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Translocator protein (18 kDa) TSPO: an emerging therapeutic target in neurotrauma

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Abstract

Traumatic brain injury (TBI) induces physical, cognitive, and psychosocial deficits that affect millions of patients. TBI activates numerous cellular mechanisms and molecular cascades that produce detrimental outcomes, including neuronal death and loss of function. The mitochondrion is one of the major targets of TBI, as seen by increased mitochondrial activity in activated and proliferating microglia (due to high energy requirements and/or calcium overload) as well as increased reactive oxygen species, changes in mitochondrial permeability transition, release of cytochrome c, caspase activation, reduced ATP levels, and cell death in neurons. Translocator protein (TSPO) is an 18-kDa outer mitochondrial membrane protein that interacts with the mitochondria permeability transition pore and binds with high affinity to cholesterol and various classes of drug ligands, including some benzodiazepines such as 4′-chlorodiazepam (Ro5-4864). Although TSPO levels in the brain are low, they are increased after brain injury and inflammation. This finding has led to the proposed use of TSPO expression as a marker of brain injury and repair. TSPO drug ligands have been shown to participate in the control of mitochondrial respiration and function, mitochondrial steroid and neurosteroid formation, as well as apoptosis. This review and commentary will outline our current knowledge of the benefits of targeting TSPO for TBI treatment and the mechanisms underlying the neuroprotective effects of TSPO drug ligands in neurotrauma.

Keywords

Traumatic brain injury; Spinal cord injury; Translocator protein; Peripheral benzodiazepine receptor; Cell death; Regeneration; Neurogenesis; Neurosteroids

Traumatic brain injury (TBI)

TBI is a major health issue and has considerable socioeconomic impact. It is recognized as a leading cause of mortality and morbidity in young adults in industrialized countries (Fu and Tummala, 2005; Guha 2004; Vink and Nimmo, 2009). TBI is caused by both direct neural tissue damage and secondary (delayed) sequelae (reviewed by Fu and Tummala, 2005; Guha 2004; Jagannathan and Jagannathan, 2008; Vink and Nimmo, 2009). Primary injury is irreversible and leads to neuronal injury and vascular damage with immediate clinical effects. Secondary injury results from a time-dependent sequence of activation of multiple cellular,

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biochemical, and molecular mechanisms following the initial insult. These mechanisms lead into hypoxia, ischemia, production of proinflammatory cytokines, increased excitotoxicity, accumulation of free radicals, and energy failure, resulting in neuronal cell death and loss of function.

Neurotrauma affects both glia (microglia, astrocytes, and oligodendrocytes) and neurons. Glia are at the origin of neuroinflammation (Skarper, 2007). These cells exhibit dysfunctional and maladaptive responses to injury that consist of reactive astrogliosis, microglial activation and proliferation, loss of oligodendrocytes, and disconnection of glial-neuronal interactions. This injury response, termed “gliopathy” (Hulsebosch, 2008), is a major contributor to neuronal dysfunction and death. Events underlying this neuronal dysfunction (and hallmarks of this transformation) include changes in neuronal metabolism, increased glutamate-activated accumulation of reactive oxygen species (ROS) and reactive nitrogen species, lipid peroxidation and degradation, changes in intracellular calcium levels, reduced mitochondrial respiration, decreased ATP synthesis, and activation of caspase 3 and 9.

Mitochondria appear to be targeted by many deleterious biochemical pathways triggered during neurotrauma. These organelles provide the major energy source supporting these biochemical processes in injury-activated and proliferating microglia. In injury-affected oligodendrocytes and neurons, mitochondria exhibit uncoupling of oxidative phosphorylation, generation of ROS, and permeability transition due to calcium overload, resulting in mitochondrial cytochrome c release, caspase activation, and apoptosis (Fiscum, 2004; Haberlein, 2004).

During the last decade, a number of therapeutic targets and treatments for TBI have been identified (reviewed by Fu and Tummala, 2005; Stoica and Barnes, 2009; Vink and Nimmo, 2009; Wang et al., 2006). These strategies target diverse functions with varying importance in neurotrauma. For example, (i) NMDA and AMPA antagonists have been used to suppress excitotoxicity associated with TBI. (ii) Immunophilin ligands, such as cyclosporine, have been used to regulate the mitochondrial permeability transition state. (iii) Erythropoietin has been used as an anti-inflammatory agent to protect against apoptosis and induce neurogenesis. (iv) Similarly, kinin antagonists and Toll-like receptor agonists have been used to target neuroinflammation. (v) Caspase inhibitors have been used to block apoptosis and calpain inhibitors to block necrosis and caspase-independent cell death. (vi) Various other processes affected by TBI have been targeted by cell cycle inhibitors as well as thyrotropin-releasing hormone and analogs. (vii) Antioxidants such as the antibiotic minocyclin, the cannabinoid dexanabinol, vitamin E, and Ginkgo biloba extract (EGb761) have been used for their antioxidant and free radical scavenging properties. (viii) Magnesium has been used as an NMDA antagonist and a regulator of calcium levels. (ix) The cholesterol-lowering statins have been shown to offer neuroprotection and enhance neurogenesis and synaptogenesis in TBI. (x) Progesterone and estrogen also offer therapeutic potential for TBI. These hormones exert both neuroprotective and neurotrophic effects, acting via the classical nuclear receptors and membrane effector sites. Progesterone also acts on caspase activation to inhibit apoptosis, while estrogen also has antioxidant properties. (xi) Neurosteroids, such as the progesterone metabolite allopregnanolone (which acts on GABA receptors), have been used to suppress excitotoxicity. (xii) Finally, progenitor/stem cell therapy was recently proposed as a means to replace dead neurons following neurotrauma (Obermaier et al., 2008; Walker et al., 2009). These strategies are not only aimed at targets with diverse functions, but they also entail the use of chemically diverse and multifunctional compounds. In addition, encouraging results have been obtained with these approaches in animal models. Despite this, no successful treatments for improving the clinical outcome of the detrimental sequelae of TBI have been identified.

Translocator protein (18 kDa) TSPO in the brain and neuropathology

Translocator protein (TSPO) is an 18-kDa protein, previously known as the peripheral-type benzodiazepine receptor. TSPO is a high-affinity cholesterol and drug ligand that is primarily localized at the outer mitochondrial membrane and is present in many tissues throughout the body (Papadopoulos et al., 2006a). Decades of study of mammalian TSPO has revealed that this protein participates in a variety of cellular functions, including cholesterol transport, steroid hormone synthesis, mitochondrial respiration, permeability transition pore opening, apoptosis, and cell proliferation (Casellas et al., 2002; Gavish et al., 1999; Papadopoulos et al. 2006a, Veenman et al., 2007). In accord with its diverse functions, changes in TSPO expression have been linked to multiple disease, including cancer, endocrine diseases, and neurological diseases.

In the normal brain, overall TSPO expression is low, and TSPO is mainly found in glia and at very low levels in neurons (Chen and Guilarte, 2008; Cosenza-Nashat et al., 2008; Papadopoulos et al., 2006b; Veenman and Gavish, 2000). In the abnormal brain, TSPO is mainly expressed in glia, some hypertrophic astrocytes, infiltrating macrophages, and at low levels in neurons (Chen and Guilarte, 2008; Cosenza-Nashat et al., 2008; Papadopoulos et al., 2006b; Veenman and Gavish, 2000). Animal and human brain imaging following administration of radiolabeled TSPO drug ligands and positron emission tomography (PET) have confirmed that TSPO expression is low in the healthy brain (Chen and Guilarte, 2008). In contrast, TSPO expression is upregulated in the brain at sites of injury and inflammation as well as following a number of neuropathological conditions in experimental animals and humans. These conditions include gliomas, stroke, herpes and HIV encephalitis, and neurodegenerative disorders such as Alzheimer's disease, multiple sclerosis, amyotrophic lateral sclerosis, Parkinson's disease, and Huntington's disease (Chen and Guilarte, 2008; Papadopoulos et al., 2006b; Veenman and Gavish, 2000). Brain diseases in which TSPO is upregulated are typically associated with microglial activation and inflammation, conditions known to lead to gliosis. The high level of TSPO expression in glia as well as the increased proliferation of microglia in gliosis suggests that TSPO could serve as an index of the state and progression of TBI. It should be noted that TSPO has also been implicated in peripheral nerve degeneration and regeneration (Lacor et al., 1999). Of even greater interest to the role of TSPO in TBI, TSPO expression has also been linked to inflammatory responses occurring in various models of inflammation and following ischemia-reperfusion injury (Papadopoulos et al. 2006a). These studies have led to the proposal that TSPO expression be used as a biomarker of active brain disease and have prompted the clinical use of labeled TSPO drug ligands as neuroimaging agents (Chen and Guilarte, 2008; Dourdoin et al., 2008; Kassiou et al., 2005).

Whether changes in TSPO expression are at the origin or an outcome of the neuropathology seen in TBI and various neurodegenerative disorders is not known. Increased levels of TSPO may contribute to TBI neuropathology, as TSPO is required for the transport of cholesterol needed for inner mitochondrial membrane biogenesis and mitochondrial biogenesis is needed to support the accelerated cell proliferation seen in reactive gliosis, a major component of TBI (Papadopoulos et al., 2006a). In actively proliferating cells, TSPO has also been observed in the perinuclear and nuclear area, though the function of TSPO in these areas is unclear (Harwick et al., 1999; Kuhlmann and Guilarte, 2000).

TSPO drug ligands in glia and neuronal function

TSPO was originally discovered due to its ability to bind the benzodiazepine diazepam with an affinity close to that shown for the γ-aminobutyric acid ($GABA_A$) receptors. However, TSPO was later found to have no other structural or pharmacological similarities to the

$GABA_A$ receptor. TSPO binds not only diazepam, but also a number of other benzodiazepines, best exemplified by the 4-chlorodiazepam Ro5-4864. It also binds isoquinoline carboxamides, such as PK 11195, with high affinity. PK 11195 and Ro5-4864 have become the drug ligands diagnostic for the presence and function of TSPO in various tissues and cells. These compounds have been used to probe the role of TSPO in mitochondrial function, calcium homeostasis, steroid biosynthesis, cell proliferation, cell differentiation, and cell death. Interestingly, analysis of the thermodynamic properties of these compounds suggested that Ro5-4864 was a TSPO agonist and PK 11195 a TSPO antagonist (Le Fur et al., 1983). However, *in vitro* and *in vivo* studies in various model systems have shown that such pharmacological assignment of these compounds is not always applicable. Today, a number of chemically diverse ligands have been found to have high affinity for TSPO. These ligands include imidazopyridines, indoleacetamides, pyrrolobenzoxazepines, and phenoxyphenyl acetamide derivatives (Veenman and Gavish, 2006). Of interest to TBI, TSPO drug ligands have been shown to affect neurosteroid synthesis, cell proliferation, and apoptosis, suggesting the TSPO participates in glial, microglial, and neuronal functions.

TSPO drug ligands have been shown to stimulate the formation of neurosteroids (Costa et al., 1994; Papadopoulos et al., 1992), which can be produced by glia in the brain (Baulieu, 1997). Multiple neurosteroids are formed in response to TSPO ligand treatment *in vivo*. Among these is allopregnanolone, which elicits antineophobic, anticonflict, and anxiolytic actions via its action on the $GABA_A$ receptor (Costa et al., 194; Herd et al., 2007). He et al. (2004a & b) demonstrated that allopregnanolone reduces neuronal loss and enhances cognitive and behavioral recovery after TBI in rats. Moreover, steroid intermediates formed during neurosteroid biosynthesis have been shown to induce neuronal stem cell differentiation (Yao et al., 2007), and allopregnanolone and other neurosteroids have been shown to induce neurogenesis (Charalampopoulos et al., 2008). Taken together, these data suggest that TSPO drug ligands protect neuronal function and induce neuroregeneration, at least in part, by inducing neurosteroid synthesis. In this case, the target cell for TSPO drug ligands in TBI would be the glial cell. Interestingly, other evidence points to microglial-specific mechanisms of neuroprotection. For example, PK 11195 has been shown to act on calcium signaling pathways and inhibit a pro-inflammatory agent induced by microglia activation (Choi et al., 2002; Hong et al., 2006). Moreover, Wilms et al (2003) showed that PK 11195 and benzodiazepine TSPO drug ligands alone and in the presence of pro-inflammatory agents inhibit microglia cell proliferation and the release of cytokines. In addition, PK 11195 was shown to inhibit growth factor-induced DNA synthesis and cell proliferation in rat astrocytes (Neary et al. 1985), a phenomenon that occurs following neurotrauma.

A detailed search of the literature has shown that the TSPO ligands, PK 11195 and Ro5-4864, are anti-apoptotic when used at concentrations close to their affinity for TSPO. On the other hand, high concentrations of these compounds elicit effects that do not appear to be related to their binding to TSPO (Veenman et al., 2007). These studies also show that TSPO ligands frequently demonstrate pro-apoptotic activity in synergy with other pro-apoptotic agents. The anti-apoptotic properties of TSPO drug ligands are important to TBI treatment. They are also now being explored for use in cancer therapy.

A number of studies have indicated that TSPO is a component of the mitochondrial permeability transition pore (MPTP) (Zamzami et al., 1997; Zoratti and Szabo, 1993). The role of TSPO in MPTP function was convincingly demonstrated in rat brain mitochondria by Azarashvili et al. (2007). Free radical production has been shown to occur following induction of MPTP opening (Zamzami et al., 1997) or the addition of TSPO drug ligands in various model systems (Chelli et al., 2001; Pastorino et al., 1994). Jayakumar et al. (2002) first showed that TSPO drug ligands induce free radical generation in neuronal cells in a cyclosporine A-inhibitable manner, indicating that MPTP mediates this effect and linking TSPO activation to

MPTP function in neurons. At the same time, TSPO drug ligands were shown to inhibit platelet-activating factor-induced changes in MPTP and cytochrome c release in brain mitochondria (Parker et al., 2002). More recently, Tarnok et al. (2008) demonstrated that Ro5-4864 blocks glutamate-induced changes in MPTP. These studies have been expanded in other systems, particularly ischemia-reperfusion injury of the heart. In this system, Ro5-4864 protects the heart against injury by limiting mitochondrial membrane permeabilization (Obame et al., 2007). This is due to a reorganization of the balance between pro-and anti-apoptotic proteins of the Bcl-2 family at the mitochondrial membrane (Obame et al., 2007). Interestingly, Ro5-4864 effectively protects against post-ischemic cardiac dysfunction when given during reperfusion (Brown et al., 2008), making it a valuable therapeutic tool. Together, these data suggest that TSPO drug ligands, and most likely Ro5-4864, could be effective in blocking injury-induced MPTP changes, cytochrome c release, and apoptosis in neurons.

TSPO ligands in neurotrauma

Soustiel et al. (2008a) recently demonstrated that, in rats subjected to dynamic cortical deformation injury, the administration of Ro5-4864, but not PK 11195, 2 days before or 30 min after injury restored the loss of mitochondrial membrane potential, reduced activation of caspase 3 and 9, and significantly increased in the number of surviving neurons. The authors linked the latter two effects to the preservation of the mitochondrial membrane potential. These data offer experimental evidence that mitochondrial TSPO is a viable therapeutic target and that specific TSPO drug ligands offer a new approach to TBI therapy. This is major step towards a better understanding of TSPO function in neurological diseases and its potential as a TBI therapeutic target.

Previous studies using animal models of sciatic nerve injury and regeneration (Lacor et al., 1999; Leonelli et al., 2005; Mills et al., 2005 & 2007) have demonstrated that Ro5-4864, but not PK 11195, promotes neuronal survival and nerve regeneration, leading to greater functional recovery. These effects are thought to result, in part, from increased neurosteroid synthesis (Lacor et al., 1999). Veiga et al. (2005) demonstrated that, in the hippocampus, pre-administration of Ro5-4864, but not PK 11195, decreases reactive gliosis and prevents neuronal loss induced by kainic acid. The same authors later demonstrated that PK 11195 reduces only microglial activation (Veiga et al., 2007). These effects were not exclusive to benzodiazepine TSPO drug ligands. Ferzaz et al. (2002) reported that the indoleacetamide derivative SSR180575, a high affinity TSPO drug ligand, promotes neuronal survival and repair in axotomy and neuropathy models of central and peripheral neurodegeneration. SSR180575 was found to increase local concentrations of neurosteroid levels in the brain and sciatic nerve suggesting that its neuroprotective effects were mediated by these neuroactive steroids. These critical studies paved the way for observations made by Soustiel et al. (2008a), further validating the development of Ro5-4864 and derivatives for neurotrauma therapy. In further studies, Soustiel et al. (2008b) reported that the neuroprotective effect of hyperbaric hyperoxia in TBI may be due to a negative regulation of the pro-apoptotic function of TSPO, suggesting that TSPO expression is subject to oxygen-dependent regulation as has been described for the *Rhodobacter sphaeroids* homologue of TSPO in photosynthesis (Yeliseev et al., 1997). The neuroprotective effect of hyperbaric hypoxia is blocked by PK 11195 (Soustiel et al., 2008b). This finding suggests that injury- or PK 11195-activated, MPTP-mediated increases in neuronal ROS (Jayakumar et al. 2002) lie at the origin of injury-induced cell death. Interestingly, increased ROS levels lead to TSPO polymerization through di-tyrosine formation (Delavoie et al., 2003), an event that correlates well with human neuropathologies associated with elevated TSPO and ROS levels (Papadopoulos et al., 2006b). The *R. sphaeroids* homologue of TSPO also forms polymers, and the TSPO dimer has been proposed to be the active form in oxygen sensing (Yeliseev and Kaplan, 2000). In agreement with these observations, TSPO polymers are also functional in mammalian cells (Delavoie et al., 2003).

In support of a role for TSPO in nerve regeneration and functional recovery, a steroid derivative, cholest-4-en-3-one oxime, has been shown to bind to the cholesterol-binding domain of TSPO and rescue motor neurons from axotomy-induced death (Bordet et al., 2007). This compound also promotes nerve regeneration and improves nerve function and survival in a mouse model of amyotrophic lateral sclerosis. These findings indicate that TSPO activation is critical for neuronal survival and nerve regeneration, though the exact role of the specific TSPO ligand-binding sites in neuroprotection remain to be elucidated. Girard et al. (2008) discovered nerve regenerative effects of yet another structurally distinct TSPO drug ligand, etifoxine, which was previously shown to induce allopregnanolone formation in the brain and exert anxiolytic properties. Specifically, they found that the anxiolytic benzoxazine derivative etifoxine promotes axonal regeneration, modulates inflammatory responses, and improves functional recovery in a number of peripheral nerve lesion paradigms.

The mechanism underlying the neuroprotective effect of Ro5-4864 in TBI is not known. Considering the information provided earlier in the review, one could speculate that a dual mechanism of action exists. That is, one mechanism may involve glial production of neurotrophic and neurogenic neurosteroids (e.g., allopregnanolone), and the other may involve a reduction in injury-induced mitochondrial membrane permeability in neurons to diminish cytochrome c release, caspase activation, and apoptosis. It is worth noting that, in a recent study by Soustiel et al. (2008a), the isoquinoline PK 11195 did not affect TBI, while it reduced microglia activation in neural inflammation models (Choi et al., 2002; Veiga et al., 2007). These differences might be due either to differences in the TSPO binding sites targeted by Ro5-4864 and PK 11195 or to the distinct TSPO microenvironment in each cell type.

Previous studies have demonstrated that both PK 11195 and Ro5-4864 bind to the 18-kDa TSPO, although maximal binding of Ro5-4864 depends on the presence of other proteins such as VDAC (Lacapere et al., 2001). TSPO ligand binding is also affected by the presence of specific lipids (Beaumont et al., 1988), and obvious differences exist between the mitochondrial membrane lipid composition of various glial cells and neurons. Furthermore, it could be affected by the presence of endogenous TSPO ligands such as the polypeptide diazepam-binding inhibitor, an acyl-CoA-binding protein, and protoporhyrin IX as well as TSPO-interacting proteins such as PBR-associated protein 1 (PRAX-1) and PBR-associated protein 7 (PAP7), which also binds the regulatory subunit I alpha of protein kinase A (Papadopoulos et al., 2006a).

In conclusion, our evolving knowledge of TSPO structure, the function of this protein in brain function, and the effects of its drug ligands suggests that TSPO could serve as a diagnostic marker and therapeutic target in TBI and spinal cord injury therapy.

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