Histol Histopathol (2014) 29: 1525-1538
DOI: 10.14670/HH-29.1525

http://www.hh.um.es

Histology and Histopathology
Cellular and Molecular Biology

Review

Therapeutic implications of melatonin in cerebral edema

Gurugirijha Rathnasamy, Eng-Ang Ling and Charanjit Kaur
Department of Anatomy, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

Summary. Cerebral edema/brain edema refers to the accumulation of fluid in the brain and is one of the fatal conditions that requires immediate medical attention. Cerebral edema develops as a consequence of cerebral trauma, cerebral infarction, hemorrhages, abscess, tumor, hypoxia, and other toxic or metabolic factors. Based on the causative factors cerebral edema is differentiated into cytotoxic, vasogenic, osmotic and interstitial cerebral edema. Treatment of cerebral edema depends on timely diagnosis and medical assistance. Pragmatic treatment strategies such as antihypertensive medications, nonsteroidal anti-inflammatory drugs, barbiturates, steroids, glutamate and N-methyl-D-aspartate receptor antagonists and trometamol are used in clinical practice. Although the above mentioned treatment approaches are being used, owing to the complexity of the mechanisms involved in cerebral edema, a single therapeutic strategy which could ameliorate cerebral edema is yet to be identified. However, recent experimental studies have suggested that melatonin, a neurohormone produced by the pineal gland, could be an effective alternative for treating cerebral edema. In animal models of stroke, melatonin was not only shown to reduce cerebral edema but also preserved the blood brain barrier (BBB) integrity. Melatonin's beneficial effects were attributed to its properties, such as being a potent anti-oxidant, and its ability to cross the BBB within minutes after its administration. This review summarizes the beneficial effects of melatonin when used for treating cerebral edema.

Offprint requests to: Professor Charanjit Kaur, Department of Anatomy, MD10, 4 Medical Drive, Yong Loo Lin School of Medicine, National Uiversity of Singapore, Singapore-117597. e-mail: antkaurc@nus.edu.sg

Key words: Cerebral edema, Melatonin, Cytotoxic cerebral edema, Vasogenic cerebral edema, BBB disruption, Vascular endothelial growth factor, Aquaporin, Matrix metalloproteinases, Nitric oxide

Introduction

Cerebral edema or brain edema refers to excess accumulation of fluid in the brain parenchyma resulting in increased brain volume. Any injury to the brain could result in cerebral edema, including conditions such as traumatic brain injury (TBI), ischemic stroke, brain hemorrhages, infections and tumors. In the above mentioned conditions, although there is a primary injury to the brain parenchyma, the subsequent occurrence of edema has been reported to contribute further to neural tissue damage, resulting in neurological dysfunction. Furthermore, cerebral edema is also reported as a secondary complication to unrelated diseases such as diabetic ketoacidosis, acute liver failure, high altitude sickness and salicylate poisoning (Adeva et al., 2012).

Cerebral edema may occur either due to the intracellular accumulation of water or due to the disruption of the BBB which results in extracellular accumulation of fluid and protein in the brain. Although cerebral edema is classified into cytotoxic, vasogenic, interstitial and osmotic edema, the common forms observed clinically are cytotoxic and vasogenic cerebral edema. Symptoms of cerebral edema are non-specific and vary depending on the cause and severity of injury. Milder forms of edema are generally reversible and the brain volume is compensated with a decrease in cerebrospinal fluid (CSF) and blood volume. However, these cerebral autoregulatory mechanisms fail as the brain fluid volume rapidly increases in severe edema,

resulting in structural alterations such as thinning of white matter, brain midline shift, cerebral ischemia and, ultimately, fatal cerebral herniation through the foramen magnum (Bosma et al., 2002; Ho et al., 2012).

Despite investigations being underway for decades an effective treatment for cerebral edema is still lacking. However, several investigations have proposed pragmatic medical treatments such as hyperventilation, osmotherapy (mannitol and hypertonic saline), diuretics, hypothermia and sedation (propofol, barbiturates) to alleviate cerebral edema (Ho et al., 2012). Corticosteroids, which are known to reduce the BBB permeability, were also proposed to be a therapeutic alternative for treating vasogenic edema. For cases that are obstinate, a decompressive craniectomy is preferred as a last resort. Recently, the use of melatonin (5-methoxy-N-acetyltrypamine), a hormone produced by the pineal gland, to reduce cerebral edema has gained importance owing to its efficacy in reducing the edema and being a potential anti-oxidant. It is highly lipophilic and has the ability to cross the BBB, which was evident with its increased concentration in the brain minutes after its administration (Le Bars et al., 1991). Although growing experimental evidence points to the fact that melatonin is effective in reducing cerebral edema arising from different etiologies, clinical studies are warranted to better understand its therapeutic abilities. In this article, we have reviewed the pathophysiology of different forms of cerebral edema and have summarized the current knowledge available on the beneficial effect of melatonin in alleviating the damage caused by cerebral edema.

Types of cerebral edema and the mechanisms involved

As mentioned above, there are four different types of cerebral edema. However, the cytotoxic and vasogenic forms of cerebral edema are well appreciated clinically. Several mediators have been implicated in the pathogenesis of cerebral edema (Fig 1). In this section, the role played by the different mediators such as aquaporin-4 (AQP4), vascular endotelial grouth factor (VEGF), nitric oxide (NO), adenosine triphosphate (ATP) etc. in causing various forms of cerebral edema is discussed.

Cytotoxic edema

Cytotoxic edema or cellular edema occurs as a result of impairment in the energy-dependant mechanisms, a common observation documented in several forms of brain injury. It affects the grey matter more than the white matter, resulting in excess accumulation of fluid within the neurons, glial cells, axons and myelin sheaths. Being involved in the clearance of K^+ and glutamate, astrocytes are more prone to accumulate water when compared to other brain parenchymal cells (Nag et al., 2009). Cytotoxic edema is more prevalent in conditions where the brain cells undergo a hypoxic-ischemic insult, excitotoxic insult or are exposed to metabolic poisoning. Other causes of cytotoxic edema include TBI, infections and metabolic disorders of kidney and liver. In hypoxic-ischemic conditions, the cells use their stored reserves of ATP to abrogate the oxidative phosphorylation mechanisms (Heo et al., 2005). Owing to the resultant deficiency of ATP, the affected cells fail to carry out the energy dependent mechanisms and fail to maintain homeostasis. Furthermore, the lack of ATP results in superfluous entry of cations, primarily Na^+, into the cells. This inability of the cells to control the excess influx of cations is mostly attributed to the formation of cytotoxic edema. In this type of cerebral edema, while there is an excess influx of cations such as Na^+ into the neurons and glial cells, the efflux of these cations from the cells fails. The extrusion of Na^+ from the cell is essential to maintain cellular volume. Furthermore, the influx of Na^+ creates a driving force for the influx of anions such as Cl^- through the chloride channels to neutralize the ionic shift formed within the cell. The subsequent increase in osmolarity within the cell favours the inflow of water into the glial cells or neurons through the AQP channels, a water channel present on the plasma membrane, (Go, 1997; Kempski, 2001) resulting

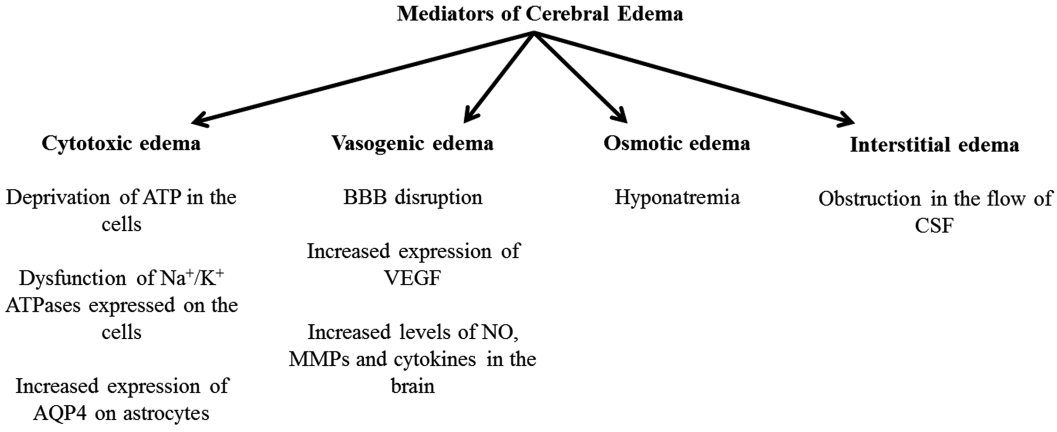

Fig. 1. An illustration summarizing the various mediators involved in causing different types of cerebral edema such as cytotoxic, vasogenic, osmotic and interstitial cerebral edema.

in cytotoxic edema. The cells further undergo morphological changes such as swelling and rupture of plasma membrane. The swelling of glial cells, especially the astrocytes, is a hallmark of cytotoxic edema. Astrocytes are known to outnumber the neurons and have the capacity to expand five times more than their original volume. Also, the presence of AQP4 on the astrocytic foot processes has been implicated in this (Manley et al., 2000). This was also evident with findings from AQP4 null-mice which demonstrated reduced astrocytic swelling and increased survival in mice subjected to water intoxication (Manley et al., 2000) and ischemic stroke (Manley et al., 2000). Despite having normal levels of AQP4, reduced astrocytic swelling was reported in dystrophin null *mdx-βgeo* transgenic mouse and the α-syntrophin null mouse subjected to ischemia. Since AQP4 requires dystrophin and α-syntrophin for its membrane localization, the lack of these molecules in the above mentioned mice models meant that AQP4 is less expressed on astrocytic foot processes. Furthermore, there was reportedly reduced cerebral edema in the above mentioned experimental models, which implies that AQP4 could have a role in causing cytotoxic edema (Frigeri et al., 2001; Vajda et al., 2002; Amiry-Moghaddam et al., 2003). In addition to hypoxia and ischemia, cellular poisoning could also lead to the development of cytotoxic edema. For example, cellular intoxications with exposure to chemicals such as methionine sulfoximine and cuprizone isoniazid were reported to cause swelling of astrocytes. Triethyltin and hexachlorophene intoxications cause accumulation of water in intramyelinic clefts and produce striking white matter edema, whereas axonal swelling is a hallmark of exposure to hydrogen cyanide (Nag et al., 2009). Cytotoxic edema is itself not fatal, but the ionic gradient created in the extracellular space due to the excess intracellular accumulation of water leads to transport of molecules across the BBB. During the initial stages of cytotoxic edema the BBB remains intact. Subsequently, during the chronic phase the BBB disrupts resulting in vasogenic edema.

Vasogenic edema

BBB is crucial for maintaining homeostasis in the brain microenvironment. Any damage to the BBB could result in increased vascular permeability, leading to vasogenic edema. Contrary to cytotoxic edema, in vasogneic edema the white matter is more prone to accumulate fluid than the grey matter owing to the presence of loose extracellular spaces (ECS). Vasogenic edema is known to occur as a consequence of disorders such as stroke, cardiac arrest, respiratory distress and carbon monoxide poisoning. Unlike the capillaries in the rest of the body the brain microvasculature lacks fenestrations and contains very few endocytic vesicles, suggesting limited transendothelial transport (Cornford and Cornford, 2002). Studies using molecular trackers have shown that the BBB is only permeable to small lipophilic molecules while the rest are generally actively transported across the BBB via specialized mechanisms/pathways (Nau et al., 2010). Thus the presence of vasogneic edema has been demonstrated clinically and experimentally by immunostaining for whole serum proteins, albumin, fibrinogen or fibronectin. Furthermore, in experimental animals the breakdown of the BBB is also assessed with the help of tracers such as Gadolinium DPTA, 125Iodine-labeled serum albumin, Evans blue, horseradish peroxidase (HRP), Rhodamine isothiocyanate (RhIC) and dextrans (Nag, 2003).

The BBB is formed by tight junctions between the capillary endothelial cells, which rest on a basal lamina. The basal lamina is surrounded by astrocytic end feet, which have specialized channels and transporters known to be essential in maintaining BBB function (Zador et al., 2007), and pericytes. Based on the fact that vasogenic cerebral edema is due to the disruption of BBB followed by a leakage of intravascular fluid into the brain and lack of mechanisms to clear the excess fluid, the hypothesis that water channels of astrocytes, especially the AQP4 channels, might have a role in the formation of vasogenic edema was put forth. Furthermore, this hypothesis was supported with findings from AQP4 null mice which reported an increased intracranial pressure associated with increased brain water and subsequent mortality (Papadopoulos et al., 2004; Bloch et al., 2005). Models in which vasogenic edema was a predominant form of edema, including cortical cold injury, tumor implantation and brain abscess models, ascertained a role for AQP4 in clearing the fluid accumulated in the extracellular space (Papadopoulos et al., 2004; Bloch et al., 2005), as AQP4-null mice used for the above mentioned conditions were shown to accumulate more water in the brain when compared to wild-type mice. Irrespective of the way the water enters the brain the main route of exit from the brain to the blood has been suggested to be via the AQP4 channels expressed on the astrocytic foot process (Nag et al., 2009).

Additionally, factors such as VEGF, NO, inflammatory mediators and reactive oxygen species (ROS) have been reported to be responsible for BBB disruption. VEGF is known to increase BBB permeability (Hermann and Zechariah, 2009); however, the mechanism involved in increasing vascular permeability has not been completely elucidated. In conditions such as hypoxia and cerebral ischemia, VEGF has been documented to increase cerebral vascular permeability and thereby induce vasogenic cerebral edema (Zhang et al., 2000; Harrigan et al., 2002; Kaur et al., 2006a; Kaur and Ling, 2008). Consistent with this is the finding that either systemic or intracerebroventricular administration of VEGF during the early hours of post ischemic phase could increase BBB leakage and tissue damage (Zhang et al., 2000; Abumiya et al., 2005; Kaya et al., 2005). However, efforts to inhibit VEGF had remarkable neuroprotective effects, which included

reduced BBB permeability, reduced risk of hemorrhagic transformation following focal cerebral ischemia, decreased infarct volume and cerebral edema (van Bruggen et al., 1999; Harrigan et al., 2003; Kaya et al., 2005; Kimura et al., 2005; Chi et al., 2007; Kumai et al., 2007; Chiba et al., 2008; Koyama et al., 2010). VEGF is known to act via its two receptors VEGF receptor 1 (VEGFR1) also known as fms-like tyrosine kinase 1 (Flt-1) and VEGF receptor 2 (VEGFR2) also known as fetal liver kinase 1 (Flk-1). Both the receptors for VEGF, VEGFR1 and VEGFR2 have been shown to have a role in maintaining BBB permeability (Kilic et al., 2006; Vogel et al., 2007; Abdul Muneer et al., 2012; Mendonca et al., 2013). Schreurs et al (2012) demonstrated that VEGF requires both VEGFR1 and VEGFR2 to enhance the permeability of blood vessels. In the blood samples collected from women suffering from pre-eclampsia, levels of VEGFR1, a soluble VEGF receptor, was found to be elevated and it was suggested to increase BBB permeability in these women (Amburgey et al., 2010). In the postmortem brains of patients with multiple sclerosis, the increased expression of VEGF by astrocytes and VEGFR2 by endothelial cells was correlated to increased BBB permeability (Argaw et al., 2006). In animal models of CD8 T-cell induced BBB disruption, inhibition of neuropilin, a co-receptor for VEGFR2/Flk-1 activation, was demonstrated to decrease BBB disruption (Suidan et al., 2012). In brain microvessel endothelial cell (BMVEC) cultures, inhibition of Flt-1 effectively decreased the increased permeability (Argaw et al., 2009). Although the mechanism by which VEGF exerts destructive effects on the BBB still remains elusive, studies have proposed a role for VEGF in diminishing tight junction proteins in the brain vascular endothelium (Argaw et al., 2009; Morin-Brureau et al., 2011). In cultured BMVEC, VEGF was found to decrease the transendothelial electrical resistance and the expression of proteins such as zona occludens-1 and occludin, which are components of tight junctions between vascular endothelial cells. Argaw et al (2009) demonstrated that VEGF could reduce the expression of tight junction component claudin-5 leading to BBB breakdown. Additionally, VEGF is known to influence the phosphorylation of proteins including those containing receptor phosphotyrosine Src homology 2 domains (Guo et al., 1995; Wang et al., 2001). As phosphorylation of proteins is essential for assembly and maintenance of tight junctions, excess VEGF could be speculated to interfere with tight junction assembly and disruption. These findings provide evidence that VEGF reportedly up-regulated in conditions such as cerebral ischemia (Lennmyr et al., 1998), TBI (Shore et al., 2004) and tumors (Senger et al., 1994), could contribute significantly to the disruption of the BBB and in the initiation of vasogenic edema. Furthermore, VEGF has been found to increase the permeability of the BBB by inducing NO production (Mayhan, 1999). *In vitro* studies have also shown that it causes enhanced vacuolations of the endothelial cells (Julien et al., 2008) resulting in enhanced transendothelial transport of serum derived substances (Kaur et al., 2006a).

NO, which is known to modulate the transport of ions, nutrients, and other molecules, is also known to regulate the function of the BBB (Janigro et al., 1994). However, excess production of NO has been shown to increase the permeability of the BBB (Shukla et al., 1996; Thiel and Audus, 2001). Administration of NO donors and nitric oxide synthase (NOS) inhibitors was helpful in understanding the contribution of NO in causing BBB disruption and subsequent vasogenic edema (Boje, 1995, 1996; Koedel et al., 1995). In mice administered with lipo-polysaccharide, NO produced from inducible NOS (iNOS) was shown to enhance the permeability of BBB (Minami et al., 1998). The permeability of cerebrovascular endothelium cultures increased when they were treated with NO donors (Utepbergenov et al., 1998). Factors such as histamine, VEGF and glutamate, which are known to enhance the permeability of the BBB mediate their action through NOS and NO (Mayhan, 1996, 1999; Mayhan and Didion, 1996). In addition, NO is believed to mediate bradykinin and tumour necrosis factor-α (TNF-α) induced BBB disruption (Nakano et al., 1996; Worrall et al., 1997). These findings support the notion that synthesis/release of NO could contribute to increased BBB permeability and thereby vasogenic edema.

Apart from the above factors, matrix metalloproteinases (MMPs), zinc- and calcium-dependent endopeptidases, are known to degrade all kinds of extracellular matrix proteins, including fibronectin, laminin, proteoglycans and type IV collagen (Sternlicht and Werb, 2001; Rosenberg, 2002). Growing evidence from both experimental and clinical studies suggests that MMPs are involved in weakening and rupturing the brain vasculature, thereby increasing the risk of cerebral haemorrhage/vascular leakage (Rosell et al., 2008; Rosell and Lo, 2008). The type IV collagenase which belongs to the MMP proteolytic family is capable of degrading the basal lamina of blood vessels and is implicated in the development of vasogenic edema in conditions including multiple sclerosis, bacterial meningitis and ischemic stroke (Leppert et al., 2001; Nag et al., 2009). Different forms of MMPs are reported to be expressed in different cell types; for example MMP-9 is known to be expressed on endothelial cells whereas astrocytes express MMP-2 (Candelario-Jalil et al., 2007). Several studies have demonstrated that the expression of MMP-9 is increased following a brain injury. Furthermore, MMP-9 is known to be activated by ROS and its expression is likely to be regulated by oxidative stress (Rajagopalan et al., 1996; Mori et al., 2004; Pustovrh et al., 2005). In patients suffering from ischemic stroke the levels of MMP-9 remained elevated even after months following the episode (Clark et al., 1997). In animal models of cerebral ischemia, MMP-9 levels were found to be elevated, and associated with this there was BBB disruption (Aoki et al., 2002; Tejima et al., 2009). In mice subjected to white matter damage

Seo et al. (2013) demonstrated the increased synthesis of MMP-9 by oligodendrocyte progenitor cells and the subsequent reduction in BBB integrity. In spontaneously hypertensive rats, both permanent and temporary middle cerebral artery occlusion resulted in increased production of MMP-9 and MMP-2 (Rosenberg et al., 1996; Yang et al., 2007). Associated with this, the expression of tight junction proteins claudin-5 and occludin was reduced (Yang et al., 2007) suggesting disruption of the BBB and the subsequent development of vasogenic cerebral edema. However, treatment using inhibitors for MMPs, MMP neutralizing antibodies and knockout studies have shown a significant reduction in BBB damage (Asahi et al., 2000, 2001; Yang et al., 2007). Asahi et al (2000) reported that in animal models of focal cerebral ischemia, the BBB was preserved when the gene for MMP-9 was knocked out. Taken together, these findings add support to the point that MMPs have a role in the development of vasogenic edema.

Hypoxic-ischemic conditions are also associated with an inflammatory response in the central nervous system (CNS) (Bona et al., 1999; Cowell et al., 2002) resulting in disruption of the BBB (Tu et al., 2011). Chemokines and cytokines, produced by glial and endothelial cells in hypoxic-ischemic conditions, enhance lymphocyte migration across the BBB (Bona et al., 1999) and also increase the permeability of the blood vessels (Glabinski and Ransohoff, 1999). TNF-α, which is synthesized in the brain in response to middle cerebral artery occlusion, hypoxia, TBI, bacterial meningitis etc. has been reported to cause disruption of the BBB (Yang et al., 1999). In rats, intracisternal injections of TNF-α resulted in increased transport of radiolabelled albumin across the BBB suggesting disruption of the BBB (Kim et al., 1992). In bovine BMVEC, TNF-α was found to enhance permeability by inducing the production of cyclooxygenase-2 (COX-2) and prostaglandins (Mark et al., 2001). In rats, prostaglandin E_2, which is produced by COX-2 when injected intracerebrally enhances the permeability of the BBB (Schmidley et al., 1992). In a rat cranial window model, selective inhibition of COX-2 reduced TNF-α mediated BBB breakdown (Trickler et al., 2005). Besides TNF-α, interleukin (IL)-1β has also been reported to alter BBB permeability (Argaw et al., 2006). In autopsy brain samples from patients suffering from multiple sclerosis Argaw et al (2006) demonstrated the increased concentration of IL-1β , hypoxia inducible factor -1α (HIF-1α) and VEGF. They speculated that IL-1β, by activating HIF-1α and its target VEGF, could increase BBB permeability. The IL-1β-induced BBB breakdown is likely to be mediated by cytokine-induced neutrophil chemoattractant -1, which is known to attract neutrophils (Anthony et al., 1998). Similar to TNF-α, IL-1β was also reported to favour BBB breakdown by inducing COX-2 and prostaglandin synthesis (Moore et al., 2004). Furthermore, studies have suggested that TNF-α and/or IL-1β could favour BBB breakdown by inducing MMP-9 expression via the nuclear factor-κB (NF-κB) signalling pathway in different types of cells (Esteve et al., 2002; Xie et al., 2004; Liang et al., 2007). COX induced by both TNF-α/IL-1β has been shown to increase the expression of MMP-9 (Candelario-Jalil et al., 2007).

Osmotic edema

In this type of edema there exists an osmotic gradient between the blood and the brain tissue while the BBB remains intact. Osmotic edema is more common in subjects having diabetic ketoacidosis, inappropriate secretion of anti-diuretic hormone, acute dilutional hyponatremia and in patients undergoing excessive hemodialysis (Sterns et al., 1986; Glaser, 2001). In the above mentioned conditions, the serum Na^+ ions drop below normal values and when the serum Na^+ is less than 120 mmol/L, the intravascular fluid enters into the brain (Arieff et al., 1976). Development of osmotic edema might lead to an increase in the CSF volume in the ventricles by seepage of fluid from the brain (DiMattio et al., 1975). Osmotic edema is also possible when the brain tissue osmolality is high and the plasma osmolality is normal, a condition which is prevalent following brain haemorrhage, infarction and contusions (Nag et al., 2009).

Interstitial edema

Interstitial edema is another rare form of edema and is best characterized in noncommunicating hydrocephalus and hepatic encephalopathy (Kale et al., 2006). Although the pathogenesis of interstitial cerebral edema is still unknown, studies on animal models of hydrocephalus have thrown light on the molecular mechanisms involved. In kaolin-induced hydrocephalus, although the cerebral blood flow was above the ischemic levels, the development of interstitial edema impaired the oxidative metabolism at a very early stage (Kawamata et al., 2003). The rise in the intraventricular pressure results in the migration of CSF into the white matter and thereby increase the extracellular fluid volume (Milhorat et al., 1970). The reduction in the expression of AQP4 in the brain is implicated in the reduced clearance of the excess extracellular fluid, ultimately leading to cerebral edema (Bloch et al., 2006). In more advanced stages, there is destruction of myelin and axons followed by activation of microglia in the white matter, leading to a thinning of white matter (Del Bigio, 1993). Associated with this there might be disruption of ependyma and distortion of cerebral vessels (Del Bigio, 1993).

Melatonin

Melatonin (5-methoxy-N-acetyltryptamine) is a derivative of amino acid tryptophan and was first discovered by Lerner and his co-workers (Lerner et al., 1958). Melatonin was, however reported to be synthesized by other tissues such as retina (Dubocovich,

1983), Harderian gland (Buzzell et al., 1990; Djeridane and Touitou, 2001), bone marrow (Conti et al., 2000), platelets (Champier et al., 1997), gastrointestinal tract (Bubenik, 2002), skin (Slominski et al., 2005) and lymphocytes (Carrillo-Vico et al., 2004). In addition, brains from immature rats of age between embryonic day 18 and postnatal day 7 were demonstrated to synthesize melatonin without the influence of the pineal gland (Jimenez-Jorge et al., 2007). Melatonin is a chronobiotic substance known to regulate circadian rhythms (Redman et al., 1983; Armstrong et al., 1986) and is known to participate in a wide range of physiological functions (Pandi-Perumal et al., 2006). It is a potent anti-oxidant (Reiter et al., 2003) and an immune-regulator (Carrillo-Vico et al., 2013). Clinically, melatonin has been used to treat sleep disorders (Cummings, 2012; Ferracioli-Oda et al., 2013), and has also been documented to have anti-convulsant action (Champney et al., 1996), anti-ageing property (Poeggeler, 2005) and oncostatic effect (Srinivasan et al., 2008).

Administration of melatonin has been proven to be beneficial in conditions such as Parkinson's disease (Mayo et al., 2005; Borah and Mohanakumar, 2009), Alzheimer's disease (Feng et al., 2004), ischemic brain injury (Pei et al., 2003; Pei and Cheung, 2004; Carloni et al., 2008), and neuropsychiatric disorders (Srinivasan et al., 2006b). In these conditions, melatonin protected the neurons by ameliorating the adverse effects caused by oxidative stress, inflammation and mitochondrial dysfunction (Sharma et al., 2006; Srinivasan et al., 2006a; Lin et al., 2008, 2013). Melatonin's ability to activate the AKT pathway and inhibit apoptotic signalling was attributed to its protective property (Koh et al., 2008). In addition, melatonin was demonstrated to prevent free-radical mediated injury by enhancing anti-oxidants such as superoxide dismutase, peroxidase, enzymes involved in glutathione synthesis (Hardeland, 2005), and by down-regulating pro-oxidant systems. Pro-oxidants such as 5- and 12-lipo-oxygenases (Manev et al., 1998; Uz and Manev, 1998; Zhang et al., 1999) and NOS (Pozo et al., 1994; Bettahi et al., 1996) were shown to be inhibited by melatonin. Furthermore, melatonin was documented to protect the retina by reducing the death of retinal ganglion cells and other neurons in conditions such as age related macular degeneration (Liang and Godley, 2003), glaucoma (Belforte et al., 2010) and ischemia reperfusion injury (Park et al., 2012). Apart from the above mentioned pathologies, melatonin was also shown to reduce cerebral edema. Experimental studies have documented that melatonin was effective in reducing edema of the brain formed as a consequence of ischemia-reperfusion (Kondoh et al., 2002), TBI (Mesenge et al., 1998) and excitotoxicity (Lee et al., 2000). In rat models of kainate induced excitotoxicity, melatonin was shown to reduce the levels of polyamines, which are speculated to play a role in the development of cerebral edema. Also, in rats exposed to hypoxia, melatonin effectively reduced the expression of factors known to increase vascular permeability such as VEGF, AQP4 and NO, and disruption of BBB (Kaur et al., 2010; Yawno et al., 2012). Although investigations are under way, in the forthcoming sections we have summarized the available evidence on the potential of melatonin in ameliorating different kinds of cerebral edema.

Melatonin and cerebral edema

One of the early symptoms following ischemic injury is the formation of cerebral edema. It is essential to abate the cerebral edema to avoid subsequent chronic neural damage (Kondoh et al., 2002). Several studies have shown the effectiveness of melatonin in reducing cerebral edema following ischemic insults (Lee et al., 2004, 2005). Administration of melatonin to animal models of ischemia has been proven beneficial as melatonin inhibited the activation of microglia and prevented the transmigration of leukocytes into the ischemic brain (Lee et al., 2007). Melatonin was also shown to maintain the integrity of the BBB following ischemic stroke (Chen et al., 2006). In Mongolian gerbils, melatonin was demonstrated to reduce the brain water content which was increased following ischemia (Cuzzocrea et al., 2000). Since cytotoxic cerebral edema and vasogenic cerebral edema are the most common forms of edema found in a clinical set up, the beneficial effect of melatonin in treating these types of edema are detailed below.

Melatonin and cytotoxic edema

Melatonin has been proven effective in reducing the cellular changes associated with cytotoxic edema. For example, in rats subjected to cold-induced brain injury melatonin significantly reduced the swelling of neurons and axoplasm, and prevented the disruption of the plasma membrane (Gorgulu et al., 2001). In addition, the cellular organelles such as nucleus and mitochondria were protected from degenerative changes (Gorgulu et al., 2001). In hippocampus of neonatal rats, following hypoxic exposure, there were swollen dendrites, axons and astrocyte processes (Kaur et al., 2008). However, these changes were reported to have subsided following melatonin administration to hypoxic rats (Kaur et al., 2008). A similar finding was reported by Kaur et al. (2006b) in the cerebellum of hypoxic rats, wherein melatonin reduced hypoxia-induced swelling of astrocytes and AQP4 expression on them, suggesting a reduced water uptake by these cells, and hence, decreased edema formation. Melatonin was shown to facilitate the down-regulation of AQP4 by activating protein kinase C (Bhattacharya et al., 2014). In animal models of middle cerebral artery occlusion, melatonin was shown to remarkably reduce the death of glial cells at the ischemic core (Borlongan et al., 2000). In hippocampal slice cultures treated with amyloid beta (Aβ), melatonin was shown to prevent structural

changes, including edema and necrotic profiles (Clapp-Lilly et al., 2001). Furthermore, in the brains of Anabas testudineus, melatonin has been reported to have an influencial effect on the Na^+/K^+ ATPases (Divya et al., 2006) which is essential for preventing cytotoxic edema. In rats subjected to cerebral ischemia, administration of melatonin restored down-regulated Na^+/K^+ ATPases activity in the brain (Toklu et al., 2009). The remarkable ability of melatonin to interact with mitochondrial complexes and to enhance electron flow (Martin et al., 2002) could also be attributed to the potential of melatonin in inhibiting cytotoxic edema. Taking all of the above into consideration, it could be speculated that melatonin could inhibit/prevent cytotoxic edema by enhancing energy flow or by influencing Na^+/K^+ ATPase.

Melatonin and vasogenic edema

Melatonin, as mentioned above, is a potent anti-oxidant and because of this property it has been shown to be effective in reducing vascular permeability and thereby the vasogenic edema (Cuzzocrea et al., 1997; Bilici et al., 2002). Moreover, melatonin was shown to reduce the increased vascular permeability by interacting with endothelial cells (Lotufo et al., 2006) and inhibiting the binding of neutrophils to endothelial cells (Lotufo et al., 2001). Alternatively, melatonin is also reported to exert its suppressive effects on the tissue concentration of VEGF (Kaur et al., 2006b, 2007; Sivakumar et al., 2008) resulting in reduced vascular permeability and edema in many parts of the CNS (Kaur et al., 2006b). Studies on different kinds of cancers have revealed that melatonin has the potential to decrease the serum concentrations of VEGF (Lissoni et al., 2001; Pandi-Perumal, 2006). In rats subjected to hypoxia, increased expression of VEGF and NO was a hallmark finding suggesting edema. Melatonin has been shown to suppress these factors and thereby the vasogenic edema in different regions of the brain including periventricular white matter, hippocampus, cerebellum, ventrolateral medulla, nucleus tractus solitarius and choroid plexus (Kaur et al., 2006b, 2008, 2010, 2011; Sivakumar et al., 2008). In hypoxic brains, melatonin not only reduced the production of VEGF and NO, but also reduced the vascular leakage which was evident with reduced uptake of rhodium isothiocyante (RhIC) and horseradish peroxidase (HRP) injected intraperitoneally or intravenously (Kaur et al., 2006b, 2008). In addition, in hypoxic neonatal rats melatonin effectively reduced the expression of Flt-1 and Flk-1 expression on the retinal vasculature (Kaur et al., 2013) and also in the brain (unpublished data). This could be attributed to the efficacy of melatonin in preserving the integrity of the BBB.

In animal models of ischemia, melatonin was demonstrated to decrease the expression of iNOS and neural NOS (nNOS) (Koh, 2008). In the brains of Mongolian gerbils melatonin was shown to prevent the increase in NO concentration and peroxynitrite concentration which is implicated in causing damage to the BBB (Guerrero et al., 1997). Melatonin prevented N-methyl-D-aspartate induced excitotoxicity by inhibiting nNOS (Escames et al., 2004) and subsequent NO production. N1-acetyl-5-methoxykynuramine (AMK), a metabolite of melatonin in the brain, was reported to be the active compound against nNOS and NO production (Leon et al., 2006). Melatonin was speculated to either directly scavenge NO or to inhibit nNOS activity by interacting with calmodulin, a molecule required for NO production from nNOS (Bettahi et al., 1996; Pozo et al., 1997). The inhibition of NO production is of major significance as it can hinder the generation of free radicals and peroxynitrite (Pandi-Perumal et al., 2006) which are associated with BBB breakdown.

Melatonin was shown to be beneficial in cerebellar edema by down-regulating AQP4 expression in the astrocytes (Kaur et al., 2006b) following hypoxic injury. In rat models of subarachnoid haemorrhage (SAH) administration of melatonin was found to significantly reduce mortality. This was accompanied with a reduction in brain water content (Ayer et al., 2008). This could be attributed to the ability of melatonin to influence the expression of proteins such as VEGF and AQP4, which are up-regulated in SAH (Badaut et al., 2003; Josko, 2003) and which are known to play a role in causing edema. These findings imply that melatonin protects the integrity of BBB.

Besides VEGF and AQP4, melatonin has the remarkable ability in ischemic brains to reduce MMP-9 levels, which are known to play a role in BBB breakdown. The mechanism by which melatonin reduces the MMP-9 levels remains to be completely elucidated. However, the ability of melatonin to inhibit the activation of NF-κB (Beni et al., 2004; Qin et al., 2012) and increase the expression of tissue inhibitors of metalloproteinase (TIMP)-1 (Swarnakar et al., 2007; Paul et al., 2008) has been implicated in melatonin mediated reduction of MMP-9. In human umbilical vein endothelial cells (HUVEC) treated with IL-1β, melatonin protected the integrity and permeability of the HUVEC monolayer by down regulating the NF-κB pathway and subsequent production of MMP-9 (Qin et al., 2012). In mouse models of focal cerebral ischemia, following reperfusion, melatonin was reported to increase TIMP-1 and plasminogen activator inhibitor-1 which was associated with the concomitant reduction in MMP-9 levels (Tai et al., 2010). In addition, melatonin is known to exert its protective property by activating the extracellular signal-regulated kinases (ERK1/2) pathway. Melatonin mediated ERK1/2 activation has also been implicated in TIMP-1 up-regulation, which is essential for MMP-9 down regulation (Hung et al., 2008). Furthermore, a recent study has pointed out that melatonin inhibits the catalytic activity of MMP-9 by binding to its active site (Rudra et al., 2013).

Besides the above, melatonin prevented BBB damage by inhibiting oxidative stress and inflammation.

The excess free radicals formed in any pathological condition could cause a detrimental effect on the highly lipid enriched brain by oxidatively degrading the lipids and also disrupting the BBB. However, administration of melatonin has been reported to neutralize the deleterious effects of free radicals and protect the brain. Clinically, in newborns affected by sepsis, melatonin reduced serum malondialdehyde (MDA) levels (an end product of lipid peroxidation) (Gitto et al., 2001). Similarly, melatonin, when administered prior to in-utero asphyxia, prevented the formation of highly toxic hydroxyl radicals in the brains of late gestation sheep fetus (Miller et al., 2005). In rat models of hypoxic periventricular white matter damage, melatonin administration rendered protection to the white matter by significantly reducing the MDA levels, which were elevated due to hypoxia (Kaur et al., 2010). A similar finding was reported by Cuzzocrea et al (2000) in the brains of melatonin treated post-ischemic Mongolian gerbils. Furthermore, accumulating evidence, both clinically and experimentally, has shown the efficacy of melatonin in reducing inflammation in the brain (Gitto et al., 2001; Welin et al., 2007; Hutton et al., 2009). In asphyxiated neonatal rats, melatonin treatment was demonstrated to reduce the number of activated microglia, which have a pivotal role in the inflammatory cascade (Welin et al., 2007). Melatonin was found to inhibit the inflammatory process by preventing cytokine production in activated microglia (Min et al., 2012). In LPS-stimulated Raw264.7 cells, melatonin inhibited the excess production of TNF-α, IL-1β, IL-6, IL-8 and IL-10 production (Xia et al., 2012). Melatonin was reported to impede NF-κB translocation (Min et al., 2012) which is essential for cytokine production. Melatonin when provided in combination with electroacupunture, effectively decreased the expression to two primary inflammatory mediators TNF-α and COX-2 (Liu and Cheung, 2013).

Taken together, it could be stated that melatonin, either by influencing the expression of factors such as VEGF, NO and AQP4 or by directly scavenging the free radicals and reducing inflammatory mediators could protect the integrity of the BBB and prevent vasogenic cerebral edema.

Conclusion

Molecular mechanisms leading to cerebral edema are multifaceted and require further research to understand the complexity involved. Although research in the past decades led to the identification of molecules involved in the pathogenesis of cerebral edema, an effective treatment remains to be fully explored owing to the contributions from multiple pathways. A single therapeutic agent which could ameliorate all the pathologies associated with cerebral edema is clearly desirable. Recent findings have suggested that melatonin could be a therapeutic molecule of interest as it has been proven beneficial in reducing cerebral edema and associated pathologies. Although melatonin has been proven beneficial in experimental studies involving animals, clinical studies are warranted to better understand the efficacy of melatonin. In view of the beneficial effects of melatonin it is justified to suggest that melatonin might be a potential therapeutic agent for treatment of cerebral edema arising from different etiologies.

References

Abdul Muneer P.M., Alikunju S., Szlachetka A.M. and Haorah J. (2012). The mechanisms of cerebral vascular dysfunction and neuroinflammation by mmp-mediated degradation of vegfr-2 in alcohol ingestion. Arterioscler. Thromb. Vasc. Biol. 32, 1167-1177.

Abumiya T., Yokota C., Kuge Y. and Minematsu K. (2005). Aggravation of hemorrhagic transformation by early intraarterial infusion of low-dose vascular endothelial growth factor after transient focal cerebral ischemia in rats. Brain Res. 1049, 95-103.

Adeva M.M., Souto G., Donapetry C., Portals M., Rodriguez A. and Lamas D. (2012). Brain edema in diseases of different etiology. Neurochem. Int. 61, 166-174.

Amburgey O.A., Chapman A.C., May V., Bernstein I.M. and Cipolla M.J. (2010). Plasma from preeclamptic women increases blood-brain barrier permeability: Role of vascular endothelial growth factor signaling. Hypertension 56, 1003-1008.

Amiry-Moghaddam M., Otsuka T., Hurn P.D., Traystman R.J., Haug F.M., Froehner S.C., Adams M.E., Neely J.D., Agre P., Ottersen O.P. and Bhardwaj A. (2003). An alpha-syntrophin-dependent pool of aqp4 in astroglial end-feet confers bidirectional water flow between blood and brain. Proc. Natl. Acad. Sci. USA 100, 2106-2111.

Anthony D., Dempster R., Fearn S., Clements J., Wells G., Perry V.H. and Walker K. (1998). Cxc chemokines generate age-related increases in neutrophil-mediated brain inflammation and blood-brain barrier breakdown. Curr. Biol. 8, 923-926.

Aoki T., Sumii T., Mori T., Wang X. and Lo E.H. (2002). Blood-brain barrier disruption and matrix metalloproteinase-9 expression during reperfusion injury: Mechanical versus embolic focal ischemia in spontaneously hypertensive rats. Stroke 33, 2711-2717.

Argaw A.T., Gurfein B.T., Zhang Y., Zameer A. and John G.R. (2009). Vegf-mediated disruption of endothelial cln-5 promotes blood-brain barrier breakdown. Proc. Natl. Acad. Sci. USA 106, 1977-1982.

Argaw A.T., Zhang Y., Snyder B.J., Zhao M.L., Kopp N., Lee S.C., Raine C.S., Brosnan C.F. and John G.R. (2006). Il-1beta regulates blood-brain barrier permeability via reactivation of the hypoxia-angiogenesis program. J. Immunol. 177, 5574-5584.

Arieff A.I., Llach F. and Massry S.G. (1976). Neurological manifestations and morbidity of hyponatremia: Correlation with brain water and electrolytes. Medicine. 55, 121-129.

Armstrong S.M., Cassone V.M., Chesworth M.J., Redman J.R. and Short R.V. (1986). Synchronization of mammalian circadian rhythms by melatonin. J. Neural Transm. Suppl. 21, 375-394.

Asahi M., Asahi K., Jung J.C., del Zoppo G.J., Fini M.E. and Lo E.H. (2000). Role for matrix metalloproteinase 9 after focal cerebral ischemia: Effects of gene knockout and enzyme inhibition with bb-94. J. Cereb. Blood Flow Metab. 20, 1681-1689.

Asahi M., Wang X., Mori T., Sumii T., Jung J.C., Moskowitz M.A., Fini M.E. and Lo E.H. (2001). Effects of matrix metalloproteinase-9 gene knock-out on the proteolysis of blood-brain barrier and white matter

components after cerebral ischemia. J. Neurosci. 21, 7724-7732.
Ayer R.E., Sugawara T., Chen W., Tong W. and Zhang J.H. (2008). Melatonin decreases mortality following severe subarachnoid hemorrhage. J. Pineal Res. 44, 197-204.
Badaut J., Brunet J.F., Grollimund L., Hamou M.F., Magistretti P.J., Villemure J.G. and Regli L. (2003). Aquaporin 1 and aquaporin 4 expression in human brain after subarachnoid hemorrhage and in peritumoral tissue. Acta Neuroch. Suppl. 86, 495-498.
Belforte N.A., Moreno M.C., de Zavalía N., Sande P.H., Chianelli M.S., Keller Sarmiento M.I. and Rosenstein R.E. (2010). Melatonin: A novel neuroprotectant for the treatment of glaucoma. J. Pineal Res. 48, 353-364.
Beni S.M., Kohen R., Reiter R.J., Tan D.X. and Shohami E. (2004). Melatonin-induced neuroprotection after closed head injury is associated with increased brain antioxidants and attenuated late-phase activation of nf-kappab and ap-1. FASEB J. 18, 149-151.
Bettahi I., Pozo D., Osuna C., Reiter R.J., Acuna-Castroviejo D. and Guerrero J.M. (1996). Melatonin reduces nitric oxide synthase activity in rat hypothalamus. J. Pineal Res. 20, 205-210.
Bhattacharya P., Pandey A.K., Paul S. and Patnaik R. (2014). Melatonin renders neuroprotection by protein kinase c mediated aquaporin-4 inhibition in animal model of focal cerebral ischemia. Life Sci. 100, 97-109.
Bilici D., Suleyman H., Banoglu Z.N., Kiziltunc A., Avci B., Ciftcioglu A. and Bilici S. (2002). Melatonin prevents ethanol-induced gastric mucosal damage possibly due to its antioxidant effect. Digest. Dis. Sci. 47, 856-861.
Bloch O., Papadopoulos M.C., Manley G.T. and Verkman A.S. (2005). Aquaporin-4 gene deletion in mice increases focal edema associated with staphylococcal brain abscess. J. Neurochem. 95, 254-262.
Bloch O., Auguste K.I., Manley G.T. and Verkman A.S. (2006). Accelerated progression of kaolin-induced hydrocephalus in aquaporin-4-deficient mice. J. Cereb. Blood Flow Metab. 26, 1527-1537.
Boje K.M. (1995). Inhibition of nitric oxide synthase partially attenuates alterations in the blood-cerebrospinal fluid barrier during experimental meningitis in the rat. Eur. J. Pharmacol. 272, 297-300.
Boje K.M. (1996). Inhibition of nitric oxide synthase attenuates blood-brain barrier disruption during experimental meningitis. Brain Res. 720, 75-83.
Bona E., Andersson A.L., Blomgren K., Gilland E., Puka-Sundvall M., Gustafson K. and Hagberg H. (1999). Chemokine and inflammatory cell response to hypoxia-ischemia in immature rats. Pediatr. Res. 45, 500-509.
Borah A. and Mohanakumar K.P. (2009). Melatonin inhibits 6-hydroxydopamine production in the brain to protect against experimental parkinsonism in rodents. J. Pineal Res. 47, 293-300.
Borlongan C.V., Yamamoto M., Takei N., Kumazaki M., Ungsuparkorn C., Hida H., Sanberg P.R. and Nishino H. (2000). Glial cell survival is enhanced during melatonin-induced neuroprotection against cerebral ischemia. FASEB J. 14, 1307-1317.
Bosma J.J., Kumaran N. and May P.L. (2002). Cerebral oedema following evd insertion for delayed hydrocephalus after foramen magnum decompression in chiari i malformation. Child's Nervous System. 18, 474-477.
Bubenik G.A. (2002). Gastrointestinal melatonin: Localization, function, and clinical relevance. Dig. Dis. Sci. 47, 2336-2348.
Buzzell G.R., Menendez-Pelaez A., Troiani M.E., McNeill M.E. and Reiter R.J. (1990). Effects of short-day photoperiods and of n-(2,4-dinitrophenyl)-5-methoxytryptamine, a putative melatonin antagonist, on melatonin synthesis in the harderian gland of the syrian hamster, mesocricetus auratus. J. Pineal Res. 8, 229-235.
Candelario-Jalil E., Taheri S., Yang Y., Sood R., Grossetete M., Estrada E.Y., Fiebich B.L. and Rosenberg G.A. (2007). Cyclooxygenase inhibition limits blood-brain barrier disruption following intracerebral injection of tumor necrosis factor-alpha in the rat. J. Pharmacol. Exp. Ther. 323, 488-498.
Carloni S., Perrone S., Buonocore G., Longini M., Proietti F. and Balduini W. (2008). Melatonin protects from the long-term consequences of a neonatal hypoxic-ischemic brain injury in rats. J. Pineal Res. 44, 157-164.
Carrillo-Vico A., Calvo J.R., Abreu P., Lardone P.J., García-Mauriño S., Reiter R.J. and Guerrero J.M. (2004). Evidence of melatonin synthesis by human lymphocytes and its physiological significance: Possible role as intracrine, autocrine, and/or paracrine substance. FASEB J. 18, 537-539.
Carrillo-Vico A., Lardone P.J., Alvarez-Sanchez N., Rodriguez-Rodriguez A. and Guerrero J.M. (2013). Melatonin: Buffering the immune system. Int. J. Mol. Sci. 14, 8638-8683.
Champier J., Claustrat B., Besançon R., Eymin C., Killer C., Jouvet A., Chamba G. and Fèvre-Montange M. (1997). Evidence for tryptophan hydroxylase and hydroxy-indol-o-methyl-transferase mrnas in human blood platelets. Life Sci. 60, 2191-2197.
Champney T.H., Hanneman W.H., Legare M.E. and Appel K. (1996). Acute and chronic effects of melatonin as an anticonvulsant in male gerbils. J. Pineal Res. 20, 79-83.
Chen T.Y., Lee M.Y., Chen H.Y., Kuo Y.L., Lin S.C., Wu T.S. and Lee E.J. (2006). Melatonin attenuates the postischemic increase in blood-brain barrier permeability and decreases hemorrhagic transformation of tissue-plasminogen activator therapy following ischemic stroke in mice. J. Pineal Res. 40, 242-250.
Chi O.Z., Hunter C., Liu X. and Weiss H.R. (2007). Effects of anti-vegf antibody on blood-brain barrier disruption in focal cerebral ischemia. Exp. Neurol. 204, 283-287.
Chiba Y., Sasayama T., Miyake S., Koyama J., Kondoh T., Hosoda K. and Kohmura E. (2008). Anti-vegf receptor antagonist (vga1155) reduces infarction in rat permanent focal brain ischemia. Kobe J. Med. Sci. 54, E136-146.
Clapp-Lilly K.L., Smith M.A., Perry G., Harris P.L., Zhu X. and Duffy L.K. (2001). Melatonin acts as antioxidant and pro-oxidant in an organotypic slice culture model of alzheimer's disease. Neuroreport. 12, 1277-1280.
Clark A.W., Krekoski C.A., Bou S.S., Chapman K.R. and Edwards D.R. (1997). Increased gelatinase a (mmp-2) and gelatinase b (mmp-9) activities in human brain after focal ischemia. Neurosci. Lett. 238, 53-56.
Conti A., Conconi S., Hertens E., Skwarlo-Sonta K., Markowska M. and Maestroni J.M. (2000). Evidence for melatonin synthesis in mouse and human bone marrow cells. J. Pineal Res. 28, 193-202.
Cornford E.M. and Cornford M.E. (2002). New systems for delivery of drugs to the brain in neurological disease. Lancet Neurol. 1, 306-315.
Cowell R.M., Xu H., Galasso J.M. and Silverstein F.S. (2002). Hypoxic-ischemic injury induces macrophage inflammatory protein-1alpha expression in immature rat brain. Stroke 33, 795-801.
Cummings C. (2012). Melatonin for the management of sleep disorders in children and adolescents. Paediatrics Child Health 17, 331-336.

Cuzzocrea S., Zingarelli B., Gilad E., Hake P., Salzman A.L. and Szabo C. (1997). Protective effect of melatonin in carrageenan-induced models of local inflammation: Relationship to its inhibitory effect on nitric oxide production and its peroxynitrite scavenging activity. J. Pineal Res. 23, 106-116.

Cuzzocrea S., Costantino G., Gitto E., Mazzon E., Fulia F., Serraino I., Cordaro S., Barberi I., De Sarro A. and Caputi A.P. (2000). Protective effects of melatonin in ischemic brain injury. J. Pineal Res. 29, 217-227.

Del Bigio M.R. (1993). Neuropathological changes caused by hydrocephalus. Acta Neuropathol. 85, 573-585.

DiMattio J., Hochwald G.M., Malhan C. and Wald A. (1975). Effects of changes in serum osmolarity on bulk flow of fluid into cerebral ventricles and on brain water content. Pflugers Archiv. 359, 253-264.

Divya L., Vijayasree A.S., Sreejith P., Beyo R.S., Smita M. and Oommen O.V. (2006). Does melatonin have a time-dependent effect on brain and gill ionic metabolism in a teleost, anabas testudineus (bloch)? Indian J. Exp. Biol. 44, 635-639.

Djeridane Y. and Touitou Y. (2001). Melatonin synthesis in the rat harderian gland: Age- and time-related effects. Exp. Eye Res. 72, 487-492.

Dubocovich M.L. (1983). Melatonin is a potent modulator of dopamine release in the retina. Nature 306, 782-784.

Escames G., Leon J., Lopez L.C. and Acuna-Castroviejo D. (2004). Mechanisms of n-methyl-d-aspartate receptor inhibition by melatonin in the rat striatum. J. Neuroendocrinol. 16, 929-935.

Esteve P.O., Chicoine E., Robledo O., Aoudjit F., Descoteaux A., Potworowski E.F. and St-Pierre Y. (2002). Protein kinase c-zeta regulates transcription of the matrix metalloproteinase-9 gene induced by il-1 and tnf-alpha in glioma cells via NF-kappa b. J. Biol. Chem. 277, 35150-35155.

Feng Z., Chang Y., Cheng Y., Zhang B.L., Qu Z.W., Qin C. and Zhang J.T. (2004). Melatonin alleviates behavioral deficits associated with apoptosis and cholinergic system dysfunction in the app 695 transgenic mouse model of alzheimer's disease. J. Pineal Res. 37, 129-136.

Ferracioli-Oda E., Qawasmi A. and Bloch M.H. (2013). Meta-analysis: Melatonin for the treatment of primary sleep disorders. PLoS One 8, e63773.

Frigeri A., Nicchia G.P., Nico B., Quondamatteo F., Herken R., Roncali L. and Svelto M. (2001). Aquaporin-4 deficiency in skeletal muscle and brain of dystrophic mdx mice. FASEB J. 15, 90-98.

Gitto E., Karbownik M., Reiter R.J., Tan D.X., Cuzzocrea S., Chiurazzi P., Cordaro S., Corona G., Trimarchi G. and Barberi I. (2001). Effects of melatonin treatment in septic newborns. Pediatr. Res. 50, 756-760.

Glabinski A.R. and Ransohoff R.M. (1999). Sentries at the gate: Chemokines and the blood-brain barrier. J. Neurovirol. 5, 623-634.

Glaser N. (2001). Cerebral edema in children with diabetic ketoacidosis. Curr. Diabet Rep. 1, 41-46.

Go K.G. (1997). The normal and pathological physiology of brain water. Adv. Tech. Standards Neurosurg. 23, 47-142.

Gorgulu A., Palaoglu S., Ismailoglu O., Tuncel M., Surucu M.T., Erbil M. and Kilinc K. (2001). Effect of melatonin on cerebral edema in rats. Neurosurgery. 49, 1434-1441; discussion 1441-1432.

Guerrero J.M., Reiter R.J., Ortiz G.G., Pablos M.I., Sewerynek E. and Chuang J.I. (1997). Melatonin prevents increases in neural nitric oxide and cyclic gmp production after transient brain ischemia and reperfusion in the mongolian gerbil (*Meriones unguiculatus*). J. Pineal Res. 23, 24-31.

Guo D., Jia Q., Song H.Y., Warren R.S. and Donner D.B. (1995). Vascular endothelial cell growth factor promotes tyrosine phosphorylation of mediators of signal transduction that contain sh2 domains. Association with endothelial cell proliferation. J. Biol. Chem. 270, 6729-6733.

Hardeland R. (2005). Antioxidative protection by melatonin: Multiplicity of mechanisms from radical detoxification to radical avoidance. Endocrine. 27, 119-130.

Harrigan M.R., Ennis S.R., Masada T. and Keep R.F. (2002). Intraventricular infusion of vascular endothelial growth factor promotes cerebral angiogenesis with minimal brain edema. Neurosurgery 50, 589-598.

Harrigan M.R., Ennis S.R., Sullivan S.E. and Keep R.F. (2003). Effects of intraventricular infusion of vascular endothelial growth factor on cerebral blood flow, edema, and infarct volume. Acta Neurochirurg. 145, 49-53.

Heo J.H., Han S.W. and Lee S.K. (2005). Free radicals as triggers of brain edema formation after stroke. Free Radic. Biol. Med. 39, 51-70.

Hermann D.M. and Zechariah A. (2009). Implications of vascular endothelial growth factor for postischemic neurovascular remodeling. J. Cereb. Blood Flow Metab. 29, 1620-1643.

Ho M.N., Rojas R. and Eisenberg R.L. (2012). Cerebral edema. Am. J. Roentgenol. 199, W258-W273.

Hung Y.C., Chen T.Y., Lee E.J., Chen W.L., Huang S.Y., Lee W.T., Lee M.Y., Chen H.Y. and Wu T.S. (2008). Melatonin decreases matrix metalloproteinase-9 activation and expression and attenuates reperfusion-induced hemorrhage following transient focal cerebral ischemia in rats. J. Pineal Res. 45, 459-467.

Hutton L.C., Abbass M., Dickinson H., Ireland Z. and Walker D.W. (2009). Neuroprotective properties of melatonin in a model of birth asphyxia in the spiny mouse (*Acomys cahirinus*). Dev. Neurosci. 31, 437-451.

Janigro D., West G.A., Nguyen T.S. and Winn H.R. (1994). Regulation of blood-brain barrier endothelial cells by nitric oxide. Circulation Res. 75, 528-538.

Jimenez-Jorge S., Guerrero J.M., Jimenez-Caliani A.J., Naranjo M.C., Lardone P.J., Carrillo-Vico A., Osuna C. and Molinero P. (2007). Evidence for melatonin synthesis in the rat brain during development. J. Pineal Res. 42, 240-246.

Josko J. (2003). Cerebral angiogenesis and expression of vegf after subarachnoid hemorrhage (sah) in rats. Brain Res. 981, 58-69.

Julien S., Kreppel F., Beck S., Heiduschka P., Brito V., Schnichels S., Kochanek S. and Schraermeyer U. (2008). A reproducible and quantifiable model of choroidal neovascularization induced by vegf a165 after subretinal adenoviral gene transfer in the rabbit. Mol. Vis. 14, 1358-1372.

Kale R.A., Gupta R.K., Saraswat V.A., Hasan K.M., Trivedi R., Mishra A.M., Ranjan P., Pandey C.M. and Narayana P.A. (2006). Demonstration of interstitial cerebral edema with diffusion tensor mr imaging in type c hepatic encephalopathy. Hepatology 43, 698-706.

Kaur C. and Ling E.A. (2008). Blood brain barrier in hypoxic-ischemic conditions. Current Neurovasc. Res. 5, 71-81.

Kaur C., Sivakumar V., Ang L.S. and Sundaresan A. (2006a). Hypoxic damage to the periventricular white matter in neonatal brain: Role of vascular endothelial growth factor, nitric oxide and excitotoxicity. J. Neurochem. 98, 1200-1216.

Kaur C., Sivakumar V., Zhang Y. and Ling E.A. (2006b). Hypoxia-

induced astrocytic reaction and increased vascular permeability in the rat cerebellum. Glia 54, 826-839.

Kaur C., Sivakumar V., Yong Z., Lu J., Foulds W.S. and Ling E.A. (2007). Blood-retinal barrier disruption and ultrastructural changes in the hypoxic retina in adult rats: The beneficial effect of melatonin administration. Journal Pathol. 212, 429-439.

Kaur C., Sivakumar V., Lu J., Tang F.R. and Ling E.A. (2008). Melatonin attenuates hypoxia-induced ultrastructural changes and increased vascular permeability in the developing hippocampus. Brain Pathol. 18, 533-547.

Kaur C., Sivakumar V. and Ling E.A. (2010). Melatonin protects periventricular white matter from damage due to hypoxia. J. Pineal Res. 48, 185-193.

Kaur C., Viswanathan S. and Ling E.A. (2011). Hypoxia-induced cellular and vascular changes in the nucleus tractus solitarius and ventrolateral medulla. J. Neuropathol. Exp. Neurol. 70, 201-217.

Kaur C., Sivakumar V., Robinson R., Foulds W.S., Luu C.D. and Ling E.A. (2013). Neuroprotective effect of melatonin against hypoxia-induced retinal ganglion cell death in neonatal rats. J. Pineal Res. 54, 190-206.

Kawamata T., Katayama Y., Tsuji N. and Nishimoto H. (2003). Metabolic derangements in interstitial brain edema with preserved blood flow: Selective vulnerability of the hippocampal ca3 region in rat hydrocephalus. Acta Neurochirurg. Supplement. 86, 545-547.

Kaya D., Gursoy-Ozdemir Y., Yemisci M., Tuncer N., Aktan S. and Dalkara T. (2005). Vegf protects brain against focal ischemia without increasing blood--brain permeability when administered intracerebroventricularly. J. Cereb. Blood Flow Metab. 25, 1111-1118.

Kempski O. (2001). Cerebral edema. Semin. Nephrol. 21, 303-307.

Kilic E., Kilic U., Wang Y., Bassetti C.L., Marti H.H. and Hermann D.M. (2006). The phosphatidylinositol-3 kinase/akt pathway mediates vegf's neuroprotective activity and induces blood brain barrier permeability after focal cerebral ischemia. FASEB J. 20, 1185-1187.

Kim K.S., Wass C.A., Cross A.S. and Opal S.M. (1992). Modulation of blood-brain barrier permeability by tumor necrosis factor and antibody to tumor necrosis factor in the rat. Lymphokine and Cytokine Res. 11, 293-298.

Kimura R., Nakase H., Tamaki R. and Sakaki T. (2005). Vascular endothelial growth factor antagonist reduces brain edema formation and venous infarction. Stroke 36, 1259-1263.

Koedel U., Bernatowicz A., Paul R., Frei K., Fontana A. and Pfister H.W. (1995). Experimental pneumococcal meningitis: Cerebrovascular alterations, brain edema, and meningeal inflammation are linked to the production of nitric oxide. Ann. Neurol. 37, 313-323.

Koh P.O. (2008). Melatonin regulates nitric oxide synthase expression in ischemic brain injury. J. Vet. Med. Sci. 70, 747-750.

Kondoh T., Uneyama H., Nishino H. and Torii K. (2002). Melatonin reduces cerebral edema formation caused by transient forebrain ischemia in rats. Life Sci. 72, 583-590.

Koyama J., Miyake S., Sasayama T., Chiba Y., Kondoh T. and Kohmura E. (2010). The novel vegf receptor antagonist, vga1155, reduces edema, decreases infarct and improves neurological function after stroke in rats. Kobe J. Med. Sci. 56, E1-11.

Kumai Y., Ooboshi H., Ibayashi S., Ishikawa E., Sugimori H., Kamouchi M., Kitazono T., Egashira K. and Iida M. (2007). Postischemic gene transfer of soluble flt-1 protects against brain ischemia with marked attenuation of blood-brain barrier permeability. J. Cereb. Blood Flow Metab. 27, 1152-1160.

Le Bars D., Thivolle P., Vitte P.A., Bojkowski C., Chazot G., Arendt J., Frackowiak R.S. and Claustrat B. (1991). Pet and plasma pharmacokinetic studies after bolus intravenous administration of [11c]melatonin in humans. Int J. Rad. Applications Instrumentation. Part B, Nuclear Med. Biol. 18, 357-362.

Lee Y.K., Lee S.R. and Kim C.Y. (2000). Melatonin attenuates the changes in polyamine levels induced by systemic kainate administration in rat brains. J. Neurol. Sci. 178, 124-131.

Lee E.J., Wu T.S., Lee M.Y., Chen T.Y., Tsai Y.Y., Chuang J.I. and Chang G.L. (2004). Delayed treatment with melatonin enhances electrophysiological recovery following transient focal cerebral ischemia in rats. J. Pineal Res. 36, 33-42.

Lee E.J., Lee M.Y., Chen H.Y., Hsu Y.S., Wu T.S., Chen S.T. and Chang G.L. (2005). Melatonin attenuates gray and white matter damage in a mouse model of transient focal cerebral ischemia. J. Pineal Res. 38, 42-52.

Lee M.Y., Kuan Y.H., Chen H.Y., Chen T.Y., Chen S.T., Huang C.C., Yang I.P., Hsu Y.S., Wu T.S. and Lee E.J. (2007). Intravenous administration of melatonin reduces the intracerebral cellular inflammatory response following transient focal cerebral ischemia in rats. J. Pineal Res. 42, 297-309.

Lennmyr F., Ata K.A., Funa K., Olsson Y. and Terent A. (1998). Expression of vascular endothelial growth factor (vegf) and its receptors (flt-1 and flk-1) following permanent and transient occlusion of the middle cerebral artery in the rat. J. Neuropathol. Exp. Neurol. 57, 874-882.

Leon J., Escames G., Rodriguez M.I., Lopez L.C., Tapias V., Entrena A., Camacho E., Carrion M.D., Gallo M.A., Espinosa A., Tan D.X., Reiter R.J. and Acuna-Castroviejo D. (2006). Inhibition of neuronal nitric oxide synthase activity by n1-acetyl-5-methoxykynuramine, a brain metabolite of melatonin. J. Neurochem. 98, 2023-2033.

Leppert D., Lindberg R.L., Kappos L. and Leib S.L. (2001). Matrix metalloproteinases: Multifunctional effectors of inflammation in multiple sclerosis and bacterial meningitis. Brain Res. Brain Res. Rev. 36, 249-257.

Lerner A.B., Case J.D., Takahashi Y., Lee T.H. and Mori W. (1958). Isolation of melatonin, the pineal gland factor that lightens melanocytes 1. J. Am. Chem. Soc. 80, 2587-2587.

Liang F.Q. and Godley B.F. (2003). Oxidative stress-induced mitochondrial DNA damage in human retinal pigment epithelial cells: A possible mechanism for rpe aging and age-related macular degeneration. Exp. Eye Res. 76, 397-403.

Liang K.C., Lee C.W., Lin W.N., Lin C.C., Wu C.B., Luo S.F. and Yang C.M. (2007). Interleukin-1beta induces mmp-9 expression via p42/p44 mapk, p38 mapk, jnk, and nuclear factor-kappab signaling pathways in human tracheal smooth muscle cells. J. Cell Physiol. 211, 759-770.

Lin C.H., Huang J.Y., Ching C.H. and Chuang J.I. (2008). Melatonin reduces the neuronal loss, downregulation of dopamine transporter, and upregulation of d2 receptor in rotenone-induced parkinsonian rats. J. Pineal Res. 44, 205-213.

Lin L., Huang Q.-X., Yang S.-S., Chu J., Wang J.-Z. and Tian Q. (2013). Melatonin in alzheimer's disease. Int. J. Mol. Sci. 14, 14575-14593.

Lissoni P., Rovelli F., Malugani F., Bucovec R., Conti A. and Maestroni G.J. (2001). Anti-angiogenic activity of melatonin in advanced cancer patients. Neuroendocrinol. Lett. 22, 45-47.

Liu L. and Cheung R.T. (2013). Effects of pretreatment with a combination of melatonin and electroacupuncture in a rat model of transient focal cerebral ischemia. Evid. Based Complement.

Alternat. Med. 2013, 953162.

Lotufo C.M., Lopes C., Dubocovich M.L., Farsky S.H. and Markus R.P. (2001). Melatonin and N-acetylserotonin inhibit leukocyte rolling and adhesion to rat microcirculation. Eur. J. Pharmacol. 430, 351-357.

Lotufo C.M., Yamashita C.E., Farsky S.H. and Markus R.P. (2006). Melatonin effect on endothelial cells reduces vascular permeability increase induced by leukotriene b4. Eur. J. Pharmacol. 534, 258-263.

Manev H., Uz T. and Qu T. (1998). Early upregulation of hippocampal 5-lipoxygenase following systemic administration of kainate to rats. Restorative Neurol. Neurosci. 12, 81-85.

Manley G.T., Fujimura M., Ma T., Noshita N., Filiz F., Bollen A.W., Chan P. and Verkman A.S. (2000). Aquaporin-4 deletion in mice reduces brain edema after acute water intoxication and ischemic stroke. Nat. Med. 6, 159-163.

Mark K.S., Trickler W.J. and Miller D.W. (2001). Tumor necrosis factor-alpha induces cyclooxygenase-2 expression and prostaglandin release in brain microvessel endothelial cells. J. Pharmacol. Exp. Ther. 297, 1051-1058.

Martin M., Macias M., Leon J., Escames G., Khaldy H. and Acuna-Castroviejo D. (2002). Melatonin increases the activity of the oxidative phosphorylation enzymes and the production of atp in rat brain and liver mitochondria. Int. J. Biochem. Cell Biol. 34, 348-357.

Mayhan W.G. (1996). Role of nitric oxide in histamine-induced increases in permeability of the blood-brain barrier. Brain Res. 743, 70-76.

Mayhan W.G. (1999). VEGF increases permeability of the blood-brain barrier via a nitric oxide synthase/cgmp-dependent pathway. Am. J. Physiol. 276, C1148-1153.

Mayhan W.G. and Didion S.P. (1996). Glutamate-induced disruption of the blood-brain barrier in rats. Role of nitric oxide. Stroke. 27, 965-969; discussion 970.

Mayo J.C., Sainz R.M., Tan D.X., Antolin I., Rodriguez C. and Reiter R.J. (2005). Melatonin and parkinson's disease. Endocrine 27, 169-178.

Mendonca M.C., Soares E.S., Stavale L.M., Raposo C., Coope A., Kalapothakis E. and da Cruz-Hofling M.A. (2013). Expression of vegf and flk-1 and flt-1 receptors during blood-brain barrier (bbb) impairment following phoneutria nigriventer spider venom exposure. Toxins 5, 2572-2588.

Mesenge C., Margaill I., Verrecchia C., Allix M., Boulu R.G. and Plotkine M. (1998). Protective effect of melatonin in a model of traumatic brain injury in mice. J. Pineal Res. 25, 41-46.

Milhorat T.H., Clark R.G., Hammock M.K. and McGrath P.P. (1970). Structural, ultrastructural, and permeability changes in the ependyma and surrounding brain favoring equilibration in progressive hydrocephalus. Arch. Neurol. 22, 397-407.

Miller S.L., Yan E.B., Castillo-Melendez M., Jenkin G. and Walker D.W. (2005). Melatonin provides neuroprotection in the late-gestation fetal sheep brain in response to umbilical cord occlusion. Dev. Neurosci. 27, 200-210.

Min K.J., Jang J.H. and Kwon T.K. (2012). Inhibitory effects of melatonin on the lipopolysaccharide-induced cc chemokine expression in bv2 murine microglial cells are mediated by suppression of akt-induced nf-kappab and stat/gas activity. J. Pineal Res. 52, 296-304.

Minami T., Okazaki J., Kawabata A., Kawaki H., Okazaki Y. and Tohno Y. (1998). Roles of nitric oxide and prostaglandins in the increased permeability of the blood-brain barrier caused by lipopolysaccharide. Environ. Toxicol. Pharmacol. 5, 35-41.

Moore A.H., Olschowka J.A. and O'Banion M.K. (2004). Intraparenchymal administration of interleukin-1beta induces cyclooxygenase-2-mediated expression of membrane- and cytosolic-associated prostaglandin e synthases in mouse brain. J. Neuroimmunol. 148, 32-40.

Mori K., Shibanuma M. and Nose K. (2004). Invasive potential induced under long-term oxidative stress in mammary epithelial cells. Cancer Res. 64, 7464-7472.

Morin-Brureau M., Lebrun A., Rousset M.C., Fagni L., Bockaert J., de Bock F. and Lerner-Natoli M. (2011). Epileptiform activity induces vascular remodeling and zonula occludens 1 downregulation in organotypic hippocampal cultures: Role of vegf signaling pathways. J. Neurosci. 31, 10677-10688.

Nag S. (2003). Blood-brain barrier permeability using tracers and immunohistochemistry. Methods Mol. Med. 89, 133-144.

Nag S., Manias J.L. and Stewart D.J. (2009). Pathology and new players in the pathogenesis of brain edema. Acta Neuropathol. 118, 197-217.

Nakano S., Matsukado K. and Black K.L. (1996). Increased brain tumor microvessel permeability after intracarotid bradykinin infusion is mediated by nitric oxide. Cancer Res. 56, 4027-4031.

Nau R., Sorgel F. and Eiffert H. (2010). Penetration of drugs through the blood-cerebrospinal fluid/blood-brain barrier for treatment of central nervous system infections. Clin. Microbiol. Rev. 23, 858-883.

Pandi-Perumal S.R., Srinivasan V., Maestroni G.J.M., Cardinali D.P., Poeggeler B. and Hardeland R. (2006). Melatonin: Nature's most versatile biological signal? FEBS J. 273, 2813-2838.

Papadopoulos M.C., Manley G.T., Krishna S. and Verkman A.S. (2004). Aquaporin-4 facilitates reabsorption of excess fluid in vasogenic brain edema. FASEB J. 18, 1291-1293.

Park S.W., Lee H.S., Sung M.S. and Kim S.J. (2012). The effect of melatonin on retinal ganglion cell survival in ischemic retina. Chonnam Med. J. 48, 116-122.

Paul S., Sharma A.V., Mahapatra P.D., Bhattacharya P., Reiter R.J. and Swarnakar S. (2008). Role of melatonin in regulating matrix metalloproteinase-9 via tissue inhibitors of metalloproteinase-1 during protection against endometriosis. J. Pineal Res. 44, 439-449.

Pei Z. and Cheung R.T. (2004). Pretreatment with melatonin exerts anti-inflammatory effects against ischemia/reperfusion injury in a rat middle cerebral artery occlusion stroke model. J. Pineal Res. 37, 85-91.

Pei Z., Pang S.F. and Cheung R.T. (2003). Administration of melatonin after onset of ischemia reduces the volume of cerebral infarction in a rat middle cerebral artery occlusion stroke model. Stroke 34, 770-775.

Poeggeler B. (2005). Melatonin, aging, and age-related diseases: Perspectives for prevention, intervention, and therapy. Endocrine 27, 201-212.

Pozo D., Reiter R.J., Calvo J.R. and Guerrero J.M. (1994). Physiological concentrations of melatonin inhibit nitric oxide synthase in rat cerebellum. Life Sci. 55, PL455-460.

Pozo D., Reiter R.J., Calvo J.R. and Guerrero J.M. (1997). Inhibition of cerebellar nitric oxide synthase and cyclic gmp production by melatonin via complex formation with calmodulin. J. Cell Biochem. 65, 430-442.

Pustovrh M.C., Jawerbaum A., Capobianco E., White V., Martinez N., Lopez-Costa J.J. and Gonzalez E. (2005). Oxidative stress promotes the increase of matrix metalloproteinases-2 and -9 activities in the feto-placental unit of diabetic rats. Free Radic. Res.

39, 1285-1293.

Qin W., Lu W., Li H., Yuan X., Li B., Zhang Q. and Xiu R. (2012). Melatonin inhibits il1β-induced mmp9 expression and activity in human umbilical vein endothelial cells by suppressing nf-κb activation. J. Endocrinol. 214, 145-153.

Rajagopalan S., Meng X.P., Ramasamy S., Harrison D.G. and Galis Z.S. (1996). Reactive oxygen species produced by macrophage-derived foam cells regulate the activity of vascular matrix metalloproteinases in vitro. Implications for atherosclerotic plaque stability. J. Clin. Invest. 98, 2572-2579.

Redman J., Armstrong S. and Ng K.T. (1983). Free-running activity rhythms in the rat: Entrainment by melatonin. Science 219, 1089-1091.

Reiter R.J., Tan D.-X., Manchester L.C., Lopez-Burillo S., Sainz R.M. and Mayo J.C. (2003). Melatonin: Detoxification of oxygen and nitrogen-based toxic reactants. Adv. Exp. Med. Biol. 527, 539-548.

Rosell A. and Lo E.H. (2008). Multiphasic roles for matrix metalloproteinases after stroke. Curr. Opin. Pharmacol. 8, 82-89.

Rosell A., Cuadrado E., Ortega-Aznar A., Hernandez-Guillamon M., Lo E.H. and Montaner J. (2008). Mmp-9-positive neutrophil infiltration is associated to blood-brain barrier breakdown and basal lamina type iv collagen degradation during hemorrhagic transformation after human ischemic stroke. Stroke 39, 1121-1126.

Rosenberg G.A. (2002). Matrix metalloproteinases in neuroinflammation. Glia 39, 279-291.

Rosenberg G.A., Navratil M., Barone F. and Feuerstein G. (1996). Proteolytic cascade enzymes increase in focal cerebral ischemia in rat. J. Cereb. Blood Flow Metab. 16, 360-366.

Rudra D.S., Pal U., Maiti N.C., Reiter R.J. and Swarnakar S. (2013). Melatonin inhibits matrix metalloproteinase-9 activity by binding to its active site. J. Pineal Res. 54, 398-405.

Schmidley J.W., Dadson J., Iyer R.S. and Salomon R.G. (1992). Brain tissue injury and blood-brain barrier opening induced by injection of lge2 or pge2. Prostaglandins Leukot Essent Fatty Acids 47, 105-110.

Schreurs M.P., Houston E.M., May V. and Cipolla M.J. (2012). The adaptation of the blood-brain barrier to vascular endothelial growth factor and placental growth factor during pregnancy. FASEB J. 26, 355-362.

Senger D.R., Brown L.F., Claffey K.P. and Dvorak H.F. (1994). Vascular permeability factor, tumor angiogenesis and stroma generation. Invasion Metast. 14, 385-394.

Seo J.H., Miyamoto N., Hayakawa K., Pham L.D., Maki T., Ayata C., Kim K.W., Lo E.H. and Arai K. (2013). Oligodendrocyte precursors induce early blood-brain barrier opening after white matter injury. J. Clin. Invest. 123, 782-786.

Sharma R., McMillan C.R., Tenn C.C. and Niles L.P. (2006). Physiological neuroprotection by melatonin in a 6-hydroxydopamine model of parkinson's disease. Brain Res. 1068, 230-236.

Shore P.M., Jackson E.K., Wisniewski S.R., Clark R.S., Adelson P.D. and Kochanek P.M. (2004). Vascular endothelial growth factor is increased in cerebrospinal fluid after traumatic brain injury in infants and children. Neurosurgery 54, 605-611; discussion 611-602.

Shukla A., Dikshit M. and Srimal R.C. (1996). Nitric oxide-dependent blood-brain barrier permeability alteration in the rat brain. Experientia. 52, 136-140.

Sivakumar V., Lu J., Ling E.A. and Kaur C. (2008). Vascular endothelial growth factor and nitric oxide production in response to hypoxia in the choroid plexus in neonatal brain. Brain Pathol. 18, 71-85.

Slominski A., Wortsman J. and Tobin D.J. (2005). The cutaneous serotoninergic/melatoninergic system: Securing a place under the sun. FASEB J. 19, 176-194.

Srinivasan V., Pandi-Perumal S.R., Cardinali D.P., Poeggeler B. and Hardeland R. (2006a). Melatonin in alzheimer's disease and other neurodegenerative disorders. Behav. Brain Funct. 2, 15.

Srinivasan V., Smits M., Spence W., Lowe A.D., Kayumov L., Pandi-Perumal S.R., Parry B. and Cardinali D.P. (2006b). Melatonin in mood disorders. World J. Biol. Psych. 7, 138-151.

Srinivasan V., Spence D.W., Pandi-Perumal S.R., Trakht I. and Cardinali D.P. (2008). Therapeutic actions of melatonin in cancer: Possible mechanisms. Integr. Cancer Ther. 7, 189-203.

Sternlicht M.D. and Werb Z. (2001). How matrix metalloproteinases regulate cell behavior. Annu. Rev. Cell Dev. Biol. 17, 463-516.

Sterns R.H., Riggs J.E. and Schochet S.S. Jr (1986). Osmotic demyelination syndrome following correction of hyponatremia. N. Engl. J. Med. 314, 1535-1542.

Suidan G.L., Dickerson J.W., Johnson H.L., Chan T.W., Pavelko K.D., Pirko I., Seroogy K.B. and Johnson A.J. (2012). Preserved vascular integrity and enhanced survival following neuropilin-1 inhibition in a mouse model of cd8 t cell-initiated cns vascular permeability. J. Neuroinflammation 9, 218.

Swarnakar S., Mishra A., Ganguly K. and Sharma A.V. (2007). Matrix metalloproteinase-9 activity and expression is reduced by melatonin during prevention of ethanol-induced gastric ulcer in mice. J. Pineal Res. 43, 56-64.

Tai S.H., Chen H.Y., Lee E.J., Chen T.Y., Lin H.W., Hung Y.C., Huang S.Y., Chen Y.H., Lee W.T. and Wu T.S. (2010). Melatonin inhibits postischemic matrix metalloproteinase-9 (mmp-9) activation via dual modulation of plasminogen/plasmin system and endogenous mmp inhibitor in mice subjected to transient focal cerebral ischemia. J. Pineal Res. 49, 332-341.

Tejima E., Guo S., Murata Y., Arai K., Lok J., van Leyen K., Rosell A., Wang X. and Lo E.H. (2009). Neuroprotective effects of overexpressing tissue inhibitor of metalloproteinase timp-1. J. Neurotrauma. 26, 1935-1941.

Thiel V.E. and Audus K.L. (2001). Nitric oxide and blood-brain barrier integrity. Antioxid. Redox Signal. 3, 273-278.

Toklu H., Deniz M., Yüksel M., Keyer-Uysal M., Şener G. and (2009). The protective effect of melatonin and amlodipine against cerebral ischemia/reperfusion-induced oxidative brain injury in rats. Marmara Med. J. 22, 34-44.

Trickler W.J., Mayhan W.G. and Miller D.W. (2005). Brain microvessel endothelial cell responses to tumor necrosis factor-alpha involve a nuclear factor kappa b (nf-kappab) signal transduction pathway. Brain Res. 1048, 24-31.

Tu Y.F., Tsai Y.S., Wang L.W., Wu H.C., Huang C.C. and Ho C.J. (2011). Overweight worsens apoptosis, neuroinflammation and blood-brain barrier damage after hypoxic ischemia in neonatal brain through jnk hyperactivation. J. Neuroinflammation. 8, 40.

Utepbergenov D.I., Mertsch K., Sporbert A., Tenz K., Paul M., Haseloff R.F. and Blasig I.E. (1998). Nitric oxide protects blood-brain barrier in vitro from hypoxia/reoxygenation-mediated injury. FEBS Lett. 424, 197-201.

Uz T. and Manev H. (1998). Circadian expression of pineal 5-lipoxygenase mrna. Neuroreport 9, 783-786.

Vajda Z., Pedersen M., Fuchtbauer E.M., Wertz K., Stodkilde-Jorgensen H., Sulyok E., Doczi T., Neely J.D., Agre P., Frokiaer J. and Nielsen S. (2002). Delayed onset of brain edema and mislocalization of

aquaporin-4 in dystrophin-null transgenic mice. Proc. Natl. Acad. Sci. USA 99, 13131-13136.

van Bruggen N., Thibodeaux H., Palmer J.T., Lee W.P., Fu L., Cairns B., Tumas D., Gerlai R., Williams S.P., van Lookeren Campagne M. and Ferrara N. (1999). Vegf antagonism reduces edema formation and tissue damage after ischemia/reperfusion injury in the mouse brain. J. Clin. Invest. 104, 1613-1620.

Vogel C., Bauer A., Wiesnet M., Preissner K.T., Schaper W., Marti H.H. and Fischer S. (2007). Flt-1, but not flk-1 mediates hyperpermeability through activation of the pi3-k/akt pathway. J. Cell. Physiol. 212, 236-243.

Wang W., Dentler W.L. and Borchardt R.T. (2001). Vegf increases bmec monolayer permeability by affecting occludin expression and tight junction assembly. Am. J. Physiol. 280, H434-H440.

Welin A.-K., Svedin P., Lapatto R., Sultan B., Hagberg H., Gressens P., Kjellmer I. and Mallard C. (2007). Melatonin reduces inflammation and cell death in white matter in the mid-gestation fetal sheep following umbilical cord occlusion. Pediatr. Res. 61, 153-158.

Worrall N.K., Chang K., LeJeune W.S., Misko T.P., Sullivan P.M., Ferguson T.B. Jr and Williamson J.R. (1997). TNF-alpha causes reversible in vivo systemic vascular barrier dysfunction via no-dependent and -independent mechanisms. Am. J. Physiol. 273, H2565-2574.

Xia M.Z., Liang Y.L., Wang H., Chen X., Huang Y.Y., Zhang Z.H., Chen Y.H., Zhang C., Zhao M., Xu D.X. and Song L.H. (2012). Melatonin modulates tlr4-mediated inflammatory genes through myd88- and trif-dependent signaling pathways in lipopolysaccharide-stimulated raw264.7 cells. J. Pineal Res. 53, 325-334.

Xie Z., Singh M. and Singh K. (2004). Differential regulation of matrix metalloproteinase-2 and -9 expression and activity in adult rat cardiac fibroblasts in response to interleukin-1beta. J. Biol. Chem. 279, 39513-39519.

Yang G.Y., Gong C., Qin Z., Liu X.H. and Lorris Betz A. (1999). Tumor necrosis factor alpha expression produces increased blood-brain barrier permeability following temporary focal cerebral ischemia in mice. Brain Res. Mol. Brain Res. 69, 135-143.

Yang Y., Estrada E.Y., Thompson J.F., Liu W. and Rosenberg G.A. (2007). Matrix metalloproteinase-mediated disruption of tight junction proteins in cerebral vessels is reversed by synthetic matrix metalloproteinase inhibitor in focal ischemia in rat. J. Cereb. Blood. Flow. Metab. 27, 697-709.

Yawno T., Castillo-Melendez M., Jenkin G., Wallace E.M., Walker D.W. and Miller S.L. (2012). Mechanisms of melatonin-induced protection in the brain of late gestation fetal sheep in response to hypoxia. Dev. Neurosci. 34, 543-551.

Zador Z., Bloch O., Yao X. and Manley G.T. (2007). Aquaporins: Role in cerebral edema and brain water balance. Prog. Brain Res. 161, 185-194.

Zhang H., Akbar M. and Kim H.Y. (1999). Melatonin: An endogenous negative modulator of 12-lipoxygenation in the rat pineal gland. Biochem. J. 344 Pt 2, 487-493.

Zhang Z.G., Zhang L., Jiang Q., Zhang R., Davies K., Powers C., Bruggen N. and Chopp M. (2000). Vegf enhances angiogenesis and promotes blood-brain barrier leakage in the ischemic brain. J. Clin. Invest. 106, 829-838.

Accepted May 29, 2014