefit in patients will require careful, rigorous

clinical trials. Whereas in the past, such studies were often developed within the pharmaceutical industry, and their protocols to some extent imposed upon clinical investigators, it is now being recognized that clinicians must take a prominent role in the planning and execution of clinical trials.

Two new clinical organizations have developed in response to the issues raised by the clinical application of the agents derived from the years of research and development by industry. These are the American Brain Injury Consortium and the European Brain Injury Consortium. Each consists of a large number of investigators working in centers committed to high-quality clinical research aimed at improving outcome of head injuries. Each has an administrative structure, coordinating the group's activities through a central 'hub' – in America in Richmond, Virginia, in Europe in Glasgow, UK. Head injury is a new area for many pharmaceutical companies. The Consortia provide a way of harnessing the accumulated wisdom of experienced clinical investigators, backed by the influence of the large number of cooperating centers, with the aim of ensuring that trials are carried out in the most rigorous, relevant and clinically influential manner. This is achieved through developing studies in partnership with industry, discussing and, if need be, negotiating over the specifics of the protocol, patient population, data to be collected, method of analysis and eventual reporting.

This wealth of clinical experience and potential patient population in the American and European consortia, combined with the major resources being allocated to neuroprotection of head injury by industry, should guide the clinical application of neuroprotection. It will be crucial that this leads to results that are relevant and comprehensible to individual clinicians, and most importantly that it maximizes the likelihood of translating the effects seen preclinically from neuroprotection treatment to benefits for patients with severe head injury.

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