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The Mitochondrial Permeability Transition in Neurologic Disease

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Abstract

Mitochondria, being the principal source of cellular energy, are vital for cell life. Yet, ironically, they are also major mediators of cell death, either by necrosis or apoptosis. One means by which these adverse effects occur is through the mitochondrial permeability transition (mPT) whereby the inner mitochondrial membrane suddenly becomes excessively permeable to ions and other solutes, resulting in a collapse of the inner membrane potential, ultimately leading to energy failure and cell necrosis. The mPT may also bring about the release of various factors known to cause apoptotic cell death. The principal factors leading to the mPT are elevated levels of intracellular Ca^{2+} and oxidative stress. Characteristically, the mPT is inhibited by cyclosporin A. This article will briefly discuss the concept of the mPT, its molecular composition, its inducers and regulators, agents that influence its activity and describe the consequences of its induction. Lastly, we will review its potential contribution to acute neurological disorders, including ischemia, trauma, and toxic-metabolic conditions, as well as its role in chronic neurodegenerative conditions such as Alzheimer's disease, Parkinson's disease, Huntington's disease and amyotrophic lateral sclerosis.

Keywords

Alzheimer's disease; ammonia; amyotrophic lateral sclerosis; apoptosis; calcium homeostasis; cell death; cyclosporin A; excitotoxicity; hepatic encephalopathy; Huntington's disease; ischemia; manganese; mitochondria; mitochondrial permeability transition; oxidative stress; Parkinson's disease; Reye's syndrome; trauma

1. Introduction

Mitochondria play a central role in cellular bioenergetics and are often referred to as the "powerhouse" of the cell due to their primary role in the generation of ATP required for

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cellular functions. Approximately 98% of oxygen in the cell is consumed by mitochondria through oxidative phosphorylation in order to generate ATP (Hatefi, 1985). Such continuous oxidative reactions also produces reactive oxygen species (ROS) that are implicated in various pathological conditions (Salganik et al., 1994). Mitochondria also act as high-capacity Ca^{2+} sinks by transporting calcium from the cytosol for the regulation of key enzymes (dehydrogenases) of the citric acid cycle, and they also act as temporary stores of this ion (Nicholls and Budd 2000; Nicholls, 2005). The Ca^{2+} from the cytosol is normally transported into mitochondria by an electrogenic uniporter while its efflux from mitochondria is mediated by the Na^{+}/Ca^{2+} exchanger (Gunter and Gunter, 2001).

Recent studies have also implicated mitochondria in cell death mechanisms, since mitochondrial dysfunction results in the release of factors that initiate, amplify and execute various signals resulting in apoptotic cell death (Kroemer and Reed, 2000). Additionally, mitochondrial dysfunction and associated bioenergetic failure can lead to abnormal cellular ion homeostasis, as a result of which cells undergo swelling and cellular disruption, eventually leading to necrotic death (Nieminen, 2003).

The outer membrane of mitochondria is permeable to small solutes and ions, while the inner membrane is virtually impermeable and forms a barrier between the cytosol and mitochondrial matrix. Electrons are transferred from reduced nucleotides to various intermediates of the electron transport chain during which protons are pumped across the inner membrane from the matrix into the inter membrane space. This proton transport creates a transmembrane potential ($\Delta\Psi m$) (Tedeschi, 1980) which provides the motive force required for ATP synthesis, as well as for facilitating the selective entry of ions such as Ca^{2+} (Siliprandi et al., 1983).

In conditions of increased Ca^{2+} loading, especially when accompanied by oxidative stress and a fall in adenine nucleotides, mitochondria undergo a phenomenon referred to as the permeability transition (mPT). The mPT is traditionally defined as a phenomenon associated with the opening of a proteinaceous permeability transition pore (referred to as the pore in the rest of the article) located in the inner mitochondrial membrane allowing solutes with molecular masses of up to 1500 Da to enter or exit the mitochondrial matrix. This opening results in osmotic swelling of the mitochondrial matrix, dissipation of the $\Delta\Psi m$, cessation of the ATP synthesis, and the release of cytochrome *c* and other apoptogenic factors (Zoratti and Szabo, 1995).

2. The mitochondrial permeability transition

While the concept that mitochondria undergo swelling in the presence of various substances was known for the past 50 years, it was not until the classic work of Haworth and Hunter (1979) who demonstrated that Ca^{2+} induces swelling in mitochondria, a phenomenon they referred to as a "Ca^{2+}-induced transition", that the mPT acquired scientific interest. Such transition (i.e., transition to swelling) appeared to be directly proportional to the external Ca^{2+} concentration.

Interest in the mPT increased further when it was shown that the mPT could be specifically blocked by the immunosuppressive agent cyclosporin A (CsA) (Crompton at al., 1988).

Such inhibition of the mPT by CsA involves its interaction with the mitochondrial matrix protein cyclophilin D (CyP-D) thereby preventing it from binding to the adenine nucleotide translocator (ANT) (Halestrap et al., 1997a). It should be emphasized that the action of CsA on the mPT is not mediated by its well known calcineurin inhibitory effect (Liu et al., 1991) (its mode of action in immunosuppression), but rather by its direct interaction with components of the pore.

2.1. Composition of the mitochondrial permeability transition pore

Despite extensive studies, the precise composition of the pore is still unknown. The pore is believed to be a voltage-dependent channel that is formed by a set of mitochondrial proteins located on the inner membrane, mitochondrial matrix, as well as on the outer membrane (Zoratti and Szabo, 1995). While the proteins involved in pore formation remain to be defined, they are generally believed to include the voltage-dependent anion channel (VDAC), an outer mitochondrial membrane protein (Szabo and Zoratti, 1993); the ANT, an inner mitochondrial membrane protein (Halestrap and Davidson, 1990); and CyP-D, residing in the mitochondrial matrix (Griffiths and Halestrap, 1991). Under conditions favorable for the mPT, component proteins assemble to form the pore. It has been suggested that binding of the matrix protein CyP-D with the ANT changes the conformation of the ANT, allowing it to interact with the VDAC located at contact sites of the outer and inner mitochondrial membranes thereby creating the pore (Crompton et al., 2002). A schematic diagram depicting the putative structure of pore is shown in Figure 1.

VDAC is a 32 kDa protein that exists as dimer on the outer mitochondrial membrane that allows the entry and exit of various metabolites required for mitochondrial metabolism (Shoshan-Barmatz and Gincel, 2003). While VDAC has been shown to interact with the ANT in pore formation (Szabo and Zoratti, 1993), its involvement in the pore has been recently questioned since mitochondria isolated from VDAC knock-out mice undergo a similar degree of mitochondrial swelling induced by Ca^{2+} (Krauskopf et al., 2006). While this study argues against the participation of VDAC in pore formation, these authors nevertheless suggested the possibility that more than one isoform of VDAC may be involved in pore formation.

The ANT is a 30 kDa protein located on the inner mitochondrial membrane, which is mainly involved in the exchange of ATP with ADP. The ANT appears to be involved in pore formation and such involvement is related to its binding with the matrix protein CyP-D (Woodfield et al., 1998). Several studies employing reconstituted ANT (Brustovetsky and Klingenberg, 1996), inhibitors of the ANT (Ruck et al., 1998), and mPT inducers (Checler, 1999) have shown the involvement of ANT in pore formation. However, Kokozska et al. (2004) demonstrated that mitochondria isolated from liver of ANT null mice still underwent Ca^{2+}-induced swelling. These authors proposed instead that the ANT may be a regulator of the pore. The precise role of ANT in pore formation still needs to be better defined.

Cyclophilin-D (CyP-D) is an 18 kDa mitochondrial matrix protein, which as noted above, has been proposed to represent the major target of CsA's inhibitory action on mPT. The binding of CyP-D to the ANT is largely regulated by matrix Ca^{2+} which acts as a signal for the translocation of CyP-D to the inner membrane (Connern and Halestrap, 1994).

Consistent with this view, recent studies employing transgenic mice in which the CyP-D gene has been deleted, showed a critical role of CyP-D in pore opening. Nakagawa et al. (2005) and Baines et al. (2005) reported that mitochondria isolated from transgenic mice lacking Cyp-D are resistant to CsA-sensitive induction of the mPT as compared to wild type mitochondria. Basso et al. (2005) have shown that mitochondria derived from CyP-D deficient mice continue to undergo mPT but the Ca^{2+} requirement for mPT induction was twice as high as that of normal mitochondria.

Other proteins implicated in the pore formation include the peripheral benzodiazepine receptor, an outer mitochondrial membrane protein (McEnery et al., 1992) and hexokinase (Beutner, et al., 1998), but their precise involvement in pore formation is still not clear. Creatine kinase has also been proposed to be a component of the pore by its interaction with VDAC and the ANT (see Figure 1) (Brdiczka et al., 1998). Creatine can stabilize creatine kinase into an octomeric forms and such octomers have been shown to inhibit activation of the mPT (O'Gorman et al., 1996).

He and Lemasters (2002) have recently put forward a novel concept that two modes of the mPT exist - a CsA-sensitive mode, and an unregulated (CsA-insensitive) mPT that appears to result from the aggregation of multiple integral membrane proteins as a result of oxidative damage. How these aggregates interact with the “traditional” members of the pore is not clear.

2.2 Measurement of the mPT

Opening of the pore has been widely demonstrated in isolated mitochondrial fractions. Crompton et al. (1998) were the first to establish that such preparations when exposed to various concentrations of Ca^{2+} undergo swelling in a CsA-sensitive manner and such swelling can be assayed as a decrease in optical density. Another in vitro assay measures the CsA-sensitive dissipation of the membrane potential by determining extramitochondrial levels of triphenylphosphonium ion (TPP^+) with a TPP^+-sensitive electrode (Ross et al., 2005).

Measurement of the mitochondrial $\Delta\Psi m$ in intact cells was made possible with the advent of potentiometric fluorescent dyes. These include rhodamine 123, terametylrhodamine ethyl ester (TMRE) and its methylated form TMRM, 5,5',6,6'-tretachloro-1,1',2,3'-tetraethylbenzamidazoocarbocyanine (JC1), DiOC6 and DASPMI. An example of this methodology is shown in Figure 2. These cationic lipophilic dyes accumulate in the mitochondria following the Nernst equation, as changes in the $\Delta\Psi m$ alter the distribution of these dyes between cytosol and mitochondria (Duchen, 2004).

Petronilli et al. (1999) first employed the calcein fluorescence method to demonstrate the induction of the mPT. This method allows one to directly visualize permeability changes in mitochondria *in situ*. Kerr et al. (1999) developed the 2-deoxy-glucose-6-phosphate (2-DG-6-P) entrapment method to determine pore opening. This method may be particularly useful when investigating the mPT in vivo.

2.3 Inducers of the mPT

In conditions associated with high cytosolic levels of Ca^{2+}, mitochondria have a great capacity to accumulate Ca^{2+} via the uniporter, an inner membrane protein channel that transports Ca^{2+} as a function of the $\Delta\Psi m$ (Siliprandi et al., 1983). Under conditions of heightened cytosolic calcium content, the uniporter can transport large quantities of Ca^{2+} (as it may not be saturated due to its channel properties), resulting in a Ca^{2+} overload of mitochondria and opening of the pore (Halestrap, 2006). How increased mitochondrial Ca^{2+} induces pore opening is not clear. One proposed mechanism involves the facilitation of CyP-D binding to the ANT by Ca^{2+} (Halestrap and Brennerb, 2003).

Oxidative stress is another major factor in the induction of the mPT (Halestrap et al., 1997b; Kowaltowski et al., 2001). It had been earlier shown that the release of Ca^{2+} from mitochondria (a phenomenon later confirmed as the mPT) was accelerated by oxidation of pyridine nucleotides (NADPH) (Lehninger et al., 1978), suggesting that mPT induction is strongly dependent on the redox state of the mitochondria. Such oxidation of pyridine nucleotides also diminishes glutathione levels, thereby decreasing the activity of glutathione peroxidase and resulting in free radical production and induction of the mPT (Kowaltowski et al., 2001). Additionally, ROS-mediated oxidation of thiol groups on mitochondrial proteins associated with the pore has been shown to result in pore opening (Halestrap et al., 1997b).

Additional factors important in the opening of the pore include an alkaline matrix pH, diminution of the adenine nucleotide pools, and reduction of inorganic phosphate (Pi) levels (Bernardi et al., 1992).

2.4 Agents that regulate the mPT

In addition to CsA, bongkrekic acid, an inhibitor of the ANT, is a potent inhibitor of the mPT (Brustovetsky et al., 1996). Several other agents are known to inhibit the mPT, however, the specificity of these agents to the mPT is doubtful. For instance, creatine (O'Gorman et al., 1997) and carnitine (Zanelli et al., 2005) are reported to inhibit the mPT, however, both are also known to increase high-energy phosphate stores (Ratnakumari et al., 1993; Brustovetsky et al., 2001; Klivenyi et al., 2004). Similarly, minocycline, a tetracycline derivative, inhibits the mPT and mPT-associated events such as the mitochondrial release of cytochrome *c* (Wang et al., 2003). However, it is also able to inhibit caspase-inducible form of nitric oxide synthase, as well as p38 MAP kinase (see (Mecocci et al., 1994; Zhu et al., 2002) and references therein), and such effects appear not to be mediated by the mPT. Other agents, including coenzyme Q (Fontaine et al., 1998), tamoxifen (Kimelberg et al., 2003), tricyclics and heterocyclics (desipramine, trifluoperazine) (Stavrovskaya et al., 2004), melatonin (Andrabi et al., 2004), promethazine (Stavrovskaya et al., 2004) all have to variable extent been shown to inhibit the mPT, but many of these agents also have antioxidant properties. The precise mechanisms by which these agents exert inhibitory effects on the mPT (directly or indirectly) still need to be more carefully assessed.

2.5 Consequences of the mPT

The major consequence of the opening of the MPT pore is dissipation of the mitochondrial inner membrane potential resulting in uncoupling of the oxidative phosphorylation and failure to synthesize ATP. Such malfunction of the electron transport chain results in ROS production (Votyakova and Reynolds, 2005). Thus, while oxidative stress is a major cause of the mPT, it can also be a consequence of the mPT.

The involvement of the mPT in the apoptotic cell death pathway has largely been studied by examining the release of cytochrome *c* (Liu et al., 1996) which activates procaspase 9 to stimulate downstream events related to apoptosis (Jemmerson et al., 2005). Additionally, certain apoptotic factors such as AIF and Smac/Diablo are also released (Brustovetsky et al., 2005). The efflux of cytochrome *c* involves members of the pro-apoptotic Bcl-2 family such as BAX, BAD and BID (Green and Reed, 1998). However, the mechanism by which BID and BAX association causes cytochrome *c* efflux is still not clear and whether such an event is mediated by the mPT remains controversial. While disagreement exist regarding the precise role of the mPT in mediating apoptosis, CsA has been shown to block this process (Crompton, 2003;Green and Kroemer, 2004). Recent studies by Schinzel et al. (2005) demonstrated that apoptosis continues to occur in embryonic fibroblasts in CyP-D null mice which have not undergone the mPT after a calcium stimulus, suggesting that the mPT is not important in the mediation of apoptosis.

Induction of the mPT can clearly result in necrotic cell death since the mPT leads to cessation of the ATP synthesis leading to loss of ion homeostasis, cell disintegration and death.

3. Neurological disorders

Many acute and chronic CNS disorders have common pathogenetic factors, including the involvement of excitotoxicity, oxidative stress, disturbances in calcium homeostasis and mitochondrial dysfunction. All these factors create an ideal environment for induction of the mPT. The discovery that CsA was able to inhibit the mPT initiated a flurry of research activity aimed at not only better understanding this process, but more importantly, investigating its possible involvement in disease and its potential as a therapeutic target.

The following sections briefly summarizes contemporary knowledge regarding the role of the mPT in neurological diseases. It must be cautioned that much of the supporting evidence implicating the mPT in disease is largely based on the protective effect of CsA and other mPT inhibiting agents. While such protection is suggestive, it is not definitive as CsA possesses other effects, in particular calcineurin inhibition (Liu et al., 1991). Unfortunately, many in vivo studies have not excluded calcineurin inhibitory effects. Agents inhibiting the mPT other than CsA have been used that are far less specific than CsA as mPT inhibitors, so that invoking the mPT based on beneficial therapeutic action may not be sufficient. Further, many of the studies have employed cell cultures. Although crucial in teasing apart mechanistic considerations, such studies do not prove that mechanistic events identified in culture are operative in vivo. Taking these caveats into account, a body of data has nevertheless emerged indicating that the mPT may be a major factor in disease pathogenesis.

3.1 Excitotoxicity

Excitotoxicity represents a cascade of events triggered by glutamate and other NMDA receptor agonists resulting in the excessive entry of Ca^{2+} ions into neurons, leading to the activation of destructive hydrolytic enzymes, mitochondrial injury, ROS formation and ultimately cell death (Choi, 1992; Coyle Putterfarcken, 1993). White and Reynolds (1996) and Dubinsky and Levi (1998) showed that such treatment resulted in the accumulation of large quantities of Ca^{2+} within mitochondria causing a dissipation of the $\Delta\Psi m$. The mitochondrial depolarization was blocked by CsA, indicating the probable involvement of the mPT. Schinder et al. (1996) further showed that CsA provided cytoprotection against excitotoxic injury in neuronal cultures. However, Ruiz et al., (2000) noted that while CsA protects against excitotoxicity, CsA derivatives that do not bind to calcineurin had a smaller effect on survival than CsA, suggesting that calcineurin inhibition by CsA also plays a part in such neuroprotection. FK506, a calcineurin inhibitor that has no effect on the mPT (Liu et al., 1991), has also been shown to protect against excitotoxicity (Dawson et al., 1993; Ankarcrona et al., 1996) indicating that calcineurin-mediated events also contribute to excitotoxic neuronal death. Thus, while it is clear that mPT represents an important component of the NMDA receptor-mediated excitotoxic cascade, it is by no means the only factor responsible for such injury.

In vivo studies examining the role of the mPT have been hampered by the limited transport of CsA across the BBB. Nevertheless, in vivo support for the role of the mPT in excitotoxic injury was provided by Santos et al. (2003) who systemically injected mice with the excitotoxin kainic acid, a procedure well known to cause cell death of hippocampal neurons. This study showed that CsA almost completely eliminated neuronal cell death, whereas FK506 had no effect. However, Maciel et al. (2003) observed no protection by CsA in an in vivo model of quinolinic acid-mediated excitotoxic lesions in rodents. The reason for the failure of CsA to protect against quinolinic acid is not known.

3.2 Ischemia

The involvement of mitochondria in ischemic cell death is well known, and has been recently extensively reviewed (Fiskum et al., 1999; Kristian, 2004). In the ischemic core mitochondria depolarize and their capacity for oxidative phosphorylation is acutely and irreversibly lost (Siesjö, 1992). Ischemia is consequently associated with a severe energy crisis leading to a profound drop in ATP/ADP levels, a build up of lactic acid, and a fall in intracellular pH (Siesjö, 1985, 1992). Such energy failure also leads to a disruption of Ca^{2+} homeostasis resulting in an elevation of intracellular Ca^{2+} levels (Kruman and Mattson, 1999). However, little of this calcium will enter mitochondria as the latter have become depolarized thus removing the driving force for Ca^{2+} entry into that organelle.

Consequently, during the ischemic phase, conditions may not be optimal for induction of the mPT as calcium is not able to enter mitochondria in sufficient amounts to create the mPT, and because of the acidosis which is known to inhibit the mPT (Friberg and Wieloch, 2002; Kristian, 2004). Rather, it is during the period of reperfusion that Ca^{2+} can be sequestered in re-energized mitochondria (Hansen and Zeuthen, 1981) and stimulate the formation of ROS. pH will briefly return to normal as lactic acid levels decrease and the activation of pH

regulatory pumps occur (Halestrap, 2006). All of these conditions now create an ideal environment for opening of the pore. It should be noted that while acidosis inhibits the mPT, in the setting of ischemia, there in an increased matrix influx of inorganic phosphate. The increase in phosphate, which is known to promote the mPT, appears to overcome the inhibitory effect of acidosis on the mPT (Kristian et al., 2001).

Oxygen-glucose deprivation (OGD) represents a useful in vitro model of ischemia (Goldberg and Choi, 1993). Khaspekov et al. (1999) showed that mouse hippocampal neuronal cultures transiently exposed to OGD for 90 min, followed by 24 h of reoxygenation, exhibited extensive neuronal degeneration. Preincubation of these cultures with CsA diminished neuronal death by 30–50%. Likewise, the CsA analogue, *N*-methyl-valine-4-cyclosporin A (*N*-Me-Val-CsA), a potent blocker of the mPT with no significant calcineurin inhibitory activity, decreased cell death by an even greater amount (70–80%). Such findings clearly establish a vital role of the mPT in ischemic cell death in vitro. Using the OGD model of ischemia, MacGregor et al. (2003) showed that CsA afforded similar protection against edema formation whereas FK506 did not. The mPT was detected in cultured astrocytes after OGD exposure, although it took much longer for it to occur as compared to cultured neurons (Reichert et al., 2001).

Consistent with the above findings, CsA has been shown to exert potent neuroprotection in global, as well as in focal ischemia (reviewed in Friberg and Wieloch, 2002). Because of the limited capacity of CsA to cross the BBB, investigators inserted a syringe needle into the brain parenchyma so as to disrupt the BBB. To address the issue of whether the effect of CsA was mediated by closure of the pore or by calcineurin inhibition, the investigators employed *N*-Me-Val-CsA and found that this agent also diminished infarct size (Matsumoto et al., 1999). The same group subsequently showed that CsA, but not FK506, blocked the mPT after middle cerebral artery occlusion (Yoshimoto et al., 2001).

A major advance in this field occurred with the development of transgenic mice deficient in CyP-D. As CyP-D is a critical component of the pore (see above), the use of these mice obviates many of the difficulties associated with mPT inhibitors. These mice were not susceptible to the mPT induced by the addition of calcium, and displayed a dramatic reduction in brain infarct size after acute middle cerebral artery occlusion and reperfusion, strongly supporting a central role of the mPT in cerebral ischemia (Schinzel et al., 2005).

A number of agents that have mPT inhibitory effects were reported to have beneficial effects in models of stroke, including bongkrekic acid (Muranyi and Li, 2005), melatonin (Andrabi et al., 2004), tricyclics and heterocyclics (e.g., desipramine, trifluoperazine), the antihistaminic promethazine and minocycline (Yrjanheikki et al., 1998; Stavrovskaya et al., 2004). Tamoxifen has mPT inhibitory effects (Moreira et al., 2005) and has recently been shown to have neuroprotective properties in stroke (Kimelberg et al., 2003; Feng et al., 2004). The specificity of these agents to the mPT is doubtful. Nevertheless, these studies support the concept that the mPT is a critical aspect of tissue injury associated with ischemia.

3.3 Hypoglycemia

In contrast to ischemia, cerebral blood flow is maintained in hypoglycemia, and there is also no lactic acid accumulation (Auer and Siesjö, 1988). When severe, membrane ionic gradients cannot be maintained, intracellular Ca^{2+} levels increase (Harris et al., 1984) the intracellular redox state shifts towards oxidation (Auer and Siesjö, 1988), and oxidative stress develops (Liu et al., 2003). All of these events may eventually cause the mPT. Indeed, Friberg et al. (1998) showed that CsA significantly reduced brain damage when administered prior to insulin-induced hypoglycemic coma. The marked swelling of dendrites and mitochondria in neurons of the dentate gyrus of the hypocampus was abrogated by CsA, while FK506 exhibited no protection.

3.4 Trauma

Mechanisms responsible for tissue injury in CNS trauma remain poorly understood. The initial mechanical injury (primary insult) results in the loss of membrane integrity and membrane depolarization, thereby initiating a cascade of molecular and cellular events over the succeeding hours and days (secondary insult) and resulting in the loss of ion homeostasis (in particular Ca^{2+}), development of brain edema, ischemia, hyperthermia, inflammation, glutamate-induced excitotoxicity, mitochondrial dysfunction, energy failure, and production of free radicals. All of these events will ultimately result in cell/tissue injury and death. For general reviews on pathogenetic mechanisms in traumatic brain injury (TBI), see Rey et al. (2002) and Raghupathi (2004). It is of interest that many of the factors believed to be instrumental in the mechanism TBI, are also known to induce the mPT.

Investigations into the role of the mPT in TBI were initiated by Povlishock and colleagues (Okonkwo et al., 1999; Buki et al., 1999) who found that CsA was able to attenuate trauma-induced axonal lesions. A follow-up study by the same group, however, found that FK506 was as effective as CsA (Singleton et al., 2001). Although not excluding the involvement of the mPT in these lesions, calcineurin inhibition appears to, at least in part, explain the beneficial effects of CsA.

Scheff and Sullivan (1999) observed that CsA significantly reduced the amount of cortical damage following TBI in rats and mice, while FK506 failed to protect against the cortical damage. The same research group subsequently identified the mPT in mitochondria isolated from traumatized brain (Sullivan et al., 1999). Improvement in mitochondrial function was shown by Signoretti et al. (2004). Together, these findings clearly indicate that a significant portion of the cortical damage after TBI is mediated by the mPT.

Interestingly, CsA was shown not to be effective in spinal cord trauma (Rabchevsky, et al., 2001). While explanations for the disparity between brain and spinal cord with regard to the involvement of the mPT following trauma is not known, differences between cord and brain mitochondria were subsequently identified that might explain the differential responsiveness to CsA (Sullivan et al., 2004). These investigators found that superoxide production, lipid peroxidation, and mitochondrial DNA oxidation were higher in spinal cord mitochondria as compared to cortical mitochondria. Complex I enzyme activity and respiration in spinal cord

mitochondria was also found to be reduced and the threshold for calcium-induced mPT was also reduced.

3.5. Toxic-metabolic

(a) Hepatic encephalopathy—Hepatic encephalopathy (HE) is a complex neuropsychiatric syndrome resulting from severe liver failure. It may manifest in a chronic form (portal-systemic encephalopathy), which usually occurs in the setting of alcoholic liver cirrhosis. HE may also occur acutely (acute liver failure) following viral hepatitis, and drug-induced hepatotoxicity. Acute HE has an extremely poor prognosis with a mortality rate of about 90%, and the only effective treatment is an emergency liver transplantation. For review of clinical aspects of HE, see Jones and Weissenborn, 1997).

Although mechanisms responsible for HE remain elusive, ammonia is generally considered a key factor in its pathogenesis (Hazell and Butterworth, 1999), with astrocytes being the principal target of ammonia neurotoxicity (Norenberg, 1998). The involvement of astrocytes is likely due to the fact that ammonia in brain is primarily metabolized by glutamine synthetase (Cooper and Plum, 1987), an enzyme predominantly localized in astrocytes (Norenberg and Martinez-Hernandez, 1979). Accordingly, high levels of glutamine in brain is a characteristic feature of HE (Albrecht and Norenberg, 2006).

Many factors that are conducive to the induction of the mPT are also known to be implicated in the mechanism of HE, including oxidative/nitrosative stress (Norenberg et al., 2004), elevation in intracellular Ca^{2+} (Rose et al., 2005), and alkaline pH (Cooper and Plum, 1987). Recent studies have demonstrated the induction of the mPT by pathophysiological concentrations of ammonia in cultured astrocytes (Bai et al., 2001; Rama Rao et al., 2003b; Rama Rao et al., 2005b) (see Figure 2). Such ammonia-induced free radical production and the mPT were both blocked methionine sulfoximine (Murthy et al., 2001; Bai et al., 2001), an inhibitor of glutamine synthetase, invoking the possibility that glutamine rather than ammonia per se is responsible for these events. Studies employing clinically relevant concentrations of glutamine (6–8 mM), have shown that glutamine causes free radical production (Jayakumar et al. 2004), and induces the mPT in cultured astrocytes (Rama Rao et al., 2003c), but not in cultured neurons (Rama Rao et al., 2005a). These changes were blocked by 6-diazo-5-oxo-L-norleucine (DON), an inhibitor of mitochondrial phosphate-activated glutaminase, suggesting that the hydrolysis of glutamine in mitochondria represents the basis for the free radical production and the mPT in ammonia-treated astrocytes (reviewed in Albrecht and Norenberg, 2006).

Induction of the mPT by ammonia has been shown to exert a major impact on astrocyte properties (Rama Rao et al., 2003b; Norenberg et al., 2005), including the development of cell swelling, a critical component of the brain edema associated with acute HE (Norenberg, 1977; Traber et al., 1987), as well as inhibition of glutamate uptake (Jayakumar et al., 2006). CsA was shown to reduce both ammonia-induced astrocyte swelling (Rama Rao et al., 2003a) as well as correct the glutamate uptake inhibition in cultured astrocytes (Jayakumar et al., 2006). While the direct role of the mPT in in vivo models of HE has not been established, recent unpublished studies (Jayakumar et al.) have shown that CsA protected against brain edema in an acute model of HE, and that such protection was not detected with

FK506, supporting the involvement of the mPT in the brain edema associated with acute HE.

(b) Manganese—Manganese is known to cause CNS injury leading to Parkinson's disease-like neurological abnormalities (parkinsonism) (Wennberg et al., 1992). Manganese also has been implicated in the pathogenesis of chronic hepatic encephalopathy (Hazell and Butterworth, 1999). Manganism is also an occupational health problem in workers employed in welding factories, manganese mines and ferro-alloy plants (Kaiser, 2003a). The widespread use of the manganese derivative, methylcyclopentadienyl manganese tricarbonyl (MMT) as an anti-knock agent in gasoline has evolved into a major environmental issue (Kaiser, 2003b).

Although mechanisms of manganese neurotoxicity are not completely understood, chronic exposure of various cell types to manganese resulted in oxidative stress and mitochondrial energy failure, factors implicated in the induction of the mPT. Neurotoxic concentrations of manganese (Mn^{3+}) induce the mPT in cultured astrocytes, while in cultured neurons such induction is delayed and less severe (Rama Rao et al., 2004). This differential effect could be due to the inherently higher capacity of astrocytes to accumulate manganese as compared to neurons (Aschner et al., 1992). Studies also demonstrated that various antioxidants significantly blocked manganese-induced mPT, supporting a role of oxidative stress in this process (Rama Rao et al., 2004).

(c) Reye's syndrome—Reye's syndrome is a lethal childhood disorder that usually occurs following viral infections. Mitochondria in brain and liver had been shown to be structurally and morphologically affected in Reye's syndrome patients (Partin et al., 1971). Aspirin has been strongly implicated in the pathogenesis of Reye's syndrome (Trost and Lemasters, 1996), and salicylate, the hydrolyzed product of aspirin, has been shown to induce the mPT in mitochondria (Trost and Lemasters, 1996).

3.6. Degenerative diseases

Neurodegenerative disorders comprise a heterogeneous group of chronic, age-related conditions that are associated with a disease-specific topographic loss of neurons, astrogliosis and microgliosis. These conditions are inexorably progressive, of unknown etiology and unfortunately, without known cures. Common features to neurodegenerative conditions appear to be mitochondrial dysfunction and bioenergetic failure (Fiskum et al., 1999; Cassarino et al., 1999), oxidative stress (Lin and Beal, 2006) (possibly related to bioenergetic failure), and iron deposition (Zecca et al., 2004) which is commonly involved in the generation of ROS (Fenton reaction).

A factor common to the degenerative diseases is aging, which represents the greatest risk factor for these disorders. The aging process is associated with the accumulation of mitochondrial DNA mutations and appears to be the chief source of ROS (Lin and Beal, 2006). In normal aging mitochondrial DNA damage accumulates (Mecocci et al., 1993) and mitochondrial respiratory function decreases (Yen et al., 1989). Aged cells have been shown to have elevated intracellular calcium levels (Squier and Bigelow, 2000) and the activation of the mPT by calcium is enhanced with age (Mather and Rottenberg, 2000).

A number of events associated with neurodegenerative conditions, acting in concert, create conditions conducive to induction of the mPT. These include mitochondrial failure, oxidative stress, disruption of calcium homeostasis and aging, all of which will be highlighted in conditions to be presented in the following sections.

(a) Alzheimer's disease—Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the leading cause of late-onset dementia in adults. About 10% of cases are familial with mutations in the amyloid precursor protein (APP), and presenilin-1 and -2, which may be part of the γ-secretase complex. The pathological hallmarks of AD are extracellular amyloid "neuritic" plaques (Glenner, 1989), which are composed of aggregates of β-amyloid (Aβ), a 39–42 amino acid peptide derived from the proteolytic breakdown of APP (Selkoe, 2001).

Oxidative stress has been increasingly recognized as a factor in the pathogenesis of AD (see Behl, 1999; Perry et al., 2000). There is abundant evidence that Aβ is toxic and plays a crucial role in AD pathogenesis (Selkoe, 2000), and that such toxicity is enhanced when the Aβ peptide becomes aggregated (Puttfarcken et al., 1996). A major aspect of Aβ toxicity is the promotion of oxidative stress. The Aβ peptide appears to be an important source of free radicals, which in turn, enhances Aβ aggregation (Dyrks et al., 1992), thereby making Aβ more toxic. Additional sources of free radicals in AD may come from activation of NADPH oxidase, a source of superoxide anion and H_2O_2, possibly derived from glial activation (Abramov et al., 2004), as well as from mitochondrial dysfunction (see below). Noteworthy, there is evidence of oxidative damage to mitochondrial DNA in Alzheimer's disease (Mecocci et al., 1994; Rodrigues et al., 2001), and such oxidative damage to mitochondria may bring about additional free radical formation.

Aβ, including its aggregated form, is also known to bring about a dysregulation of Ca^{2+} homeostasis (Mattson et al., 1992; Sheehan et al., 1997). Such dyregulation may contribute to the mitochondrial impairment observed in AD (Lin and Beal, 2006) and after exposure of cells to Aβ (Pereira et al., 1998; Parks et al., 2001). Recent studies have identified Aβ in mitochondria (Anandatheerthavarada et al., 2003; Hansson et al., 2004; Manczak et al., 2006) as well as presenilins and the γ-secretase complex (Hansson et al., 2004). These proteins likely exert untoward effects on mitochondria.

As documented above, AD and Aβ have been associated with oxidative stress, calcium dysregulation and mitochondrial dysfunction, thereby making conditions ripe for mPT induction. It is therefore not surprising that several studies have shown that exposure of isolated mitochondria to neurotoxic Aβ peptides lead to a drop in $\Delta\Psi m$, matrix swelling and impaired respiration in the presence of Ca^{2+} (Parks et al., 2001; Moreira et al., 2002). These changes were blocked by CsA. Additionally, use of PC12 cell lines expressing the presenilin-1 mutation (L286V) exhibited increased sensitivity to apoptosis when exposed to complex II inhibitors, and such action of mutant presenilin-1 was prevented by CsA (Keller et al., 1998).

(b) Parkinson's disease—Parkinson's disease (PD) is characterized by progressive rigidity, poverty of movement (bradykinesia), tremor, and postural instability. The condition

is due to the loss of melanin-containing dopaminergic neurons in the substantia nigra and other sites. Other histopathological features include Lewy bodies, which are eosinophilic cytoplasmic inclusions composed largely of α-synuclein (Lang and Lozano, 1998). The mechanism responsible for the neurodegeneration in PD is not known. Environmental factors and genetic susceptibility, however, are strongly suspected to be involved, and oxidative stress and mitochondrial dysfunction have emerged as critical mediators of the neuronal damage in PD (for reviews, see Blum et al., 2001; Beal, 2003). There is also evidence for excitotoxicity in the mechanism of PD (Beal, 1998).

Mitochondrial involvement in PD was initially proposed when it was shown that the parkinsonian toxin, 1-methyl-4-phenyl pyridinium ion (MPP^+) derived from 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), inhibits complex I of the mitochondrial electron transport chain (Nicklas et al., 1985). MPTP has proven to be an excellent agent to clarify pathogenetic mechanisms in PD (Kopin, 1992; Singer et al., 1993). Its administration to primates and rodents recapitulates many of the clinical, biochemical and pathological features of PD.

A reduction in complex I activity, impaired cellular energy metabolism and mitochondrial function along with excessive production of ROS were identified in patients with PD (Beal, 2000). MPP^+ has been shown to cause mitochondrial depolarization (Cleren et al., 2005), and rotanone, another complex I inhibitor, has also been shown to cause similar clinical and pathological changes to that seen in humans with PD (Greenamyre et al., 2003). A number of genes have been associated with PD including α-synuclein, parkin, UCH-L1, DJ-1 and others, and all appear to have important interactions with mitochondria (reviewed in Lin and Beal, 2006).

Since oxidative stress and mitochondrial dysfunction are features of both human and experimental PD, it was reasonable to expect that the mPT might be involved in PD. MPP^+ causes mitochondrial swelling and the release of cytochrome *c*, which was inhibited by CsA (Cassarino and Bennett, 1999). Packer et al. (1996) showed that exposure of MPP^+ to mitochondria to caused a CsA-sensitive calcium efflux and membrane depolarization. Additionally, another parkinsonian neurotoxin, N-methyl(R)salsolinol, aminoindan, was shown to mediate an mPT-dependent apoptosis, while CsA attenuated the degeneration of dopaminergic neurons induced by 6-hydroxydopamine in mice (Akao et al., 2002). Both rotenone and MPP^+ have been shown to induce apoptosis in PC12 cells, and such effect was attenuated by CsA and *N*-Me-4-Val-CsA (Seaton et al., 1998). DOPAL (3,4-dihydroxyphenylacetaldehyde), a monoamine oxidase metabolite of dopamine, also has been shown to be a potent inducer of the mPT in isolated mitochondria derived from PC12 cells (Kristal et al., 2001).

A number of agents with mPT inhibitory effects have been shown to attenuate the toxic effects of parkinsonian toxins. Promethazine, an antihistamine known to delay the onset of the mPT (Stavrovskaya et al., 2004), prevented the MPP^+-induced mitochondrial depolarization, inhibited the Ca^{2+}-induced mPT in isolated brain mitochondria and markedly attenuated the loss of nigral neurons (Cleren et al., 2005). Creatine has been shown to protect against MPP^+-induced neuronal loss (Matthews et al., 1999; Andres et al., 2005) and

against 6-hydroxydopamine neuronal loss (Andres et al., 2005). Similarly, minocycline was found to exert neuroprotective effects against MPTP toxicity both in vivo and in vitro (Du et al., 2001; Wu et al., 2002).

(c) Huntington's disease—Huntington's disease (HD) is a hereditary autosomal dominant progressive neurodegenerative fatal disorder with an onset at 35–40 years and an average survival of 15–20 years after the onset of the disease. It is clinically characterized by progressive motor disorder (choreiform movements) and behavioral and cognitive impairments. The disease largely affects the striatum and to a lesser extent the cerebral cortex (Vonsattel and DiFiglia, 1998).

The disease is due to a mutation in the *huntingtin (htt)* gene located on chromosome 4 resulting in expanded CAG repeats (coding for glutamine) (The Huntington's Disease Collaborative Research Group, 1993). Patients with HD have CAG repeats varying from 36–86 (average 46). The length of the polyglutamine extensions correlates with lower age of onset, severity of the disease and the higher density of ubiquitin-positive neuronal intranuclear inclusions (Walling et al., 1998). The prevailing hypothesis is that expanded glutamine repeats confers a toxic "gain of function".

Functional disturbances in mitochondrial bioenergetics are a common feature of HD models and humans with PD (for review, see Grunewald and Beal, 1999). The complex II inhibitors 3-nitropropionic acid (3-NPA) and malonate cause striatal lesions and energy impairment similar to HD (Beal et al., 1993; Andreassen et al., 2000). Lymphoblasts from patients with HD treated with complex II or IV inhibitors had greater mitochondrial depolarization than control lymphoblasts. Interestingly, the severity of depolarization correlated with length of glutamine repeats and with the ability of mitochondria to depolarize at lower calcium concentration than control mitochondria (Sawa et al., 1999; Panov et al., 2002). As in other neurodegenerative diseases, there is a substantial role for oxidative stress (Browne et al., 1999) and excitotoxicity in HD (for reviews, see Whetsell and Shapira 1993; Beal, 1994).

Precisely how Htt brings about these mitochondrial changes is not well understood, although recent studies provide important clues. Mutant Htt has been found to be associated with various cellular organelles, including mitochondria (Gutekunst et al., 1998). Bae et al (2005) presented evidence for the involvement of the transcription factor p53 in the mitochondria-associated cellular dysfunction. Mutant Htt with expanded polyglutamine bound to p53 and upregulated levels of nuclear p53 in neuronal cultures. The p53 levels were also found to be increased in the brains of *Htt* transgenic mice and HD patients. Inhibiting p53 with pifithrin-alpha, RNA interference, or genetic deletion prevented the mitochondrial membrane depolarization and cytotoxicity in HD cells, as well as the decreased respiratory complex IV activity of transgenic mice. This important study provides a crucial link between nuclear and mitochondrial events in HD. Similarly, Choo et al. (2004) showed that the mutant Htt may directly interact with the outer mitochondrial membrane and affect its functions. They further demonstrated that mutant Htt induced the mPT in isolated mouse liver mitochondria as well as promoted cytochrome *c* release, both of which were blocked by CsA. Mutant Htt also significantly decreased the Ca^{2+} threshold necessary to trigger mPT pore opening.

Disturbances in calcium homestasis have been identified in HD. In a transgenic model of HD, the calcium buffering capacity of neurons expressing mutant Htt was found to be impaired (Hodgson et al., 1999; Panov et al., 2003). Synthetic peptides containing glutamine repeats capable of crossing the plasma and nuclear membranes of sympathetic neurons brought about elevated cytosolic Ca^{2+} levels, and decreased ATP levels (Suzuki and Koike, 2005).

There is evidence that HD neurotoxins and cells carrying the mutant *Htt* gene are prone to develop the mPT. The complex II inhibitor malonate has been shown to induce the mPT in isolated brain mitochondria (Fernandez-Gomez et al., 2005), while CsA protected striatal neurons in vitro and in vivo from 3-NPA toxicity. Synthetic peptides containing glutamine repeats capable of crossing the plasma and nuclear membranes were able to induce the mPT (Suzuki and Koike, 2005). Striatal neurons carrying the HD transgene were more susceptible to cell death after treatment with 3-NPA (Ruan et al., 2004), and such treatment was associated with a greater loss of $\Delta\Psi m$ compared with wild-type cells. CsA diminished 3-NPA-induced cell death and prevented the loss of $\Delta\Psi m$. Mutant Htt was also shown to induce mPT pore opening which was associated with the release of cytochrome *c* and was blocked by CsA (Choo et al., 2004). Zeron et al. (2004) found that primary striatal neurons carrying mutant *Htt* were more sensitive to NMDA receptor-mediated neurotoxicity than were normal neurons, and that such toxicity was attenuated by either CsA or bongkrekic acid.

In keeping with the potential involvement of the mPT in various models of HD, creatine was found to protect against malonate and 3-NPA in vivo models of HD (Matthews et al., 1998), as well as in transgenic mouse models of HD (Ferrante et al., 2000; Andreassen et al., 2001). Minocycline was reported to delay disease progression and to inhibit caspase-1 and caspase-3 mRNA upregulation in the R6/2 mouse model of HD (Chen et al., 2000).

(d) Amyotrophic lateral sclerosis—Amyotrophic lateral sclerosis (ALS) is an age-dependent progressive disorder resulting from degeneration of motor neurons in the ventral horns of the spinal cord, brainstem and motor cortex, along with associated degeneration of the corticospinal tract. This leads to progressive skeletal muscle atrophy, weakness, paralysis, and death frequently due to respiratory failure within 2 to 5 years of onset (Rowland and Schneider, 2001). About 10% of ALS cases are familial and approximately 20% of these have mutations in superoxide dismutase 1 (SOD1) (Rosen et al., 1993). Familial and sporadic forms have indistinguishable clinical and histopathological features (Gurney et al., 1994; Wong et al., 1995). Over 90 different SOD1 mutations have been identified, the majority of which show normal SOD1 activity (Radunovic and Leigh, 1996), suggesting that the mutations lead to a “gain of function”. The cause of motor neuron death in ALS is unknown (for reviews on potential mechanisms involving mitochondria, calcium, oxidative stress and excitotoxicity, see Cleveland and Rothstein, 2001; Menzies et al., 2002).

The involvement of mitochondria in ALS have been recently reviewed by (Menzies et al., 2002; Xu et al., 2004). Such involvement in ALS was initially suggested by the widespread mitochondrial vacuolation identified in the early phase of motor neuron degeneration (Gurney et al., 1994; Wong, et al., 1995; Higgins et al., 2003). Similar structural

mitochondrial abnormalities have been observed in humans with sporadic and familial ALS (Sasaki et al., 1990; Siklos et al., 1996).

Cells expressing the G93A SOD1 mutation show a significant loss of mitochondrial membrane potential, an increase in cytosolic Ca^{2+} concentration (Carri et al., 1997). Mutant SOD1 (a cytosolic protein) has been shown to be imported into mitochondria (Okado-Matsumoto and Fridovich, 2001; Jaarsma et al., 2001; Mattiazzi et al., 2002; Higgins et al., 2002), and it has been suggested that this localization may induce cell death (Takeuchi et al., 2002). Higgins et al. (2003) found that the mitochondrial vacuolar patterns in transgenic mice expressing mutant SOD1G93A originate from the expansion of the mitochondrial intermembrane space and that these vacuoles were bounded by SOD1. As mutated SOD1 has a propensity to undergo aggregation (Julien, 2001), the authors speculated that aggregation of mutant SOD1 may elicit mitochondrial degeneration. Mattiazzi et al. (2002) found mitochondrial abnormalities in oxidative phosphorylation in mice possessing the G93A mutated SOD1.

Using a transgenic mouse model of ALS (SOD1-G93A) in which weakness appears at 3 months of age, and death by 5 months, Keep et al. (2001) and Karlsson et al. (2004) showed that intraventricular administration of CsA prolonged the survival of these mice as compared to vehicle-treated controls. Histologically, there was significant preservation of cervical and lumbar spine motor neurons

The effectiveness of minocycline in mice with ALS expressing the mutant human G93A SOD1 transgene has been examined (Zhu et al., 2002). Minocycline delayed the onset of the disease and extended the survival time. These authors also found that minocycline inhibited the mPT-mediated cytochrome *c* release as well as blocked mitochondrial swelling upon the addition of Ca^{2+}. Klivenyi et al. (1999) found that G93A transgenic mice treated with creatine showed a dose-dependent improvement in motor performance, an extended survival time and displayed a reduction in oxidative cellular injury.

4. Concluding remarks

The mPT has evolved over the past decade as major factor in the mediation of cell injury and death. Factors associated with its induction include loss of calcium homeostasis leading to elevated intracellular calcium levels, oxidative stress, mitochondrial dysfunction and energy failure. These events are common in many CNS disorders and are often triggered by excitotoxicity. When sufficiently severe, these events may coalesce to create the permeability transition, adding further insult to an already compromised cell.

Much data has accrued to implicate the mPT in a host of acute and chronic neurological conditions. Nevertheless, caution must be exercised when interpreting the results of these studies. There are technical difficulties, and caveats to be considered when determining the presence of the mPT in vivo as well as in cultured cells. Additionally, much of the current data implicating the mPT in neurologic disease has come from cell culture studies exposed to putative neurotoxins which, while suggestive, still leaves unanswered the significance of

the mPT in the in vivo condition. Lastly, it is often less than clear whether the mPT was the cause or the consequence of the disorder being investigated.

With these reservations aside, the potential involvement of the mPT in neurological conditions adds an exciting new dimension to mechanisms of neurologic disease and provides attractive and novel approaches for the therapy of these devastating CNS disorders for which no cures are currently available.

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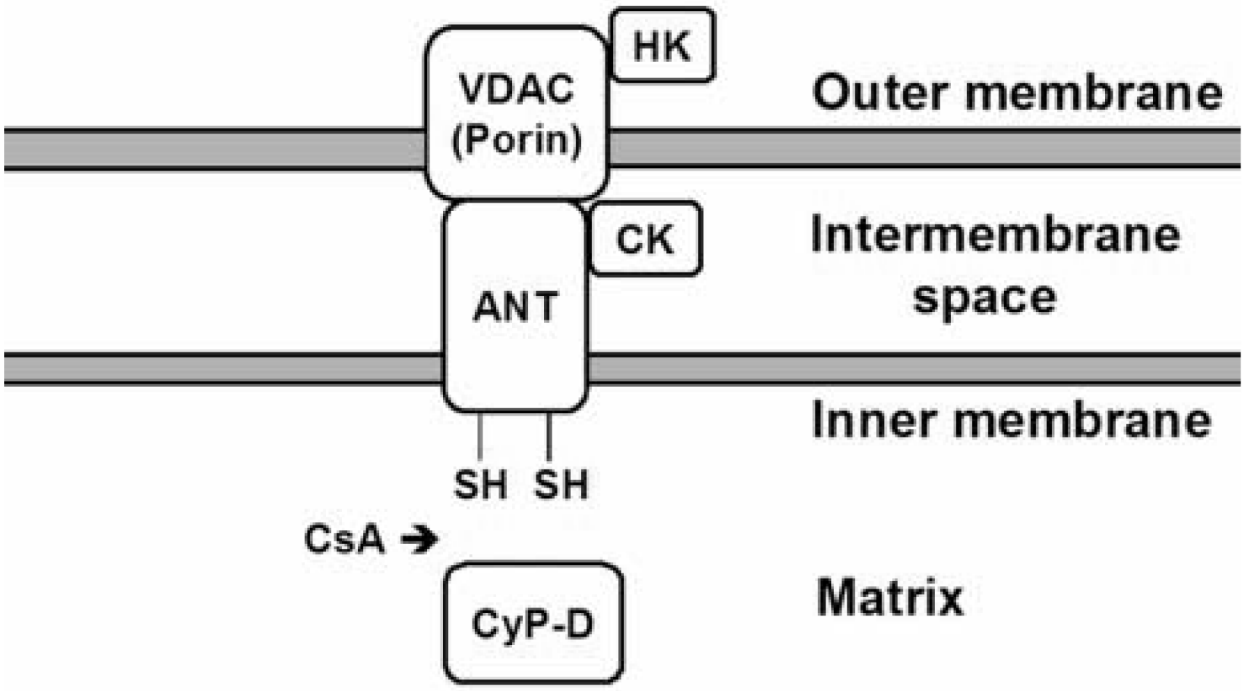

Figure 1.

Proposed structure of the PT pore. CsA blocks pore opening by inhibiting the binding of cyclophilin D (CyP-D) to the adenine nucleotide translocator (ANT). VDAC, voltage-dependent anion channel; HK, hexokinase; CK, creatine kinase. Modified from Rama Rao et al., Metab. Brain Dis. 18, 113–127, 2003.

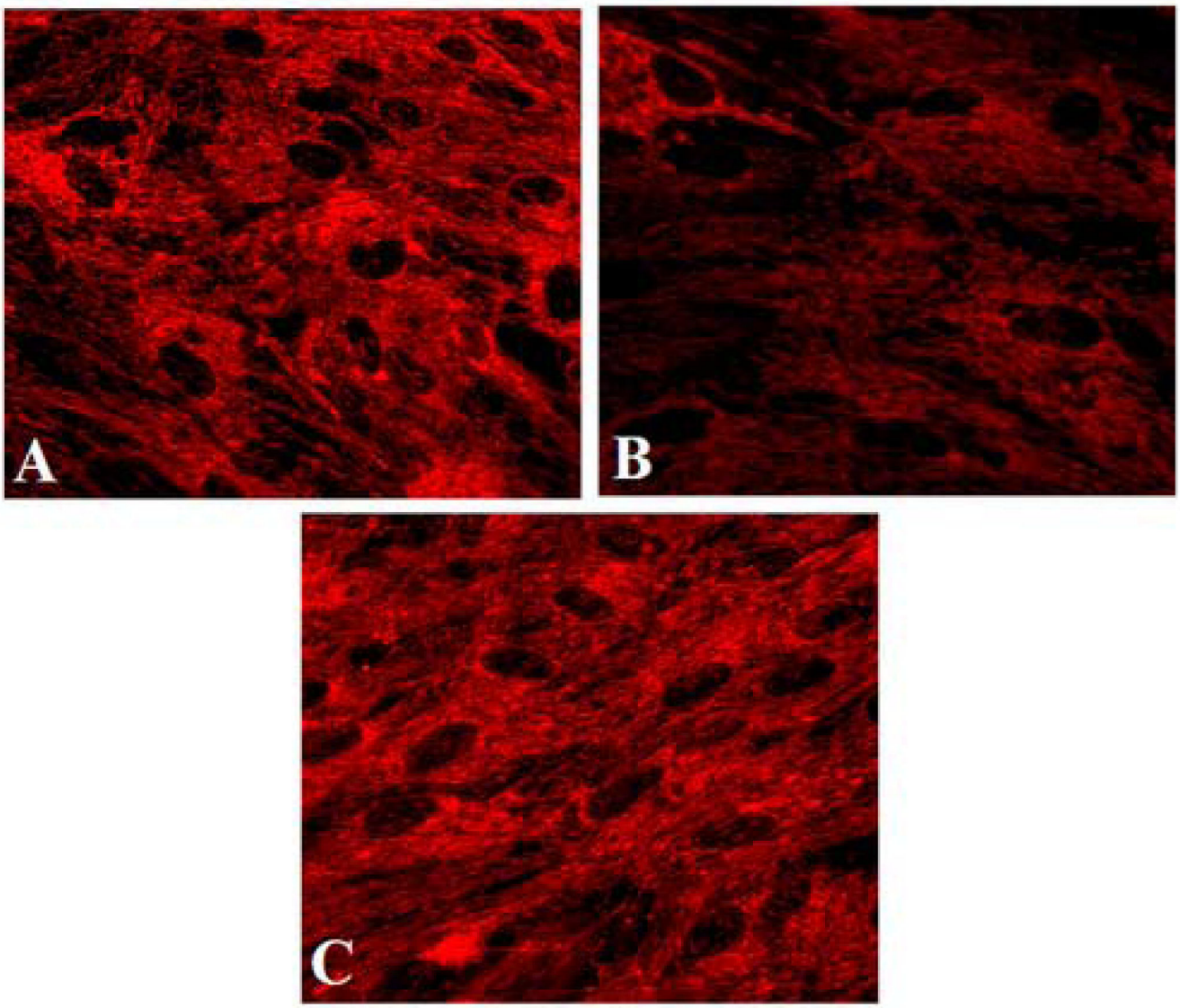

Figure 2.

Fluorescence images of cultured astrocytes treated with ammonia for 24 h. Astrocytes were loaded with TMRE (25 nM; 15 min) and images were captured and examined with a fluorescence microscope. A. Control astrocytes show prominent fluorescence. B. Astrocytes treated with ammonia show decreased fluorescence, consistent with depolarization of the mitochondrial membrane potential. C. Astrocytes treated with CsA (1 μM) show fluorescence similar to that of the control.