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Multiple sclerosis: The role of melatonin and *N*-acetylserotonin

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Abstract
Multiple sclerosis (MS) is an immune mediated disorder that is under intensive investigation in an attempt to improve on available treatments. Many of the changes occurring in MS, including increased mitochondrial dysfunction, pain reporting and depression may be partly mediated by increased indoleamine 2,3-dioxygenase, which drives tryptophan to the production of neuroregulatory tryptophan catabolites and away from serotonin, *N*-acetylserotonin and melatonin production. The consequences of decreased melatonin have classically been attributed to circadian changes following its release from the pineal gland. However, recent data shows that melatonin may be produced by all mitochondria containing cells to some degree, including astrocytes and immune cells, thereby providing another important MS treatment target. As well as being a powerful antioxidant, anti-inflammatory and antinociceptive, melatonin improves mitochondrial functioning, partly via increased oxidative phosphorylation. Melatonin also inhibits demyelination and increases remyelination, suggesting that its local regulation in white matter astrocytes by serotonin availability and apolipoprotein E4, among other potential factors, will be important in the etiology, course and treatment of MS.

Abbreviations: 4HNE, 4-hydroxy-2-nonena 1; AA-NAT, arylalkylamine *N*-acetylatransferase; AFMK, *N*1-acetyl-*N*2-formyl-5-methoxykynuramine; AHr, aryl hydrocarbon receptor; AMK, *N*1-acetyl-5-methoxykynuramine; Apo, apolipoprotein; cAMP, cyclic adenosine monophosphate; B2-adr, beta2-adrenergic receptor; BBBp, blood-brain barrier permeability; BDNF, brain derived neurotrophic factor; EAE, experimental autoimmune encephalomyelitis; FTO, fat mass and obesity-associated; GA, glatiramer acetate; GSH, glutathione; HIOMT, hydroxyindole *O*-methyltransferase; IDO, indoleamine 2, 3-dioxygenase; **IL**, interleukin; IFN-γ, interferon-gamma; KYNA, kynurenic acid; LIF, leukaemia inhibitory facto; LXR, liver X receptor; MAOi, monoamine oxidase inhibitor; MeCP2, methyl-CpG-binding protein 2; miR, microRNA; MTr, melatonin receptor; **NAS**, *N*-acetylserotonin; NE, norepinephrine; NF-κB, nuclear factor-kappa beta; NK, natural killer; NK-1r, neurokinin-1 receptor; O&NS, oxidative and nitrosative stress; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator-1alpha; RegT, regulatory T cells; S1P, sphingosine-1-phosphate; SMase, sphingomyelinase; SNP, single nucleotide polymorphism; SSRI, selective serotonin reuptake inhibitor; SubP, substance P; Th, T-helper; TIMP 1, tissue inhibitor of metalloproteinase-; TLR, toll-like receptor; **TNF-α**, tumor necrosis factor-alpha; TrkB, tyrosine receptor kinase beta; TRYCAT, tryptophan catabolites; YY1, yin yang 1

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Here we review the role of local melatonin and its precursors, *N*-acetylserotonin and serotonin, in MS.

1. Introduction

Multiple sclerosis (MS) is an immune mediated disorder (Wootla et al., 2012), with predominantly white matter, but also grey matter, loss. This is driven by increased T-helper (Th)17 and Th1 T cells, coupled to a decrease in regulatory T cells (RegT). Indoleamine 2,3-dioxygenase (IDO) activation in dendritic cells may increase RegT cell levels (Chen et al., 2008), whereas its activation in other cell types predominantly takes tryptophan down the tryptophan catabolite (TRYCAT) pathways and away from serotonin, *N*-aceylserotonin (NAS) and melatonin production (Maes et al., 2011a). It is the activation of IDO and TRYCATs that is thought to drive increased depression prior to disease exacerbations in MS (Akpinar et al., 2008).

Measures of melatonin in MS have focused on pineal gland synthesis and efflux, spurred by data showing MS susceptibility genes in tryptophan hydroxylase-2 and melatonin receptors, which are associated with primary and secondary progressive MS (Natarajan et al., 2012). When given to secondary progressive MS patients melatonin decreases the oxidative stress in red blood cells, as indicated by decreased lipid peroxidation and increased endogenous antioxidants, superoxide dismutase and glutathione peroxide (Miller et al., 2013). Vitamin D supplementation is very common in MS and will modulate melatonin production in beta-interferon (IFN-β) treated MS patients (Golan et al., 2013), which the authors suggest indicates a role of melatonin in modulating the effects of vitamin D. Previously we suggested efficacious interactions of vitamin D and melatonin with valproate in MS treatment, especially in the case of emergent seizures (Anderson and Rodriguez, 2011). Such accumulating data suggests a potential role for melatonin in the etiology, course and treatment of MS, as in other immune mediated disorders (Lin et al., 2013). However, the role of melatonin in MS may be dependent on local glia melatonin synthesis and release (Liu et al., 2012), rather than on pineal derived melatonin. Here we review recent data on the production of central melatonin and its relevance in MS. First we say something on melatonin.

2. Melatonin and MS

2.1. Melatoninergic pathway regulation

N-Acetyl-5-methoxytryptamine (melatonin) is a methoxyindole that is produced at night by the pineal gland. Pineal nighttime melatonin production is mediated by norepinephrine (NE), and is a powerful circadian regulator. Melatonin is a potent antioxidant, anti-inflammatory, immune regulator and inducer of endogenous anti-oxidants, as well as optimizing mitochondrial oxidative phosphorylation (Hardeland et al., 2011). Melatonin production is dependent on the availability of serotonin, which is converted by arylalkylamine *N*-acetylatransferase (AA-NAT) to *N*-acetylserotonin (NAS), which is further converted to melatonin by hydroxyindole *O*-methyltransferase (HIOMT) (also known as acetylserotonin *O*-methyltransferase). In melatonin producing cells both NAS and melatonin are readily effluxed and, being lipophilic, readily cross cell membranes; see Fig. 1.

The metabolites of melatonin, including *N*1-acetyl-*N*2-formyl-5-methoxykynuramine (AFMK) and *N*1-acetyl-5-methoxykynuramine (AMK), also have anti-inflammatory, anti-oxidant and immuno-regulatory effects (Hardeland et al., 2011). Melatonin readily passes through cell membranes often accumulating in intracellular organelles, especially mitochondria. However, many of its effects are driven by the activation of melatonin receptors (MT1r and MT2r). Decreased melatonin, melatoninergic pathway enzymes and melatonin receptor single nucleotide polymorphisms (SNP) are common to many disorders, including MS (Natarajan et al., 2012), but also bipolar disorder (Etain et al., 2012),

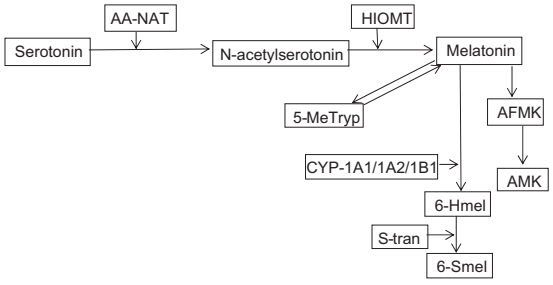

Fig. 1 Astrocyte release of NAS and melatonin will have significant impacts on neighbouring microglia, macrophages and oligodendrocytes. By decreasing microglia and macrophage reactivity and inducing a phagocytic phenotype, astrocyte derived melatonin will have anti-inflammatory effects, contributing to decreased BBB permeability. Either or both NAS and melatonin will increase BDNF, sirtuins, MeCP2 and possibly miR-7 in oligodendrocytes, decreasing the likelihood of demyelination, whilst also increasing oligodendrocyte progenitor maturation and remyelination. As well as the proven effects of serotonin availability and ApoE4 in the regulation of astrocyte NAS and melatonin efflux, other factors, known to regulate NAS and melatonin in other cell types, are likely to influence their efflux from astrocytes, including B2-adr, cAMP, 14-3-3, leptin, YY1 and other processes involved in reactivation. Medications are likely to act on such NAS/melatonin modulators to influence their efflux. Stress and peripheral inflammation, by increasing IDO and TDO will decrease serotonin availability; thereby decreasing NAS and melatonin efflux in conjunction with increased risk of depression, somatization, fatigue and TRYCAT induced cognitive deficits. Oligodendrocytes, microglia and macrophages will also produce melatonin to some degree, although not included for clarity. Acronyms are detailed in the main text.

depression (Galecka et al., 2011) and cancer (Ekmekcioglu, in press). A number of factors modulate NE induced pineal melatonin production, which is increased by 14-3-3, whilst being decreased by tumor necrosis factor-alpha (TNF-α) and substance P (SubP), as well as being variably regulated by leptin (Pontes et al., 2007; Gupta et al., 2010).

Increased homocysteine occurs in MS, especially in association with the fat mass and obesity-associated (FTO) SNP rs9939609, with homocysteine being decreased by folate supplementation (Davis et al., 2014). Increased homocysteine and decreased folate decrease S-adenosyl-methionine, in turn depriving the methyl source that is necessary for melatonin formation from NAS. Increased homocysteine and decreased melatonin would then contribute to elevated risk of cardiovascular disorders in MS (Wens et al., 2013). As such, increased homocysteine and decreased folate, as with increased TNF-α, contribute to decreased melatonin in MS.

Latitude effects in MS susceptibility, typically attributed to changes in seasonal sunlight induced vitamin D (Alcalde-Cabero et al., 2013), may also interact with melatonin levels, which also seasonally vary by latitude (Stokkan and Reiter, 1994).

Overall, a number of factors can influence the regulation of melatonin synthesis, some of which are altered in MS. However, much of the work on melatonin has focused on its synthesis and release by the pineal gland. Recent work shows melatonin to be produced by many other cells.

2.2. Glia, immune cell and local melatonin synthesis

Many cells can produce melatonin and NAS, including macrophages (Muxel et al., 2012), astrocytes (Liu et al., 2007), fibroblasts and skin cells (Liu et al., 2013). In astrocytes the availability of serotonin and the apolipoprotein (Apo) E4 allele significantly regulate astrocyte melatonin efflux (Liu et al., 2012). The role for known regulators of pineal NAS and melatonin synthesis, such as NE, cyclic adenosine monophosphate (cAMP), 14-3-3, leptin and SubP awaits investigation. Given its powerful protective effects in cells, local astrocyte melatonin regulation is a significant treatment target for a range of central conditions, including MS (Anderson and Maes, 2014a). NAS is a brain derived neurotrophic factor (BDNF) mimic, activating the BDNF receptor, tyrosine receptor kinase beta (TrkB) (Jang et al., 2010). As such, NAS is also likely to have protective effects, although different to those of melatonin, suggesting that the melatonin/NAS ratio may be of some biological significance.

Recent conceptualizations of non-pinealocyte melatonin synthesis suggest that mitochondria, and therefore almost all eukaryotic cells, produce melatonin to some degree (Tan et al., 2013). Mitochondria evolved from bacteria that produce melatonin in a circadian rhythm, especially rhodospirillum rubrum (Manchester et al., 1995). Over evolution melatonin biosynthetic ability has become integrated into the nuclear genome, although mitochondria may still produce melatonin (Tan et al., 2013). The localization of the MT1r (Wang et al., 2011) and AA-NAT to mitochondria provides some support for this (Kerenyi et al., 1975). Deficits in mitochondrial functioning are evident in many psychiatric and neurodegenerative conditions, including MS. In a viral MS model, we have previously shown mitochondrial dysfunction to correlate with axonal loss (Sathornsumetee et al., 2000), highlighting the importance of mitochondrial dysfunction. As such, melatonin and NAS synthesis may be intimately associated with mitochondrial function across a range of cell types.

2.3. Astrocytes, melatonin and inflammation in MS

Although grey matter losses are evident in MS, most evidence shows a loss of white matter. In white matter astrocytes, densely positioned around the nodes of Ranvier, the beta2-adrenergic receptor (B2-adr) is decreased (De Keyser et al., 1999), which regulates pinealocytes melatonin synthesis in some animals (Zubidat and Haim, 2007). The loss of astrocyte B2-adr alters energy regulation and increases immuno-inflammatory processes (Dong et al., 2012; Cambron et al., 2012), suggesting that these may be co-ordinated with decreased astrocyte melatonin. Any such, decreases in astrocyte melatonin synthesis would contribute to lowering oligodendrocyte protection and the increased remyelination afforded by astrocytes (Moore et al., 2011; De Keyser et al., 2010), as well as by melatonin (Villapol et al., 2011; Tai et al., 2010; Mishra et al., 2011).

However, astrocyte activation in the MS preclinical model, experimental autoimmune encephalomyelitis (EAE), decreases disease severity (Toft-Hansen et al., 2011). It is of note that only reactive astrocytes express the transcription factor yin yang1 (YY1) (Nowak et al., 2006), which increases retina melatoninergic pathways (Bernard and Voisin, 2008). This could suggest that the dampening effects of reactive astrocytes in the course of EAE may be via YY1 driven increased melatonin and/or NAS synthesis. This will be dependent on the availability of local melatonin precursors, including serotonin, suggesting that the reactivity process in astrocytes will be altered in conditions of decreased serotonin availability, as in depression.

The loss of astrocyte reactivity increases the infiltration of macrophages over T cells in EAE (Toft-Hansen et al., 2011), suggesting that astrocyte reactivity and fluxes may modulate the nature of the central immune cells present in EAE/MS. Melatonin is a significant driver of a phagocytic phenotype in many cell types, including macrophages, where nuclear factor-kappa beta (NF-κB) activation induces melatonin efflux, with resultant autocrine effects that decrease macrophage inflammatory responses, whilst increasing their phagocytic activity (Muxel et al., 2012). As such variation in local astrocyte melatonin production is likely to modulate the nature of chemoattracted immune cells and their responses in the course of demyelination and remyelination.

Studies looking for the factors regulating local melatonin and NAS are urgently required. Of the known regulators of astrocyte melatonin production, increased serotonin availability should modulate immune cell responses in MS and EAE, including in the nature of the macrophage response. To some degree this is supported by the efficacy of the monoamine oxidase inhibitor (MAOI), phenelzine, in EAE, where it decreases serotonin metabolism (Musgrave et al., 2011), thereby increasing serotonin availability for NAS and melatonin synthesis.

Interleukin (IL)-6 is classically associated with MS and the EAE model, where it can increase Th17 cell levels, thereby significantly contributing to immuno-inflammatory processes

(Serada et al., 2008). Increased IL-6 signalling on CD4+ effector T cells attenuates their inhibition by immuno-suppressive RegT cells (Schneider et al., 2013). In the EAE model, astrocyte derived IL-6, in the absence of systemic IL-6, allows EAE to be induced (Giralt et al., 2013), suggesting a significant role for central IL-6 regulation in the etiology and course of MS. IL-6 is also a significant inducer of IDO, thereby increasing neuroregulatory TRYCATs and decreasing serotonin, NAS and melatonin. Melatonin epigenetically down-regulates IL-6 via the induction of methyl-CpG-binding protein 2 (MeCP2) (Sharma et al., 2008), thereby inhibiting some important immuno-inflammatory processes in MS, as in other neurodegenerative conditions (Michaud et al., 2013). As well as decreasing IL-6, melatonin may also bind and regulate the activity and transcription of another Th17 cell modulator, the retinoic acid receptor-related orphan receptor-alpha (Lardone et al., 2011). As such melatonin, although associated with increased Th1 activation and natural killer (NK) cell cytotoxicity (Pioli et al., 1993; del Gobbo et al., 1989), will decrease levels of the more damaging Th17 cells evident in MS and autoimmune disorders, partly via the regulation of IL-6.

Degenerated white matter leads to increased ingestion of lipids by macrophages and microglia. As to whether NF-κB induced melatonin in macrophages, via MeCP2 induction, drives the myelin-ingested macrophage suppression of IL-6, requires investigation. The ingestion of lipids by macrophages also increases cholesterol efflux via liver X receptor-beta (LXR-β) activation (Bogie et al., 2012). It is unknown if LXR activation in macrophages and glia modulates or interacts with NAS and melatonin production. Should this occur, the wide protective effects of LXR activation in neurodegenerative conditions would then be modulated by variations in serotonin availability and NAS/melatonin efflux. Also myelin basic protein, a component of the myelin sheath, increases blood-brain barrier permeability (BBBp) (D'Aversa et al., 2013). Melatonin can inhibit BBBp (Chen et al., 2006), as well as the consequences of peripheral inflammation on central immuno-inflammatory processes (Chen et al., 2012). As such variations in local melatonin/NAS production by glia and immune cells will modulate processes classically associated with MS.

2.4. ApoE4 and melatonin regulation of MS cognitive deficits

Currently, the only other known regulator of astrocyte melatonin production is the apolipoprotein (Apo)E4 allele, which increases melatonin efflux (Liu et al., 2012). The ApoE4 allele also increases susceptibility to a more severe MS course (Tamam et al., 2011) leading to an exacerbation of cognitive decline (Shi et al., 2011) and grey matter volume loss (Horáková et al., 2010), which is in line with the ApoE4 allele being a susceptibility factor for Alzheimer's disease, where it interacts with stress to heighten cognitive decline (Sheffler et al., 2014). However, a meta-analysis of ApoE4 on MS susceptibility per se shows no significant effect (Xuan et al., 2011). ApoE4 synergistically interacts with depression, anxiety and stressful life events to increase cognitive decline and dementia susceptibility (Metti et al., 2013; Michels et al., 2012; Comijs et al., 2011; Robertson et al., 2005; Kim et al., 2011). The relevance of an ApoE4 allele interaction with stress/depression in the regulation of cognitive decline in MS requires investigation.

ApoE4 increases astrocyte melatonin synthesis (Liu et al., 2012). ApoE4 can also increase many neurotoxic processes, including the loss of white matter integrity (Ryan et al., 2011; Bartzokis et al., 2007). This suggests that increased astrocyte melatonin synthesis by ApoE4 may be necessary to offset its neurotoxic effects. Depression and chronic stress, by decreasing serotonin availability for melatonin synthesis, may then differentially heighten ApoE4 neurotoxicity, including the severity of cognitive decline, and perhaps relapse risk, in MS.

2.5. Depression and melatonin in MS

White matter changes are also evident in depression, which highly associates with MS, with decreased levels of oligodendrocytes coupled to increased white matter hyperintensities evident at post-mortem and in neuroimaging studies of depressed patients (Tham et al., 2011). Depression is classically associated with decreased serotonin availability, suggesting a decrease in the synthesis of melatonin and NAS that, in turn, contributes to the increased immuno-inflammation evident in depressed patients (Anderson and Maes, 2014b). Recent data shows significant changes in the levels of serotonin transporter in MS patients (Hesse et al., 2014), suggesting that variations in the availability of central serotonin for NAS and melatonin synthesis is likely to occur in both depressed and MS patients.

With melatonin modulating myelination and remyelination, depression is likely to be more than a simple psychiatric comorbidity of MS, but rather may be an integral part of the disease process, as suggested for other neurodegenerative conditions (Anderson and Maes, 2014c; Maes et al., 2011b). Peripheral and central inflammation induced cytokines, including IL-1β, IL-6, IL-18 and TNF-α, but especially interferon-gamma (IFN-γ), increase IDO, thereby depleting serotonin, NAS and melatonin (Campbell et al., 2014). This could suggest a wider role for increased systemic inflammation and oxidative and nitrosative stress (O&NS), which are evident in MS (Christensen et al., 2013; Murta and Ferrari, 2013), in increasing IDO.

O&NS and peripheral inflammation induce IDO, thereby decreasing serotonin availability and increasing depression susceptibility, whilst concurrently increasing the likelihood of demyelination and lowering remyelination. Somatization strongly associates with depression, and is driven by increased IDO coupled to an increased kynurenine/kynurenic acid (KYNA) ratio (Maes and Rief, 2012; Anderson et al., 2012a). As well as having effects on peripheral sensory processing, kynurenine is also readily taken up over the BBB, increasing central TRYCATs that contribute to depression, somatization and fatigue (Anderson et al., 2012b). As to how relevant these changes are to the high levels of somatization, fatigue and pain reported in MS requires investigation.

2.6. Depression, gut permeability, melatonin and MS

Recent data shows an increase in gut permeability in depression, which can be driven by a number of factors, including diet, alcohol and stress associated cortisol (Anderson and Maes, in press; Mariadason et al., 1999; Vanuytsel et al.,

2014). Increased gut permeability allows gut bacteria and tiny bits of partially digested food to trigger an immune response, thereby contributing to systemic immuno-inflammation, which is thought to contribute to depression, including by increasing IDO and decreasing serotonin, NAS and melatonin availability. Such systemic inflammation can alter the macrophage and microglia phenotype in EAE (Moreno et al., 2011), highlighting the relevance of systemic inflammation in the etiology and course of MS. The gut microbiome and gut permeability have recently been proposed to be major contributors to demyelinating disorders, especially MS (Joscelyn and Kasper, 2014). In the EAE model, increased gut permeability is an early event, prior to neurological symptoms, with heightened immuno-inflammatory activity contributing to these gut changes.

In this context, it is of note that melatonin is far more highly expressed in the gut, especially in enterochromaffin cells, than in the pineal gland (Raikhlin and Kvetnoy, 1976). Melatonin significantly decreases gut permeability under a number of inflammatory conditions, including binge and chronic alcohol intake in rodents (Sommansson et al., 2013). As such, melatoninergic pathway susceptibility genes and decreased serotonin and melatonin in MS would be expected to contribute not only to circadian and local glia/immune cell melatonin synthesis, but also to gut melatonin synthesis and thereby to gut permeability mediated immuno-inflammatory processes. The ensuing increase in immuno-inflammatory processes, perhaps especially TNF (Pontes et al., 2007), but also homocysteine, drive down pineal melatonin release, thereby impacting on a wide array of processes, including circadian, sleep, O&NS and immune cell activity, which are all altered in MS as well as in depression.

Emphasizing the occluded role of melatonin and NAS in different organs and cells, including in the pineal gland, gut and glia/immune cells, has implications for wider data in MS, as well as in the mechanisms of action of current treatments (see Fig. 2).

3. Melatonin and NAS in wider MS associated pathways

A number of proteins and pathways have been associated with the etiology and/or course of MS, but have not been well integrated within current conceptualizations of this condition.

3.1. Leptin, obesity and melatonin

Increased obesity in early adulthood increases MS risk, suggesting a role for raised levels of leptin, leptin resistance and obesity induced inflammation in the etiology and course of MS (Munger et al., 2009; Hedström et al., 2012), including by increasing gut permeability (Cox et al., in press). Extravasated immune cells can also release local leptin, which may act to regulate glia NAS/melatonin synthesis, as in the pineal gland (Gupta et al., 2010).

In non-obese and non-leptin resistant rodents, melatonin increases leptin levels (Song and Chen, 2009), which, in the absence of leptin resistance, has neuroprotective effects. This is reciprocated, as leptin also increases pineal AA-NAT activity in fed but not fasted animals (Gupta et al., 2010).

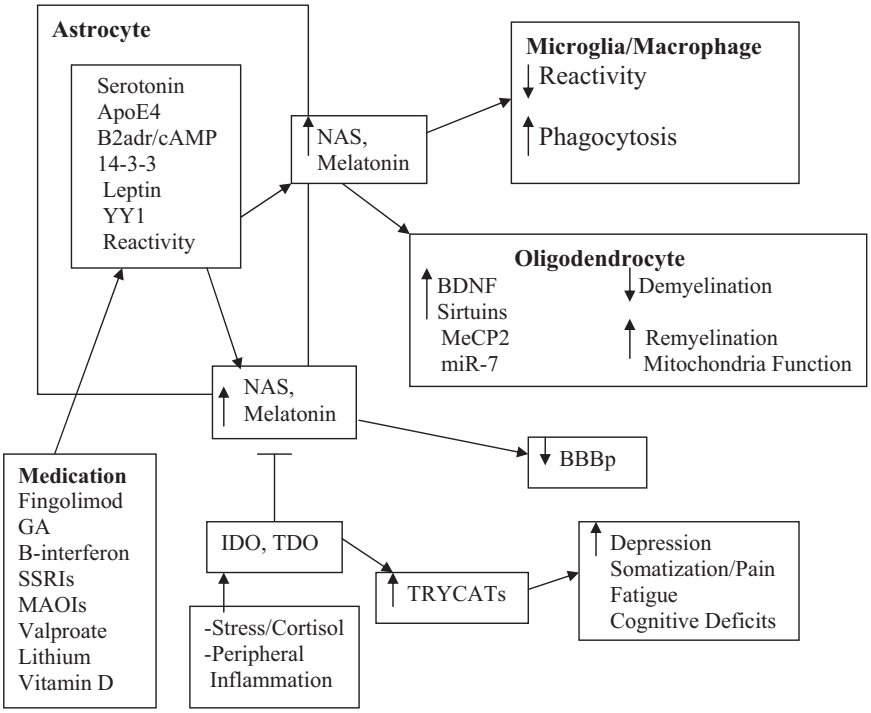

Fig. 2 Serotonin is converted to *N*-acetylserotonin by AA-NAT, which is then enzymatically converted to melatonin by HIOMT. Melatonin is further degraded to a number of products, including AFMK and AMK, which have also anti-oxidant qualities. At least three cytochrome P450 enzymes (CYP1A1, CYP1A2, CYP1B2) convert melatonin to 6-hydroxymelatonin (6-Hmel), which can be further metabolized to 6-sulfomelatonin (6-Smel) by sulphotransferase (S-tran). Melatonin is also in equilibrium with 5-methyltryptamine (5-MeTryp), which is regulated by AA-NAT, aryl acylamidase and melatonin deacetylase (not shown). See main text for other acronyms.

As to whether leptin regulates local melatonin and NAS in human glia, immune and gut cells requires investigation.

Leptin has diverse effects in MS/EAE, both accelerating and inhibiting MS disease processes (Hsuchou et al., 2013). Increased leptin in MS relapses, independent of body mass index (Matarese et al., 2005) correlates with decreased RegT cells (Kraszula et al., 2012). In contrast, the loss of leptin signalling in EAE astrocytes worsens disease progression, being associated with increased leukocyte extravasation, demyelination and altered astrocyte effluxes (Mishra et al., 2013). As to whether astrocyte NAS or melatonin are altered when EAE is induced in this astrocyte leptin receptor KO model requires investigation.

In obesity and metabolic syndrome, increased leptin release leads to leptin resistance. Leptin resistance is mediated by increased cAMP/Epac levels (Fukuda et al., 2011). Given that the cAMP pathway is a significant regulator of pineal melatoninergic synthesis enzymes, it will be important to determine as to how leptin and leptin resistance modulate astrocyte NAS and melatonin production at different CNS sites, including as to how this is co-ordinated with other cAMP regulated processes in astrocytes, such as KYNA production. Central KYNA inhibits the alpha 7 nicotinic acetylcholine receptor activity, leading to decreased cortex glutamate, dopamine and acetylcholine release, in turn decreasing cognition (Luchowska et al., 2009). Some of the effects of melatonin in mitochondria are mediated via the alpha 7 nicotinic receptor (Parada et al., in press), which are expressed in mitochondria (Gergalova et al., 2012), with the circadian rhythm of these nicotinic receptors being regulated by melatonin (Markus et al., 2010). As such, cAMP induced leptin resistance will impact on cognition as well as wider astrocyte processes and effluxes. The association of leptin and leptin resistance in interaction with serotonin availability in modulating astrocyte NAS and melatonin production requires investigation.

3.2. Substance P

SubP is increased in depression and a number of neurodegenerative and psychiatric conditions (Herpfer and Lieb, 2003). SubP effects are mediated via the neurokinin-1 receptor (NK-1r), which increases cAMP. The NK-1r is also upregulated by cAMP. SubP is a major activator of mast cells, thereby increasing BBBp, a major event in MS. In the EAE model of MS, SubP promotes the maintenance of inflammation (Reinke et al., 2006). In the pineal gland, SubP inhibits NE induced pineal NAS and melatonin production (Mukda et al., 2009). As with leptin, the significant role of SubP in the regulation of MS/EAE is long recognised but not integrated into current conceptualizations of the biological underpinnings of MS. As to how SubP modulates astrocyte and gut NAS and melatonin synthesis requires investigation, including within white matter astrocytes and in conditions of increased cAMP/Epac in leptin resistance.

3.3. Mitochondria, melatonin and MS

Accumulating data shows mitochondrial defects and an energy deficient state in the pathogenesis of MS (Campbell et al., 2012). In myelinated axons over 90% of mitochondria are located within juxtaparanodal and internodal axoplasm. Following demyelination the number of mitochondria increases, which is maintained even after remyelination. It remains to be determined as to whether these changes in axonal mitochondria content have any impacts on axonal mitochondria melatonin synthesis and as to whether an increased astrocyte production of melatonin would normalize axonal mitochondria number and functioning. Deficits in mitochondrial respiratory chain function are evident in lesion associated oligodendrocytes, hypertrophied astrocytes and axons in MS (Mahad et al., 2008) and MS models (Sathornsumetee et al., 2000), suggesting that local melatonin synthesis will have beneficial effects in a diverse range of lesion-associated cells, in part via the optimization of mitochondrial functioning.

Damage to myelin and mitochondria are partly mediated by increased microglia and macrophage reactivity (Fischer et al., 2012), which the stimulation of the autocrine and paracrine effects of astrocyte and macrophage local melatonin synthesis would also decrease. As such local melatonin may inhibit the immune cell activations that drive mitochondrial damage, as well as increasing mitochondrial functioning per se, in different lesion-associated cells.

O&NS driven lipid peroxidation, readily measured by products such as 4-hydroxy-2-nonenal (4HNE) has been proposed as an early event in the etiology of MS (Wang et al., 2014), as well as in the EAE model (Ljubisavljevic et al., 2013). 4HNE can induce conformational changes in sirtuin-3 that decrease sirtuin-3 function (Fritz et al., 2011). Sirtuin-3 is mitochondria located and a significant regulator of mitochondrial functioning. Sirtuin-3, like sirtuin-1, is increased by nicotinamide. Melatonin is a significant inducer of sirtuin-1 (Carloni et al., 2014), suggesting that it will have concurrent impacts on levels of sirtuin-3. Both these sirtuins are longevity associated, with sirtuin-1 also having positive mitochondria regulating effects via its activation of the master mitochondrial co-ordinator peroxisome proliferator-activated receptor gamma coactivator-1alpha (PGC-1α). The role of altered sirtuins in MS has still to be fully examined, with data showing that sirtuin-1 is expressed in a number of lesion-associated cells of MS patients, including CD4(+) and CD68(+) leukocytes, as well as in oligodendrocytes and astrocytes (Tegla et al., 2014). These authors also showed a statistically significant decrease in sirtuin-1 mRNA and protein expression in peripheral blood mononuclear cells during relapses versus levels in controls and in stable MS patients.

There is a growing interest in the role of microRNAs (miRNA) in MS (Ma et al., 2014), with miR-132 regulation of sirtuin-1 a significant determinant of aberrant cytokine production in the course of relapsing remitting MS (Miyazaki et al., 2014). Melatonin regulates sirtuin-1 (Carloni et al., 2014) and a number of miRNAs in cancer cell lines (Lee et al., 2011), as well as being regulated by miRNAs (Zhu et al., 2014; Clokie et al., 2012). As such, many of the effects of melatonin, including in the regulation of sirtuins and mitochondrial functioning, may be in association with miRNA alterations.

If indeed astrocytes have a co-ordinating and perhaps controlling role in their interactions with neurons and other CNS cells (Anderson, 2011), the state of astrocyte melatonin and NAS synthesis may be relevant as to how neighbouring cells are strengthened or weakened, as in the case of neurons and oligodendrocytes, or have their reactivity threshold regulated, as in the case of microglia and infiltrating leukocytes. As such

B-adr, ApoE4 and serotonin availability as well as other yet to be identified NAS and melatonin regulators in white matter astrocytes may be having significant impacts on oligodendrocyte survival and microglia reactivity in the etiology and course of MS, partly via astrocyte melatonin's regulation of mitochondria functioning in these cells.

Overall, given the high accumulation of exogenous and extracellular derived melatonin around mitochondria, it is likely that extracellular sources of melatonin supplement mitochondrial sources with positive impacts on mitochondrial functioning and compartmental anti-oxidant co-ordination. As indicated above this is likely to be co-ordinated with the regulation of sirtuins. This may allow astrocytes to have a integrating and regulatory role in the CNS, in part via variations in NAS and melatonin efflux.

4. Melatonin and MS treatments

Given the wide range of melatonin's effects in different cell types and tissues, it is likely that melatonin will be relevant to the effects of current medications, as well as to the development of new treatments.

4.1. Fingolimod

Fingolimod is a recently developed treatment for MS, where its benefits include decreasing the thymic egress of T cells (Noguchi and Chun, 2011). Phosphorylated fingolimod binds to four of the five sphingosine-1-phosphate (S1P) receptors, with its regulation of astrocyte S1P1r being crucial to its efficacy in EAE (Choi et al., 2011). S1Pr activation is intimately involved in the activation of glia, where S1P1r activation leads to Rac1, which can activate NADPH Oxidase, leading to superoxide release, which is rapidly converted to hydrogen peroxide, in turn leading to neutral sphingomyelinase (SMase), ceramide and lipid raft reorganization (Anderson and Ojala, 2010). The initial activation of the S1P1r may be followed by a fivefold increase in S1P3r (Singleton et al., 2005). S1P3r activation is necessary for the maintenance of astrocyte reactivity (Fischer et al., 2011). Reactive astrocytes in MS patients also show increased levels of acidic SMase, which increases ceramide and drives increased BBBp (van Doorn et al., 2012). Fingolimod decreases the induction of SMase and ceramide in reactive astrocytes, thereby decreasing levels of S1P availability, as well as decreasing BBBp (van Doorn et al., 2012). As to whether fingolimod modulates the maintenance of astrocyte reactivation, either directly via impacts on S1P3r or via inhibiting the initial role of S1P1r in driving lipid raft plasticity that includes the shifting of the S1P3r into rafts, requires investigation. Certainly part of the efficacy of fingolimod is mediated by its regulation of astrocyte reactivity (Colombo et al., 2014), with YY1, a known inducer of the melatoninergic pathways, inhibiting S1Pr activation (Stuebe et al., 2008). As such, fingolimod has wide effects on glia activation processes (Wu et al., 2013). As to whether this is co-ordinated with astrocyte NAS and melatonin production requires investigation.

Fingolimod also increases BDNF and glia derived neurotrophic factor release from activated microglia, concurrently decreasing IL-1β, IL-6 and TNF-α (Noda et al., 2013). BDNF is protective in EAE, perhaps especially in the early stages or where levels of disease activity are mild (Lee et al., 2012; Song et al., 2013). As well as being a BDNF receptor agonist, NAS also increases BDNF release (Yoo et al., 2011). By increasing the extracellular kinase-1/2 pathway (Xiao et al., 2012), the activation of the BDNF receptor, TrkB, is an important inducer of oligodendrocyte myelination (Wong et al., 2013). However, SNPs in the BDNF gene that are known to alter function are not associated with MS susceptibility or clinical course (Mero et al., 2012), suggesting that variations in glia NAS and NAS/melatonin ratio may be more important to TrkB activation and myelination levels. BDNF levels are increased in the cerebral spinal fluid in MS (Mashayekhi et al., 2012), likely indicative of processes driving increased myelination, although site and cellular source of production have still to be ascertained. Serum levels of BDNF are also increased and further raised by IFN-β treatment (Yoshimura et al., 2010). As such, TrkB activation is an important inducer of oligodendrocyte myelination and may be activated by NAS or BDNF, including NAS induced BDNF. The impact of fingolimod on glia NAS, melatonin and NAS/melatonin ratio requires investigation, including as to whether factors increasing serotonin availability, such as SSRIs and MAOIs, would be useful adjunctives to fingolimod. It is of note that fingolimod, as with sphingosine, can bind and regulate the function of 14-3-3 (Woodcock et al., 2010), a known modulator of pineal AA-NAT (Maronde et al., 2011), suggesting fingolimod impacts on the melatoninergic pathways.

4.2. Glatiramer acetate

Glatiramer acetate (GA) is another commonly used treatment in MS, although it mode of efficacy is still under investigation and may involve the induction of regulatory CD8+ T cells (Tyler et al., 2013). Some of the efficacy of GA is via the regulation of astrocytes (Li et al., 2001) and by increasing the phagocytic capacity of monocytes (Pul et al., 2012), as well as in the normalization of dysregulated miRNAs in MS (Waschbisch et al., 2011). GA also has efficacy in the treatment of the MeCP2 knockout model of Rett syndrome (Ben-Zeev et al., 2011), where is actions, like fingolimod in this model, are thought to be mediated via increased BDNF in neurons. However, given that the effects of MeCP2 knockout in driving Rett syndrome features seem to be mediated in astrocytes and microglia (Derecki et al., 2013: Lioy et al., 2011), it is not unlikely that GA has significant impacts via glia functioning in MS (Li et al., 2001). With melatonin being a significant inducer of a phagocytic phenotype, which is also induced by GA in monocytes (Pul et al., 2012), the impact of GA on astrocyte and immune cell NAS and melatonin synthesis and its interactions with serotonin availability require investigation.

4.3. Valproate and lithium

Both lithium and valproate, classical mood stabilizers in the treatment of bipolar disorder, have significant efficacy in the treatment of EAE (De Sarno et al., 2008; Zhang et al., 2012). Some of their effects may be mediated by the regulation of melatonin, which is also significantly decreased, as well as being a genetic susceptibility factor, in bipolar disorder (Etain

et al., 2012). Valproate significantly regulates the melatoninergic pathways in astrocytes (Castro et al., 2005). Lithium and valproate, like SSRIs, increase 14-3-3 (Choi et al., 2012; Nanavati et al., 2011), which increases the stability of AA-NAT, leading to increased NAS and melatonin production (Pozdeyev et al., 2006). The effects of lithium and valproate on astrocyte and immune cell melatoninergic pathways require investigation.

4.4. Interferon-beta

IFN-β has been extensively used in the treatment of MS. IFN-β increases the levels of melatonin metabolites in the urine of MS patients (Melamud et al., 2012), which the authors show is associated with improved sleep and decreased fatigue. Fatigue is an important debilitating symptom in MS and, as highlighted above, has biological underpinnings that closely link it to depression (Maes and Rief, 2012). Melatonin is also decreased in treatment naïve MS patients (Melamud et al., 2012). As highlighted above the efficacy of adjunctive vitamin D in IFN-β treated patients may be mediated by alterations in melatonin synthesis (Golan et al., 2013). Some of the efficacy of IFN-β may also be mediated by increased BDNF (Yoshimura et al., 2010), suggesting that efficacy may also occur by increasing melatonin's precursor, NAS, thereby activating BDNF's TrkB receptor. Overall, as with other MS treatments, some of the efficacy of IFN-β may be mediated by the regulation of the melatoninergic pathways.

5. Conclusions

The occluded role of NAS and melatonin in the etiology, course and treatment of MS is highlighted above. The targeting of astrocyte, gut and immune cell NAS and melatonin synthesis are likely to be significant pharmacological treatment goals in MS.

Conflicts of interest

Neither author has any relevant conflicts of interest to declare.

References

Akpinar Z, Tokgöz S, Gökbel H, Okudan N, Uğuz F, Yilmaz G. The association of nocturnal serum melatonin levels with major depression in patients with acute multiple sclerosis. (Nov 30). Psychiatry Res 2008;161(2):253–7.

Alcalde-Cabero E, Almazán-Isla J, García-Merino A, de Sá J, de Pedro-Cuesta J. Incidence of multiple sclerosis among European Economic Area populations, 1985–2009: the framework for monitoring. (Jun 12). BMC Neurol 2013:13–58.

Anderson G, Maes M. The gut-brain axis: the role of melatonin in linking psychiatric, inflammatory and neurodegenerative conditions. Adv Integr Med in press.

Anderson G, Maes M. Local melatonin regulates inflammation resolution: a common factor in neurodegenerative, psychiatric and systemic inflammatory disorders. CNS Neurol Disord Drug Targets 2014a;13(5):817–27.

Anderson G, Maes M. Oxidative/nitrosative stress and immuno-inflammatory pathways in depression: treatment implications. Curr Pharm Des 2014b;20(23):3812–47.

Anderson G, Maes M. TRYCAT pathways link peripheral inflammation, nicotine, somatization and depression in the etiology and course of Parkinson's disease. (Feb). CNS Neurol Dis 2014c;13(1):137–49.

Anderson G, Maes M, Berk M. Biological underpinnings of the commonalities in depression, somatization, and chronic fatigue syndrome. Med Hypotheses 2012a;78:752–6.

Anderson G, Maes M, Berk M. Inflammation-related disorders in the tryptophan catabolite (TRYCAT) pathway in depression and somatization. Adv Protein Chem Struct Biol 2012b;88:27–48.

Anderson G. Neuronal-immune interactions in mediating stress effects in the etiology and course of schizophrenia: role of the amygdala in developmental co-ordination. Med Hypotheses. 2011;76:54–60.

Anderson G, Rodriguez M. Multiple sclerosis, seizures and anti-epileptics: role of IL-18, IDO and melatonin. (May). Eur J Neurol 2011;18(5):680–5.

Anderson G, Ojala JO. Alzheimer's and seizures: interleukin-18, indoleamine 2,3-dioxygenase and quinolinic acid. Int J Tryptophan Res 2010;3:169–73.

Bartzokis G, Lu PH, Geschwind DH, Tingus K, Huang D, Mendez MF, et al. Apolipoprotein E affects both myelin breakdown and cognition: implications for age-related trajectories of decline into dementia. (Dec 15). Biol Psychiatry. 2007;62(12):1380–7.

Ben-Zeev B, Aharoni R, Nissenkorn A, Arnon R. Glatiramer acetate (GA, Copolymer-1) an hypothetical treatment option for Rett syndrome. Med Hypotheses. 2011 Feb;76(2):190–3.

Bernard M, Voisin P. Photoreceptor-specific expression, light-dependent localization, and transcriptional targets of the zinc-finger protein Yin Yang 1 in the chicken retina. (May). J Neurochem. 2008;105(3):595–604.

Bogie JF, Timmermans S, Huynh-Thu VA, Irrthum A, Smeets HJ, Gustafsson JÅ, et al. Myelin-derived lipids modulate macrophage activity by liver X receptor activation. PLoS One 2012;7(9):e44998.

Cambron M, D'Haeseleer M, Laureys G, Clinckers R, Debruyne J, De Keyser J. White-matter astrocytes, axonal energy metabolism, and axonal degeneration in multiple sclerosis. (Mar). J Cereb Blood Flow Metab. 2012;32(3):413–24.

Campbell BM, Charych E, Lee AW, Möller T. Kynurenines in CNS disease: regulation by inflammatory cytokines. (Feb). Front Neurosci 2014;6:8–12.

Campbell GR, Ohno N, Turnbull DM, Mahad DJ. Mitochondrial changes within axons in multiple sclerosis: an update. (Jun). Curr Opin Neurol. 2012;25(3):221–30.

Carloni S, Albertini MC, Galluzzi L, Buonocore G, Proietti F, Balduini W. Melatonin reduces endoplasmic reticulum stress and preserves sirtuin 1 expression in neuronal cells of newborn rats after hypoxia-ischemia. (Sep). J Pineal Res. 2014;57(2):192–9.

Castro LM, Gallant M, Niles LP. Novel targets for valproic acid: up-regulation of melatonin receptors and neurotrophic factors in C6 glioma cells. J Neurochem. 2005;95:1227–36.

Chen YC, Sheen JM, Tain YL, Chen CC, Tiao MM, Huang YH, et al. Alterations in NADPH oxidase expression and blood-brain barrier in bile duct ligation-treated young rats: effects of melatonin. (Jun). Neurochem Int. 2012;60(8):751–8.

Chen W, Liang X, Peterson AJ, Munn DH, Blazar BR. The indoleamine 2,3-dioxygenase pathway is essential for human plasmacytoid dendritic cell-induced adaptive T regulatory cell generation. (Oct 15). J Immunol. 2008;181(8):5396–404.

Chen TY, Lee MY, Chen HY, Kuo YL, Lin SC, Wu TS, et al. Melatonin attenuates the postischemic increase in blood-brain barrier permeability and decreases hemorrhagic transformation of tissue-plasminogen activator therapy following ischemic stroke in mice. (Apr). J Pineal Res. 2006;40(3):242–50.

Choi MR, Hwang S, Park GM, Jung KH, Kim SH, Das ND, et al. Effect of fluoxetine on the expression of tryptophan hydroxylase and

14-3-3 protein in the dorsal raphe nucleus and hippocampus of rat. (Mar). J Chem Neuroanat. 2012;43(2):96–102.
Choi JW, Gardell SE, Herr DR, Rivera R, Lee CW, Noguchi K, et al. FTY720 (fingolimod) efficacy in an animal model of multiple sclerosis requires astrocyte sphingosine 1-phosphate receptor 1 (S1P1) modulation. (Jan 11). Proc Natl Acad Sci USA. 2011;108 (2):751–6.
Christensen JR, Börnsen L, Ratzer R, Piehl F, Khademi M, Olsson T, et al. Systemic inflammation in progressive multiple sclerosis involves follicular T-helper, Th17- and activated B-cells and correlates with progression. PLoS One 2013;8(3):e57820.
Clokie SJ, Lau P, Kim HH, Coon SL, Klein DC. MicroRNAs in the pineal gland: miR-483 regulates melatonin synthesis by targeting arylalkylamine *N*-acetyltransferase. (Jul 20). J Biol Chem. 2012;287(30):25312–24.
Colombo E, Di Dario M, Capitolo E, Chaabane L, Newcombe J, Martino G, et al. Fingolimod may support neuroprotection via blockade of astrocyte nitric oxide. (Sep). Ann Neurol. 2014;76 (3):325–37.
Comijs HC, van den Kommer TN, Minnaar RW, Penninx BW, Deeg DJ. Accumulated and differential effects of life events on cognitive decline in older persons: depending on depression, baseline cognition, or ApoE epsilon4 status? (Jul). J Gerontol B Psychol Sci Soc Sci 2011;66(Suppl 1):i111–20.
Cox A.J., West N.P., Cripps A.W. Obesity, inflammation, and the gut microbiota. Lancet Diabetes Endocrinol. in press.
D'Aversa TG, Eugenin EA, Lopez L, Berman JW. Myelin basic protein induces inflammatory mediators from primary human endothelial cells and blood-brain barrier disruption: implications for the pathogenesis of multiple sclerosis. (Apr). Neuropathol Appl Neurobiol. 2013;39(3):270–83.
Davis W, van Rensburg SJ, Cronje FJ, Whati L, Fisher LR, van der Merwe L, et al. The fat mass and obesity-associated FTO rs9939609 polymorphism is associated with elevated homocysteine levels in patients with multiple sclerosis screened for vascular risk factors. (Jun). Metab Brain Dis. 2014;29(2):409–19.
De Keyser J, Laureys G, Demol F, Wilczak N, Mostert J, Clinckers R. Astrocytes as potential targets to suppress inflammatory demyelinating lesions in multiple sclerosis. (Nov). Neurochem Int. 2010;57(4):446–50.
De Keyser J, Wilczak N, Leta R, Streetland C. Astrocytes in multiple sclerosis lack beta-2 adrenergic receptors. (Nov 10). Neurology 1999;53(8):1628–33.
del Gobbo V, Libri V, Villani N, Caliò R, Nisticò G. Pinealectomy inhibits interleukin-2 production and natural killer activity in mice. Int J Immunopharmacol. 1989;11(5):567–73.
Derecki NC, Cronk JC, Kipnis J. The role of microglia in brain maintenance: implications for Rett syndrome. (Mar). Trends Immunol 2013;34(3):144–50.
De Sarno P, Axtell RC, Raman C, Roth KA, Alessi DR, Jope RS. Lithium prevents and ameliorates experimental autoimmune encephalomyelitis. J Immunol 2008;1:338–45.
Dong JH, Chen X, Cui M, Yu X, Pang Q, Sun JP. Beta2-adrenergic receptor and astrocyte glucose metabolism. (Oct). J Mol Neurosci. 2012;48(2):456–63.
Ekmekcioglu C. Expression and putative functions of melatonin receptors in malignant cells and tissues. Wien Med Wochenschr. 2014;164(21–22):472–8.
Etain B, Dumaine A, Bellivier F, Pagan C, Francelle L, Goubran-Botros H, et al. Genetic and functional abnormalities of the melatonin biosynthesis pathway in patients with bipolar disorder. (Sep 15). Hum Mol Genet. 2012;21(18):4030–7.
Fischer MT, Sharma R, Lim JL, Haider L, Frischer JM, Drexhage J, et al. NADPH oxidase expression in active multiple sclerosis lesions in relation to oxidative tissue damage and mitochondrial injury. (Mar). Brain 2012;135(Pt 3):886–99.
Fischer I, Alliod C, Martinier N, Newcombe J, Brana C, Pouly S. Sphingosine kinase 1 and sphingosine 1-phosphate receptor 3 are functionally upregulated on astrocytes under pro-inflammatory conditions. PLoS One 2011;6(8):e23905.
Fritz KS, Galligan JJ, Smathers RL, Roede JR, Shearn CT, Reigan P, et al. 4-Hydroxynonenal inhibits SIRT3 via thiol-specific modification. (May 16). Chem Res Toxicol. 2011;24(5):651–62.
Fukuda M, Williams KW, Gautron L, Elmquist JK. Induction of leptin resistance by activation of cAMP-Epac signaling. Cell Metab. 2011;13:331–9.
Galecka E, Szemraj J, Florkowski A, Galecki P, BiekiewiczM Karbownik-LewinskaM, et al. Single nucleotide polymorphisms and mRNA expression for melatonin MT(2) receptor in depression. Psychiatry Res. 2011;189(3):472–4.
Gergalova G, Lykhmus O, Kalashnyk O, Koval L, Chernyshov V, Kryukova E, et al. Mitochondria express α7 nicotinic acetylcholine receptors to regulate Ca2+ accumulation and cytochrome *c* release: study on isolated mitochondria. PLoS One 2012;7(2): e31361.
Giralt M, Ramos R, Quintana A, Ferrer B, Erta M, Castro-Freire M, et al. Induction of atypical EAE mediated by transgenic production of IL-6 in astrocytes in the absence of systemic IL-6. (Apr). Glia 2013;61(4):587–600.
Golan D, Staun-Ram E, Glass-Marmor L, Lavi I, Rozenberg O, Dishon S, et al. The influence of vitamin D supplementation on melatonin status in patients with multiple sclerosis. (Aug). Brain Behav Immun. 2013;32:180–5.
Gupta BB, Yanthan L, Singh KM. In vitro effects of 5-hydroxytryptophan, indoleamines and leptin on arylalkylamine *N*-acetyltransferase (AA-NAT) activity in pineal organ of the fish, *Clarias gariepinus* (Burchell, 1822) during different phases of the breeding cycle. (Aug). Indian J Exp Biol. 2010;48(8):786–92.
Hardeland R, Cardinali DP, Srinivasan V, Spence DW, Brown GM, Pandi-Perumal SR. Melatonin—a pleiotropic, orchestrating regulator molecule. Prog Neurobiol. 2011;93:350–84.
Hedström AK, Olsson T, Alfredsson L. High body mass index before age 20 is associated with increased risk for multiple sclerosis in both men and women. (Sep). Mult Scler. 2012;18(9):1334–6.
Herpfer I, Lieb K. Substance P and Substance P receptor antagonists in the pathogenesis and treatment of affective disorders. (Apr). World J Biol Psychiatr 2003;4:56–63.
Hesse S, Moeller F, Petroff D, Lobsien D, Luthardt J, Regenthal R, et al. Altered serotonin transporter availability in patients with multiple sclerosis. (May). Eur J Nucl Med Mol Imaging. 2014;41 (5):827–35.
Horáková D, Kýr M, Havrdová E, Doležal O, Lelková P, Pospíšilová L, et al. Apolipoprotein E ε4-positive multiple sclerosis patients develop more gray-matter and whole-brain atrophy: a 15-year disease history model based on a 4-year longitudinal study. Folia Biol (Praha) 2010;56(6):242–51.
Hsuchou H, Mishra PK, Kastin AJ, Wu X, Wang Y, Ouyang S, et al. Saturable leptin transport across the BBB persists in EAE mice. J Mol Neurosci. 2013;51(2):364–70.
Jang SW, Liu X, Pradoldeja S, Tosini G, Chang Q, Iuvone PM, et al. *N*-Acetylserotonin activates TrkB receptor in circadian rhythm. PNAS 2010;107(8):3876–81.
Joscelyn J, Kasper LH. Digesting the emerging role for the gut microbiome in central nervous system demyelination. (Oct). Mult Scler. 2014;20(12):1553–9.
Kerenyi NA, Sotonyi P, Somogyi E. Localizing acetylserotonin transferase by electron microscopy. Histochemistry 1975;46:77–80.
Kim JM, Stewart R, Kim SY, Kim SW, Bae KY, Yang SJ, et al. Synergistic associations of depression and apolipoprotein E genotype with incidence of dementia. (Sep). Int J Geriatr Psychiatry 2011;26(9):893–8.
Kraszula L, Jasińska A, Eusebio M, Kuna P, Głąbiński A, Pietruczuk M. Evaluation of the relationship between leptin, resistin, adiponectin and natural regulatory T cells in relapsing-remitting multiple sclerosis. (Jan-Feb). Neurol Neurochir Pol. 2012;46(1):22–8.

Lardone PJ, Guerrero JM, Fernández-Santos JM, Rubio A, Martín-Lacave I, Carrillo-Vico A. Melatonin synthesized by T lymphocytes as a ligand of the retinoic acid-related orphan receptor. (Nov). J Pineal Res. 2011;51(4):454–62.

Lee DH, Geyer E, Flach AC, Jung K, Gold R, Flügel A, et al. Central nervous system rather than immune cell-derived BDNF mediates axonal protective effects early in autoimmune demyelination. (Feb). Acta Neuropathol. 2012;123(2):247–58.

Lee SE, Kim SJ, Youn J-P, Hwang SY, Park C-S, Park YS. MicroRNA and gene expression analysis of melatonin-exposed human breast cancer cell lines indicating involvement of the anticancer effect. J. Pineal Res. 2011;51:345–52.

Li QQ, Burt DR, Bever CT. Glatiramer acetate inhibition of tumor necrosis factor-alpha-induced RANTES expression and release from U-251 MG human astrocytic cells. (Jun). J Neurochem. 2001;77(5):1208–17.

Lin GJ, Huang SH, Chen SJ, Wang CH, Chang DM, Sytwu HK. Modulation by melatonin of the pathogenesis of inflammatory autoimmune diseases. (May 31). Int J Mol Sci. 2013;14(6):11742–66.

Lioy DT, Garg SK, Monaghan CE, Raber J, Foust KD, Kaspar BK, et al. A role for glia in the progression of Rett's syndrome. (Jun 29). Nature 2011;475(7357):497–500.

Liu YJ, Meng FT, Wu L, Zhou JN. Serotoninergic and melatoninergic systems are expressed in mouse embryonic fibroblasts NIH3T3 cells. Neuro Endocrinol Lett 2013;34(3):236–40.

Liu YJ, Meng FT, Wang LL, Zhang LF, Cheng XP, Zhou JN. Apolipoprotein E influences melatonin biosynthesis by regulating NAT and MAOA expression in C6 cells. (May). J Pineal Res. 2012;52(4):397–402.

Liu YJ, Zhuang J, Zhu HY, Shen YX, Tan ZL, Zhou JN. Cultured rat cortical astrocytes synthesize melatonin: absence of a diurnal rhythm. (Oct). J Pineal Res. 2007;43(3):232–8.

Ljubisavljevic S, Stojanovic I, Pavlovic D, Milojkovic M, Sokolovic D, Stevanovic I, et al. Suppression of the lipid peroxidation process in the CNS reduces neurological expression of experimentally induced autoimmune encephalomyelitis. Folia Neuropathol. 2013;51(1):51–7.

Luchowska E, Kloc R, Olajossy B, Wnuk S, Wielosz M, Owe-Larsson B, et al. Beta-adrenergic enhancement of brain kynurenic acid production mediated via cAMP-related protein kinase A signalling. Prog. Neuropsychopharmacol. Biol Psychiatry. 2009;33(3):519–29.

Ma X, Zhou J, Zhong Y, Jiang L, Mu P, Li Y, et al. Expression, regulation and function of microRNAs in multiple sclerosis. (Jun 2). Int J Med Sci. 2014;11(8):810–8.

Maes M, Rief W. Diagnostic classifications in depression and somatization should include biomarkers, such as disorders in the tryptophan catabolite (TRYCAT) pathway. Psychiatry Res. 2012;196:243–9.

Maes M, Leonard BE, Myint AM, Kubera M, Verkerk R. The new '5-HT' hypothesis of depression: cell-mediated immune activation induces indoleamine 2,3-dioxygenase, which leads to lower plasma tryptophan and an increased synthesis of detrimental tryptophan catabolites (TRYCATs), both of which contribute to the onset of depression. (Apr 29). Prog Neuropsychopharmacol Biol Psychiatry. 2011a;35(3):702–21.

Maes M, Kubera M, Obuchowiczwa E, Goehler L, Brzeszcz J. Depression's multiple comorbidities explained by (neuro)inflammatory and oxidative & nitrosative stress pathways. Neuroendocrinol Lett 2011b;32(1):7–24.

Mahad D, Ziabreva I, Lassmann H, Turnbull D. Mitochondrial defects in acute multiple sclerosis lesions. (Jul). Brain 2008;131(Pt 7):1722–35.

Manchester LC, Poeggeler B, Alvares FL, Ogden GB, Reiter RJ. Melatonin immunoreactivity in the photosynthetic prokaryote *Rhodospirillum rubrum*: implications for an ancient antioxidant system. Cell Mol Biol Res 1995;41:391–5.

Mariadason JM, Catto-Smith A, Gibson PR. Modulation of distal colonic epithelial barrier function by dietary fibre in normal rats. (Mar). Gut 1999;44(3):394–9.

Markus RP, Silva CL, Franco DG, Barbosa Jr EM, Ferreira ZS. Is modulation of nicotinic acetylcholine receptors by melatonin relevant for therapy with cholinergic drugs? (Jun). Pharmacol Ther 2010;126(3):251–62.

Maronde E, Saade A, Ackermann K, Goubran-Botros H, Pagan C, Bux R, et al. Dynamics in enzymatic protein complexes offer a novel principle for the regulation of melatonin synthesis in the human pineal gland. (Aug). J Pineal Res. 2011;51(1):145–55.

Mashayekhi F, Salehi Z, Jamalzadeh HR. Quantitative analysis of cerebrospinal fluid brain derived neurotrophic factor in the patients with multiple sclerosis. Acta Medica (Hradec Kralove) 2012;55(2):83–6.

Matarese G, Carrieri PB, La Cava A, Perna F, De Rosa V, Aufiero D, et al. Leptin increase in multiple sclerosis associates with reduced number of CD4CD25 regulatory T cells. PNAS 2005;102:5150–5.

Melamud L, Golan D, Luboshitzky R, Lavi I, Miller A. Melatonin dysregulation, sleep disturbances and fatigue in multiple sclerosis. (Mar 15). J Neurol Sci 2012;314(1–2):37–40.

Mero IL, Smestad C, Lie BA, Lorentzen ÅR, Sandvik L, Landrø NI, et al. Polymorphisms of the BDNF gene show neither association with multiple sclerosis susceptibility nor clinical course. (Mar). J Neuroimmunol. 2012;244(1–2):107–10.

Metti AL, Cauley JA, Newman AB, Ayonayon HN, Barry LC, Kuller LM, et al. Plasma beta amyloid level and depression in older adults. (Jan). J Gerontol A Biol Sci Med Sci 2013;68(1):74–9.

Michaud M, Balardy L, Moulis G, Gaudin C, Peyrot C, Vellas B, et al. Proinflammatory cytokines, aging, and age-related diseases. (Dec). J Am Med Dir Assoc. 2013;14(12):877–82.

Michels A, Multhammer M, Zintl M, Mendoza MC, Klünemann HH. Association of apolipoprotein E ε4 (ApoE ε4) homozygosity with psychiatric behavioral symptoms. J Alzheimers Dis 2012;28(1):25–32.

Miller E, Walczak A, Majsterek I, Kędziora J. Melatonin reduces oxidative stress in the erythrocytes of multiple sclerosis patients with secondary progressive clinical course. (Apr 15). J Neuroimmunol 2013;257(1–2):97–101.

Mishra PK, Hsuchou H, Ouyang S, Kastin AJ, Wu X, Pan W. Loss of astrocytic leptin signaling worsens experimental autoimmune encephalomyelitis. (Nov). Brain Behav Immun. 2013;34:98–107.

Mishra A, Paul S, Swarnakar S. Downregulation of matrix metalloproteinase-9 by melatonin during prevention of alcohol-induced liver injury in mice. (May). Biochimie 2011;93(5):854–66.

Miyazaki Y, Li R, Rezk A, Misirliyan H, Moore C, Farooqi N, et al. CIHR/MSSC new emerging team grant in clinical autoimmunity; MSSRF Canadian B cells in MS team. A novel microRNA-132-surtuin-1 axis underlies aberrant B-cell cytokine regulation in patients with relapsing-remitting multiple sclerosis. (Aug 19). PLoS One 2014;9(8):e105421.

Moore CS, Milner R, Nishiyama A, Frausto RF, Serwanski DR, Pagarigan RR, et al. Astrocytic tissue inhibitor of metalloproteinase-1 (TIMP-1) promotes oligodendrocyte differentiation and enhances CNS myelination. (Apr 20). J Neurosci. 2011;31(16):6247–54.

Moreno B, Jukes JP, Vergara-Irigaray N, Errea O, Villoslada P, Perry VH, et al. Systemic inflammation induces axon injury during brain inflammation. (Dec). Ann Neurol. 2011;70(6):932–42.

Mukda S, Møller M, Ebadi M, Govitrapong P. The modulatory effect of substance P on rat pineal norepinephrine release and melatonin secretion. (Sep 25). Neurosci Lett. 2009;461(3):258–61.

Munger KL, Chitnis T, Ascherio A. Body size and risk of MS in two cohorts of US women. Neurology 2009;73:1543–50.

Murta V, Ferrari CC. Influence of Peripheral inflammation on the progression of multiple sclerosis: evidence from the clinic and

experimental animal models. (Mar). Mol Cell Neurosci. 2013;53:6–13.
Musgrave T, Benson C, Wong G, Browne I, Tenorio G, Rauw G, et al. The MAO inhibitor phenelzine improves functional outcomes in mice with experimental autoimmune encephalomyelitis (EAE). (Nov). Brain Behav Immun. 2011;25(8):1677–88.
Muxel SM, Pires-Lapa MA, Monteiro AWA, Cecon E, Tamura EK, Floeter-Winter LM, et al. NF-kB drives the synthesis of melatonin in RAW 264.7 macrophages by inducing the transcription of the arylalkylamine-*N*-acetyltransferase (AA-NAT) gene. PLoS One 2012;7(12):e52010.
Nanavati D, Austin DR, Catapano LA, Luckenbaugh DA, Dosemeci A, Manji HK, et al. The effects of chronic treatment with mood stabilizers on the rat hippocampal post-synaptic density proteome. (Nov). J Neurochem. 2011;119(3):617–29.
Natarajan R, Einarsdottir E, Riutta A, Hagman S, Raunio M, Mononen N, et al. Melatonin pathway genes are associated with progressive subtypes and disability status in multiple sclerosis among Finnish patients. (Sep 15). J Neuroimmunol. 2012;250(1–2):106–10.
Noda H, Takeuchi H, Mizuno T, Suzumura A. Fingolimod phosphate promotes the neuroprotective effects of microglia. (Mar 15). J Neuroimmunol. 2013;256(1–2):13–8.
Noguchi K, Chun J. Roles for lysophospholipid S1P receptors in multiple sclerosis. (Feb). Crit Rev Biochem Mol Biol. 2011;46(1):2–10.
Nowak K, Lange-Dohna C, Zeitschel U, Günther A, Lüscher B, Robitzki A, et al. The transcription factor Yin Yang 1 is an activator of BACE1 expression. (Mar). J Neurochem. 2006;96(6):1696–707.
Parada E., Buendia I., León R., Negredo P., Romero A., Cuadrado A., et al.Neuroprotective effect of melatonin against ischemia is partially mediated by alpha-7 nicotinic receptor modulation and HO-1 overexpression. J Pineal Res. in press.
Pioli C, Caroleo MC, Nistico G, Doria G. Melatonin increases antigen presentation and amplifies specific and non specific signals for T-cell proliferation. Int J Immunopharmacol 1993;15:463–8.
Pontes GN, Cardoso EC, Cameiro-Sampaio MM, Markus RP. Pineal melatonin and the innate immune response: the TNF-alpha increase after Cesarean sections suppresses nocturnal melatonin production. J Pineal Res. 2007;43:365–71.
Pozdeyev N, Taylor C, Haque R, Chaurasia SS, Visser A, Thazyeen A, et al. Photic regulation of arylalkylamine *N*-acetyltransferase binding to 14-3-3 proteins in retinal photoreceptor cells. (Sep 6). J Neurosci 2006;26(36):9153–61.
Pul R, Morbiducci F, Skuljec J, Skripuletz T, Singh V, Diederichs U, et al. Glatiramer acetate increases phagocytic activity of human monocytes in vitro and in multiple sclerosis patients. PLoS One 2012;7(12):e51867.
Raikhlin NT, Kvetnoy IM. Melatonin and enterochromaffine cells. Acta Histochem. 1976;55(1):19–24.
Reinke EK, Johnson MJ, Ling C, Karman J, Lee J, Weinstock JV, et al. Substance P receptor mediated maintenance of chronic inflammation in EAE. (Nov). J Neuroimmunol. 2006;180(1–2):117–25.
Robertson J, Curley J, Kaye J, Quinn J, Pfankuch T, Raber J. apoE isoforms and measures of anxiety in probable AD patients and Apoe−/− mice. Neurobiol Aging. 2005 May;26(5):637–43.
Ryan L, Walther K, Bendlin BB, Lue LF, Walker DG, Glisky EL. Age-related differences in white matter integrity and cognitive function are related to APOE status. (Jan 15). NeuroImage 2011;54(2):1565–77.
Sathornsumetee S, McGavern DB, Ure DR, Rodriguez M. Quantitative ultrastructural analysis of a single spinal cord demyelinated lesion predicts total lesion load, axonal loss, and neurological dysfunction in a murine model of multiple sclerosis. Am J Pathol 2000;157:1365–76.
Schneider A, Long SA, Cerosaletti K, Ni CT, Samuels P, Kita M, et al. In active relapsing-remitting multiple sclerosis, effector T cell resistance to adaptive T(regs) involves IL-6-mediated signaling. (Jan 30). Sci Transl Med 2013;5(170):170ra15.
Serada S, Fujimoto M, Mihara M, Koike N, Ohsugi Y, Nomura S, et al. IL-6 blockade inhibits the induction of myelin antigen-specific Th17 cells and Th1 cells in experimental autoimmune encephalomyelitis. (Jul 1). PNAS 2008;105(26):9041–6.
Sharma R, Ottenhof T, Rzeczkowska PA, Niles LP. Epigenetic targets for melatonin: induction of histone H3 hyperacetylation and gene expression in C17.2 neural stem cells. (Oct). J Pineal Res 2008;45(3):277–84.
Sheffler J, Moxley J, Sachs-Ericsson N. Stress, race, and APOE: understanding the interplay of risk factors for changes in cognitive functioning. Aging Ment Health. 2014;18(6):784–91.
Shi J, Tu J, Gale SD, Baxter L, Vollmer TL, Campagnolo DI, et al. APOE ε4 is associated with exacerbation of cognitive decline in patients with multiple sclerosis. (Sep). Cogn Behav Neurol. 2011;24(3):128–33.
Singleton PA, Dudek SM, Chiang ET, Garcia JG. Regulation of sphingosine 1-phosphate-induced endothelial cytoskeletal rearrangement and barrier enhancement by S1P1 receptor, PI3 kinase, Tiam1/Rac1, and alpha-actinin. (Oct). FASEB J. 2005;19(12):1646–56.
Sommansson A, Saudi WS, Nylander O, Sjöblom M. Melatonin inhibits alcohol-induced increases in duodenal mucosal permeability in rats in vivo. (Jul 1). Am J Physiol Gastrointest Liver Physiol. 2013;305(1):G95–105.
Song F, Bandara M, Deol H, Loeb JA, Benjamins J, Lisak RP. Complexity of trophic factor signaling in experimental autoimmune encephalomyelitis: differential expression of neurotrophic and gliotrophic factors. (Sep 15). J Neuroimmunol. 2013;262(1–2):11–8.
Song YM, Chen MD. Effects of melatonin administration on plasma leptin concentration and adipose tissue leptin secretion in mice. (Dec). Acta Biol Hung. 2009;60(4):399–407.
Stokkan KA, Reiter RJ. Melatonin rhythms in Arctic urban residents. (Jan). J Pineal Res. 1994;16(1):33–6.
Stuebe S, Wieland T, Kraemer E, Av Stritzky, Schroeder D, Seekamp S, et al. Sphingosine-1-phosphate and endothelin-1 induce the expression of rgs16 protein in cardiac myocytes by transcriptional activation of the rgs16 gene. (Jan). Naunyn Schmiedebergs Arch Pharmacol. 2008;376(5):363–73.
Tai SH, Chen HY, Lee EJ, Chen TY, Lin HW, Hung YC, et al. 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. (Nov). J Pineal Res. 2010;49(4):332–41.
Tamam Y, Tasdemir N, Yalman M, Tamam B. Association of apolipoprotein E genotypes with prognosis in multiple sclerosis. (Oct). Eur Rev Med Pharmacol Sci. 2011;15(10):1122–30.
Tan DX, Manchester LC, Liu X, Rosales-Corral SA, Acuna-Castroviejo D, Reiter RJ. Mitochondria and chloroplasts as the original sites of melatonin synthesis: a hypothesis related to melatonin's primary function and evolution in eukaryotes. J. Pineal Res. 2013;54:127–38.
Tegla CA, Azimzadeh P, Andrian-Albescu M, Martin A, Cudrici CD, Trippe 3rd R, et al. SIRT1 is decreased during relapses in patients with multiple sclerosis. (Apr). Exp Mol Pathol. 2014;96(2):139–48.
Tham MW, Woon PS, Sum MY, Lee TS, Sim K. White matter abnormalities in major depression: evidence from post-mortem, neuroimaging and genetic studies. (Jul). J Affect Disord. 2011;132(1–2):26–36.
Toft-Hansen H, Füchtbauer L, Owens T. Inhibition of reactive astrocytosis in established experimental autoimmune encephalomyelitis favors infiltration by myeloid cells over T cells and enhances severity of disease. (Jan). Glia 2011;59(1):166–76.

Tyler AF, Mendoza JP, Firan M, Karandikar NJ. CD8+ T cells are required for Glatiramer acetate therapy in autoimmune demyelinating disease. (Jun 21). PLoS One 2013;8(6):e66772.

van Doorn R, Nijland PG, Dekker N, Witte ME, Lopes-Pinheiro MA, van het Hof B, et al. Fingolimod attenuates ceramide-induced blood-brain barrier dysfunction in multiple sclerosis by targeting reactive astrocytes. (Sep). Acta Neuropathol. 2012;124(3):397–410.

Vanuytsel T, van Wanrooy S, Vanheel H, Vanormelingen C, Verschueren S, Houben E, et al. Psychological stress and corticotropin-releasing hormone increase intestinal permeability in humans by a mast cell-dependent mechanism. (Aug). Gut 2014;63(8):1293–9.

Villapol S, Fau S, Renolleau S, Biran V, Charriaut-Marlangue C, Baud O. Melatonin promotes myelination by decreasing white matter inflammation after neonatal stroke. (Jan). Pediatr Res. 2011;69(1):51–5.

Wang P, Xie K, Wang C, Bi J. Oxidative stress induced by lipid peroxidation is related with inflammation of demyelination and neurodegeneration in multiple sclerosis. (Sep 30). Eur Neurol. 2014;72(3–4):249–54.

Wang X, Sirianni A, Pei Z, Cormier K, Smith K, Jiang J. The melatonin MT1 receptor axis modulates mutant Huntingtin-mediated toxicity. J Neurosci. 2011;31:14496–507.

Waschbisch A, Atiya M, Linker RA, Potapov S, Schwab S, Derfuss T. Glatiramer acetate treatment normalizes deregulated microRNA expression in relapsing remitting multiple sclerosis. PLoS One 2011;6(9):e24604.

Wens I, Dalgas U, Stenager E, Eijnde BO. Risk factors related to cardiovascular diseases and the metabolic syndrome in multiple sclerosis—a systematic review. (Oct). Mult Scler. 2013;19(12):1556–64.

Wong AW, Xiao J, Kemper D, Kilpatrick TJ, Murray SS. Oligodendroglial expression of TrkB independently regulates myelination and progenitor cell proliferation. (Mar 13). J Neurosci. 2013;33(11):4947–57.

Woodcock JM, Ma Y, Coolen C, Pham D, Jones C, Lopez AF, et al. Sphingosine and FTY720 directly bind pro-survival 14-3-3 proteins to regulate their function. Cell Signal. 2010;22:1291–9.

Wootla B, Eriguchi M, Rodriguez M. Is multiple sclerosis an autoimmune disease? Autoimmune Dis 2012;2012:969657.

Wu C, Leong SY, Moore CS, Cui QL, Gris P, Bernier LP, et al. Dual effects of daily FTY720 on human astrocytes in vitro: relevance for neuroinflammation. (Mar 19). J Neuroinflammation 2013:10–41.

Xiao Z, Wang J, Chen W, Wang P, Zeng H, Chen W. Association studies of several cholesterol-related genes (ABCA1, CETP and LIPC) with serum lipids and risk of Alzheimer's disease. (Nov 26). Lipids Health Dis. 2012:11–163.

Xuan C, Zhang BB, Li M, Deng KF, Yang T, Zhang XE. No association between APOE ε 4 allele and multiple sclerosis susceptibility: a meta-analysis from 5472 cases and 4727 controls. (Sep 15). J Neurol Sci. 2011;308(1-2):110–6.

Yoo DY, Nam SM, Kim W, Lee CH, Won MH, Hwang IK, et al. *N*-Acetylserotonin increases cell proliferation and differentiating neuroblasts with tertiary dendrites through upregulation of brain-derived neurotrophic factor in the mouse dentate gyrus. J Vet Med Sci. 2011;73(11):1411–6.

Yoshimura S, Ochi H, Isobe N, Matsushita T, Motomura K, Matsuoka T, et al. Altered production of brain-derived neurotrophic factor by peripheral blood immune cells in multiple sclerosis. (Oct). Mult Scler. 2010;16(10):1178–88.

Zhang Z, Zhang ZY, Wu Y, Schluesener HJ. Valproic acid ameliorates inflammation in experimental autoimmune encephalomyelitis rats. (Sep 27). Neuroscience 2012:140–50221 2012:140–50.

Zhu HQ, Li Q, Dong LY, Zhou Q, Wang H, Wang Y. MicroRNA-29b promotes high-fat diet-stimulated endothelial permeability and apoptosis in apoE knock-out mice by down-regulating MT1 expression. (Oct 20). Int J Cardiol. 2014;176(3):764–70.

Zubidat AE, Haim A. The effect of alpha- and beta-adrenergic blockade on daily rhythms of body temperature, urine production, and urinary 6-sulfatoxymelatonin of social voles *Microtus socialis*. (Oct). Comp Biochem Physiol A Mol Integr Physiol 2007;148(2):301–7.