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SIRT1 and NAD+ precursors: Therapeutic targets in multiple sclerosis a review

Vamshi K.C. Nimmagadda[a,b,1], **Tapas K. Makar**[a,b,c,1], **Krish Chandrasekaran**[a], **Avinash Rao Sagi**[a], **Jayanta Ray**[a], **James W. Russell**[a,b], and **Christopher T. Bever Jr.**[a,b,c,*]

[a]Department of Neurology, University of Maryland, Baltimore, MD 21201, USA

[b]Research Service, VA Maryland Health Care System, Baltimore, MD 21201, USA

[c]VA Multiple Sclerosis Center of Excellence East, Baltimore, MD 21201, USA

Abstract

Neurodegeneration is an important determinant of disability in multiple sclerosis (MS) but while currently approved treatments reduce inflammation, they have not been shown to reduce neurodegeneration. SIRT1, a NAD dependent protein deacetylase, has been implicated in the pathogenesis of neurodegeneration in neurological diseases including MS. We have studied the role of SIRT1 in experimental autoimmune encephalomyelitis (EAE) and found evidence for a neuroprotective role. In this review we summarize the most recent findings from the use of SIRT1 activators and SIRT1 overexpression in transgenic mice. These data support provide a rational for the use of SIRT1 activators in MS.

Keywords

Multiple sclerosis; EAE; Neurodegeneration; NAD; SIRT1

1. Neurodegeneration in multiple sclerosis

Neurodegeneration has become the focus of research into multiple sclerosis (MS) therapy because currently approved drugs, while reducing inflammation, have not eliminated neurodegeneration which appears linked to progressive disease and disability (Noseworthy et al., 2000). Pathologically, MS is characterized by both white matter and gray matter inflammation (Bo et al., 2003; Cifelli et al., 2002; Dutta and Trapp, 2007; Stadelmann et al., 2011; Steinman et al., 2002) which is believed to be initiated by autoreactive T cells activated in the periphery (Steinman et al., 2002). These cells are thought to migrate across the blood brain barrier where they recruit lymphocytes and monocytes, activate microglia, and stimulate the deposition of immunoglobulins and complement inducing a hypoxia-like insult (Henderson et al., 2009; Lucchinetti et al., 2000). Neurodegeneration appears to occur early in the disease process and be linked to the inflammatory process (Frischer et al., 2009;

*Corresponding author at: VA MS CoE – East, 10 N Greene Street (151), Baltimore, MD 21201., United States. christopher.bever@va.gov (C.T. Bever).

[1]Equal Contribution.

Magliozzi et al., 2010). Most of the current disease modifying therapies in MS reduce inflammation and the number of clinical relapses but do not prevent neurodegeneration or the development of progressive disease suggesting that the neurodegeneration is not dependent on ongoing inflammation. This has led to a search for new therapies for MS that are neuroprotective.

2. Mitochondrial changes in MS

Mitochondrial dysfunction with reduced nicotinamide dinucleotide (NAD+) appears to play a role in neurodegeneration in MS pathogenesis (Campbell et al., 2012, 2014; Carvalho, 2013; Kalman et al., 2007; Lassmann et al., 2012; Lu et al., 2000; Mao and Reddy, 2010; Penberthy and Tsunoda, 2009; Witte et al., 2010; Zambonin et al., 2011). Mitochondrial damage, triggered by inflammation may play a role in demyelination and neurodegeneration (Lassmann et al., 2012). The discovery of mitochondrial abnormalities in MS has led to the hypothesis that mitochondrial dysfunction may lead to impaired oxidative energy metabolism in the neuron resulting in an inability to maintain neuronal and axonal function and integrity, leading to axonal degeneration and/or neuronal death (Su et al., 2009; van et al., 2012; Witte et al., 2010). Neuropathological studies on experimental re-myelination in vivo showed an increase in mitochondrial content in re-myelinated axons which was associated with an increase in mitochondrial respiratory chain complex IV activity (Campbell et al., 2012, 2014; Zambonin et al., 2011). A significant increase in the number of stationary mitochondria was seen in re-myelinated axons compared with myelinated and demyelinated axons in In vitro studies (Campbell et al., 2012, 2014; Zambonin et al., 2011). It has been further suggested that inflammation may induce oxidative stress-related mitochondrial DNA deletions in neurons, which could contribute to neurodegeneration in MS (Campbell et al., 2014; Campbell and Mahad, 2012). In chronic MS lesions, a decline of energy metabolism in affected cells resulting in decreased ATP synthesis could ultimately lead to degeneration and cell death (Campbell et al., 2012, 2014; Lu et al., 2000). Determining the order in which events occur in this pathway and defining the putative initiation and execution phases are key aims to help to identify the best steps to target therapeutically. In this review we will discuss the evidence supporting the use of mitochondrial activators, sirtuins and supplementation of NAD+ precursors as therapeutic targets in MS.

3. SIRTuins

Mammals have seven sirtuins (SIRT1–7) which are found in different subcellular locations, including the nucleus (SIRT1, SIRT6, and SIRT7), cytosol (SIRT2), and mitochondria (SIRT3, SIRT4, and SIRT5). Surtuins 1–3 and 5 -7 are part of a larger group of protein deacetylases while SIRT4 acts to ADP-ribosylate a target protein. Sirtuins, unlike other protein deacetylases, require NAD+ as a cofactor in the deacetylation and ADP-ribosylation reaction (Imai et al., 2000). NAD is an essential cofactor which is involved in cellular redox reactions and is a substrate for NAD-dependent enzymes. The link among NAD+ and sirtuin activity suggested that sirtuins are likely to act as a sensor of energetic status and NAD+ levels may act as a signaling molecule of axonal integrity (Imai and Guarente, 2010). This may particularly be true in the mitochondria, where levels of NAD and NADH are high and

where a disproportionate fraction of proteins appear to be acetylated (Kim et al., 2006). SIRT1 is studied extensively because it is considered to be one of the determining factors in lifespan extension induced by caloric restriction (CR), a phenomenon observed in many organisms including yeast, worm, fruit fly, and mouse (Howitz et al., 2003; Kaeberlein et al., 1999; Rogina and Helfand, 2004; Tissenbaum and Guarente, 2001).

4. SIRT1

SIRT1 is an NAD + –dependent protein deacetylase that catalyzes the removal of acetyl groups from lysine residues in substrate proteins. SIRT1 contains 741 amino acids in humans with a predicted molecular weight of 81 kDa and Western blot show a size of ~120 kDa. Although SIRT1 lacks a DNA-binding domain, it recruits transcriptional machinery to target promoters to induce transcriptional changes. Histones are the primary substrate of SIRT1 (Smith et al., 2000; Tanny et al., 1999) particularly acetylation of histone H4 in lysine 16 (H4K16Ac) and acetylation of histone *H3* in lysine 9 (H3K9Ac). The effect on transcriptional regulation is dependent on the gene involved and may be either inhibition or activation and seem to relate to the intracellular energy state of the cell. The molecules and the pathways that are regulated by SIRT1 are shown in Table 1. In addition to histones, SIRT1 also deacetylates a number of non-histone histone substrates. SIRT1 regulates activity of circadian clock proteins CLOCK/Per (Aguilar-Arnal et al., 2015; Asher et al., 2008; Bellet et al., 2013; Chang and Guarente, 2013; Nakahata et al., 2008, 2009, p53) (Luo et al., 2001) and peroxisome proliferator-activated receptor γ (PPARγ) coactivator-1α (PGC-1α); (Nemoto et al., 2005), and FOXO (Xiong et al., 2011), nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB; (Salminen et al., 2008). The deacetylating activity of SIRT1, in turn, regulates diverse biological processes related to axonal integrity (Araki et al., 2004), cell differentiation (Fulco et al., 2003), apoptosis (Luo et al., 2001), autophagy (Lee et al., 2008), development (Cheng et al., 2003) and metabolism (Li, 2013).

SIRT1 is expressed at high levels in the brain, spinal cord, and dorsal root ganglia (Sakamoto et al., 2004). In adult rodent brains, SIRT1 mRNA is abundantly expressed in metabolically relevant areas, the hypothalamic arcuate, ventromedial, dorsomedial, and paraventricular nuclei, the area postrema and the nucleus of the solitary tract in the hindbrain (Ramadori et al., 2008). In addition to these sites, SIRT1 mRNA was also abundant in the piriform cortex, hippocampus, cerebellum and low levels in white matter (Ramadori et al., 2008). SIRT1 is predominantly expressed in neurons (Ramadori et al., 2008; Sakamoto et al., 2004). At the subcellular level, SIRT1 is located mostly in the nucleus. For example, transfection with SIRT1 cDNA shows nuclear localization in monkey kidney COS-7 cells (Sakamoto et al., 2004; Tanno et al., 2007). However, the cytoplasmic localization of SIRT1 has also been reported recently in murine pancreatic β-cells and neonatal rat cardiomyocytes (Chen et al., 2006; Moynihan et al., 2005). Two nuclear localization signals and two nuclear export signals are identified in SIRT1 protein (Tanno et al., 2007). In neural precursor cells isolated from the embryonic brain, SIRT1 is transiently localized to nucleus in response to differentiation stimuli and then translocates to the cytoplasm (Hisahara et al., 2008). SIRT1 is also predominantly expressed in the cytoplasm of some NeuN+ neurons in the gray matter (Hisahara et al., 2008). While the function of nuclear SRT1 has been shown to influence the transcription of genes, the function of cytoplasmic SIRT1 in neurons, if any, is unknown.

5. NAD+ and axonal degeneration

The role of NAD+ in axonal protection is best exemplified by the model of Wallerian degeneration. C57BL/WldS (Wallerian degeneration slow mutant) mice have prolonged survival of the distal stumps of transected axons both in the peripheral nervous system (PNS) and the CNS (Ludwin and Bisby, 1992; Lunn et al., 1989; Perry et al., 1990). Transected axons from wild type dorsal root ganglion (DRG) neurons degenerate in less than 24 h. By contrast transected WldS neurons survive for up to 4 weeks (Conforti et al., 2014). WldS mice are protected from Wallerian degeneration by a mutation, an 85-kb tandem triplication on mouse chromosome 4 (Perry et al., 1990). WldS encodes a fusion protein containing 70 N-terminal amino acids of ubiquitination factor Ube4b, full-length NAD + – synthesizing enzyme nicotinamide mono-nucleotide adenylyltransferase 1 (Nmnat1), and a unique 18-aminoacid joining sequence (Conforti et al., 2014). WldS is a gain of function mutant; however, new studies using mutations that results in a loss of function have begun to ask how Wallerian degeneration is initiated and which proteins are required for its completion.

For example, the removal of one endogenous NMNAT isoform that is present in axons, NMNAT2, causes WLDS-sensitive axon degeneration. On the other hand, deletion of SARM1 gene delays Wallerian degeneration to the same extent as WldS, SARM 1 causes degradation of NAD+, suggesting NAD+ metabolism a function in axon death signaling (Gerdts et al., 2015). Likewise, loss of PHR1 (also known as MYCBP2, an ubiquitin ligase) has a protective effect in vivo that approaches the same level as that of SARM1 and WldS (Babetto et al., 2013). Phr1 depletion increases the axonal level of the axon survival molecule nicotin-amide mononucleotide adenyltransferase 2 (NMNAT2), and NMNAT2 is necessary for Phr1-dependent axon stability (Babetto et al., 2013). Thus, these results suggest a primary role for NAD+ in axonal protection and is supported by the findings that exogenous NAD + mimics the protection of neurites by WldS (Araki et al., 2004; Wang et al., 2005).

Although NAD+ can be synthesized de novo from the amino acid tryptophan derived from the diet, the main source of NAD+ is produced through the so-called NAD+ salvage pathways (Young and Kirkland, 2008). This requires the dietary uptake of NAD+ precursors, such as the niacin-derived nicotinic acid (NA), nicotinamide (Nam) and nicotinamide riboside (NR), which in mammals are converted into NAD through the salvage pathway. In mammals Nam is directly converted to NMN (Nicotinamide mononucleotide) by the enzyme Nicotinamide phospho ribosyl transferase (NAMPT). NAMPT is a regulator of the intracellular NAD pool. Through its NAD-biosynthetic activity, NAMPT induces the activity of NAD-dependent enzymes, thereby regulating cellular function. NMN is subsequently converted to NAD by the enzyme Nmnat. Mammalian NMNATs have distinct subcellular localizations: NMNAT1 is a nuclear protein with a predicted nuclear localization signal, NMNAT2 is enriched in numerous membrane compartments, including synaptic terminals and synaptic vesicles and NMNAT3 is predominantly localized in mitochondria and its first 25 residues encode a mitochondrial targeting sequence (Ali et al., 2013). Thus, increased nuclear NAD biosynthesis and SIRT1 activation are important to prevent axonal degeneration (Araki et al., 2004).

6. SIRT1 – MS and EAE

Studies of animal models of demyelinating and neurodegenerative diseases have shown that SIRT1 induction can ameliorate the course of the disease. A neuroprotective effect in optic neuritis was shown by intravitreal injection of SRT647 and SRT501, two structurally and mechanistically distinct activators of SIRT1 (Shindler et al., 2007). Experimental allergic encephalomyelitis (EAE) was induced by immunization with Proteolipid peptide in SJL/J mice. Intravitreal injection of SIRT1 activators significantly attenuated retinal ganglion cell (RGC) loss in a dose-dependent manner. This neuroprotective effect was blocked by sirtinol, a SIRT1 inhibitor. Treatment with either SIRT1 activator did not prevent EAE or optic nerve inflammation, suggesting that neuroprotection occurs without immunosuppression (Shindler et al., 2007). This group also showed in the same mouse strain that oral administration of SRT501 or SRT1720 prevented neuronal loss during optic neuritis. In addition, the spinal cords from SRT501-treated mice had significantly higher axonal density than vehicle-treated mice suggesting protection against neurological dysfunction (Shindler et al., 2010). Similar neuro-protection by SIRT1 activators against optic neuritis induced with a neurotropic strain of mouse hepatitis virus, MHV-A59, or chronic EAE induced by immunization with MOG peptide is observed in C57/Bl6 mice (Fonseca-Kelly et al., 2012; Khan et al., 2014). SIRT1 activators are shown to significantly reduce ROS levels and increase mitochondrial metabolism (Fonseca-Kelly et al., 2012; Khan et al., 2014). These studies support a role for SIRT1 in EAE.

Studies by Rus et al. support a role for SIRT1 in MS. SIRT1 was found to be elevated in lesions in the brains of MS patients. SIRT1 expression was shown to be elevated in cells in both acute and chronic active lesions from MS patients. SIRT1 co-localized with CD4+, CD68+, oligo-dendrocytes (OLG), and glial fibrillary acidic protein (GFAP) positive cells in MS plaques. In addition, studies of peripheral blood mononuclear cells (PBMCs) showed a significant decrease in SIRT1 mRNA and protein in PBMCs during relapses when compared to the levels in controls and stable MS patients. These results suggest a role for SIRT1 in MS and that modulation of SIRT1 could be a therapeutic strategy to treat MS (Martin et al., 2015; Tegla et al., 2014),

We studied EAE in transgenic mice with neuron specific over expression of SIRT1, and found evidence supporting a protective role of SIRT1. SIRT1 over expression in chronic EAE induced by immunization of C57BL/6 mice with MOG peptide suppressed EAE clinical symptoms compared with wild-type EAE mice and prevented or altered the phenotype of inflammation in spinal cords; as a result, demyelination and axonal injury were reduced. Significant neuroprotective effects are observed, with fewer apoptotic cells found in the spinal cords of SIRT1 over expressing EAE mice associated with increased brain-derived neurotrophic factor (BDNF) and NAD levels (Nimmagadda et al., 2013). Delivery of BDNF using transformed bone marrow stem cells (BMSC) in mice is shown to have reduced clinical impairment compared to control mice receiving BMSC that did not produce BDNF (Makar et al., 2014). A reduction in inflammatory infiltrating cells; apoptotic cells, cleaved Caspase-3 staining is observed suggesting that BDNF reduces clinical severity, inflammation (Makar et al., 2012, 2014). Furthermore, we have shown that BDNF delivery increased SIRT1 expression in EAE animals (Makar et al. 2012). SIRT1 regulates BDNF expression

via its epigenetic pathway of deacetylation of histones and other transcription factors (Smith et al., 2000; Tanny et al., 1999). SIRT1 deacetylates methyl-CpG binding protein 2 (MeCP2) thereby controls MeCP2 binding activity to the BDNF promoter and promotes its expression (Jiang et al., 2012; Zocchi and Sassone-Corsi, 2012). On the other hand, generation of oligodendrocytes-the myelin-forming cells, from neural stem cells (NSCs) in adult mouse brain is shown to increase following inactivation of SIRT1 and SIRT1 inactivation ameliorates remyelination and delays paralysis in mouse models of demyelinating injuries (Rafalski et al., 2013). Therefore, distinctive pharmacological approaches designed for NAD-complementation or targeting NAD-centric proteins such as SIRT1 are needed to determine which approach may work best in the context of clinical application.

7. MS disease modifying therapies and SIRT1

We studied the effect of glatiramer acetate (GA), a widely used MS DMT, in EAE and found that treatment increased SIRT1 expression. EAE was induced in 10 week old C57 BL/6 J mice with MOG peptide as reported previously (57). Mice were treated daily with GA (150 μg/mouse/day) by subcutaneous injection following onset of disease symptoms. The clinical severity of disease up to day 30 was reduced at which time mice were euthanized. Pathological examination of spinal cord sections showed a reduction in inflammation and axonal loss. Immunohistochemistry analysis showed increased expression of SIRT1, SIRT3 and NAMPT compared to untreated EAE (unpublished data).

Further, we studied the effect of IFN-β, another widely used MS DMT, treatment in EAE and found similar effects. Because the activity of IFN-β is limited by a short serum half-life and limited ability to cross the blood brain barrier we used genetically engineered bone marrow stem cell for drug delivery (Makar et al., 2008) in EAE mice and showed increased SIRT1 expression in spinal cord (lumbar region, gray matter) in both acute and chronic stages of EAE (Unpublished data). These results are consistent with a reduction in inflammation caused by GA and IFN-β treatment allowing compensatory increases in NAD + production resulting in reduced neuronal loss.

8. Conclusions

Approved disease modifying therapies for MS are not effective in progressive MS and have not eliminated neurodegeneration in MS patients. Evidence of mitochondrial damage in MS has led to the hypothesis that neurodegeneration results for energy depletion in neurons. This, in turn, led to studies designed to understand the changes occurring in mitochondria to identify potential therapeutic targets. Depletion of NAD+ has been identified as an important mediator reflecting the energy state of the cell which can regulate gene expression through sirtuins. Studies of MS showed that SIRT1 is upregulated in acute and chronic brain lesions and reduced in the peripheral blood during MS exacerbations. Studies of EAE have shown that SIRT1 agonists and SIRT1 overexpression are neuroprotective. Studies of MS DMTs in EAE show increases in SIRT1 associated with clinical improvements. These studies support further studies of SIRT1 activation as a potential treatment for neurodegeneration in MS.

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Table 1

Molecular pathways regulated by SIRT1.

SUBSTRATE	LOCATION	FUNCTION
Circadian Clock Bmal1 (Aryl hydrocarbon receptor nuclear translocator-like, also known as Arntl, Bmal1, or Mop3)	Nucleus	SIRT1-promotes circadian transcription. SIRT1 physically interacts with CLOCK, a key clock regulator that forms heterodimers with BMAL1, and deacetylates BMAL1 and histone *H3* in a circadian manner at the promoters of circadian clock genes.
Per2 (Period circadian protein homolog 2)	Mainly nuclear, cytoplasm (perinuclear region)	SIRT1 also interacts with and deacetylates Period Protein, PER2, which heterodimerizes with Cryptochrome, CRY proteins and inhibits the CLOCK: BMAL1 function, and promotes its degradation. SIRT1 thus establishes a circadian clock feedback loop through NAD+.
Metabolism Peroxisome proliferator activated receptor-γ co-activator-1α (PGC-1α)	Nucleus.	SRT1 regulates the expression and activity of PGC-1α and help in oxidative metabolism and calorie restriction.
UCP3 (Uncoupling protein 3)	Mitochondrial inner membrane.	SIRT1 results in histone deacetylation of ucp3 promoter in response to glucocorticoids in skeletal and cardiac muscle.
CRTC2(TORC2)-(CREB regulated transcription coactivator2)	Cytoplasm, nucleus	Fasting induced switch consisting of SIRT1 and histone acetyltransferase p300 causing induction of CRTC2 & FOXO1.
HNF 4alpha (Hepatocyte nuclear factor 4 alpha)	Nucleus	SIRT1 activation inhibits transcription of the gene for PEPCK-C (Cytosolic Form of Phosphoenolpyruvate Carboxykinase) in part by deacetylation of HNF4a. SIRT1 activation is indirectly proportional to HNF4 activation and glucokinase activity.
LKB1(Liver Kinase *B*1)	Mitochondria; membrane; cytoplasm; nucleus; cytosol	SIRT1 regulates LKB1 and in turn influences its intracellular localization associated with STRAD, Kinase activity & ability to activate AMPK, which maintains energy homeostasis.
AceCS (acetyl-coenzyme A (acetyl-CoA) synthetase)	Mitochondrial matrix and/or cytoplasm	SIRT1 deacetylates and activates mammalian acetyl-CoA synthetases and increased AceCS1-dependent fatty-acid synthesis from acetate.
Axonal Pathways B-Catenin (Cadherin associated protein - Beta)	Cytoplasm (cytoskeleton), nucleus	SIRT1 deacetylates β-catenin to promote its accumulation in the nucleus leading to transcription of genes for MSC (mesenchymal stem cells) differentiation. Also deacetylation is an important step in carrying out the various functions of B-catenin like cell-cell adhesion, cell proliferation, cell survival, apoptosis, early embryonic patterning, stem cell renewal, maintenance of mitochondrial homeostasis, etc.
Mef2 (Myocyte enhancer factor2)	Nucleus	SIRT1 represses the muscle differentiation program by deacetylating Mef2, which is an important regulator of cardiac and skeletal muscle development and remodeling. MEF2 activity negatively regulates excitatory synapse density in part by promoting activity-dependent synapse elimination.
Zyxin	Cytoplasm (cytoskeleton), Nucleus (in presence of HESX1).	Zyxin is one of the downstream effectors necessary for SIRT1 to execute some biological functions in the developing brain and various adult tissues and regulates signal transmission from ECM to the nucleus.
Development and Degeneration Smad7 (Mothers against decapentaplegic homolog 7)	Nucleus, Cytoplasm	SIRT1 directly interacts with Smad7 and inhibits the p300-mediated acetylation of the lysine residues of Smad7. Persistent expression of Smad7 in SIRT1- leads to defective embryonic stem cell differentiation.
Androgen Receptor	Predominantly cytoplasm, Also in nucleus upon ligand binding.	SIRT1 binds and deacetylates the AR at a conserved lysine motif and offers protection against polyQ- expanded AR and in neurodegenerative diseases.
Cortactin(Cortical Acting Binding protein)	Cytoplasm	Deacetylation of cortactin by SIRT1 promotes cell migration by affecting recruitment of Arp2/3 complex proteins to existing actin microfilaments, facilitating and stabilizing nucleation sites for actin branching.