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REGULATION OF INTRACELLULAR FREE MAGNESIUM IN CENTRAL NERVOUS SYSTEM INJURY

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1. ABSTRACT

Traumatic injury to the central nervous system (CNS) initiates an autodestructive cascade of biochemical and pathophysiological changes that ultimately results in irreversible tissue damage. Known as secondary injury, this delayed injury process is multifactorial in nature and it is generally thought that the simultaneous attenuation of a number of the secondary injury factors will be required for interventional therapies to have a significant beneficial effect on outcome. This review summarizes the growing body of evidence that suggests that magnesium plays a pivotal role in the secondary injury process following CNS trauma, affecting a number of secondary injury factors including neurotransmitter release and activity, ion changes, oxidative stress, protein synthesis, and energy metabolism. By having effects on such a range of secondary injury factors following trauma, pharmacological studies have shown that magnesium may be an effective therapy following neurotrauma, improving survival, motor outcome and alleviating cognitive deficits.

2. INTRODUCTION

A number of studies have now demonstrated that magnesium plays a critical role in the injury process following traumatic injury to the Central Nervous System (CNS). Indeed, alterations in free magnesium concentration associated with the development of a functional deficit was first demonstrated in traumatic brain injury. Following this initial observation in brain, it has become generally accepted that the concentration of the free ion can indeed change *in vivo*, and that such changes can have functional effects in a variety of tissues. The discovery that free magnesium is not constant in the body under pathophysiological conditions has now opened the door to interventional studies that are only now being conducted. One area under intense investigation is brain injury.

3. BRAIN INJURY

Injury to the brain with subsequent development of neurologic deficits may be the result of various insults including hypoxia, anoxia, stroke, hypoglycemia and trauma, amongst others. Traumatic injury, in itself, may in fact encompass all of the other insults as a consequence the initial traumatic event. Accordingly, it is one of the most complicated forms of brain injury and, not surprisingly, no pharmacologic intervention has been developed to date that is generally accepted as an effective therapy. A number of animal models have been devised to study the mechanisms associated with formation of irreversible tissue damage after trauma in the hope of developing an effective therapeutic intervention. A complete description of these various models is beyond the scope of the present review and readers are referred to some excellent articles elsewhere (1-3). Suffice to say that all of these models produce the resultant neurologic deficits though two broadly defined mechanisms: primary mechanisms and secondary mechanisms (4, 5). Primary mechanisms include those mechanical events that occur at the time of the traumatic insult including hemorrhage, axonal stretching, shearing, tearing and laceration (6). While these events can be prevented with the use of helmets, seat belts and other protective devices, no therapeutic interventions targeting the primary mechanisms can be initiated after the traumatic primary event. Secondary events, on the other hand, occur between minutes and days after the primary

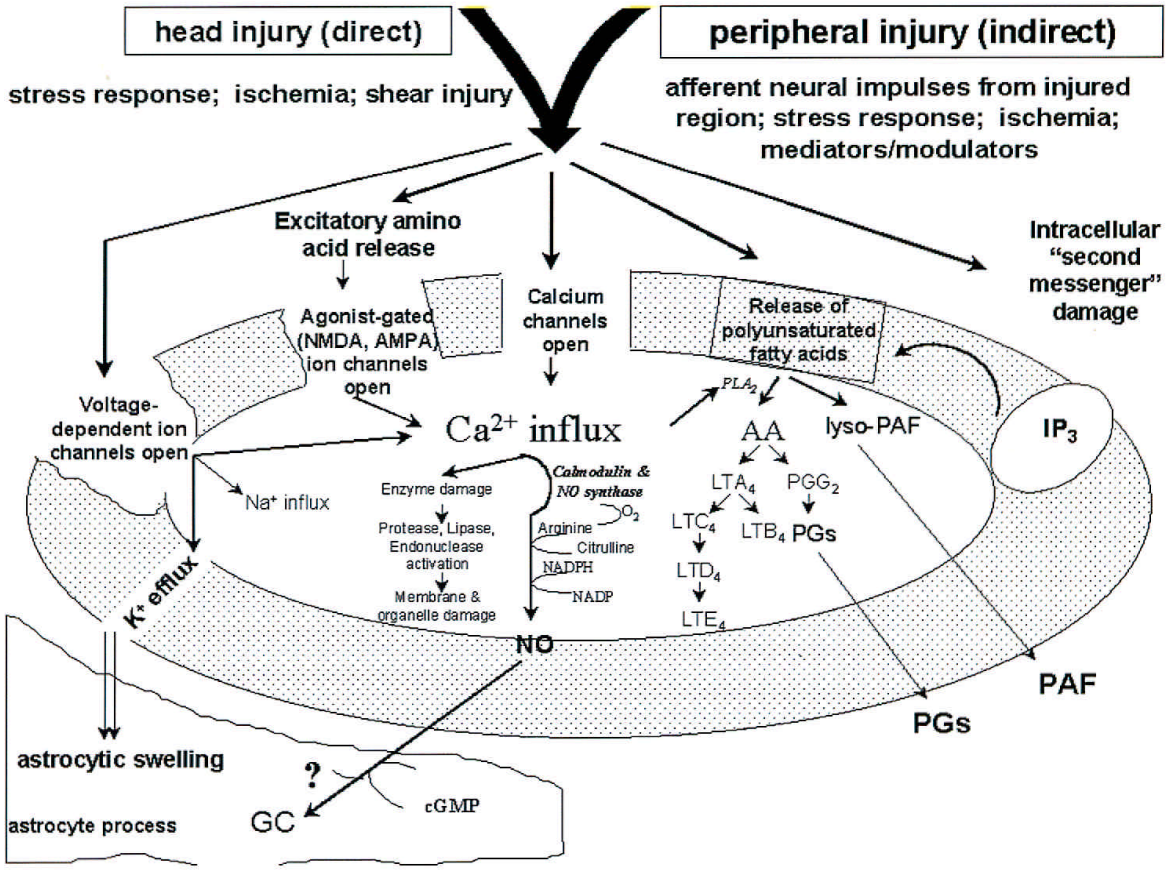

Figure 1. Schematic diagram of cellular secondary responses to both direct and indirect neurotrauma.

insult and include biochemical and physiologic iterations that are initiated at the time of trauma (5, 7). These secondary events include, but are not limited to, changes in neurotransmitters, ions, oxidative stress, blood flow, edema and energy failure (Figure 1). Moreover, secondary injury mechanisms need not be activated exclusively by direct primary injury to the brain. Indeed, they may also be initiated in the CNS following peripheral injury. For example, peripheral blast trauma results in secondary alterations in the brain (8) presumably by the action of, amongst others, autacoids that are released into the systemic circulation, by afferent hyperexcitability, or by enhanced neurotransmitter release. Irrespective of whether the secondary mechanisms associated with brain injury were initiated by either direct or indirect means, there exists an opportunity to prevent, or at least attenuate, the damage that results to the brain from the delayed secondary injury cascade using appropriate pharmacologic interventions (9). However, given the multifactorial nature of the secondary injury process, it is unlikely that targeting a single factor will result in any significant improvement in outcome, particularly in human brain injury. Hence, targeting several factors using an interventional cocktail, or using drugs that affect a number of secondary factors, is considered the most likely method of improving outcome (10). Recent evidence suggests one such multifactorial intervention is the magnesium cation which has been reported to have affects on a number of secondary injury factors (11, 12).

3.1. Magnesium in brain injury

Over the past decade, a number of studies in brain injury have conclusively demonstrated that magnesium decline after trauma is associated with neuronal cell death and functional impairment (8, 11, 13, 14). The first of these was reported in 1987 by Vink et al. (15). These authors used *in vivo* magnetic resonance spectroscopy to demonstrate that intracellular brain free magnesium declined by up to 60% following moderate traumatic brain injury in rats. While the significance of this decline may not at face value be obvious to many researchers, when converted into a logarithmic scale and compared to a more familiar parameter such as pH, the magnitude of the change after trauma is clearly very significant (Figure 2). Few would challenge the philosophy that pH changes of this magnitude in the brain would need urgent correction. In contrast, changes of this magnitude in free magnesium concentration were not considered critical largely because of the belief that magnesium was

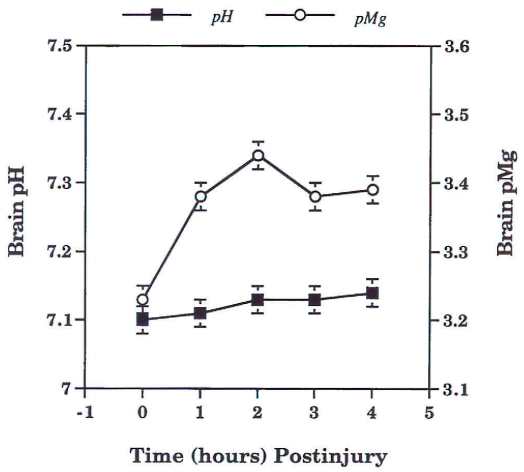

Figure 2. Changes in pH and pMg following moderate traumatic brain injury in rats. No significant changes in brain pH occurred after trauma. In contrast, changes in intracellular magnesium concentration were highly significant at all time points.

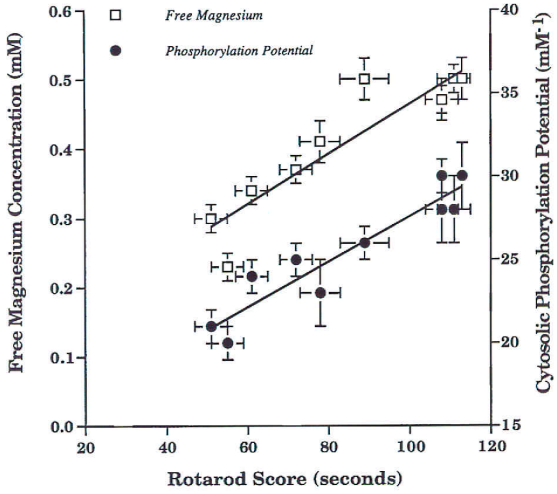

Figure 3. Linear correlation between brain free magnesium changes, phosphorylation potential and neurologic motor outcome following traumatic brain injury in rats. Each point represents the mean and standard error from six animals assessed over a one week period.

functionally insignificant. However, because magnetic resonance spectroscopy is a noninvasive technique, the same authors were able to clearly demonstrate in a follow-up study (16) that the decline in brain intracellular free magnesium concentration was associated with the development of functional deficits in neurologic motor outcome. Indeed, subsequent studies by the same group (16-18) demonstrated that depleting tissue magnesium concentration resulted in an exacerbated neurologic deficit while attenuation of the decline with parenteral magnesium administration prior to the injury significantly improved subsequent neurologic outcome.

The decline in free magnesium after trauma was reflected in a much smaller decline in tissue total magnesium concentration which was limited to the injury zone and did not extend to non-injured tissue (19). Thus the magnesium decline was thought to be indicative of cellular injury. Analysis of the bioenergetic implications of such intracellular changes in free magnesium concentration demonstrated that by affecting the equilibrium constants of the creatine kinase reaction in particular, but also the adenylate kinase and ATPase reactions, there would be significant affects of the ion on posttraumatic bioenergetic state (20, 21). Indeed, a linear relationship between intracellular free magnesium concentration and cytosolic phosphorylation potential following traumatic brain injury was described. Thus, magnesium decline after traumatic brain injury results in a decreased ability of the cell to provide sufficient energy to restore disrupted ion gradients and to repair itself. Consistent with this, magnesium decline following indirect neurotrauma correlated with decline in activity of the Na+ / K+ ATPase and the associated edema development (22). A similar association between magnesium concentration and edema development has been described following direct neurotrauma (19, 23). It is therefore not surprising that both intracellular free magnesium concentration and cytosolic phosphorylation potential are linearly associated with neurologic motor outcome after traumatic brain injury (Figure 3).

While the early studies of direct brain trauma were limited to fluid percussion traumatic brain injury (24, 25), a number of more recent studies have subsequently described similar declines in magnesium concentration following other focal models of injury (26) and even the more diffuse models of acceleration induced brain injury (13, 27). The declines reported in brain intracellular free magnesium concentration ranged between 40% and 60%. The fact that magnesium does decline following trauma irrespective of the injury model suggests that magnesium decline is a ubiquitous feature of central nervous system injury. In support of this hypothesis, declines in magnesium concentration have now also been reported in spinal cord injury (28), drug intoxication (29, 30) and even migraine (31). However, it is notable that the free magnesium decline in any condition never exceeds a minimum value of approximately 0.2 mM, suggesting that this concentration may be a threshold below which the ion cannot fall under physiological conditions. Since free magnesium changes were related to much smaller changes in total tissue magnesium (16), buffering by intracellular ligands presumably prevents any further decline.

The declines in brain free magnesium have been shown to persist for at least 4 days following traumatic brain injury and with increasing severity of injury, out to 7 days (32). Thus, it is not the magnitude of decline that is related to outcome but rather the time period for which magnesium is depressed. This seems to be consistent with observations of magnesium decline following different insults. For example, acute alcohol consumption causes a significant but transient decline in brain free magnesium concentration which does not result in a permanent

neurologic deficit (30). In contrast, chronic alcohol consumption, which is known to cause neurologic deficit, causes a persistent decline in brain free magnesium concentration (30, 33). Similarly, mild levels of traumatic brain injury (approaching concussion) result in transient yet significant declines in brain free magnesium concentration and minimal recordable deficits but severe injury results in more prolonged magnesium declines and severe neurologic deficits (16).

3.2. Blood free magnesium following brain injury

The availability of ion selective electrodes for magnesium has meant that blood free magnesium concentration can also be readily measured after brain injury. Similar to brain free magnesium concentration, blood levels of free magnesium in rats significantly decline from a mean preinjury level of approximately 0.50 mM to 0.35 mM by 30 minutes after traumatic brain injury (34). This decline in magnesium persists for at least four days following trauma before recovering to preinjury levels by six days after injury. The temporal profile of blood free magnesium changes was similar to the cytosolic changes observed in rat brain using magnetic resonance techniques. As with the brain determinations, there was a pattern whereby milder levels of injury resulted in transient declines in blood free magnesium while more severe injury caused persistent declines. However, unlike the brain determinations, a relationship between blood free magnesium and outcome only existed for the more severe injury levels. Thus, there was not a clear relationship between blood free magnesium concentration and motor outcome following less severe injury. This is in contrast to brain free magnesium and neurologic outcome (see Figure 3). It therefore appears that it is the brain level of magnesium that is associated with neurologic recovery, suggesting that neuronal effects of magnesium may dominate over non-neuronal effects. Nonetheless, such a simple bedside measure of free magnesium homeostasis may be a convenient prognostic indicator of outcome following severe trauma.

4. EXPERIMENTAL TREATMENT STRATEGIES FOLLOWING BRAIN INJURY

4.1. Magnesium therapy

Therapies targeting the restoration of magnesium homeostasis have demonstrated beneficial effects on neurologic outcome following traumatic brain injury. The first studies examined whether administration of magnesium salts prior to injury could indeed improve neurologic outcome (16, 17). These studies showed that administration of magnesium sulfate prior to injury improved motor outcome after moderate traumatic brain injury. Moreover, the administration of the salt attenuated the decline of brain intracellular free magnesium concentration after trauma, suggesting that the traumatic event permits the entry of blood magnesium into the brain. Later studies demonstrated that magnesium could be administered 30 minutes after the traumatic event and still have beneficial effects on outcome (18). Moreover, it was not just the motor outcome that showed significant improvement with magnesium therapy. Significant improvements in cognitive performance also resulted with magnesium sulfate administered intravenously at 30 minutes posttrauma (35) suggesting that the cation is also protective with respect to the hippocampus following trauma. This is consistent with demonstrated neuroprotective properties of magnesium in the hippocampus against a variety of insults (36-40). Heath and Vink (41, 42) subsequently compared the magnesium sulfate and magnesium chloride salts and conclusively demonstrated that both salts improve brain intracellular free magnesium concentration following traumatic brain injury with a resultant improvement in neurologic motor outcome. Moreover, such an improvement in outcome was noted irrespective of the route of administration provided that the blood free magnesium concentration was increased to approximately 1 mM. Thus, administration of a magnesium salt after brain injury will result an improvement in brain free magnesium concentration with resultant improvement in functional outcome.

Dose response studies using both the sulfate and chloride salts have demonstrated that they both improve neurologic motor outcome when administered up to 24 hours after injury (43). The best outcome was, however, achieved when the cation was delivered in the first 12 hours after injury (43). Parenteral administration of the drug was noted to increase both plasma free magnesium concentration and brain intracellular free magnesium concentration confirming that the sulfate and chloride salts of magnesium readily cross the blood brain barrier after trauma. This is consistent with previous pharmacokinetic studies of magnesium salts in neurosurgical patients (44). Moreover, a single bolus of magnesium was as effective as repeated administration in improving motor outcome following diffuse brain trauma (43) with the degree of improvement in motor outcome following drug administration being linearly correlated with brain free magnesium concentration. Thus, the critical period in which to restore magnesium homeostasis appears to occur within the first 24 hours after trauma. Improvement in brain free magnesium concentration during this phase results in a sustained improvement in brain free magnesium homeostasis and subsequent improvement in neurologic outcome.

4.2. Other treatment strategies

One of the most intriguing observations in traumatic brain injury has been the association between brain intracellular magnesium concentration and neurologic outcome irrespective of the treatment strategy (45). In other words, pharmacologic interventions that have been shown to improve motor outcome following traumatic brain injury have all caused in an improvement in brain free magnesium concentration after drug administration. For example, thyrotropin releasing hormone analogues (46), n-methyl-D-aspartate antagonists (19, 47), opiate antagonists (48, 49), adenosine agonists (25), apovincaminic acid derivatives (26) and phospholipase C inhibitors (50) have all been shown to increase brain free magnesium concentration after trauma with an associated improvement in neurologic outcome as assessed by motor tests. Conversely, therapeutic interventions that have not shown

any benefit upon brain free magnesium concentration have also not improved neurologic outcome (51). Clearly magnesium is critically involved in a diversity of secondary injury mechanisms. Targeting any of these secondary injury factors will therefore affect magnesium homeostasis and should a large shift in magnesium concentration take place, then a number of other injury factors will also be affected. Given the multifactorial nature of traumatic brain injury, it may be more beneficial to give magnesium salts rather than a single factor inhibitor.

5. THE ROLE OF MAGNESIUM

Although the mechanisms by which magnesium is beneficial to outcome following traumatic brain injury are largely unknown, extensive studies have been conducted in an effort to characterize the relationship between magnesium decline and the development of irreversible tissue damage. Magnesium has long been recognized as an important cation necessary for the functioning of over 300 key enzymes involved in energy transformation, protein synthesis, and lipid and nucleic acid metabolism (52). Moreover, any reaction that either produces or consumes ATP has a mandatory requirement for magnesium (53). This includes the enzymes of glycolysis and oxidative phosphorylation. Thus, any decline in magnesium concentration following neurotrauma will adversely affect the cells ability to maintain membrane potential and repair itself.

Magnesium is also essential for the stability and normal functioning of the cell membranes (54). Indeed, magnesium depletion has been reported to increase membrane turnover and fluidity and to increase lipid peroxidation (55). Increased lipid peroxidation is indicative of oxidative stress suggesting that magnesium may also play a central role in this process. Hydrolysis of membrane phospholipids and activation of the free fatty acid cascade is strongly related to the generation of reactive oxygen species. These reactive oxygen species initiate further cell damage, in part, through peroxidation of membrane components (56). Moreover, peroxidative reactions themselves initiate complex chain-reactions which generate even more free radicals (57). These free radicals, along with other damaging neurochemical events, have been shown to play an important role in the pathophysiology of CNS injury (58, 59). Indeed, the increase in reactive oxygen species in the brain soon after CNS injury correlates with formation of cerebral oedema, secondary ischemia, and impairment of microvascular regulation (56, 60-63). Regan and colleagues (64) have suggested that the vulnerability of neurons to iron-dependent oxidative injury is an inverse function of the extracellular magnesium concentration. Their studies demonstrated that magnesium at high concentration directly inhibits lipid peroxidation, most probably by competing with iron for phospholipid binding sites. However, at low magnesium concentrations, increased cell death may be result of to the combined effect of increased n-methyl-D-aspartate receptor activity, impairment of antioxidant defense, and direct potentiation of the oxidative stress. Nonetheless, magnesium's direct impact on free radicals has been recently confirmed (65). Therefore, specific free radical scavenging therapies may be of some utility as a treatment intervention following experimental traumatic brain injury. Certainly these therapies, particularly those using combination magnesium and antioxidant agents, have met with some success in cerebral ischemia (66-68). Recent results from our laboratory support the beneficial effects of magnesium administration in attenuating oxidative stress following indirect neurotrauma. Specifically, magnesium sulfate administered immediately following peripheral trauma in rabbits reduced posttraumatic superoxide anion generation in a number of brain structures. The generation of superoxide anions is generally thought to be the early phase in the development of oxidative stress that culminates in the generation of lipid peroxidation by-products.

The membrane-stabilizing properties of magnesium don't only affect lipid peroxidation and generation of reactive oxygen species, but also impact upon the release of neurotransmitters and other mediators/modulators. Indeed, both glutamate release (69) and acetylcholine release (70) are reduced by the administration of magnesium. Both of these transmitters are increased after trauma (71). Magnesium's effect on glutamate release is perhaps indirect arising largely from the cation's membrane-stabilizing properties. The amount of the acetylcholine released, however, has been shown to be dependent upon Ca2+ and Mg2+-concentrations. While Ca2+ increases acetylcoholine release during neuronal depolarisation, Mg2+ decreases acetylcholine release by stabilizing the membranes of presynaptic vesicles (70). Significant elevations in neurotransmitters, and particularly the excitatory amino acids including glutamate, are among the most important autodestructive responses occurring during the early posttraumatic period after trauma (47, 71). In particular, glutamate activation of n-methyl-D-aspartate (NMDA) and -amino-3-hydroxy-5-methylisoxazole-4-proprionate / kainate receptors leads to increased intracellular calcium and sodium concentrations which activates a complex cascade of interactive biochemical alterations and subsequent cell death (72). Indeed, the NMDA channel has been implicated as a critical factor in the development of cellular injury following neurotrauma (47). A considerable body of evidence indicates that the magnesium cation is the endogenous regulator of NMDA channel activity (73, 74). It is the specific effects of the ion on the activity of the NMDA channel that has been recently reported to be critical to outcome following central nervous system trauma (75). These authors demonstrate in an in vitro study that the magnesium block of the NMDA channel is reduced after neural injury, and that this reduction may be linked to either a decline in magnesium levels, or a change in the structure of the NMDA channel. Indeed, increasing the magnesium level in culture was neuroprotective. Moreover, other studies have reported that peripherally administered magnesium sulfate results in a significant reduction of the NMDA receptor binding capacity in the rat brain (76). Thus as an endogenous blocker of both NMDA and voltage-gated calcium channels (77), magnesium regulates calcium concentration within a cell and modulates posttraumatic neurochemical changes mediated by these elevated intracellular calcium levels.

Elevations in intracellular calcium concentration not only occur through ionotropic receptors, but also through second-messenger linked receptors. Abundant experimental evidence exists demonstrating that neurotransmitters, hormones and even mechanical damage also increase intracellular calcium concentration through activation of phospholipase C and subsequent hydrolysis of phosphatidyl inositol 4,5-bisphosphate into inositol 1,4,5-triphosphate (IP3) (78). IP3 is an an intracellular messenger with regulatory effects on nerve cell excitability, neurotransmitter secretion, posttetanic potentiation and differentiation, both in physiological and pathological conditions (79). Magnesium modifies the activity of the IP3-messenger system mainly by reducing the affinity of the receptor for IP3 (80, 81). Therefore, magnesium's role in the defense mechanisms following traumatic brain injury can be partially explained by its activity as an intracellular calcium antagonist acting on IP3-sensitive channels. Bearing in mind that the phosphatidylinositol cycle is involved as a second messenger system in the regulation of various endogenous mediators/modulators, the importance of magnesium's influence on IP3-sensitive calcium channels is evident.

It is now generally accepted that calcium ion influx and its intracellular redistribution are key events following brain injury (82). One of the consequences of calcium influx is initiation of pathways involved in breakdown of lipid membrane constituents and subsequent accumulation of free fatty acids, particularly arachidonic acid (83). At high concentrations, arachidonic acid can inhibit Na+ / K+-ATPase activity and induce cerebral edema, as well as increasing release of neurotransmitters like glutamate and its reuptake (84). There is now strong evidence that magnesium has an important role in the regulation of arachidonic acid metabolism (85). Depletion of intracellular Mg2+ has been shown to reduce incorporation of exogenous arachidonic acid into tissue phospholipids, perhaps by reducing synthesis of arachidonyl CoA and thus modifying the first phase in the incorporation of exogenous fatty acids into membrane phospholipids (86). Moreover, Mg2+ binding to its specific binding site on protein kinase C causes reduced activity of this enzyme, suggesting that some of the effects of intracellular Mg2+ depletion may be mediated through protein kinase C activation. Increased PKC-mediated phosphorylation of enzymes which are involved in arachidonic acid incorporation (CoA synthetase, lysophosphatidylcholine acyl transferase) reduces their activities and subsequently increases the concentration of the free arachidonic acid and its metabolites (85). The relationship between magnesium and phospholipid/arachidonic acid metabolism in traumatic brain injury has been confirmed in our previous study demonstrating that phospholipase C inhibitor neomycin administered immediately prior to traumatic brain injury in rats significantly improved free magnesium concentration, bioenergetic state and neurological outcome (50). Our results thus suggest that phospholipase C-activated second messenger pathways may affect magnesium homeostasis. Phospholipase C is not the only phospholipase enzyme that contributes to neuronal cell death after CNS injury. It has been established that platelet-activating factor synthesized through the actions of phospholipase A2 significantly contributes to posttraumatic ischaemia, inflammatory changes and the impairment of the cerebral blood flow in much the same way as the products of the arachidonic acid metabolic cascade (87, 88). The fact that phospholipase-induced products may also act to chelate magnesium (89) suggests a possible role of phospholipae activity in the posttraumatic depletion of free magnesium and impairments of cellular bioenergetic state (85).

In addition to the cellular effects described above, magnesium has also been shown to affect physiologic functions after trauma such as blood flow. Experimental data have demonstrated that magnesium sulfate administration increases cerebral blood flow velocity in the normal intact cerebral vasculature, accompanied by increased arterial carbon dioxide tension (90). On the other hand, magnesium deficiency has been found to sensitize the vascular epithelium to prostanoids and induces rapid calcium-mediated vasospastic responses in cerebral blood vessels (91). Administration of magnesium decreases vascular resistance and causes vascular dilation (92). Furthermore, recent experimental data have demonstrated that magnesium sulfate injection reverses pressor effects and cerebral vasoconstriction previously induced by noradrenaline (93). These authors suggest direct effects of Mg2+ on the actions of noradrenaline in the cerebral and peripheral vasculature leading to subsequent vasodilation and decrease in vascular resistance. Experimental data published by Chi et al. (94) have described beneficial effects of magnesium on cerebral blood flow in the ischemic brain region, which was superior than the effects of nimodipine. Others have reported that magnesium administration dramatically attenuates myocardial dysfunction associated with brain damage and caused by excessive release of catecholamines and calcium ion overload (95). Finally, clinical studies have shown that magnesium's effect on the cerebral vascular bed may contribute to the neuroprotection observed following stroke (96). Indeed, the increased blood flow in the penumbral tissue is thought to reduce the size of the eventual infarction.

6. CLINICAL STUDIES

Recent evidence in clinical neurotrauma also supports the concept that significant declines in free magnesium concentration occur after penetrating and non-penetrating head injury and that such a decline may be an important factor determining posttraumatic course and outcome. Significant declines in blood free magnesium concentration have been reported following both direct (97) and indirect clinical neurotrauma (98). These data show that both direct and indirect neurotrauma cause significant changes in divalent cation balance, and that following indirect neurotrauma, these changes are correlated to alterations in oxidative status/antioxidant defense. The fact that the alterations in magnesium homeostasis and oxidative stress were closely related suggests common mechanisms involved in their pathogenesis. Dose-dependency of plasma ionized magnesium decline and head

injury severity implicates that measurement of plasma free magnesium should be included in evaluation of patients with traumatic brain injury, planning of treatment and determining prognosis.

7. MECHANISTIC CONSIDERATIONS

Few studies have examined how brain total and free magnesium may decline following injury to the central nervous system. It was generally assumed that changes in ligand binding of the ion would regulate free magnesium concentration in keeping with the role that these ligands play in buffering the cation. Thereafter, loss of cells during necrosis or apoptosis might explain the total tissue losses. In support of the free magnesium decline, Vink (89) demonstrated that phospholipase C activity results in decline in free magnesium levels in ATP loaded membrane vesicles. This could only have occurred by increasing the magnesium binding sites in the membranes. However, this would not explain total tissue losses. Moreover, histologic examination of injured tissue does not support the loss of over 10% of the total tissue which is what the total tissue magnesium loss amounts to. Therefore, there must be some active transport of magnesium out of the brain thereby reducing total CNS content. In keeping with the finding that increased adenylate cyclase activity results in loss of total magnesium content from mitochondria (99, 100), one possibility is that activation of this enzyme results in extrusion of mitochondrial magnesium with subsequent loss from the cell down its concentration gradient. Although this is simply conjecture at this point of time, characterisation of magnesium transporters and the development of specific antagonists may not only rationalise the changes in tissue magnesium, but also lead to an entire new therapeutic strategy to be investigated.

8. CONCLUSION

In conclusion, we have summarized a growing body of both experimental and clinical evidence indicating that magnesium decline plays a critical role in the development of irreversible tissue damage following direct and indirect neurotrauma. Moreover, the fact that magnesium has now been shown to be neuroprotective in both focal and diffuse forms of brain injury suggests that the magnesium ion plays a ubiquitous role in determining functional outcome following brain injury.

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