Acta Neurol. Belg., 2010, **110**, 26-35

Endogenous neuroprotection in multiple sclerosis

R. E. GONSETTE
National Centre for Multiple Sclerosis, Melsbroek, Belgium

Abstract

Endogenous neuroprotection was mostly investigated in stroke, trauma and neurodegenerative diseases. However, several endogenous neuroprotective mechanisms have been identified recently in multiple sclerosis: protective autoimmunity, direct low molecular weight antioxidants, indirect antioxidants inducing cytoprotective proteins, kynurenine pathways, ischemic preconditioning, integrated cell response, cannabinoids and complement system.

Numerous endogenous neuroprotective strategies are investigated in animal models but the translation into the clinic of positive results obtained in the laboratory has been disappointing so far.

Endogenous neuroprotection is the net result of complex and interconnected mechanisms and modulating an individual neuroprotective pathway will likely yield a partial benefit, if any.

Another concern, consistently observed in multiple sclerosis and its animal models, is that the same cells and the same chemical mediators can initiate degenerative cascades and/or neuroprotective pathways. The final outcome depends on the local microenvironment but most of the regulatory mechanisms that control the balancing of protective versus detrimental responses are unknown at present.

Before experimental strategies are to become approved treatments further studies are necessary to understand the precise molecular mechanisms underlying neuroprotective pathways and their complex interconnections.

Key words: Multiple sclerosis; neuroprotection; antioxidants; kynurenine; ischemic preconditioning; integrated cell response; cannabinoids; complement system.

Introduction

Common intrinsic mechanisms have evolved in all organisms to counteract damaging effects of endogenous and/or exogenous toxic agents. Endogenous protective mechanisms have been mainly investigated in diverse pathological states such as vascular diseases, trauma and cancer. More recently, endogenous neuroprotection has been identified in neurodegenerative diseases including multiple sclerosis (MS). Given that exogenous pharmacological neuroprotective strategies failed to be proven clinically useful so far, interest has turned to endogenous protective mechanisms. This review is meant to update our current understanding of endogenous neuroprotection in MS as well as of therapeutic approaches developed to enhance their efficacy.

1. PROTECTIVE AUTOIMMUNITY

Both the cellular and humoral components of the immune system associated with inflammatory reactions may have beneficial effects in certain conditions. Regulatory T cells (CD4+CD25+-FoxP3-Treg) block autoreactive Th1 CD4+ cells ability to produce inflammatory mediators and stimulate secretion of immunosuppressive cytokines. A distinct CD8+ T cell population exerts suppressive functions and participates to beneficial immunity (Zozulya and Wiendl, 2008). Regulatory B cells can produce IL-10 and TGFβ (Mizoguchi and Bhan, 2006) as well as neuroprotective antibodies (Ab) (Graber and Dhib-Jalbut, 2009). Natural autoantibodies react to self antigens, induce extensive remyelination by stimulating oligodendrocyte development and are currently investigated in a phase I trial in MS patients (Rodriguez *et al.*, 2009).

Boosting protective immunity however can lead to untoward immune reactions. Treg cells exhibit defective regulatory properties in MS patients (Frisullo *et al.*, 2009). To expand the size and enhance the activity of Treg cell compartment, a superagonistic mAb (CD28SA) was developed. In contrast to conventional monoclonal antibodies (mAbs), CD28SA simultaneously provides the two signals required for T cell activation. Very effective to protect human primates against EAE induction (Beyersdorf *et al.*, 2005), this fully humanized

superagonistic mAb (TGN1412) induced a life-threatening cytokine release syndrome in a phase I trial in humans (Suntharalingam *et al.*, 2006) for still elusive reasons (Schraven and Kalinke, 2008).

Another dilemma is the Janus face of immunocompetent cells. It has been recently observed that, during chronic inflammation, Treg cells can be converted in aggressive Th17 cells in the presence of IL-1 and IL-2 (Deknuydt *et al.*, 2009).

2. Low molecular weight antioxidants (LMWA)

Low molecular weight antioxidants include two classes of endogenous, closely interactive molecules. Direct antioxidants react directly with reactive oxygen and nitrogen intermediates (e.g. α tocopherol, ascorbic acid, uric acid). They are consumed or chemically modified in the process and have to be replenished or regenerated. Indirect antioxidants involve genetically induced cytoprotective proteins that act catalytically and have long half-life. Cytoprotective proteins comprise non-enzymatic oxidants (e.g. thioredoxin) as well as some other conjugating enzymes (e.g. glutathione transferase) and enzymatic (phase 2) antioxidants (e.g. superoxide dismutase, catalase) (Dinkova-Kostova and Talalay, 2008).

2.1. *Direct LMWA*

Uric acid (UA) is the major component of the direct LMWA. Uric acid represents about 70% of total human serum antioxidant activity (Becker, 1993). Uric acid has pro-oxidant capacities in certain conditions. Its reaction with hydroxyl radical or peroxynitrite leads to the formation of radical intermediates that are neutralized by ascorbic acid (Kuzkaya *et al.*, 2005). There is thus a close cooperative interaction between the two most important direct LMWA.

Numerous clinical observations and experimental data provide persuasive evidence for an active role of UA not only in MS but also in other neurodegenerative diseases. Since the seminal publication of Hooper (Hooper *et al.*, 1998), decreased UA levels in serum or in biological fluids have been reported in several autoimmune diseases: MS (Drulovic *et al.*, 2001; Spitsin, 2001; Toncev *et al.*, 2000; Zamani *et al.*, 2008) optic neuritis (Knapp *et al.*, 2004), Crohn's disease (Rezaie *et al.*, 2006), myasthenia gravis and Guillain-Barré (Peng *et al.*, 2008) as well as in neurodegenerative processes: Parkinson's (PD) (Annanmaki *et al.*, 2007; Larumbe Ilundain *et al.*, 2001), Alzheimer's (AD) (Kim *et al.*, 2006; Polidori *et al.*, 2004; Rinaldi *et al.*, 2003) and Huntington's (HD) diseases (Insarova *et al.*, 1978).

In MS, serum UA level variations do not seem to correlate with clinical phenotypes (Ramsaransing *et al.*, 2005) but most observations demonstrate lower serum UA levels during clinical and/or radiological disease activity (Deretzi *et al.*, 2003; Drulovic *et al.*, 2001; Guerrero *et al.*, 2008; Koch and De Keyser, 2006; Mostert *et al.*, 2005; Rentzos *et al.*, 2006; Sotgiu *et al.*, 2002; Toncev *et al.*, 2002; Tsakiri *et al.*, 2008). The lower serum UA concentration in MS may represent a primary, constitutive loss of protection against oxidative stress (Rentzos *et al.*, 2006) or a deficit secondary to UA consumption during oxidative radical scavenging (Koch and De Keyser, 2006).

The neuroprotective role of UA is substantiated by observations showing that increased serum UA levels appear to be associated with a lower risk of developing MS (Hooper *et al.*, 1997), PD (Alonso *et al.*, 2007; Annanmaki *et al.*, 2007; Davis *et al.*, 1996; de Lau *et al.*, 2005; Gao *et al.*, 2008; Weisskopf *et al.*, 2007) and dementia (Euser *et al.*, 2009). On the other hand, increased serum UA levels were reported during treatments with drugs whose efficacy is recognized in MS: glatiramer acetate (Constantinescu *et al.*, 2000; Guerrero *et al.*, 2008), high dose methylprednisolone (Deretzi *et al.*, 2003; Guerrero *et al.*, 2008), IFNβs (Deretzi *et al.*, 2003; Guerrero *et al.*, 2008; Toncev *et al.*, 2007) and natalizumab (Handouk *et al.*, 2008).

Lastly, increased serum UA levels were found effective to reduce clinical and pathological signs in various experimental models: EAE (Hooper *et al.*, 1997), PD (Anderson and Harris, 2003; Duan *et al.*, 2002), spinal cord injury (Scott *et al.*, 2005), focal brain ischemia (Yu *et al.*, 1998) and experimental meningitis (Kastenbauer *et al.*, 2001).

Despite convincing experimental and clinical data showing a marked neuroprotective efficacy in several animal models, an asymptomatic hyperuricemia maintained for 2 years did not provide any additional benefit on accumulation of disability in relapsing-remitting MS patients compared with IFNβ alone (Gonsette *et al.*, in press).

2.2. *Indirect (phase 2) LMWA: theNrF2-ARE pathway*

Indirect endogenous LMWA are cytoprotective, phase 2 enzymes expressed under the control of the transcription factor "nuclear factor erythroid 2-related factor 2" (Nrf2). This unstable protein is constitutively degraded via ubiquitination by Kelch-like ECH associated protein 1 (Keap1). Recent data show that Nrf2 was observed to localize in the nucleus in the absence of any stress. The accumulation of Nrf2

in the nucleus in response to stress and the consequent activation of the antioxidant response element (ARE) likely results from a decrease in the rate of its degradation (Nguyen *et al.*, 2009). Numerous cytoprotective proteins induced by ARE genes are upregulated in MS (Schreibelt *et al.*, 2007) and reflect an activation of the Nrf2-ARE pathway: superoxide dismutases and glutathione peroxidase (Tajouri *et al.*, 2003), catalase and quinone oxidoreductases (van Horssen *et al.*, 2008), peroxiredoxins (Holley *et al.*, 2007), heme oxygenases (Mehindate *et al.*, 2001). Those cytoprotective proteins exert beneficial effects on lipid peroxidation, intracellular calcium overload, excitotoxicity and mitochondriopathy. ARE driven genes are preferentially expressed in astrocytes which provide neuroprotection to neighbouring neurons (Johnson *et al.*, 2008). Interestingly, EAE is exacerbated in Nrf2-knock out mice (Johnson *et al.*, 2009). The response of the Nrf2-ARE pathway might be inadequate in chronic MS. Recent observations suggest that acute oxidative stress upregulates Nrf2 and activates neuroprotective mechanisms, whereas chronic oxidative stress downregulates Nrf2 and concurrently decreases energy metabolism (Pandit *et al.*, 2009).

Harnessing Nrf2-ARE pathways would induce the synthesis of numerous indirect (phase 2) LMWA but the chemistry and the pharmacology of Nrf2-ARE inducers are far from being completely understood. Distinct inducers of the Nfr2-ARE system activate different neuroprotective genes depending on the nature of the inducer. Numerous chemicals and natural products, safe and crossing the blood brain barrier, are potential candidates (e.g. dimethylfumarate, sulforaphane, 3-hydroxycoumarin). Only limited clinical trials have been performed with detoxifying phase 2 enzymes inducers. Fumaric acid derivatives have been investigated in EAE and have marked anti-inflammatory effects (Schilling *et al.*, 2006). One derivative (BG0012) reduces MRI active lesions in relapsing-remitting MS (Schimrigk *et al.*, 2006; Kappos *et al.*, 2008).

3. The kynurenine system

Kynurenic acid (KYNA) is the only endogenous excitotoxicity antagonist. The tryptophan-catabolizing enzyme indoleamine 2,3-dioxygenase (IDO) generates KYNA along with quinoleic acid (QUIN) and other metabolites.

The kynurenine pathway is associated with the pathogenesis of neurodegenerative diseases including MS (Vamos *et al.*, 2009). KYNA is produced at the L-kynurenin stage by L-kynurenine aminotransferases (KAT) I and primarily by KAT II. KYNA is a potent antagonist of all three excitatory amino acid (EAA) receptors. QUIN is the end product of the kynurenine pathway. It acts as an agonist of the excitatory amino acid (EAA) receptors and generates toxic free radicals (Kwidzinki and Bechmann, 2007). The kynurenine pathway can thus be neuroprotective or neurotoxic according to the balance between KYNA and QUIN production (Rozsa *et al.*, 2008).

Data concerning alterations of the kynurenine pathway in MS are scarce. In stable patients, CSF KYNA levels are lower than in patients with other neurological diseases and increased during relapses (Rejdak *et al.*, 2002, 2007). Kat I, KAT II and KINA were found increased in red blood cells and plasma of MS patients (Hartai *et al.*, 2005).

Exogenous administration of KYNA was the first tentative to boost endogenous neuroprotection against cerebral ischemic damage (Nozaki and Beal, 1992). In MS, neuronal damage results, at least in part, from the subsequent synthesis of toxic metabolites of tryptophan, notably the QUIN molecule (Kwidzinski and Bechmann, 2007). Boosting KYNA production to counteract QUIN toxicity might shift the balance in favour of neuroprotection. KYNA does not easily cross the BBB but systemic administration of high doses in animal experiments exerts protective effects after carotid occlusion (Salvati *et al.*, 1999). KYNA analogues (e.g. glucosamine-KYNA) cross the BBB, disengage in the brain and release KYNA that can antagonize excitotoxicity (Nemeth *et al.*, 2006). Another possibility would be the blockade of the kynurenin pathway at the L-kynurenine stage with a kynurenine-3-hydroxylase inhibitor (Ro 61-8048) that enhances KYNA synthesis, decreases QUIN production and provides neuroprotection (Chiarugi *et al.*, 2001). A synthetic tryptophan metabolite has been found effective in EAE (Platten *et al.*, 2005). Interestingly, quinoline carboxamides (linomide, laquinimod) with structural homology to this metabolite have shown some efficacy in MS patients (Comi *et al.*, 2008).

4. Preconditioning (HIF-α)

Tissue preconditioning was first described after heart ischemia (Janoff, 1964) and more recently after brain transient ischemic episodes (Kitagawa *et al.*, 1990).

In normoxia, the protein levels of hypoxia-inducible factor-1α (HIF-1α) are highly linked to oxygen tension and remain stable due to HIF-1α steadily degradation via ubiquitination. During hypoxia, HIF-1α escapes ubiquitination and translocates to the nucleus where it binds to HIF-β to transactivate the expression of hypoxia-response genes (Freeman

and Barone, 2005). The proteins encoded by HIF-1α genes are mainly involved in energy metabolism and cell survival (e.g. erythropoietine, trophic factors, anti-apoptotic proteins) (Dirnagl and Meisel, 2008). It has been recently discovered that Toll-like receptors (TLR) play an important role in preconditioning and ischemic tolerance (Leung *et al.*, 2009).

Hypoxia-like tissue injury associated with nuclear expression of hypoxia-inducible factor1α (HIF-1α) has been reported in active lesions with pattern III characteristics supporting the view of its intervention in a subset of MS patients (Aboul-Enein *et al.*, 2003).

In MS, microarray studies from cortical and white matter tissue confirm upregulation of genes involved in ischemic preconditioning (Graumann *et al.*, 2003; Mahad *et al.*, 2008).

Neuroprotective proteins are detected in oligodendrocytes and neurons at the border of acute lesions and in the adjacent normal white matter (Marik *et al.*, 2007). Due to their neuroprotective effects, the tissue where they are expressed becomes resistant to further damage and this may explain the preserved layers in the Balö type of MS (Stadelmann *et al.*, 2005; Mowry *et al.*, 2007). Mitochondrial dysfunction and energy failure due to ATP depletion certainly play a role in the hypoxia-like injury (Aboul-Enein and Lassmann, 2005; Mahad *et al.*, 2008). The concept of "virtual hypoxia" due to reduced ATP supply and dysfunction of the Na+ pump leading to the same pathomechanisms as those observed in true ischemic axoglial injuries, has been extended to axonal demyelination in MS (Trapp and Stys, 2009). Redox imbalance or virtual hypoxia might be responsible for endothelial cell activation and angiogenesis initiation recently observed in MS brains (Holley *et al.*, 2009).

Boosting preconditioning would have the potential advantage of regulating the expression of a large number of genes involved in endogenous neuroprotection. It seems difficult however to apply the principle of a preconditioning insult in neurological diseases. TLR ligands and inflammatory cytokines are known to induce conditioning tolerance but the boundaries between stimulus intensities that elicit ischemic tolerance and those that induce damage are not clearly defined (Dirnagl *et al.*, 2008). A number of small molecules have been developed that can stabilize HIF-1α and induce HIF gene expression and have protective effects (Yao *et al.*, 2008).

5. Integrated stress response

The endoplasmic reticulum (ER) is a membranous labyrinthine network involved in the folding and processing of membrane proteins, lipids, cellular calcium storing and cell signalling. Oligodendrocytes synthesize a large amount of membrane proteins and lipids and are highly sensitive to ER dysfunction. Impairment of the ER has been reported in neurodegenerative diseases (Lindholm *et al.*, 2006) and in MS (Mhaille *et al.*, 2008). Dysfunction of ER can be caused by nitric oxide, TNFα and IFNγ leading to the "integrated stress response" (ISR) also named "unfold protein response". The ISR is mediated by activation of the pancreatic ER kinase (PERK) (Lu *et al.*, 2004) which couples protein folding in the ER with protein synthesis by phosphorylation of the alpha subunit of eukaryotic translation initiation factor 2 (elf2α). The PERK-elf2α pathway promotes the expression of cytoprotective genes against oxidative stress and other immune-mediated damages. Endoplasmic reticulum markers are increased in MS lesions (Mhaille *et al.*, 2008). Expressed in oligodendrocytes, astrocytes and macrophages, they are mainly observed in the centre and periphery of acutely demyelinating lesions. There is a link between ER and excitotoxicity as ERS inhibition protects against excitotoxic neuronal injury (Sokka *et al.*, 2007). It is noteworthy that ER markers can also be associated with the hypoxia-related protein D-110. Experimental data suggest that the ISR induced by IFNγ is involved in the pathogenesis of immune-mediated demyelination. Importantly, the outcomes of the ISR induced by endogenous IFNγ in oligodendrocytes are determined by the differentiation of the cells. During EAE evolution in adult mice, IFNγ protects mature oligodendrocytes that maintain myelin. In contrast, in young mice, low doses of IFNγ results in the death of developing or remyelating oligodendrocytes (Lin *et al.*, 2007). It appears thus that myelinating cells respond in a different manner from other cell types.

The ISR likely participates to neuroprotection in MS. Manipulating the PERK-Elf2α pathways may offer interesting therapeutic avenues. Several chemical chaperones, such as vaticanol B, prevent ISR-induced apoptosis. A specific inhibitor of the elf2α dephosphorylation (salubrinal) protects against IFNγ induced oligodendrocyte loss and hypomyelination (Lin *et al.*, 2008). A considerable amount has been learned about signalling pathways of the ISR but it will be several more years before clinical trials enable us to judge the interest of therapeutic strategies enhancing the PERK-elf 2α pathways (Lin and Popko, 2009).

6. Endogenous cannabinoid system

The endogenous cannabinoid system includes cannabinoid receptors (CB1 and CB2), the

endocannabinoid (eCBs) family, most notably anandamide (AEA) and 2arachidonoylglycerol (2AG) serving as receptor ligands, as well as enzymes for their synthesis and degradation. CB1 receptors are found mainly on neurons and CB2 receptors primarily on central and peripheral immune cells (macrophages, DC and NK cells) (Pandey *et al.*, 2009) and on immature bone marrow myeloid progenitor cells (Palazuelos *et al.*, 2008). Importantly, eCBs may have CB-receptor-independent effects whose mechanisms remain unclear. In addition to controlling motor and psychic functions, the eCB system also modulates the immune system. Endocannabinoids are produced on demand from lipid precursors and removed by cellular uptake. They exert several important functions: antioxidant activity and prevention of excitotoxicity by modulation of glutamate synthesis, activation of cytoprotective pathways, reduction of Ca^{2}+ overload and decrease in TNFα production (Centonze *et al.*, 2007).

Several therapeutic approaches have been shown effective in EAE: exogenous CB1 agonists (Pryce *et al.*, 2003), synthetic CBs (Arevalo-Martin *et al.*, 2003), inhibition of eCB transporter (Mestre *et al.*, 2005), inhibition of fatty acid amide hydrolase (an eCB deactivating enzyme) (Hwang *et al.*, 2009), inhibition of AEA reuptake (Ligresti *et al.*, 2006) and increased synthesis of eCBs after P2X7 stimulation (Stella, 2004). In contrast with experimental ischemia and brain tissue injury, no increase in eCBs is observed in EAE even though CB receptors remain functional. In fact IFNγ, released by activated T cells, blocks purinergic receptors P2X7, a key player in eCBs synthesis. The conserved CB receptor functionality provides support for CB-based treatment in MS (Shohami and Mechoulam, 2006; Witting *et al.*, 2006).

In MS acute lesions, CB2 receptor-immunoreactivity was found increased in activated microglia and macrophages (Yiangou *et al.*, 2006). CB2-positive microglial cells are evenly distributed within active plaques and located in the periphery of chronic active plaques (Benito *et al.*, 2007). These authors have also shown that CB1 receptors are expressed in cortical neurons, oligodendrocytes and oligodendrocyte precursors whereas CB2 receptors are present in T lymphocytes, astrocytes and perivascular reactive microglia.

AEA concentrations are higher in acute than in silent lesions but 2AG is only moderately elevated. Beside neurons, microglia and macrophages can produce AEA. In the CSF AEA, but not 2AG, is increased in patients with inflammatory activity at the MRI as a result of an increased synthesis and reduced degradation of AEA (Centonze *et al.*, 2007). These observations suggest that AEA and 2AG have different regulatory mechanisms and that AEA is preferentially involved in MS neuroprotection. Recently, AEA was found to inhibit IL-12p70 and IL-23 production (Correa *et al.*, 2009) and to enhance IL-10 synthesis (Correa *et al.*, 2010) by human microglia.

It has been observed in a viral EAE model of MS that an endogenous AEA increase does not cause maximal neuroprotection as further increased concentrations with exogenous administration of AEA result in additional neuroprotection (Mestre *et al.*, 2005). Administration of delta 9-tetrahydrocannabinol (Δ^{9} –THC) was the first therapeutic approach with cannabinoid-based drugs in EAE (Lyman *et al.*, 1989). Since then, numerous compounds were found effective to prevent clinical signs and pathological lesions. So far therapeutic applications of CBs in MS were limited to spasticity and tremor. They yielded weak and disappointing effects possibly because of dose-limiting psychoactive side effects. New compounds, with limited psychotropic activity that represents the main hindrance to their therapeutic use should be developed and could exploit the neuroprotective properties of eCBs (Baker and Pryce, 2008).

7. The complement system

There is evidence for antibody- and complement-mediated demyelination in MS (Storch *et al.*, 1998). The fragmenting myelin staining for the C5b-9n membranolytic complement complex is observed in various CNS pathological states and is not specific for MS. The only identified complement-reactive tissue component specific for MS are elongated microglial nodules containing short C3d positive stretches of nerve fibres in unaffected tissue bordering plaques (Barnett *et al.*, 2009). A proteomic analysis indicates that serum levels of complement C4 fragments correlate with clinical relapses (Sawai *et al.*, 2009) and recently a laboratory measure of complement-mediated cell injury has shown that complement activation correlates with attack severity in patients with neuromyelitis optica (Hinson *et al.*, 2009).

In EAE, the C5b-9_{n} complex clearly participates to myelin destruction during the acute phase, but sublytic concentrations were found neuroprotective during the chronic phase (Rus *et al.*, 2006; Tegla *et al.*, 2009). Regulatory proteins, and in particular the complement factor H (fH), have been identified that attenuate inflammation in EAE and protect neurons from complement opsonization and axonal injury (Griffiths *et al.*, 2009). Pharmacological inhibition

of C5a/C3a (Li *et al.*, 2009) but not deletion of C3a and C5a receptors (Ramos *et al.*, 2009) protect against EAE.

So far a protective activity of the complement system similar to the one observed during the chronic phase of EAE has not been observed in MS but possibly exists.

Conclusions

Endogenous neuroprotection was mostly investigated in stroke, trauma and neurodegenerative diseases but recent observations demonstrate that it plays a role in MS also. The nature of inflammatory processes varies over time but inflammation is consistently associated with neurodegeneration even in the progressive stages (Frischer *et al.*, 2009). Inflammation causes nervous tissue destruction and at the same time promotes survival and repair. The same cells and the same chemical mediators can initiate the degenerative cascade and/or neuroprotective pathways. The final outcome depends on the local microenvironment varying over time but the regulatory mechanisms that control the balancing of protective versus detrimental responses are still unknown.

Given the close relationship between inflammation and neurodegeneration, a marked reduction in the inflammatory component with potent immunosuppressants reduces associated neurodegenerative processes and improves neurological deficits in the early stage of the disease (CAMMS, 08). Harnessing insufficient or dysregulated endogenous neuroprotective mechanisms appears more problematic. Endogenous neuroprotection is the net result of several complex and interconnected mechanisms. Modulating an individual neuroprotective pathway will likely yield a partial benefit, if any. Further are necessary to understand the precise molecular mechanisms underlying neuroprotective pathways and their complex interconnections. It would also be of central interest to monitor activated pathways to identify their respective roles at a certain point of time and their specific activation according to pathomechanism stages and microenvironment status.

REFERENCES

Aboul-Enein F., Lassmann H. Mitochondrial damage and histotoxic hypoxia: a pathway of tissue injury in inflammatory brain disease? Acta Neuropathol. 2005;109:49-55.

Aboul-Enein F, Rauschka H, Kornek B, Stadelmann C, Stefferl A. *et al.* Preferential loss of myelin-associated glycoprotein reflects hypoxia-like white matter damage in stroke and inflammatory brain diseases. J Neuropathol Exp Neurol. 2003;62: 25-33.

Alonso A, Rodriguez LA, Logroscino G, Hernan MA. Gout and risk of Parkinson disease: a prospective study. Neurology. 2007;69:1696-700.

Anderson RF, Harris TA. Dopamine and uric acid act as antioxidants in the repair of DNA radicals: implications in Parkinson's disease. Free Radic Res. 2003;37:1131-6.

Annanmaki T, Muuronen A, Murros K. Low plasma uric acid level in Parkinson's disease. Mov Disord. 2007;22:1133-7.

Arevalo-Martin A,Vela JM, Molina-Holgado E, Borrell J, Guaza C. Therapeutic action of cannabinoids in a murine model of multiple sclerosis. J Neurosci. 2003;23:2511-6.

Baker D, Pryce G. The endocannabinoid system and multiple sclerosis. Curr Pharm Des. 2008;23:2326-36.

Barnett MH, Parratt JD, Cho ES, Prineas JW. Immunoglobulins and complement in postmortem multiple sclerosis tissue. Ann Neurol. 2009;65:32-46.

Becker B.F. Towards the physiological function of uric acid. Free Radic Biol Med. 1993;14:615-31.

Benito C, Romero JP, Tolon RM, Clemente D, Docagne F. *et al.* Cannabinoid CB1 and CB2 receptors and fatty acid amide hydrolase are specific markers of plaque cell subtypes in human multiple sclerosis. J Neurosci. 2007;27:2396-402.

Beyersdorf N, Gaupp S, Balbach K, Schmidt J, Toyka KV. *et al.* Selective targeting of regulatory T cells with CD28 superagonists allows effective therapy of experimental autoimmune encephalomyelitis. J Exp Med. 2005;202:445-55.

CAMMS223 Trial Investigators, Coles AJ, Compston DA, Selmaj KW, Lake SL, Moran S. *et al.* Alemtuzumab vs. interferon beta-1a in early multiple sclerosis. N Engl J Med. 2008;359:1786-801.

Centonze D, Bari M, Rossi S, Prosperetti C, Furlan R. *et al.* The endocannabinoid system is dysregulated in multiple sclerosis and in experimental autoimmune encephalomyelitis. Brain. 2007;130:2543-53.

Centonze D, Finazzi-Agrò A, Bernardi G, Maccarrone M. The endocannabinoid system in targeting inflammatory neurodegenerative diseases. Trends Pharmacol Sci. 2007;28:180-7.

Chiarugi A, Cozzi A, Ballerini C, Massacesi L, Moroni F. Kynurenine 3-mono-oxygenase activity and neurotoxic kynurenine metabolites increase in the spinal cord of rats with experimental allergic encephalomyelitis. Neuroscience. 2001;102:687-95.

Christen S, Bifrare YD, Siegenthaler C, Leib SL, Tauber MG. Marked elevation in cortical urate and xanthine oxidoreductase activity in experimental bacterial meningitis. Brain Res. 2001; 900:244-51.

Comi G, Pulizzi A, Rovaris M, Abramsky O, Arbizu T. *et al.* Effect of laquinimod on MRI-monitored disease

activity in patients with relapsing-remitting multiple sclerosis: a multicentre, randomised, double-blind, placebo-controlled phase IIb study. Lancet. 2008;371:2085-92.

Constantinescu CS, Freitag P, Kappos L. Increase in serum levels of uric acid, an endogenous antioxidant, under treatment with glatiramer acetate for multiple sclerosis. Mult Scler. 2000;6:378-81.

Correa F, Docagne F, Mestre L, Clemente D, Hernangomez M. *et al.* A role for CB2 receptors in anandamide signalling pathways involved in the regulation of IL-12 and IL-23 in microglial cells. Biochem Pharmacol. 2009;77:86-100.

Correa F, Hernangomez M, Mestre L, Loria F, Spagnolo A. *et al.* Anandamide enhances IL-10 production in activated microglia by targeting CB(2) receptors: Roles of ERK1/2, JNK, and NF-kappaB. Glia. 2010;58:135-47.

Davis JW, Grandinetti A, Waslien CI, Ross GW, White LR. *et al.* Observations on serum uric acid levels and the risk of idiopathic Parkinson's disease. Am J Epidemiol. 1996;144:480-4.

De Lau LM, Koudstaal PJ, Hofman A, Breteler MM. Serum uric acid levels and the risk of Parkinson disease. Ann. Neurol. 2005;58:797-800.

Deknuydt F, Bioley G, Valmori D, Ayyoub M. IL-1beta and IL-2 convert human Treg into T(H)17 cells. Clin. Immunol. 2009;131:298-307.

Deretzi G, Pelidou SH, Zacharakis G, Kyritsis AP. Serum levels of uric acid in patients with multiple sclerosis: a biological marker in clinical course and treatment of MS. Mult Scler. 2003;9(suppl 1):S100, P412.

Dinkova-Kostova AT, Talalay P. Direct and indirect antioxidant properties of inducers of cytoprotective proteins. Mol Nutr Food Res. 2008;52:S128-38.

Dirnagl U, Meisel A. Endogenous neuroprotection: mitochondria as gateways to cerebral preconditioning? Neuropharmacology. 2008;55:334-44.

Drulovic J, Dujmovic I, Stojsavljevic N, Mesaros S, Andjelkovic S. *et al.* Uric acid levels in sera from patients with multiple sclerosis. J Neurol. 2001; 248:121-6.

Duan W, Ladenheim B, Cutler RG, Kruman II, Cadet JL. *et al.* Dietary folate deficiency and elevated homocysteine levels endanger dopaminergic neurons in models of Parkinson's disease. J Neurochem. 2002;80:101-10.

Euser SM, Hofman A, Westendorp RG, Breteler MM. Serum uric acid and cognitive function and dementia. Brain. 2009;132:377-82.

Freeman RS, Barone MC. Targeting hypoxia-inducible factor (HIF) as a therapeutic strategy for CNS disorders. Curr Drug Targets CNS Neurol Disord. 2005;4:85-92.

Frischer JM, Bramow S, Dal-Bianco A, Lucchinetti CF, Rauschka H. *et al.* The relation between inflammation and neurodegeneration in multiple sclerosis brains. Brain. 2009;132:1175-89.

Frisullo G, Nociti V, Iorio R, Patanella AK, Caggiula M. *et al.* Regulatory T cells fail to suppress CD4(+)T-bet(+) T cells in relapsing multiple sclerosis patients. Immunology. 2009;127:418-28.

Gao X, Chen H, Choi Hk, Curhan G, Schwarzschild MA. *et al.* Diet, urate, and Parkinson's disease risk in men. Am J Epidemiol. 2008;167:831-8.

Gonsette RE, Sindic C, D'hooghe MB, De Deyn P, Medaer R. *et al.* Boosting endogenous protection in multiple sclerosis:the ASIIMS trial (Association of Interferon beta and Inosine in Multiple Sclerosis). Mult Scler, 2010, epub ahead of print.

Graber JJ, Dhib-Jalbut S. Protective autoimmunity in the nervous system. Pharmacol Ther. 2009;121:147-59.

Graumann U, Reynolds R, Steck AJ, Schaeren-Wiemers N. Molecular changes in normal appearing white matter in multiple sclerosis are characteristic of neuroprotective mechanisms against hypoxic insult. Brain Pathol. 2003;13:554-73.

Griffiths MR, Neal JW, Fontaine M, Das T, Gasque P Complement factor H, a marker of self protects against experimental autoimmune encephalomyelitis. J Immunol. 2009;182:4368-77.

Guerrero AL, Martin-Polo J, Laherran E, Gutierrez F, Iglesias F. *et al.* Variation of serum uric acid levels in multiple sclerosis during relapses and immunomodulatory treatment. Eur J Neurol. 2008;15:394-7.

Handouk Y, Angeleri VA, Danni M, De Riso S, Provinciali L. Increase of serum uric acid levels in multiple sclerosis during treatment with natalizumab. Mult Scler. 2008;14(suppl 1):S281, P888.

Hartai Z, Klivenyi P, Janaky T, Penke B, Dux L. *et al.* Kynurenine metabolism in multiple sclerosis. Acta Neurol Scand. 2005;112:93-6.

Hinson SR, Mckeon A, Fryer JP, Apiwattanakul M, Lennon VA. *et al.* Prediction of neuromyelitis optica attack severity by quantitation of complement-mediated injury to aquaporin-4-expressing cells. Arch Neurol. 2009;66:1164-7.

Holley JE, Newcombe J, Winyard PG, Gutowski NJ. Peroxiredoxin V in multiple sclerosis lesions: predominant expression by astrocytes. Mult Scler. 2007;13:955-61.

Holley JE, Newcombe J, Whatmore JL, Gutowski NJ. Increased blood vessel density and endothelial cell proliferation in multiple sclerosis cerebral white matter. Neurosci Lett. 2009 [Epub ahead of print].

Hooper DC, Bagasra O, Marini JC, Zborek A, Ohnishi ST. *et al.* Prevention of experimental allergic encephalomyelitis by targeting nitric oxide and peroxynitrite: implications for the treatment of multiple sclerosis. Proc Natl Acad Sci USA. 1997;94:2528-33.

Hooper DC, Spitsin S, Kean RB, Champion JM, Dickson GM. *et al.* Uric acid, a natural scavenger of peroxynitrite, in experimental allergic encephalomyelitis and multiple sclerosis. Proc Natl Acad Sci USA. 1998;95:675-80.

Hwang J, Adamson C, Butler D, Janero DR, Makriyannis A. *et al.* Enhancement of endocannabinoid signaling by fatty acid amide hydrolase inhibition: A neuroprotective therapeutic modality. Life Sci. 2009 [Epub ahead of print].

Insarova NG, Korshunova TS, Mzhel'skaia TI, Borisova TV. Metabolic disorders in Huntington's chorea. Zh Nevropatol Psikhiatr Im S S Korsakova. 1978;78: 489-95.

Janoff A. Alterations in lysosomes (intracellular enzymes) during shock; effects of preconditioning (tolerance) and protective drugs. Int Anesthesiol Clin. 1964;2: 251-69.

Johnson JA, Johnson DA, Kraft AD, Calkins MJ, Jakel RJ. *et al.* The Nrf2-ARE pathway: an indicator and modulator of oxidative stress in neurodegeneration. Ann NY Acad Sci. 2008;1147: 61-9.

Johnson DA, Amirahmadi S, Ward C, Fabry Z, Johnson JA. The absence of the pro-antioxidant transcription factor Nrf2 exacerbates experimental autoimmune encephalomyelitis. Toxicol Sci. 2009 [Epub ahead of print].

Kanemitsu H, Tamura A, Kirino T, Karasawa S, Sano K. *et al.* Xanthine and uric acid levels in rat brain following focal ischemia. J Neurochem. 1988;51: 1882-5.

Kappos L, Gold R, Miller DH, Macmanus DG, Havrdova E. *et al.* Efficacy and safety of oral fumarate in patients with relapsing-remitting multiple sclerosis: a multicentre, randomised, double-blind, placebo-controlled phase IIb study. Lancet. 2008;372:1463-72.

Kastenbauer S, Koedel U, Becker BF, Pfister HW. Experimental meningitis in the rat: protection by uric acid at human physiological blood concentrations. Eur J Pharmacol. 2001;425:149-52.

Kim TS, Pae CU, Yoon SJ, Jang WY, Lee NJ. *et al.* Decreased plasma antioxidants in patients with Alzheimer's disease. Int J Geriatr Psychiatry. 2006;21:344-8.

Kitagawa K, Matsumoto M, Tagaya M, Hata R, Ueda H. *et al.* 'Ischemic tolerance' phenomenon found in the brain. Brain Res. 1990;528:21-4.

Knapp CM, Constantinescu CS, Tan JH, Mclean R, Cherryman GR. *et al.* Serum uric acid levels in optic neuritis. Mult Scler. 2004;10:278-80.

Koch M, De Keyser J. Uric acid in multiple sclerosis. Neurol Res. 2006;28:316-9.

Kuzkaya N, Weissmann N, Harrison DG, Dikalov S. Interactions of peroxynitrite with uric acid in the presence of ascorbate and thiols: implications for uncoupling endothelial nitric oxide synthase. Biochem Pharmacol. 2005;70:343-54.

Kwidzinski E, Bechmann I. IDO expression in the brain: a double-edged sword. J Mol Med. 2007;85:1351-9.

Larumbe Ilundain R, Ferrer Valls JV, Vines Rueda JJ, Guerrero D, Fraile P. Case-control study of markers of oxidative stress and metabolism of blood iron in Parkinson's disease. Rev Esp Salud Publica. 2001;75:43-53.

Leung PY, Packard AE, Stenzel-Poore MP. It's all in the family: multiple Toll-like receptors offer promise as novel therapeutic targets for stroke neuroprotection. Future Neurol. 2009;4:201-208.

Li Q, Nacion K, Bu H, Lin F. The complement inhibitor FUT-175 suppresses T cell autoreactivity in experimental autoimmune encephalomyelitis. Am J Pathol. 2009;175:661-7.

Ligresti A, Cascio MG, Pryce G, Kulasegram S, Beletskaya I. *et al.* New potent and selective inhibitors of anandamide reuptake with antispastic activity in a mouse model of multiple sclerosis. Br J Pharmacol. 2006;147: 83-91.

Lin W, Kunkler PE, Harding HP, Ron D, Kraig RP. *et al.* Enhanced integrated stress response promotes myelinating oligodendrocyte survival in response to interferon-γ. Am J Pathol. 2008;173:1508-17.

Lin W, Popko B. Endoplasmic reticulum stress in disorders of myelinating cells. Nat Neurosci. 2009;12:379-85.

Lin W, Bailey SL, Ho H, Harding HP, Ron D. *et al.* The integrated stress response prevents demyelination by protecting oligodendrocytes against immune-mediated damage. J Clin Invest. 2007;117:448-56.

Lindholm D, Wootz H, Korhonen L. ER stress and neurodegenerative diseases. Cell Death Differ. 2006;13:385-92.

Lu PD, Jousse C, Marciniak SJ, Zhang Y, Novoa I. *et al.* Cytoprotection by pre-emptive conditional phosphorylation of translation initiation factor 2. EMBO J. 2004;23:169-79.

Lyman WD, Sonett JR, Brosnan CF, Elkin R, Bornstein MB. Delta 9-tetrahydrocannabinol: a novel treatment for experimental autoimmune encephalomyelitis. J Neuroimmunol. 1989;23:73-81.

Mahad D, Ziabreva I, Lassmann H, Turnbull D. Mitochondrial defects in acute multiple sclerosis lesions. Brain. 2008;131:1722-35.

Marik C, Felts PA, Bauer J, Lassmann H, Smith KJ. Lesion genesis in a subset of patients with multiple sclerosis: a role for innate immunity? Brain. 2007;130:2800-15.

Mehindate K, Sahlas DJ, Frankel D, Mawal Y, Liberman A. *et al.* Proinflammatory cytokines promote glial heme oxygenase-1 expression and mitochondrial iron deposition: implications for multiple sclerosis. J Neurochem. 2001;77:1386-95.

Mestre L, Correa F, Arevalo-Martin A, Molina-Holgado E, Valenti M. *et al.* Pharmacological modulation of the endocannabinoid system in a viral model of multiple sclerosis. J Neurochem. 2005;92:1327-39.

Mhaille AN, Mcquaid S, Windebank A, Cunnea P, McMahon J. *et al.* Increased expression of endoplasmic reticulum stress-related signalling pathway molecules in multiple sclerosis lesions. J Neuropathol Exp Neurol. 2008;67:200-11.

Mizoguchi A, Bhan AK. A case for regulatory B cells. J. Immunol. 2006;176:705-10.

Moor E, Kohen R, Reiter RJ, Shohami E. Closed head injury increases extracellular levels of antioxidants in rat hippocampus in vivo: an adaptive mechanism? Neurosci Lett. 2001;316:169-72.

Mostert JP, Ramsaransing GS, Heersema DJ, Heerings M, Wilczak N. *et al.* Serum uric acid levels and leukocyte nitric oxide production in multiple sclerosis patients outside relapses. J Neurol Sci. 2005;231: 41-4.

Mowry EM, Woo JH, Ances BM. Technology insight: can neuroimaging provide insights into the role of ischemia in Baló's concentric sclerosis? Review Nat Clin Pract Neurol. 2007;3:341-8.

Nemeth H, Toldi J, Vecsei L. Kynurenines, Parkinson's disease and other neurodegenerative disorders: preclinical and clinical studies. J Neural Transm Suppl. 2006;70:285-304.

Nguyen T, Nioi P, Pickett CB. The Nrf2-antioxidant response element signaling pathway and its activation by oxidative stress. J Biol Chem. 2009; 284:13291-5.

Nozaki K, Beal MF. Neuroprotective effects of L-kynurenine on hypoxia-ischemia and NMDA lesions in neonatal rats. J Cereb Blood Flow Metab. 1992; 12:400-7.

Palazuelos J, Davoust N, Julien B, Hatterer E, Aguado T. *et al.* The CB(2) cannabinoid receptor controls myeloid progenitor trafficking: involvement in the pathogenesis of an animal model of multiple sclerosis. J Biol Chem. 2008;283:13320-9.

Pandey R, Mousawy K, Nagarkatti M, Nagarkatti P. Endocannabinoids and immune regulation. Pharmacol Res. 2009;60:85-92.

Pandit A, Vadnal J, Houston S, Freeman E, McDonough J. Impaired regulation of electron transport chain subunit genes by nuclear respiratory factor 2 in multiple sclerosis. J Neurol Sci. 2009;279:14-20.

Peng F, Zhang B, Zhong X, Li J, Xu G. *et al.* Serum uric acid levels of patients with multiple sclerosis and other neurological diseases. Mult Scler. 2008;14: 188-96.

Platten M, Ho PP, Youssef S, Fontoura P, Garren H. *et al.* Treatment of autoimmune neuroinflammation with a synthetic tryptophan metabolite. Science. 2005;310:850-5.

Polidori MC, Mattioli P, Aldred S, Cecchetti R, Stahl W. *et al.* Plasma antioxidant status, immunoglobulin g oxidation and lipid peroxidation in demented patients: relevance to Alzheimer disease and vascular dementia. Dement Geriatr Cogn Disord. 2004;18:265-70.

Pryce G, Ahmed Z, Hankey DJ, Jackson SJ, Croxford JL. *et al.* Cannabinoids inhibit neurodegeneration in models of multiple sclerosis. Brain. 2003;126: 2191-202.

Ramos TN, Wohler JE, Barnum SR. Deletion of both the C3a and C5a receptors fails to protect against experimental autoimmune encephalomyelitis. Neurosci Lett. 2009;467:234-6.

Ramsaransing GS, Heersema DJ, De Keyser J. Serum uric acid, dehydroepiandrosterone sulphate, and apolipoprotein E genotype in benign vs. progressive multiple sclerosis. Eur J Neurol. 2005;12:514-8.

Rejdak K, Bartosik-Psujek H, Dobosz B, Kocki T, Grieb P. *et al.* Decreased level of kynurenic acid in cerebrospinal fluid of relapsing-onset multiple sclerosis patients. Neurosci Lett. 2002;331:63-5.

Rejdak K, Petzold A, Kocki T, Kurzepa J, Grieb P. *et al.* Astrocytic activation in relation to inflammatory markers during clinical exacerbation of relapsing-remitting multiple sclerosis. J Neural Transm. 2007;114:1011-5.

Rentzos M, Nikolaou C, Anagnostouli M, Rombos A, Tsakanikas K. *et al.* Serum uric acid and multiple sclerosis. Clin Neurol Neurosurg. 2006;108:527-31.

Rezaie A, Ghorbani F, Eshghtork A, Zamani MJ, Dehghan G. *et al.* Alterations in salivary antioxidants, nitric oxide, and transforming growth factor-beta 1 in relation to disease activity in Crohn's disease patients. Ann N Y Acad Sci. 2006;1091: 110-22.

Rinaldi P, Polidori MC, Metastasio A, Mariani E, Mattioli P. *et al.* Plasma antioxidants are similarly depleted in mild cognitive impairment and in Alzheimer's disease. Neurobiol Aging. 2003;24: 915-9.

Rodriguez M, Warrington AE, Pease LR. Invited Article: Human natural autoantibodies in the treatment of neurologic disease. Neurology. 2009;72:1269-76.

Rózsa E, Robotka H, Vécsei L, Toldi J. The Janus-face kynurenic acid. J Neural Transm. 2008;115: 1087-91.

Rus H, Cudrici C, Niculescu F, Shin ML. Complement activation in autoimmune demyelination: dual role in neuroinflammation and neuroprotection. J Neuroimmunol. 2006;180:9-16.

Salvati P, Ukmar G, Dho L, Rosa B, Cini M. *et al.* Brain concentrations of kynurenic acid after a systemic neuroprotective dose in the gerbil model of global ischemia. Prog. Neuropsychopharmacol. Biol Psychiatry. 1999;23:741-52.

Sawai S, Umemura H, Mori M, Satoh M, Hayakawa S. *et al.* Serum levels of complement C4 fragments correlate with disease activity in multiple sclerosis: Proteomic analysis. J Neuroimmunol. 2009 [Epub ahead of print].

Schilling S, Goelz S, Linker R, Luehder F, Gold R. Fumaric acid esters are effective in chronic experimental autoimmune encephalomyelitis and suppress macrophage infiltration. Clin Exp Immunol. 2006;145:101-7.

Schimrigk S, Brune N, Hellwig K, Lukas C, Bellenberg B. *et al.* Oral fumaric acid esters for the treatment of active multiple sclerosis: an open-label, baseline-controlled pilot study. Eur J Neurol. 2006;13:604-10.

Schraven B, Kalinke U. CD28 superagonists: what makes the difference in humans? Immunity. 2008;28: 591-5.

Schreibelt G, Van Horssen J, Van Rossum S, Dijkstra CD, Drukarch B. *et al.* Therapeutic potential and biological role of endogenous antioxidant enzymes in multiple sclerosis pathology. Brain Res Rev. 2007; 56:322-30.

Scott GS, Cuzzocrea S, Genovese T, Koprowski H, Hooper DC. Uric acid protects against secondary damage after spinal cord injury. Proc Natl Acad Sci USA. 2005;102:3483-8.

Shohami E, Mechoulam R. Multiple sclerosis may disrupt endocannabinoid brain protection mechanism. Proc Natl Acad Sci USA. 2006;103:6087-8.

Sokka AL, Putkonen N, Mudo G, Pryazhnikov E, Reijonen S. *et al.* Endoplasmic reticulum stress inhibition protects against excitotoxic neuronal injury in the rat brain. J Neurosci. 2007;27:901-8.

Sotgiu S, Pugliatti M, Sanna A, Sotgiu A, Fois ML. *et al.* Serum uric acid and multiple sclerosis. Neurol Sci. 2002;23:183-8.

Spitsin S, Hooper DC, Mikheeva T, Koprowski H. Uric acid levels in patients with multiple sclerosis: analysis in mono- and dizygotic twins. Mult Scler. 2001;7:165-6.

Stadelmann C, Ludwin S, Tabira T, Guseo A, Lucchinetti CF. *et al.* Tissue preconditioning may explain concentric lesions in Baló's type of multiple sclerosis. Brain. 2005;128:979-87.

Stella N. Cannabinoid signaling in glial cells. Glia. 2004;48:267-77.

Storch MK, Piddlesden S, Haltia M, Iivanainen M, Morgan P. *et al.* Multiple sclerosis: in situ evidence for antibody- and complement-mediated demyelination. Ann Neurol. 1998;43:465-71.

Suntharalingam G, Perry MR, Ward S, Brett SJ, Castello-Cortes A. *et al.* Cytokine storm in a phase 1 trial of the anti-CD28 monoclonal antibody TGN1412. N Engl J Med. 2006;355:1018-28.

Tajouri L, Mellick AS, Ashton KJ, Tannenberg AE, Nagra RM. *et al.* Quantitative and qualitative changes in gene expression patterns characterize the activity of plaques in multiple sclerosis. Brain Res Mol Brain Res. 2003;119:170-83.

Tegla CA, Cudrici C, Rus V, Ito T, Vlaicu S. *et al.* Neuroprotective effects of the complement terminal pathway during demyelination: Implications for oligodendrocyte survival. J Neuroimmunol. 2009; 213:3-11.

Toncev G, Drakulic M, Knezevic Z. Treatment with interferon beta 1b (Betaferon) and serum uric acid levels: two year follow-up. Mult Scler. 2007; 13(suppl 2):S90, P305.

Toncev G, Milicic B, Toncev S, Samardzic G. Correlation between serum uric acid levels in multiple sclerosis patients and activity of disease. Eur J Neurol. 2000; 7(suppl 3):126 (abstract).

Toncev G, Milicic B, Toncev S, Samardzic G. Serum uric acid levels in multiple sclerosis patients correlate with activity of disease and blood-brain barrier dysfunction. Eur J Neurol. 2002;9:221-6.

Trapp BD, Stys PK. Virtual hypoxia and chronic necrosis of demyelinated axons in multiple sclerosis. Lancet Neurol. 2009;8:280-91.

Tsakiri A, Tsiantoulas D, Frederiksen J. Serum uric acid levels are decreased in patients with relapsing-remitting multiple sclerosis, in particular during relapses. Mult Scler. 2008;14(suppl 1):S289, P888.

Vamos E, Pardutz A, Klivenyi P, Toldi J, Vecsei L. The role of kynurenines in disorders of the central nervous system: Possibilities for neuroprotection. J Neurol Sci. 2009;283:21-7.

Van Horssen J, Schreibelt G, Drexhage J, Hazes T, Dijkstra CD. *et al.* Severe oxidative damage in multiple sclerosis lesions coincides with enhanced antioxidant enzyme expression. Free Radic Biol Med. 2008;45:1729-37.

Weisskopf MG, O'reilly E, Chen H, Schwarzschild MA, Ascherio A. Plasma urate and risk of Parkinson's disease. Am J Epidemiol. 2007;166:561-7.

Witting A, Chen L, Cudaback E, Straiker A, Walter L. *et al.* Experimental autoimmune encephalomyelitis disrupts endocannabinoid-mediated neuroprotection. Proc Natl Acad Sci USA. 2006;103:6362-7.

Yao SY, Soutto M, Sriram S. Preconditioning with cobalt chloride or desferrioxamine protects oligodendrocyte cell line (MO3.13) from tumor necrosis factor-alpha-mediated cell death. J Neurosci Res. 2008;86:2403-13.

Yiangou Y, Facer P, Durrenberger P, Chessell IP, Naylor A. *et al.* COX-2, CB2 and P2X7-immunoreactivities are increased in activated microglial cells/macrophages of multiple sclerosis and amyotrophic lateral sclerosis spinal cord. BMC Neurol. 2006;6:12.

Yu Z, Bruce-Keller AJ, Goodman Y, Mattson MP. Uric acid protects neurons against excitotoxic and metabolic insults in cell culture, and against focal ischemic brain injury in vivo. J Neurosci Res. 1998;53:613-25.

Zamani A, Rezaei A, Khaeir F, Hooper DC. Serum and cerebrospinal fluid uric acid levels in multiple sclerosis patients. Clin Neurol Neurosurg. 2008; 110:642-3.

Zozulya AL, Wiendl H. The role of CD8 suppressors versus destructors in autoimmune central nervous system inflammation. Hum Immunol. 2008;69: 797-804.

R. E. Gonsette,
National Centre for Multiple Sclerosis,
Vanheylenstraat 16,
B-1820 Melsbroek (Belgium).
E-mail: r.gonsette@skynet.be