 doi:10.20944/preprints202002.0396.v1

Sirtuins, Mitochondria and the Melatonergic Pathway in Alzheimer's Disease

Anderson G,[1] Maes M.[2-4]

[1] CRC Scotland & London, Eccleston Square, London, UK

[2] Dept Psychiatry, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand.

[3] Dept Psychiatry, Medical University Plovdiv, Plovdiv, Bulgaria.

[4] IMPACT Research Center, Deakin University, Geelong, Australia.

Corresponding author

George Anderson,

Head of Research, CRC Scotland & London, UK.

Email: anderson.george@rocketmail.com

 doi:10.20944/preprints202002.0396.v1

ABSTRACT

Alzheimer's disease (AD) has been the subject of extensive investigation as to its biological underpinnings. However, this has produced little of therapeutic benefit or indeed provided any accepted biomarkers that could tailor treatment. This chapter reviews data on the main pathophysiologic processes that have been widely shown to be altered in AD, including circadian dysregulation, mitochondrial dysfunction, gut dysbiosis, and immune-glia-platelet activation. It is proposed that alterations in the gut microbiome, including gut dysbiosis and increased gut permeability drive changes in mitochondrial function that are intimately associated with significant variations in sirtuin expression. Both mitochondria-located and nucleus/cytoplasm located sirtuins can act on mitochondrial function in different cells and body systems to co-ordinate the ageing-associated changes that underpin AD. The sirtuins are therefore key aspect to a developmental model of AD that is more 'holistic' in perspective, thereby providing a framework for the detection of earlier biomarkers and more successful treatment for the heterogenous nature of AD pathoetiology.

 doi:10.20944/preprints202002.0396.v1

Keywords: Alzheimer's disease; sirtuins; mitochondria; leaky gut; inflammation; neuroimmune

 doi:10.20944/preprints202002.0396.v1

INTRODUCTION

A wide array of biological factors and processes are associated with Alzheimer's disease (AD) risk and/or pathophysiology. It is generally accepted that genetic factors and epigenetic processes over the lifespan interact with ageing to drive the pathophysiological changes occurring in neurodegeneration. Consequently, AD symptomatology may arise from an array of distinct processes culminating in a common hub of neurodegeneration. This is highly suggestive of a heterogenous set of pathways, if not distinct conditions. However, within such heterogeneity a number of key processes seem to be important, including circadian dysregulation, mitochondrial dysfunction, gut dysbiosis and increased gut permeability, as well as alterations in immune, glia and platelet activity. Other factors commonly found in people with AD, including increased levels of amyloid-β42 (Aβ42), hyperphosphorylated tau, ceramide and formaldehyde and decreased levels of the short-chain fatty acid, butyrate, melatonin, pericytes and taurine may all arise as a consequence, thereafter contributing to AD pathophysiology.

Circadian dysregulation is an important aspect of AD etiology [1] and pathophysiology [2]. This is supported by work in preclinical models, where it is proposed that circadian dysregulation leads to an increase in the oxidant/antioxidant ratio, thereby contributing to neuronal apoptotic susceptibility [3]. The decrease in the night-time secretion of pineal gland melatonin in AD contributes to elevated oxidative damage, although this seems a two-way interaction, as oxidative damage and associated immune-inflammation contribute to the suppression of pineal melatonin secretion [4]. Orexin, the wake-promoting factor, is also profoundly decreased in AD, contributing to the loss of a sleep-active rhythm [5].

A large body of data also shows mitochondrial dysregulation in AD, with mitochondrial dysfunction mooted as a viable AD treatment target [6], as in many other conditions [7,8]. Targeting mitochondrial function in an AD preclinical model prevents classical AD indicants, *viz* tangle and plaque formation [9]. Notably, the circadian rhythm drives changes in mitochondrial function and mitochondrial rate-limiting enzymes [10], suggesting that circadian dysregulation impacts core aspects of metabolic function. This is especially important in immune and glia cells, where night-time melatonin switches metabolism in reactive cells from glycolysis to oxidative phosphorylation (OXPHOS), and thereby from a reactive to quiescent state. Again, this is a two-way interaction as mitochondria function and redox regulation can modulate circadian proteins and the circadian rhythm [11,12].

 doi:10.20944/preprints202002.0396.v1

Recent data indicates a role for gut dysbiosis and increased gut permeability across a wide array of medical conditions [13-5], including AD [16]. Gut dysbiosis and gut permeability are also important in the shift from mild cognitive impairment (MCI) to AD [17]. The gut contributes to AD via two main mechanisms: 1) increased gut permeability leads to elevated levels of circulating lipopolysaccharide (LPS) and exosomal high-mobility group box (HMGB)1 [18], with both LPS and HMGB1 mediating their effects via toll-like receptor (TLR)4, in association with heightened levels of oxidative stress and immune-inflammatory activity; 2) gut dysbiosis is invariably associated with a decrease in the short-chain fatty acid, butyrate. Butyrate seals the gut barrier, suppresses immune and glia cell reactivity and optimizes mitochondria functioning, including within immune and glia cells, reviewed in [14]. These are the two important routes whereby the gut interacts with AD etiology and pathophysiology, with relevance to a host of other diverse medical presentations. It is also important to note that the gut is an integral aspect of the circadian rhythm.

An increased levels of inflammation, from the activation of immune and glia cells, has long been associated with AD, highlighting the relevance of systemic processes and their interactions with CNS regulation. Variations in the platelet activity are another systemic factor associated with the circadian rhythm and showing alterations in AD and other neurodegenerative conditions [7], including as arising from the regulation of mitochondrial function [19]. As with immune and glial cells, platelet mitochondria can be regulated by histone deacetylase (HDAC) inhibitors, such as the gut microbiome-derived, butyrate [20]. As such, platelets, like glia and immune cells, are another important hub for gut-mitochondria interactions, with consequences that include the production of thrombin and fibrin(ogen), both of which can drive neurodegenerative processes in AD [21-2], as well as contribute to AD risk factors, such as cardiovascular disorders and ischaemic stroke [23-4], as well as increasing the risk of cerebral amyloid angiopathy [25]. Overall, immunity, glia and platelets contribute to AD pathophysiology partly via changes that are regulated by the circadian rhythm and gut driven changes in mitochondrial function.

Other pathophysiological changes in AD may be linked to this, including the increased levels of ceramide that are evident in AD and other neurodegenerative conditions. For example, increased gut permeability leading to LPS and HMGB1 activation of microglia and the production of peroxynitrite ($ONOO^-$) and tumor necrosis factor (TNF)-α. ONOO- activates acidic sphingomyelinase (aSMase) leading to long-chain ceramides, with ceramide and TNF-α decreasing levels of daytime orexin and night-time melatonin, resulting in the loss of orexin and melatonin optimization of mitochondrial OXPHOS and contributing to circadian dysregulation. Ceramide also increases Aβ42 levels via the stabilization of beta-site amyloid precursor protein-cleaving enzyme

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 27 February 2020 doi:10.20944/preprints202002.0396.v1

(BACE)1 [26]. The lower butyrate levels also contribute to suboptimal mitochondria functioning, including in glia and immune cells, thereby dysregulating immune-inflammatory activity. Lower butyrate levels also attenuate its suppression of ceramide. LPS and HMGB1, via TLR4, can also regulate platelet activity as can ceramide and aSMase, whilst decreased levels of butyrate will attenuate its inhibition of platelet activation, leading to increased levels of thrombin and fibrin(ogen) in AD pathoetiology. Such data can be linked in an integrative, developmental model, comprised of a gut-mitochondria-(platelet-immune-glia)-circadian axis, that incorporates an array of diverse and previously disparate data on AD.

This chapter reviews data on the circadian dysregulation, mitochondrial dysfunction, gut dysbiosis, and immune-glia-platelet activation in AD, proposing an important role for alterations in sirtuin function in all of these processes and their interactions. First, we shall briefly review the sirtuins, before integrating sirtuins in the processes and their interactions underpinning AD pathophysiology. We then show that this can provide a more integrative model of AD, with future research and treatment implications.

THE SIRTUINS

The sirtuins are a family of nicotinamide dinucleotide (NAD)+-dependent class III histone deacetylases. The sirtuins are important to metabolic and circadian regulation, with epigenetic impacts on a host of physiological and pathophysiological processes. Mammals have seven sirtuins (SIRT1–7), with SIRT1, SIRT6 and SIRT7 being predominantly expressed in the nucleus, whilst SIRT3, SIRT4 and SIRT5 are primarily mitochondria-expressed. SIRT2 is expressed in the cytoplasm. The sirtuins regulate a wide array of core cellular processes, including mitochondrial metabolism, DNA repair, adipocyte differentiation, neurogenesis, insulin sensitivity, and fatty acid oxidation, as well as inflammation, and aging-associated processes. All of these processes have been linked to AD pathophysiology.

SIRT1 has classically been referred to as the 'longevity protein', given its association with the increased lifespan in yeast and rodents. Lower SIRT1 levels are evident in insulin-resistant cells, with the induced cellular expression of SIRT1 improving insulin sensitivity. This is important in AD, which has been referred to as type III diabetes, due to the role of type II diabetes in AD pathoetiology [27]. SIRT1 also deacetylates peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α), which is commonly referred to as the mitochondria 'master regulator',

 doi:10.20944/preprints202002.0396.v1

highlighting the important role of SIRT1 in mitochondrial metabolism. SIRT1 also deacetylates and deactivates the pro-apoptotic protein, p53, with p53 being intimately linked to the effects of hyperphosphorylated tau and Aβ42 in AD-associated neuronal death [28].

SIRT2 is more highly expressed in the brain and heart than other organs. SIRT2 has some similar effects to SIRT1, including improving insulin sensitivity and deacetylating PGC1α. However, SIRT2 can also have pro-apoptotic and pro-ageing effects, with the inhibition of SIRT2 in AD preclinical models decreasing AD-like symptomatology [29]. However, recent data shows SIRT2 to deacetylate the NLR family pyrin domain containing (NLRP)3 inflammasome, which the authors propose to indicate a role in reversing, and not simply slowing, ageing [30].

SIRT3 is mitochondria matrix-located and has generated a lot or research interest due to the suboptimal mitochondrial function that is evident in AD. SIRT3 increases mitochondrial respiration, with its over-expression in cells leading to a decrease in reactive oxygen species (ROS) production. SIRT3 deacetylates, activates and complexes with acetyl-coA synthetase (AceCS2), As acetyl-CoA is an important component of the tricarboxylic acid (TCA) cycle and OXPHOS, the induction of acetyl-CoA drives core aspects of mitochondrial metabolism. As acetyl-CoA is also a necessary co-substrate for aralkylamine N-acetyltransferase (AANAT) and therefore the activation of the mitochondrial melatonergic pathway, SIRT3 may be intimately linked with mitochondrial melatonin regulation. As the effects of mitochondrial melatonergic pathway activity include the upregulation of SIRT3 and superoxide dismutase (SOD)2 [31-2], the interactions of SIRT3 with melatonin and mitochondrial metabolism may be of some importance in AD, as highlighted below.

SIRT4 seems to have greater catalytic activity for lipoyl- and biotinyl-lysine modifications, compared to its deacetylation activity [33]. SIRT4 is a significant regulator of mitochondrial PDC, and therefore of the conversion of pyruvate to acetyl-CoA, and thereby upregulating the TCA cycle, OXPHOS and the mitochondrial melatonergic pathway. However, the increase in SIRT4 in dermal fibroblasts is associated with photo-aged cellular senescence [34], whilst data in other cells indicates its association with ageing-linked suboptimal mitochondrial function arising from a decrease in mitophagy [35]. In contrast, the knockout of SIRT4 leads to decreased longevity, as shown in drosophila [36]. Although modulating insulin resistance and susceptibility to diabetes, SIRT4 has been relatively little investigated in AD [37]. The effects of SIRT4 are complicated by its apparent diverse effects in different cell types and species [38] and clearly requires further investigation as to how its interactions can be associated with such diverse effects.

 doi:10.20944/preprints202002.0396.v1

SIRT5 has been little investigated in AD or AD-associated pathophysiological processes. There is some evidence to indicate that SIRT5 may compensate the loss of SIRT3 in mitochondria in sepsis models [39], suggesting impacts on mitochondria modulation of immune responses. Anti-ageing type effects driven by SIRT1 and nuclear factor erythroid 2-related factor (Nrf)2 in C. Elegans involve SIRT5 activation [40], paralleling the effects of SIRT1 in the deacetylation and activation of mitochondria-located SIRT3. The suppression of SIRT5 attenuates mitochondrial ATP production, as well as promoting AMP-activated protein kinase (AMPK) activation when under energy stress [41]. SIRT5 suppresses pancreatic β-cells proliferation and insulin secretion, with increased SIRT5 levels evident in type II diabetes patients [42], suggesting a role for SIRT5 in the association of type II diabetes with AD. SIRT5 desuccinylates and activates SOD1 [43] and mitochondria-located SOD2 [44], indicating impacts on antioxidant defences. SIRT5 can also regulate PDC activity via the suppression of pyruvate kinase [45]. Although little investigated in AD, SIRT5 has significant impacts on AD-associated pathophysiological processes.

SIRT6 knockout in mice produces marked premature aging [46], whereas the over-expression of SIRT6 extends murine male lifespan by ~20% [47]. The post-translational regulation of SIRT6 is also important in the recruitment of poly(ADP-ribose) polymerase (PARP)1 to oxidative stress-induced DNA breaks [48]. PARP1 levels are elevated in AD, with a prolonged rise in PARP1 levels leading to NAD+, and therefore sirtuin, depletion, thereby inducing energy depletion and apoptosis [49]. As the sirtuins are NAD+ dependent, oxidative stress-induced damage and PARP1 induction, by using NAD+, will deplete all sirtuins. SIRT6 also has a number of neuroprotective functions, with SIRT6 levels decreasing over age in association with rising levels of DNA damage [50]. These authors also showed that the brain-specific loss of SIRT6 leads to an increase in the levels of phosphorylated tau in preclinical models, as well as showing a suppression of SIRT6 mRNA and protein in AD patients [50].

SIRT7 has been relatively little explored. SIRT7 expression is highest in the liver and spleen and relatively low in the brain compared to other sirtuins. The SIRT7 knockout rodent shows accelerated aging [51], with cellular data showing SIRT7 to regulate DNA repair and decrease glycolytic metabolism. The association of SIRT7 with slowed aging would indicate that SIRT7 could have a role in AD pathophysiology, perhaps especially via non-CNS effects.

We now look in more detail as to the sirtuin roles in the different areas of AD research.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 27 February 2020 doi:10.20944/preprints202002.0396.v1

GUT, SIRTUINS AND ALZHEIMER'S DISEASE

Gut dysbiosis and gut permeability have been at the cutting edge of AD research over the past five years [52], in association with an emphasis on wider systemic processes. Such work has significantly and etiologically elaborated, if not challenged, the classical neuron-centric models of AD, which have emphasized the role of central Aβ42 and hyperphosphorylated tau. Elevations in low-level systemic inflammation are evident in AD [53], to which gut dysbiosis and increased gut permeability can contribute. The gut may therefore be seen as an important aspect of a more systemic 'holistic' perspective as to the biological underpinnings of AD. The gut has two primary ways of modulating central and systemic processes relevant to AD pathophysiology*:* increased gut permeability-mediated LPS and HMGB1, leading to TLR4 activation; and gut dysbiosis-driven suppression of butyrate levels. Both of these processes can interact to drive many of the diverse aspects of AD pathophysiology, including increased ceramide levels and glia and immune cell activation as well as wider systemic processes that can be relevant to AD, including alterations in platelet function.

Alterations in sirtuins seem important as to how gut-associated changes may modulate AD. Probiotics efficacy in suppressing high-fat diet impacts on the gut microbiome and gut permeability are mediated via the upregulation of SIRT1 in intestinal epithelial cells and the liver [54]. SIRT1 knockout, specifically in intestinal epithelial cells, highlights the importance of SIRT1 in the regulation of gut dysbiosis and inflammatory activity [55]. These authors showed intestinal epithelial cell SIRT1 to modulate nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) levels in association with heightened levels of spontaneous inflammation (colitis), dramatic changes in the composition of the gut microbiome and significant alterations in bile acids, coupled to significant changes in mitochondrial metabolism and gene expressions [55]. Colitis is an AD risk factor [56], as are many other immune-mediated disorders. Wellman and colleagues also showed that Paneth and goblet cells are significantly increased when SIRT1 is knocked out [55]. Goblet cells are classically associated with providing the protective mucus lining to the gut. However, they also act as importance sensors through antigen presentation to dendritic cell function, thereby influencing the patterning of the mucosal immune response [57]. As such, SIRT1 is a key regulator of not only gut permeability, but also adaptive structural changes in the gut that can impact on mucosal immune regulation.

Such data on the role of gut SIRT1 in the regulation of the intestinal epithelial cells may be of some

 doi:10.20944/preprints202002.0396.v1

note. There is a growing recognition as to the importance of the interactions of the gut microbiome, intestinal epithelial cells and mucosal immunity in determining how the gut modulates such a wide array of diverse medical conditions. Intestinal epithelial cell SIRT1 ko decreases the Lactobacillus gut bacterial species and butyrate production [55]. Butyrate is an important positive regulator of mitochondrial function, with consequences for immune and glia reactivity and thereby on a wide array of systemic and central processes [58]. Sirtuin-driven changes in the gut can then impact on wider body processes via alterations in butyrate production, with consequences in the mitochondria of diverse body cells, including via sirtuin changes in these cells.

Decreased fecal butyrate correlates with elevated Aβ42 in MCI patients [17], indicating the pathophysiological relevance of suppressed butyrate levels in prodromal AD. Butyrate's regulation of mitochondrial function includes via PDC disinhibition [59], with PDC also being regulated by the mitochondrial sirtuins [33,60]. SIRT3 interacts with PDC to increase its enzymatic activity mediated by protein deacetylation [60]. This would suggest that gut SIRT1, via butyrate regulation, may then impact on the regulation of mitochondrial metabolism via alterations in SIRT3 and perhaps other mitochondrial sirtuins, in distant organs and tissues. As to whether butyrate's PDC disinhibition involves the regulation of mitochondrial sirtuins in different cell types requires investigation, including in glia and immune cells as well as in neurons.

Butyrate can act via its receptor as well as via HDAC inhibition. PDC disinhibition by butyrate not only increases acetyl-CoA for the TCA cycle and OXPHOS, but also for the mitochondrial melatonergic pathway [61]. The activation of the mitochondrial melatonergic pathway is proposed to underpin the shift in reactive glia and immune cells to a more quiescent phenotype via the autocrine effects of melatonin [14,62]. Melatonin can upregulate different sirtuins and may contribute to butyrate's induction of sirtuins [63]. This will be important to determine as it would suggest that a decrease in melatonin availability may attenuate the influence of gut microbiome-derived butyrate on sirtuin induction and mitochondrial function in distant cells, including immune, glia and CNS cells. For example, lower levels of serotonin as a precursor, or decreased 14-3-3 protein for the stabilization of AANAT or decreased acetyl-CoA induction will impact on the melatonergic pathway and therefore may attenuate butyrate's modulation of mitochondria and sirtuins. This would also suggest that other factors acting on such processes will regulate sirtuins and mitochondria, such as ceramide's suppression of 14-3-3 proteins or the decreased serotonin that is often evident in depression.

The interactions of mitochondrial sirtuins and the mitochondrial melatonergic pathway clearly

 doi:10.20944/preprints202002.0396.v1

require further investigation. The above would suggest their mutual induction, with excess acetyl-CoA production acting to negatively feedback on this via PDC inhibition. Recent work proposes that mitochondrial sirtuins and the melatonergic pathway have been intimate partners over the course of evolution [64], suggesting that mitochondrial sirtuins and melatonin are closely co-ordinated in the regulation of mitochondrial function. Melatonin also increases SIRT1 in many cell types, with the protective effects of melatonin against Aβ42 requiring the induction of SIRT1 [65]. These authors also showed that SIRT1 is required for melatonin's effects on mitochondria biogenesis in an AD model. As SIRT1 contributes to the deacetylation and activation of SIRT3, this would suggest melatonin effects on both cytoplasmic and mitochondrial sirtuins, with consequences for mitochondrial function. Clearly, the effects of butyrate on the melatonergic pathway may have significant impacts on sirtuins, which may be necessary for the cellular and mitochondrial effects of butyrate.

Melatonin's regulation of mitochondria is partly driven by its induction of the circadian gene, Bmal1 [66]. Bmal1 mediates exogenous melatonin's disinhibition of PDC, thereby allowing melatonin to increase the TCA cycle and OXPHOS, as well as inducing the mitochondrial melatonergic pathway. It is also of note that Bmal1 and SIRT1 can mutually induce each other, as shown in different cell types [67-8], with SIRT1 deacetylating Bmal1 and increasing its activity [67]. SIRT1 is therefore a component of the circadian rhythm with important interactions with other circadian factors. This may be particularly important in reactive cells, including glia and immune cells, as these cells are shifted to a quiescent state at night via pineal melatonin, thereby dramatically suppressing the night-time immune response. By releasing pro-inflammatory cytokines, required ongoing night-time inflammation suppresses pineal melatonin production, thereby forming the immune-pineal axis [69]. Heightened levels of immune-inflammatory activity and glia activation are core aspects of AD pathophysiology and will contribute to the circadian dysregulation associated with AD [70]. Inflammation-driven suppression of pineal melatonin will therefore attenuate melatonin's night-time suppression of immune and glia activation [71]. Future research should clarify the specifics of melatonin, Bmal1 and SIRT1/3 interactions in the regulation of glia and immune cells over the circadian rhythm.

SIRT1-6 can modulate immune and glial cell function, as shown for SIRT1 [72], SIRT2/3 [73], SIRT4 [74], SIRT5 [75] SIRT6 [76]. As indicated above, such sirtuin-driven changes in mitochondrial function and associated immune/glia reactivity thresholds and night-time immune quiescence may be key aspects of the effects of gut microbiome-derived butyrate and pineal melatonin in the pathoetiology of AD. As mitochondrial metabolism is a major determinant of

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 27 February 2020 doi:10.20944/preprints202002.0396.v1

immune and glia cell function, including reactivity thresholds and phenotype [77], alterations in the levels and regulation of sirtuin will modulate this key aspect of the longer-term course of AD pathophysiology.

The relevance of butyrate in AD is also highlighted by its impact, via HDAC inhibition, in the attenuation of hippocampus-associated memory impairments [78]. Notably, the main genetic susceptibility factor for AD, the apolipoprotein (Apo)E4 allele, is associated with a decrease in butyrate producing bacteria in AD patients [79]. As ApoE4 decreases mitochondria SIRT3 in neurons [80], the interactions of butyrate and SIRT3 with ApoE4 in other cell types will be important to determine. As such, decreases in gut microbiome-derived butyrate are correlated with the main AD genetic risk factor, with effects that seem mediated via alterations in mitochondrial sirtuins.

Butyrate and Ceramide

Heightened levels of circulating and central ceramide are evident in many neurodegenerative conditions, including AD [7,81]. Ceramide mediates its detrimental effects via mitochondrial dysfunction, and at higher levels via mitochondria-driven apoptosis. Ceramide also decreases 14-3-3, suggesting that it may contribute to a decrease in the stabilization of AANAT, and therefore decrease the activation of the melatonergic pathway [7]. Butyrate also decreases ceramide levels, including via the addition of glucosyl moiety to ceramide, leading to the glucosylceramide [82], with the administration of glucosylceramide to a preclinical AD model ameliorating memory deficits [83]. As well as directly acting on mitochondria, butyrate attenuates the negative effects of ceramide on mitochondrial function, including mitochondria circadian regulation by orexin and melatonin. However, this may be of transient benefit in preventing AD pathophysiology, as glucosylceramide is the precursor for ganglioside formation, with some gangliosides contributing to AD pathophysiology via promotion of Aβ fibril formation in the presynaptic membrane in ganglioside-enriched lipid domains [84]. As some gangliosides afford protection in AD models [85], whilst some are detrimental [86], it will be important to determine how factors that differentially regulate ganglioside formation interact with butyrate-induced glucosylceramide. Data indicates that gangliosides at the core of Aβ plaques differ from those in the Aβ plaque periphery, suggesting dynamic regulation of ganglioside in Aβ plaques [87]. The effects of butyrate in the intercellular environment of such Aβ plaques will be important to determine.

Ceramide is a major determinant of immune and glia cell reactivity, including via the suppression of

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 27 February 2020 doi:10.20944/preprints202002.0396.v1

mitochondrial OXPHOS [88-9]. Gut permeability-driven ceramide is further increased by the suppression of butyrate in AD, with consequences for glia and immune cell reactivity. As ceramide can drive down wake-promoting orexin and pineal melatonin, ceramide can also change the circadian regulation of immune and glial cells, with both orexin and melatonin increasing OXPHOS in these cells, reviewed in [7]. Ceramide, like the gut microbiome and sirtuins, also exhibits a circadian rhythm [90-1], highlighting the relevance of ceramide to the alterations in the circadian rhythm that occur over the course of AD.

Clearly, the role of sirtuins in modulating gut microbiome-derived butyrate will modulate ceramide levels and effects in AD. This requires future investigation as some data indicates that under conditions of ischaemia-reperfusion, SIRT3 deacetylates ceramide synthase, leading to an increase in ceramide synthesis [92]. The interactions of the sirtuins with the regulation of ceramide at different sites will be important to determine

Gut Permeability

As well as gut dysbiosis and associated changes in short-chain fatty acids, such as butyrate, an increase in gut permeability is another aspect of altered gut function that impacts on wide pathophysiological processes, including AD. Gut permeability arises from a slackening of intestinal epithelial cell tight junctions, leading to the transfer of LPS from the gut to the general circulation. Coupled to this is an increase in intestinal epithelial cell exosomes containing HMGB1, with both LPS and HMGB1 triggering inflammatory responses via the TLR4 [18]. The activation of TLR2/4 in microglia increases inducible nitric oxide synthase (iNOS) and superoxide, which readily interact to form $ONOO^-$ [93]. $ONOO^-$ is the major inducer of aSMase and ceramide [94]. As such, the heightened levels of central ceramide that are evident across diverse CNS conditions, including multiple sclerosis and AD [7,81], may be contributed to, if not driven by, increased gut permeability.

As noted, ceramide is damaging to mitochondria via a number of mechanisms, including decreasing mitochondrial Complex III, PDC and OXPHOS [92]. Recent work shows all factors and enzymes of the melatonergic pathway to be expressed in mitochondria [64], including AANAT, acetylserotonin methyltransferase (ASMT), 14-3-3 and acetyl-CoA, reviewed in [8]. 14-3-3 is necessary for the stabilization of AANAT, whilst acetyl-CoA is a necessary co-substrate for AANAT [95]. Exogenous melatonin increases OXPHOS, SIRT3 and SOD2, which is proposed to parallel the

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 27 February 2020 doi:10.20944/preprints202002.0396.v1

effects of mitochondrial melatonin [32,96]. The mitochondria-located SIRT3 is protective against ceramide effects in brain cells [97], indicating that any suppression of the mitochondrial melatonergic pathway will sensitize cells to ceramide-induced suboptimal mitochondrial function and decreased OXPHOS. This supported by data showing SIRT3 to suppress levels of tau accumulation in AD patients as well as in preclinical models [98], paralleling the similar effects of melatonin [99]. It is also of note that 14-3-3 suppression sensitizing cells to ceramide's apoptotic effects [100]. Ceramide's suppression of the mitochondrial melatonergic pathway will decreases melatonin's induction of, and interaction with, sirtuin-3 [64], thereby contributing to classical AD pathophysiological changes, including tau-associated tangles [98] and Aβ-associated plaques [65]. This is given some support by data showing that cerebrospinal fluid level of total tau and brain atrophy correlate with ceramide levels in AD patients [101].

The sirtuins are positive regulators of barrier maintenance, including in the gut, but also in the lung and blood-brain barrier [102-4]. As well as being a secondary bile acid, lithocholic acid is a vitamin D receptor agonist, with its effects at the vitamin D receptor in intestinal epithelial cells maintaining the gut barrier via SIRT1 upregulation [103]. The association of decreased vitamin D with AD risk has classically been seen as a consequence of vitamin D effects on immune cell function. However, such data highlights vitamin D to be a significant regulator of gut permeability, with effects that are mediated via an upregulation of SIRT1. There is a paucity of studies looking at the role of the other sirtuins in the regulation of gut permeability, although data on the role of suboptimal mitochondrial function and mitophagy in the gut permeability would indicate a role for the mitochondria-located sirtuins in its regulation [104].

Stress, Gut and AD

Heightened levels of stress have long been associated with AD etiology and pathophysiology. Classically, this was thought to be mediated by an increase in activation of the HPA axis and the effects of heightened cortisol on neurons and neurogenesis, crystalized in Sapolsky's cortisol cascade model and subsequent revisions [106]. Recent work indicates that stress quickly activates hypothalamic and amygdala corticotropin releasing hormone (CRH), with CRH acting on mucosal mast cells to increase TNFα, thereby increasing gut permeability [107]. Mucosal mast cell TNFα increases gut permeability via the downregulation of SIRT1 [103]. This is likely to be of some significance to AD pathophysiology, including as to how AD risk is increased by other medical conditions, including recurrent depression, migraine and inflammatory bowel diseases [108-9]. As well as via pathophysiological overlaps, the stress that is associated with such conditions will

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 27 February 2020 doi:10.20944/preprints202002.0396.v1

contribute to alterations in the gut, in turn impacting on AD pathoetiology [110]. Such processes underpin how stress may contribute to symptom exacerbations across such seemingly diverse conditions. Stress-induced decreases in intestinal epithelial cell SIRT1 seems an important component of such trans-diagnostic processes.

Alterations in SIRT1-6 have been associated with psychological stress in a wide array of preclinical models [37,111-4], with the effects of long-term stress in the regulation of depression proposed to be mediated by a decrease in SIRT3-SOD2 [115]. Much of this work has focussed on changes in neurons, reflective of a neuron-centric model of many disorders that may be better framed within a more holistic, developmental perspective of wider interacting systemic processes [58]. However, as indicated above, the pathophysiology of stress may be intimately associated with immune activation and gut permeability, with alterations in sirtuins at these sites contributing to, if not underpinning, stress pathophysiology.

Gut and Platelets

There is a growing interest in platelet function in AD, especially as to whether platelets can provide biomarkers that are relevant to diagnosis, progression and treatment [116]. Platelets can also be a significant source of Aβ [117]. The transfer of platelets from an AD preclinical model to control animals leads to breakdown of the BBB and microglia activation, with the authors proposing a role for AD platelets in cerebral amyloid angiopathy [118]. Both aSMase and ceramide increase platelet activation and thrombin formation [119], with aged platelets producing higher levels of aSMase and ceramide [120], thereby potentially contributing to AD pathophysiology. LPS can activate platelets, with low-dose LPS inducing an M1 phenotype in macrophages [121], indicating that gut permeability may not only activate platelets but also decrease the threshold of transition to an M1-type macrophage that can regulate platelet function. As butyrate shifts M1 macrophages to an anti-inflammatory M2-like phenotype [122] its decrease in AD will contribute to alterations in platelet-macrophage interactions. However, low-dose LPS activated platelets may also decrease immune responses, which may be dependent on specific TLR4 ligands [123]. This requires clarification in future research.

The raised levels of oxidized low-density lipoprotein (ox-LDL) in AD can also activate platelets via TLR4 [124], indicating that the association of a high fat diet with AD risk may be mediated not only via increased gut permeability [125], but also with concurrent platelet activation. HMGB1 is

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 27 February 2020 doi:10.20944/preprints202002.0396.v1

released from, and can activate, platelets [126], suggesting that HMGB1 may modulate the interactions of the gut and brain via platelets. Such processes may be relevant to AD pathoetiology. Recent data shows AD platelets to have lower levels of adhesion and activation in AD patients at initial diagnosis [127]. These authors showed that the alpha 7 nicotinic receptor (α7nAChR) levels are significantly higher in AD platelets, with the α7nAChR contributing to the alterations in platelet function in AD patients. The α7nAChR can be expressed on the plasma membrane and mitochondrial membrane, with activation of the latter suppressing apoptotic processes in mitochondria [128]. This could suggest that there is a compensatory upregulation of the α7nAChR in AD platelets and requires further investigation. Other work shows that mitochondrial function is significantly altered in AD platelets, with citrate synthase and Complex IV activity decreased, compensated by increases in other Complexes [129]. Although platelet count positively correlates with blood Aβ42 levels, platelet count is not correlated with central Aβ levels nor does the altered mitochondrial function in AD platelets correlate with the blood Aβ levels [129].
Overall, significant changes occur in AD platelets, but it is still unclear as to the significance of this in regard to AD diagnosis and management. Changes in platelets seem regulated by gut dysbiosis and increased gut permeability.

Although not extensively investigated, SIRT1-3 can regulate platelet function [124,130-1]. The relatively recent finding of an important role for acetylation in the regulation of platelet function has highlighted the need for further research on platelet sirtuins [132]. The inhibition of platelet sirtuins leads an aged-like phenotype [133], suggesting that some of the metabolic alterations in AD platelets may be intimately linked to changes in the regulation of different sirtuins and their interactions with the mitochondrial melatonergic pathway. It is also of note that aged platelets have increased production of aSMase and ceramide [120], which may be important to AD pathophysiology, including BBB breakdown and the early white matter loss that is evident in AD, as in many other CNS disorders [7]. De novo ceramide synthesis, like decreased sirtuins, can accelerate neuronal ageing [134]. The raised levels of ox-LDL in AD activate platelets via processes that include the downregulation of SIRT1, with the addition of resveratrol, a SIRT1 inducer, preventing platelet activation, aggregation and adhesion [124]. Transferring AD and MCI platelet mitochondria into other cells to form a hybrid results in decreased SIRT1 coupled to metabolic changes that are commonly seen in AD neurons [135]. Such data highlights the significant role of altered mitochondrial metabolism in AD and the importance of sirtuin regulation, including from the consequences of increased ceramide. Clearly, the interactions of raised levels of platelet activating ligands, altered mitochondrial function, sirtuins and ceramide over the course of AD requires investigation.

 doi:10.20944/preprints202002.0396.v1

CIRCADIAN DYSREGULATION: MITOCHONDRIA, BUTYRATE AND CERAMIDE

There is a growing appreciation of the relevance of circadian dysregulation in AD, as shown clinically and preclinically [1,3]. A decrease in the sleep-promoting effects of melatonin and the wake promoting effects of orexin contribute to this [5], with effects mediated by alterations in mitochondrial function. Gut microbiome-derived butyrate and ceramide differentially modulate the mitochondrial changes over the circadian rhythm in AD.

Alterations in mitochondria functioning may be at the heart of the circadian rhythm, with the effects of circadian melatonin mediated via Bmal1-SIRT1/3 [45] leading to PDC disinhibition and activation of the mitochondrial melatonergic pathway across diverse cell types [96]. This may have particular relevance in immune and glial cells [58]. As noted above, the switching of reactive cells to a quiescent phenotype at night is driven by pineal melatonin-induced Bmal1-SIRT1/3, and the switching to OXPHOS, coupled to an increase in PDC, the TCA cycle and acetyl-CoA [32,64]. Exogenous melatonin is taken up into mitochondria by active transport via the peptide transporters (PEPT)1/2, and not only by passive diffusion as previously assumed [136]. The attenuated pineal melatonin production in AD will therefore suppress this night-time dampening of immune activity and the inflammatory nature of immune mitochondria. Such circadian processes may better explain the widespread mitochondrial dysregulation that is evident in a host of diverse clinical presentations, including depression, schizophrenia, endometriosis [137], multiple sclerosis [7], and Parkinson's disease [15], all of which are associated with gut dysbiosis, circadian dysregulation, mitochondrial dysfunction and heightened immune-inflammation.

Ceramide not only dysregulates mitochondrial function, but also inhibits and induces apoptosis in the positive regulators of mitochondria OXPHOS, including melatonin and orexin neurons, respectively. Orexin levels are dramatically decreased in AD [5], coupled to a decrease in pineal melatonin. As such, the inhibition of orexin and melatonin by ceramide and pro-inflammatory cytokines [138] will contribute to the circadian dysregulation in AD. Although melatonin and orexin have opposing effects on wakefulness, data in sheep show orexin to increase pineal AANAT, and therefore pineal melatonin production [139]. This requires investigation in humans, including as to whether the orexin-induced melatonergic pathway activation occurs in mitochondria and whether this is mediated by increases in acetyl-CoA and/or 14-3-3. This will be important to determine, as it suggests that the dramatic orexin loss in AD may contribute to decreased pineal melatonin and the

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 27 February 2020 doi:10.20944/preprints202002.0396.v1

associated circadian dysregulation of mitochondrial function and immune/glia reactivity that ensues. Overall, gut permeability-mediated elevations in ceramide can be associated with circadian dysregulation via the suboptimal mitochondrial functioning arising from ceramide and cytokine suppression of daytime orexin and night-time melatonin, being driven by decreased PDC, acetyl-CoA and mitochondrial melatonergic pathway activity (see Figure 1).

As butyrate converts ceramide to glucosylceramide, the decreased butyrate levels in AD will contribute to heightened ceramide effects on mitochondria, including in immune and glial cells as well as such mitochondrial effects underpinning the suppression of circadian melatonin and orexin [7]. Interestingly, there is a circadian variation in platelets, which may be predominantly determined by pineal melatonin [140], with the inhibition of pineal melatonin occurring prior to dysregulation in wider sleep parameters in mild/moderate AD patients [141]. Notably, PDC disinhibition significant attenuates platelet activation by known activators [142]. This indicates that the utilization of pyruvate and increased production of acetyl-CoA in mitochondria decreases platelet activation, suggesting that the potentiation of the mitochondrial melatonergic pathway may be a relevant determinant of platelet activation threshold. Notably, 14-3-3ζ significantly modulates platelet mitochondrial metabolic activity and thereby metabolic activation [143]. As 14-3-3ζ also stabilizes AANAT, 14-3-3ζ regulation may be one way of modulating platelet function via the mitochondrial melatonergic pathway. It requires investigation as to whether ceramide effects in platelets are associated with a decrease in 14-3-3ζ and thereby with alterations in AANAT stabilization and associated mitochondrial function as well as the role of the platelet mitochondrial melatonergic pathway in the platelet circadian rhythm.

Sirtuins and the Circadian Rhythm

SIRT1 regulates both the central and peripheral clock genes [144]. The dimerization of the core clock genes, CLOCK and BMAL1, drives the circadian expression of a wide array of genes, including their own negative regulators, *viz* periods (PER) and cryptochromes (CRY). Likewise, the accumulation of daytime PER and CRY, along with casein kinase 1 (CK1), repress their own transcription. SIRT1 protein has a circadian rhythm, and promotes the circadian rhythm of Bmal1, Per2, and Cry1, as well as PER2 deacetylation and degradation. There is a proposed negative reciprocated interaction between PER2 and SIRT1 [145]. As a consequence of such circadian gene regulation, decreased SIRT1 in AD will contribute to alterations in mitochondrial function and associated changes in the activity of reactive cells, including immune and glial cells.

 doi:10.20944/preprints202002.0396.v1

SIRT3 is also a powerful regulator of mitochondrial function, including via the modulation of mitochondrial quality control [146]. SIRT3 also has a circadian rhythm, partly driven by an increase in SIRT1 and its deacetylation of SIRT3, with both SIRT1 and SIRT3 having their circadian rhythm regulated by NAD+ [147]. As such, nicotinamide phosphoribosyltransferase (NAMPT)-mediated NAD+ biosynthesis as an important driver of the sirtuin circadian rhythm [148]. As the sirtuins may be key regulators of AD pathophysiology, the regulation of NAD+ level is of some importance. Consequently, oxidative stress-induced DNA damage and the induction of PARP1, by driving down NAD+ availability, will desynchronize the complex interactions of gut, LPS, ceramide, butyrate, circadian rhythm, inflammation and stress in AD pathophysiology [see Figure 1].

{INSERT Figure 1 about here}

INTEGRATING SIRTUINS INTO AD PATHOPHYSIOLOGY

As shown in Figure 1, a complex series of interactions across different organs and body systems will contribute to AD risk and pathophysiology. Gut dysbiosis/permeability and its regulation of mitochondrial function, especially in glia and immune cells, seems of particular importance. This is a two-way interaction as glia and immune cells can modulate gut mitochondria to regulate gut dysbiosis/permeability. Such homeostatic-like interactions of mitochondria across organs and body systems is powerfully regulated by variations in the expression of different sirtuins. Sirtuins are an integral aspect of mitochondrial function, including via their interactions with PDC, OXPHOS, acetyl-CoA and the mitochondrial melatonergic pathway, especially in co-ordinating the role of the circadian rhythm in its powerful modulation of mitochondrial function in immune and glial cells. Gut permeability increases ceramide, which is further contributed to by a decrease in butyrate.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 27 February 2020 doi:10.20944/preprints202002.0396.v1

Changes in the gut are also relevant to platelet alterations in AD, and the potential role of platelets in AD pathophysiology and AD risk factors, such as stroke. The main genetic susceptibility for AD, the ApoE4 allele, may be having its impacts not only in the brain but also in the gut where it is associated with a decrease in sirtuins. The contribution of stress in AD may also be via gut dysbiosis and increased gut permeability, with stress interacting with ApoE4 in the regulation of emerging cognitive deficits [149]. It would seem highly likely that such stress-ApoE4 interactions involve changes in intestinal epithelial cell sirtuins, with consequences for sirtuins, Bmal1 and the melatonergic pathway in the mitochondria of central and systemic cells, including glia and immune cells. Such a perspective provides a physiological framework for a longer-term, developmental model of AD that can readily incorporate the effects of diet and lifestyle.

The above model has a number of research and treatment implications.

FUTURE RESEARCH DIRECTIONS

Longer-term, prospective studies should provide information as to the lifestyle and diet interactions with genetic and epigenetic factors in the etiology of AD. Clearly, the earlier a biomarker can be detected, the more likely that an intervention will be successful. This may require a different orientation of AD, whereby there is a focus on wider systemic physiology and a decreased emphasis on the end-point CNS changes. It would seem clear that the interactions of the sirtuins with mitochondrial Bmal1 and melatonin is important to this, especially in immune and glial cells.

Clearly further research is needed on how SIRT1-7 interact with wider cellular and intercellular processes over the course of ageing. SIRT1 and SIRT3 have been most extensively investigated. However, all sirtuins seem to have impacts on what seem core AD pathophysiological processes.

What sirtuins show alterations in intestinal epithelial cells under conditions of gut dysbiosis and increased gut permeability?

Does butyrate induction of melatonin [61] contribute to the induction of different sirtuins, including in immune and glia cells? This could give a more direct link of the gut to the sirtuin regulation of distant cells and systems. This could also suggest that the autocrine effects of melatonin in suppressing immune cell reactivity may involve sirtuin induction [62].

 doi:10.20944/preprints202002.0396.v1

How do melatonin, Bmal1 and SIRT1/3 interact in the regulation of glia and immune cells over the circadian rhythm?

Does the main AD susceptibility factor, ApoE4, contribute to sirtuin suppression in the gut, as well as in CNS cells [80]? Given that decreased SIRT3 increases gut permeability [18], this could suggest that ApoE4, as the main AD risk factor, may be at least partly acting via suppressed SIRT3 in intestinal epithelial cells and thereby via increased gut permeability and associated gut dysbiosis.

How does butyrate's conversion of ceramide to glucosylceramide regulate specific gangliosides, given the opposing effects of different gangliosides on AD neuro-pathophysiology?

Increased ceramide seems to contribute to AD pathophysiology. However, under conditions of ischaemia-reperfusion, SIRT3 deacetylates ceramide synthase, leading to an increase in ceramide synthesis [92]. Clarification as to the interactions of the sirtuins with circadian rhythm of ceramide synthesis is required, including the impact of different sirtuins on the ceramide/sphingosine-1-phosphate ratio [81].

Does ceramide decrease mitochondrial 14-3-3, thereby inhibiting the stabilization of AANAT and the activation of the mitochondrial melatonergic pathway?

How does ApoE4 interact with stress-induced decreases in SIRT1 in the regulation of gut permeability? Would this parallel the data showing ApoE4 to potentiate the effects of military trauma stress on cognitive dysfunction [149]?

How relevant are platelets to AD pathophysiology? Do butyrate and LPS regulate platelet sirtuins?

Does orexin increase pineal, and perhaps mitochondrial, melatonin via PDC disinhibition and the upregulation of acetyl-CoA and/or 14-3-3?

Does resveratrol mediate its efficacy partly by increasing SIRT1 and SIRT3 in intestinal epithelial cells?

TREATMENT IMPLICATIONS

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 27 February 2020 doi:10.20944/preprints202002.0396.v1

Sodium butyrate

Preclinical AD models have shown benefits of probiotics in decreasing AD-like symptomatology, including decreasing Aβ deposits, cognitive impairment, and microglia activation, as well as lowering TNFα and IL-1β levels [150-1]. These effects seem mediated via an increase in butyrate. This is supported by data showing the benefits of the early administration of sodium butyrate in the prevention of AD-like symptoms and Aβ levels [150]. Likewise, the effects of chronic noise stress-induced senescence are mediated via alterations in the gut microbiome [152], which may be attenuated by sodium butyrate.

As noted above, the deleterious effects of ApoE4 may be partly mediated via its suppression of gut butyrate levels [79], suggesting that the early screening of people for the ApoE4 allele should lead to advice on how to optimize their gut microbiome, if not to take sodium butyrate supplements. This may also be of importance for people with type II diabetes, with butyrate having utility in the management of metabolic heart disease, with efficacy mediated via an increase in mitochondrial ATP [153]. As noted, AD is sometimes referred to as type III diabetes, highlighting the overlapping changes in metabolism as well as the potential utility of sodium butyrate. As indicated throughout, the effects of butyrate include sirtuin upregulation [154]

Ketone Diet

Although originally developed to treat refractory epilepsy, the ketogenic diet has proved to have utility across a number of medical conditions. The ketogenic diet aims to modulate metabolism, with parallels to calorie restriction. Decreased butyrate in MCI inversely correlates with cerebrospinal fluid levels of Aβ42, with the ketogenic diet having utility in reversing this [17]. This is supported by other work showing the ketogenic diet to decrease cerebrospinal fluid levels of tau [155] and to improve cognition in a mild AD and metabolic syndrome patient [156]. Although larger controlled studies are clearly needed, it seems likely that the ketogenic diet will have some utility in MCI and AD, with effects that include an increase in gut microbiome-derived butyrate. Notably, the ketogenic diet improves mitochondrial biogenesis and bioenergetics via an increase in PGC1α-SIRT3 [157]. This seem driven increased NAD+ within a couple of days [158], with these authors showing the ketogenic diet to elevate the mRNA and protein levels of nuclear sirtuins. Such changes are associated with a decrease in PARP1 and indicants of oxidative stress [158], suggesting that the increase in NAD+ may arise partly as a consequence of a decrease in oxidative damage to DNA and therefore a decrease in NAD+ utilization by PARP1.

 doi:10.20944/preprints202002.0396.v1

Resveratrol

Resveratrol is a natural polyphenol, found at high levels in grapes and red wine, with efficacy across a number of medical conditions via its capacity to increase SIRT1. Resveratrol, via SIRT1, can decrease Aβ deposits and inflammation by increasing Th2 anti-inflammatory cytokines and suppress neuronal apoptosis by p53 [159]. Resveratrol can also increase SIRT3 and antioxidant enzymes, as shown in AD lymphocytes [160]. The effects of resveratrol, like the ketogenic diet, on mitochondrial function also has parallels to calorie restriction [161]. Resveratrol disinhibits PDC, thereby increasing acetyl-CoA and OXPHOS, as shown in the rodent cortex [162], indicating that it will activate the mitochondrial melatonergic pathway.

Interestingly, resveratrol seems in a two-way interaction with the gut microbiome [163], with preclinical data showing resveratrol to increase gut butyrate production [164]. As to whether this is mediated by an increase in SIRT1 and SIRT3 in intestinal epithelial cells will be important to determine.

Melatonin

It has been long appreciated that the antioxidant, anti-inflammatory and mitochondrial optimizing effects of melatonin [165], would allow it to have clinical utility in AD. Melatonin decreases tau levels and aggregation [99] as well as changing the composition of exosomes from cells challenged with Aβ [166]. Importantly, melatonin resets immune and glia cells in a circadian manner via it impact on mitochondrial function, including via its induction of, and two-way interactions with, the sirtuins. Lower pineal gland volume and pineal calcification are evident in AD, being accompanied by cognitive decline and dysregulated sleep circadian patterns [167]. Melatonin is cheap, readily available and side-effect free and is markedly underused across a host of conditions, including AD and MCI where it has shown efficacy [168]. The suppression of melatonin may be an important early event in MCI and AD.

Taurine

Taurine is one of the most common free amino acids in the brain. Brain taurine levels are significantly decreased in AD, thereby preventing taurine's binding to oligomeric Aβ and its cognition-enhancing effects [169]. Taurine also attenuates Aβ42-induced mitochondrial dysfunction

 doi:10.20944/preprints202002.0396.v1

via SIRT1 induction [170] as well as modulating the gut microbiome and its influence on the immune system [171]. Clearly, the role of taurine in AD can be readily incorporated into the integrated model above.

It should be noted that many factors that modulate AD risk or pathophysiology, including green tea's epigallocatechin-3-gallate, exercise, zinc, walnut and sesame seeds, can activate the melatonergic pathway and elevate sirtuin levels as well as modulate the gut microbiome [172].

CONCLUSION

AD may be better conceptualized as a lifespan developmental disorder, involving a complex series of interactions across different organs and body systems, will contribute to AD risk and pathophysiology. Gut dysbiosis/permeability and its regulation of mitochondrial function in glia and immune cells is a crucial aspect of the biological underpinnings of AD. This involves a two-way interaction, given that glia and immune cells can modulate gut mitochondria and thereby gut dysbiosis/permeability. Alterations in the regulation of SIRT1-6 are integral to such gut-systemic mitochondria interactions. A decrease in gut microbiome-derived butyrate and increase in gut permeability-associated LPS will increase ceramide, with detrimental effects mediated via a decrease in mitochondrial function and the mitochondrial melatonergic pathway. The importance of a more holistic perspective is highlighted by the effects of the main AD susceptibility allele, ApoE4, which impacts not only on CNS but also gut function, including via a decrease in sirtuins. Such a perspective also readily incorporates the effects of stress and highlights the powerful role for the circadian regulation of glia and immune cell mitochondrial function in the course of AD pathophysiology. This provides a physiological framework of reference for a lifespan developmental model of AD, which can readily incorporate the impacts of diet, stress and lifestyle on biological systems rather than endpoint levels of brain Aβ42 and hyperphosphorylated tau.

ABBREVIATIONS

α7nAChR	alpha 7 nicotinic receptor
AANAT	aralkylamine N-acetyltransferase
Aβ	amyloid-beta
AD	Alzheimer's disease
Apo	apolipoprotein
aSMase	acidic sphingomyelinase

 doi:10.20944/preprints202002.0396.v1

CRH	corticotropin releasing hormone
CRY	cryptochromes
HDAC	histone deacetylase
HMGB	high-mobility group box
LPS	lipopolysaccharide
MCI	mild cognitive impairment
NAD+	nicotinamide dinucleotide
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
NLRP	NLR family pyrin domain containing
Nrf	nuclear factor erythroid 2-related factor
OXPHOS	oxidative phosphorylation
$ONOO^-$	peroxynitrite
oxLDL	oxidized low-density lipoprotein
PARP	poly(ADP-ribose) polymerase
PER	periods
PGC	peroxisome proliferator-activated receptor gamma coactivator
SIRT	sirtuin
SOD	superoxide dismutase
TCA	tricarboxylic acid
TLR	toll-like receptor
TNF	tumor necrosis factor

ACKNOWLEDGEMENT
Not Applicable

CONFLICTS OF INTEREST
Neither author has a conflict of interest

REFERENCES

[1]. Musiek, E.S., Bhimasani, M., Zangrilli, M.A., et al. (2018). Circadian Rest-Activity Pattern Changes in Aging and Preclinical Alzheimer Disease. JAMA Neurol **75(5)**, 582-590. doi: 10.1001/jamaneurol.2017.4719.

[2]. Milán-Tomás, Á, Shapiro, C.M. (2018). Circadian Rhythms Disturbances in Alzheimer Disease: Current Concepts, Diagnosis, and Management. Alzheimer Dis Assoc Disord **32(2)**, 162-171. doi: 10.1097/WAD.0000000000000243

[3]. LeVault, K.R., Tischkau, S.A., Brewer, G.J. (2016). Circadian Disruption Reveals a Correlation of an Oxidative GSH/GSSG Redox Shift with Learning and Impaired Memory in an Alzheimer's Disease Mouse Model. J Alzheimers Dis **49(2),** 301-16. doi: 10.3233/JAD-150026.

[4]. Bedrosian, T.A., Nelson, R.J. (2012). Pro: Alzheimer's disease and circadian dysfunction: chicken or egg Alzheimers Res Ther **4(4)**, 25. doi: 10.1186/alzrt128.

[5]. Oh, J., Eser, R.A., Ehrenberg, A.J., et al. (2019). Profound degeneration of wake-promoting neurons in Alzheimer's disease. Alzheimers Dement **15(10)**, 1253-1263. doi: 10.1016/j.jalz.2019.06.3916.

[6]. Cenini, G., Voos, W. (2019). Mitochondria as Potential Targets in Alzheimer Disease Therapy: An Update. Front Pharmacol **10**, 902. doi: 10.3389/fphar.2019.00902.

[7]. Anderson, G., Rodriguez, M., Reiter, R.J. (2019). Multiple Sclerosis: Melatonin, Orexin and Ceramide Interact with Platelet Activation, Coagulation Factors and Gut-Microbiome-derived Butyrate in the Circadian Dysregulation of Mitochondria in Glia and Immune Cells. Int J Mol Sci **20(21)**, pii: E5500. doi: 10.3390/ijms20215500.

[8]. Anderson, G., Reiter, R.J. (2019). Glioblastoma:Role of Mitochondria N-acetylserotonin/Melatonin Ratio in Mediating Effects of miR-451, Aryl Hydrocarbon Receptor and in Co-ordinating Wider Biochemical Changes. Int J Tryptophan Res **2(1)**, 44-66. doi: 10.32794/mr11250011

[9]. Stefanova, N.A., Ershov, N.I., Kolosova, N.G. (2019). Suppression of Alzheimer's Disease-Like Pathology Progression by Mitochondria-Targeted Antioxidant SkQ1: A Transcriptome Profiling Study. Oxid Med Cell Longev **2019**, 3984906. doi: 10.1155/2019/3984906.

[10]. Neufeld-Cohen, A., Robles, M.S., Aviram, R., et al. (2016). Circadian control of oscillations in mitochondrial rate-limiting enzymes and nutrient utilization by PERIOD proteins. Proc Natl Acad Sci U S A **113(12)**, E1673-82. doi: 10.1073/pnas.1519650113.

[11]. Del Olmo, M., Kramer, A., Herzel, H. (2019). A Robust Model for Circadian Redox Oscillations. Int J Mol Sci **20(9)**, pii: E2368. doi: 10.3390/ijms20092368.

[12]. Rutter, J., Reick, M., Wu, L.C., McKnight, S.L. (2001). Regulation of clock and NPAS2 DNA binding by the redox state of NAD cofactors. Science **293(5529),** 510-4.

[13]. Seo, M., Anderson, G. (2019). Gut-Amygdala Interactions in Autism Spectrum Disorder: Developmental Roles via regulating Mitochondria, Exosomes, Immunity and microRNAs. Curr Pharm Des **25(41),** 4344-4356. doi: 10.2174/1381612825666191105102545.

[14]. Anderson, G. (2019). Gut Dysbiosis Dysregulates Central and Systemic Homeostasis via Decreased Melatonin and Suboptimal Mitochondria Functioning: Pathoetiological and Pathophysiological Implications. Melatonin Res **2(2)**, 70-85; doi: 10.32794/mr11250022

[15]. Anderson, G., Seo, M., Berk, M., Carvalho, A.F., Maes, M. (2016). Gut Permeability and Microbiota in Parkinson's Disease: Role of Depression, Tryptophan Catabolites, Oxidative and Nitrosative Stress and Melatonergic Pathways. Curr Pharm Des **22(40)**, 6142-6151.

[16]. D'Argenio, V., Sarnataro, D. (2019). Microbiome Influence in the Pathogenesis of Prion and

Alzheimer's Diseases. Int J Mol Sci **20(19)**, pii: E4704. doi: 10.3390/ijms20194704.

[17]. Nagpal, R., Neth, B.J., Wang, S., Craft, S., Yadav, H. (2019). Modified Mediterranean-ketogenic diet modulates gut microbiome and short-chain fatty acids in association with Alzheimer's disease markers in subjects with mild cognitive impairment. EbioMedicine **47**, 529-542. doi: 10.1016/j.ebiom.2019.08.032.

[18]. Chen, Y., Sun, H., Bai, Y., Zhi, F. (2019). Gut dysbiosis-derived exosomes trigger hepatic steatosis by transiting HMGB1 from intestinal to liver in mice. Biochem Biophys Res Commun **509(3)**, 767-772. doi: 10.1016/j.bbrc.2018.12.180.

[19]. Fišar Z, Jirák R, Zvěřová M, et al. (2019). Decreased platelet mito respiration in AD, but not corr plasma AB Plasma amyloid beta levels and platelet mitochondrial respiration in patients with Alzheimer's disease. Clin Biochem **72**, 71-80. doi: 10.1016/j.clinbiochem.2019.04.003.

[20]. Peer, C.J., Hall, O.M., Sissung, T.M., et al. (2018). A population pharmacokinetic/toxicity model for the reduction of platelets during a 48-h continuous intravenous infusion of the histone deacetylase inhibitor belinostat. Cancer Chemother Pharmacol **82(3)**, 565-570. doi: 10.1007/s00280-018-3631-7.

[21]. Merlini, M., Rafalski, V.A., Rios Coronado, P.E., et al. (2019). Fibrinogen Induces Microglia-Mediated Spine Elimination and Cognitive Impairment in an Alzheimer's Disease Model. Neuron. **101(6)**, 1099-1108.e6. doi: 10.1016/j.neuron.2019.01.014.

[22]. Grammas, P., Martinez, J.M. (2014). Targeting thrombin: an inflammatory neurotoxin in Alzheimer's disease. J Alzheimers Dis **42(4)**, S537-44. doi: 10.3233/JAD-141557.

[23]. Yu, J.H., Han, K., Park, S., et al. (In press). Incidence and Risk Factors for Dementia in Type 2 Diabetes Mellitus: A Nationwide Population-Based Study in Korea. Diabetes Metab J doi: 10.4093/dmj.2018.0216.

[24]. De Luca, C., Virtuoso, A., Maggio, N., Papa, M. (2017) Neuro-Coagulopathy: Blood Coagulation Factors in Central Nervous System Diseases. Int J Mol Sci **18(10)**, pii: E2128. doi: 10.3390/ijms18102128.

[25]. Goulay, R., Mena Romo, L., Hol, E.M., Dijkhuizen, R.M. (In press). From Stroke to Dementia: a Comprehensive Review Exposing Tight Interactions Between Stroke and Amyloid-β Formation. Transl Stroke Res doi: 10.1007/s12975-019-00755-2.

[26]. Puglielli, L., Ellis, B.C., Saunders, A.J., Kovacs, D.M. (2003). Ceramide stabilizes beta-site amyloid precursor protein-cleaving enzyme 1 and promotes amyloid beta-peptide biogenesis. J Biol Chem **278(22)**, 19777-83.

[27]. Kandimalla, R., Thirumala, V., Reddy, P.H. (2017). Is Alzheimer's disease a Type 3 Diabetes? A critical appraisal. Biochim Biophys Acta Mol Basis Dis **1863(5)**, 1078-1089. doi: 10.1016/j.bbadis.2016.08.018.

[28]. Jazvinšćak Jembrek, M., Slade, N., Hof, P.R., Šimić, G. (2018). The interactions of p53 with tau and Aß as potential therapeutic targets for Alzheimer's disease. Prog Neurobiol **168**, 104-127. doi: 10.1016/j.pneurobio.2018.05.001.

[29]. Diaz-Perdigon, T., Belloch, F.B., Ricobaraza, A, et al. (2020). Early sirtuin 2 inhibition

prevents age-related cognitive decline in a senescence-accelerated mouse model. Neuropsychopharmacology **45(2)**, 347-357. doi: 10.1038/s41386-019-0503-8.

[30]. He, M., Chiang, H.H., Luo, H., et al. (2020). An Acetylation Switch of the NLRP3 Inflammasome Regulates Aging-Associated Chronic Inflammation and Insulin Resistance. Cell Metab pii: S1550-4131(20)30009-7. doi: 10.1016/j.cmet.2020.01.009.

[31]. Anderson, G. (In press). The effects of melatonin on signaling pathways and molecules involved in glioma: Melatonin and glioblastoma: pathophysiology and treatment. Fundam Clin Pharmacol doi: 10.1111/fcp.12538.

[32]. Anderson, G. (2019). Daytime orexin and night-time melatonin regulation of mitochondria melatonin: roles in circadian oscillations systemically and centrally in breast cancer symptomatology. Melatonin Res **2(4)**, 1-8; doi: 10.32794/mr11250037

[33]. Mathias, R.A., Greco, T.M., Oberstein, A., et al. (2014). Sirtuin 4 is a lipoamidase regulating pyruvate dehydrogenase complex activity. Cell **159(7)**, 1615-25. doi: 10.1016/j.cell.2014.11.046.

[34]. Lang A, Grether-Beck S, Singh M, et al. (2016). MicroRNA-15b regulates mitochondrial ROS production and the senescence-associated secretory phenotype through sirtuin 4/SIRT4. Aging (Albany NY) **8(3)**, 484-505.

[35]. Lang, A., Anand, R., Altinoluk-Hambüchen, S., et al. (2017). SIRT4 interacts with OPA1 and regulates mitochondrial quality control and mitophagy. Aging (Albany NY) **9(10)**, 2163-2189. doi: 10.18632/aging.101307.

[36]. Parik, S., Tewary, S., Ayyub, C., Kolthur-Seetharam, U. (2018). Loss of mitochondrial SIRT4 shortens lifespan and leads to a decline in physical activity. J Biosci **43(2)**, 243-247.

[37]. Betsinger, C.N., Cristea, I.M. (2019). Mitochondrial Function, Metabolic Regulation, and Human Disease Viewed through the Prism of Sirtuin 4 (SIRT4) Functions. J Proteome Res **18(5)**, 1929-1938. doi: 10.1021/acs.jproteome.9b00086.

[38]. Min, Z., Gao, J., Yu, Y. (2019). The Roles of Mitochondrial SIRT4 in Cellular Metabolism. Front Endocrinol (Lausanne) **9,** 783. doi: 10.3389/fendo.2018.00783.

[39]. Heinonen, T., Ciarlo, E., Le Roy, D., Roger, T. (2019). Impact of the Dual Deletion of the Mitochondrial Sirtuins SIRT3 and SIRT5 on Anti-microbial Host Defenses. Front Immunol **10**, 2341. doi: 10.3389/fimmu.2019.02341.

[40]. Dehghan, E., Goodarzi, M., Saremi, B., Lin, R., Mirzaei, H. (2019). Hydralazine targets cAMP-dependent protein kinase leading to sirtuin1/5 activation and lifespan extension in C. elegans. Nat Commun ;**10(1)**, 4905. doi: 10.1038/s41467-019-12425-w.

[41]. Zhang, M., Wu, J., Sun, R., et al. (2019). SIRT5 deficiency suppresses mitochondrial ATP production and promotes AMPK activation in response to energy stress. PLoS One **14(2)**, e0211796. doi: 10.1371/journal.pone.0211796.

[42]. Ma, Y., Fei, X. (2018). SIRT5 regulates pancreatic β-cell proliferation and insulin secretion in type 2 diabetes. Exp Ther Med **16(2)**, 1417-1425. doi: 10.3892/etm.2018.6301.

[43]. Lin, Z.F., Xu, H.B., Wang, J.Y., et al. (2013). SIRT5 desuccinylates and activates SOD1 to

eliminate ROS. Biochem Biophys Res Commun **441(1)**, 191-5. doi: 10.1016/j.bbrc.2013.10.033.

[44]. Liu L, Peritore C, Ginsberg J, et al. (2015). Protective role of SIRT5 against motor deficit and dopaminergic degeneration in MPTP-induced mice model of Parkinson's disease. Behav Brain Res **281**, 215-21. doi: 10.1016/j.bbr.2014.12.035.

[45]. Wang, F., Wang, K., Xu, W., et al. (2017). SIRT5 Desuccinylates and Activates Pyruvate Kinase M2 to Block Macrophage IL-1β Production and to Prevent DSS-Induced Colitis in Mice. Cell Rep **19(11)**, 2331-2344. doi: 10.1016/j.celrep.2017.05.065.

[46]. Lombard, D.B., Schwer, B., Alt, F.W., Mostoslavsky, R. (2008). SIRT6 in DNA repair, metabolism and ageing. J Intern Med **263(2)**, 128-41. doi: 10.1111/j.1365-2796.2007.01902.x.

[47]. Kanfi Y, Naiman S, Amir G, et al. (2012). The sirtuin SIRT6 regulates lifespan in male mice. Nature 483(7388), 218-21. doi: 10.1038/nature10815.

[48]. Van Meter, M., Simon, M., Tombline, G., et al. (2016). JNK Phosphorylates SIRT6 to Stimulate DNA Double-Strand Break Repair in Response to Oxidative Stress by Recruiting PARP1 to DNA Breaks. Cell Rep **16(10)**, 2641-2650. doi: 10.1016/j.celrep.2016.08.006.

[49]. Martire, S., Mosca, L., d'Erme, M. (2015). PARP-1 involvement in neurodegeneration: A focus on Alzheimer's and Parkinson's diseases. Mech Ageing Dev **146-148**, 53-64. doi: 10.1016/j.mad.2015.04.001.

[50]. Kaluski S, Portillo M, Besnard A, et al. (2017). Neuroprotective Functions for the Histone Deacetylase SIRT6. Cell Rep **18(13)**, 3052-3062. doi: 10.1016/j.celrep.2017.03.008.

[51]. Vazquez, B.N., Thackray, J.K., Simonet, N.G., et al. (2016). SIRT7 promotes genome integrity and modulates non-homologous end joining DNA repair. EMBO J **35(14)**, 1488-503. doi: 10.15252/embj.201593499.

[52]. Anderson, G., Maes, M. The Gut-Brain Axis: The Role of Melatonin in Linking Psychiatric, Inflammatory and Neurodegenerative Conditions. Adv Integrat Med **2(1)**, 31-37.

[53]. Alexandraki, K.I., Apostolopoulos, N.V., Adamopoulos, C., et al. (2019). Differential Expression of Apoptotic and Low-Grade Inflammatory Markers in Alzheimer Disease Compared to Diabetes Mellitus Type 1 and 2. J Appl Lab Med **3(6)**, 1003-1013. doi: 10.1373/jalm.2018.027623.

[54]. Jang, H.M., Han, S.K., Kim, J.K, et al. (2019). Lactobacillus sakei Alleviates High-Fat-Diet-Induced Obesity and Anxiety in Mice by Inducing AMPK Activation and SIRT1 Expression and Inhibiting Gut Microbiota-Mediated NF-κB Activation. Mol Nutr Food Res **63(6)**, e1800978. doi: 10.1002/mnfr.201800978.

[55]. Wellman, A.S., Metukuri, M.R., Kazgan, N., et al. (2017). Intestinal Epithelial Sirtuin 1 Regulates Intestinal Inflammation During Aging in Mice by Altering the Intestinal Microbiota. Gastroenterology **153(3)**, 772-786. doi: 10.1053/j.gastro.2017.05.022.

[56]. Caini S, Bagnoli S, Palli D, et al. (2016). Total and cancer mortality in a cohort of ulcerative colitis and Crohn's disease patients: The Florence inflammatory bowel disease study, 1978-2010. Dig Liver Dis **48(10)**, 1162-7. doi: 10.1016/j.dld.2016.07.008.

[57]. Knoop, K.A., Newberry, R.D. (2018). Goblet cells: multifaceted players in immunity at

mucosal surfaces. Mucosal Immunol **11(6)**, 1551-1557. doi: 10.1038/s41385-018-0039-y.

[58]. Anderson, G., Maes, M. (In press). Gut Dysbiosis Dysregulates Central and Systemic Homeostasis via Suboptimal Mitochondrial Function: Assessment, Treatment and Classification Implications. Curr Top Med Chem doi: 10.2174/1568026620666200131094445.

[59]. Naia L, Cunha-Oliveira T, Rodrigues J, et al. (2017). Histone Deacetylase Inhibitors Protect Against Pyruvate Dehydrogenase Dysfunction in Huntington's Disease. J Neurosci **37(10)**, 2776-2794. doi: 10.1523/JNEUROSCI.2006-14.2016.

[60]. Ozden O, Park SH, Wagner BA, et al. (2014). SIRT3 deacetylates and increases pyruvate dehydrogenase activity in cancer cells. Free Radic Biol Med 7**6,** 163-172. doi: 10.1016/j.freeradbiomed.2014.08.001.

[61]. Jin CJ, Engstler AJ, Sellmann C, et al. (2016). Sodium butyrate protects mice from the development of the early signs of non-alcoholic fatty liver disease: role of melatonin and lipid peroxidation. Br J Nutr **23,** 1-12.

[62]. Muxel SM, Pires-Lapa MA, Monteiro AW, et al. (2012). NF-κB drives the synthesis of melatonin in RAW 264.7 macrophages by inducing the transcription of the arylalkylamine-N-acetyltransferase (AA-NAT) gene. PLoS One **7(12)** e52010. doi: 10.1371/journal.pone.0052010.

[63]. Liu, L., Chen, H., Jin, J., et al. (2019). Melatonin ameliorates cerebral ischemia/reperfusion injury through SIRT3 activation. Life Sci **239**, 117036. doi: 10.1016/j.lfs.2019.117036.

[64]. Reiter, R.J., Tan, D.X., Rosales-Corral, S., Galano, A., Jou, M.J., Acuna-Castroviejo, D. (2018). Melatonin Mitigates Mitochondrial Meltdown: Interactions with SIRT3. Int J Mol Sci **19(8)**, pii: E2439. doi: 10.3390/ijms19082439.

[65]. Ansari Dezfouli, M., Zahmatkesh, M., Farahmandfar, M., Khodagholi, F. Melatonin protective effect against amyloid β-induced neurotoxicity mediated by mitochondrial biogenesis; involvement of hippocampal Sirtuin-1 signaling pathway. Physiol Behav **204**, 65-75. doi: 10.1016/j.physbeh.2019.02.016.

[66]. Beker, M.C., Caglayan, B., Caglayan, A.B., et al. (2019). Interaction of melatonin and Bmal1 in the regulation of PI3K/AKT pathway components and cellular survival. Sci Rep **9(1)**, 19082. doi: 10.1038/s41598-019-55663-0.

[67]. Wang Y, Lv D, Liu W, et al. (2018). Disruption of the Circadian Clock Alters Antioxidative Defense via the SIRT1-BMAL1 Pathway in 6-OHDA-Induced Models of Parkinson's Disease. Oxid Med Cell Longev **2018**, 4854732. doi: 10.1155/2018/4854732.

[68]. Zhang J, Liu J, Zhu K, et al. (2016). Effects of BMAL1-SIRT1-positive cycle on estrogen synthesis in human ovarian granulosa cells: an implicative role of BMAL1 in PCOS. Endocrine **53(2)**, 574-84. doi: 10.1007/s12020-016-0961-2.

[69]. Markus, R.P., Fernandes, P.A., Kinker, G.S., da Silveira Cruz-Machado, S., Marçola, M. (2018). Immune pineal axis - acute inflammatory responses coordinate melatonin synthesis by pinealocytes and phagocytes. Br J Pharmacol **175(16),** 3239-3250. doi: 10.1111/bph.14083.

[70]. Homolak, J., Mudrovčić, M., Vukić, B., Toljan, K. (2018). Circadian Rhythm and Alzheimer's Disease. Med Sci (Basel) **6(3)**, pii: E52. doi: 10.3390/medsci6030052.

[71]. Anderson, G., Maes, M. (2017). How Immune-inflammatory Processes Link CNS and Psychiatric Disorders: Classification and Treatment Implications. CNS Neurol Disord Drug Targets **16(3)**, 266-278. doi: 10.2174/1871527315666161122144659.

[72]. Ma N, Deng TT, Wang Q, et al. (2019). Erythromycin Regulates Cigarette Smoke-Induced Proinflammatory Mediator Release Through Sirtuin 1-Nuclear Factor κB Axis in Macrophages and Mice Lungs. Pathobiology **86(5-6)**, 237-247. doi: 10.1159/000500628.

[73]. Heinonen, T., Ciarlo, E., Rigoni, E., et al. (2019). Dual Deletion of the Sirtuins SIRT2 and SIRT3 Impacts on Metabolism and Inflammatory Responses of Macrophages and Protects From Endotoxemia. Front Immunol **10,** 2713. doi: 10.3389/fimmu.2019.02713.

[74]. Tao, J., Zhang, J., Ling, Y., McCall, C.E., Liu, T.F. (2018). Mitochondrial Sirtuin 4 Resolves Immune Tolerance in Monocytes by Rebalancing Glycolysis and Glucose Oxidation Homeostasis. Front Immunol **9**, 419. doi: 10.3389/fimmu.2018.00419.

[75]. Heinonen, T., Ciarlo, E., Le Roy, D., Roger, T. (2019). Impact of the Dual Deletion of the Mitochondrial Sirtuins SIRT3 and SIRT5 on Anti-microbial Host Defenses. Front Immunol **10**, 2341. doi: 10.3389/fimmu.2019.02341.

[76]. Arsiwala, T., Pahla, J., van Tits, L.J., et al. (2020). Sirt6 deletion in bone marrow-derived cells increases atherosclerosis - Central role of macrophage scavenger receptor 1. J Mol Cell Cardiol **139,** 24-32. doi: 10.1016/j.yjmcc.2020.01.002.

[77]. De Biasi, S., Simone, A.M., Bianchini, E., et al. (2019). Mitochondrial functionality and metabolism in T cells from progressive multiple sclerosis patients. Eur J Immunol **49(12)**, 2204-2221. doi: 10.1002/eji.201948223

[78]. Topuz, R.D., Gunduz, O., Tastekin, E., Karadag, H.C. (In press). Effects of Hippocampal Histone Acetylation and HDAC Inhibition on Spatial Learning and Memory in the Morris Water Maze in Rats. Fundam Clin Pharmacol doi: 10.1111/fcp.12512.

[79]. Tran, T.T.T., Corsini, S., Kellingray, L., et al. (2019). APOE genotype influences the gut microbiome structure and function in humans and mice: relevance for Alzheimer's disease pathophysiology. FASEB J **33(7)**, 8221-8231. doi: 10.1096/fj.201900071R.

[80]. Yin, J., Nielsen, M., Carcione, T., Li, S., Shi, J. (2019). Apolipoprotein E regulates mitochondrial function through the PGC-1α-sirtuin 3 pathway. Aging (Albany NY) **11(23)**, 11148-11156. doi: 10.18632/aging.102516.

[81]. Czubowicz, K., Jęśko, H., Wencel, P., Lukiw, W.J., Strosznajder, R.P. (2019). The Role of Ceramide and Sphingosine-1-Phosphate in Alzheimer's Disease and Other Neurodegenerative Disorders. Mol Neurobiol **56(8)**, 5436-5455. doi: 10.1007/s12035-018-1448-3.

[82]. Yamane, M., Yamane, S. (2007). The induction of colonocyte differentiation in CaCo-2 cells by sodium butyrate causes an increase in glucosylceramide synthesis in order to avoid apoptosis based on ceramide. Arch Biochem Biophys **459(2)**, 159-68.

[83]. Lee, Y., Oliynyk, S., Jung, J.C., Han, J.J., Oh, S. (2013). Administration of glucosylceramide ameliorated the memory impairment in aged mice. Evid Based Complement Alternat Med **2013**, 824120. doi: 10.1155/2013/824120.

[84]. Matsubara, T., Yasumori, H., Ito, K., Shimoaka, T., Hasegawa, T., Sato, T. (2018). Amyloid-β fibrils assembled on ganglioside-enriched membranes contain both parallel β-sheets and turns. J Biol Chem **293(36)**, 14146-14154. doi: 10.1074/jbc.RA118.002787.

[85]. Shin MK, Choi MS, Chae HJ, et al. (2019). Ganglioside GQ1b ameliorates cognitive impairments in an Alzheimer's disease mouse model, and causes reduction of amyloid precursor protein. Sci Rep **9(1)**, 8512. doi: 10.1038/s41598-019-44739-6.

[86]. Dukhinova, M., Veremeyko, T., Yung, A.W.Y., et al. (2019). Fresh evidence for major brain gangliosides as a target for the treatment of Alzheimer's disease. Neurobiol Aging **77,** 128-143. doi: 10.1016/j.neurobiolaging.2019.01.020.

[87]. Michno, W., Wehrli, P.M., Zetterberg, H., Blennow, K., Hanrieder, J. (2019). GM1 locates to mature amyloid structures implicating a prominent role for glycolipid-protein interactions in Alzheimer pathology. Biochim Biophys Acta Proteins Proteom **1867(5)**, 458-467. doi: 10.1016/j.bbapap.2018.09.010.

[88]. Serbulea, V., Upchurch, C.M., Ahern, K.W., et al. (2018). Macrophages sensing oxidized DAMPs reprogram their metabolism to support redox homeostasis and inflammation through a TLR2-Syk-ceramide dependent mechanism. Mol Metab **7**, 23-34. doi: 10.1016/j.molmet.2017.11.002.

[89]. Scheiblich, H., Schlütter, A., Golenbock, D.T., et al. (2017). Activation of the NLRP3 inflammasome in microglia: the role of ceramide. J Neurochem **143(5)**, 534-550. doi: 10.1111/jnc.14225.

[90]. Parkar, S.G., Kalsbeek, A., Cheeseman, J.F. (2019). Potential Role for the Gut Microbiota in Modulating Host Circadian Rhythms and Metabolic Health. Microorganisms **7(2)**, pii: E41. doi: 10.3390/microorganisms7020041.

[91]. Jang, Y.S., Kang,Y.J., Kim, T.J., Bae, K. (2012). Temporal expression profiles of ceramide and ceramide-related genes in wild-type and mPer1/mPer2 double knockout mice. Mol Biol Rep **9(4),** 4215-21. doi: 10.1007/s11033-011-1207-2.

[92]. Novgorodov SA, Riley CL, Keffler JA, et al. (2016). SIRT3 Deacetylates Ceramide Synthases: IMPLICATIONS FOR MITOCHONDRIAL DYSFUNCTION AND BRAIN INJURY. J Biol Chem **291(4)**, 1957-73. doi: 10.1074/jbc.M115.668228.

[93]. Tse, J.K.Y. (2017). Gut Microbiota, Nitric Oxide, and Microglia as Prerequisites for Neurodegenerative Disorders. ACS Chem Neurosci **8(7)**, 1438-1447. doi: 10.1021/acschemneuro.7b00176.

[94]. Castillo, S.S., Levy, M., Thaikoottathil, J.V., Goldkorn, T. (2007). Reactive nitrogen and oxygen species activate different sphingomyelinases to induce apoptosis in airway epithelial cells. Exp Cell Res **313(12)**, 2680-6.

[95]. De Angelis J, Gastel J, Klein DC, Cole PA. Kinetic analysis of the catalytic mechanism of serotonin N-acetyltransferase (EC 2.3.1.87). J Biol Chem. 1998 Jan 30;273(5):3045-50.

[96]. Reiter, R.J., Sharma, R., Ma, Q., et al. (2019). Inhibition of Mitochondrial Pyruvate Dehydrogenase Kinase: A Proposed Mechanism by Which Melatonin Causes Cancer Cells to

Overcome Aerobic Glycolysis, Limit Tumor Growth and Reverse Insensitivity to Chemotherapy. Melatonin Res **2(3)**, 105-119; doi: 10.32794/mr11250033

[97]. Novgorodov, S.A., Voltin, J.R., Gooz, M.A., et al. (2018). Acid sphingomyelinase promotes mitochondrial dysfunction due to glutamate-induced regulated necrosis. J Lipid Res **59(2)**, 312-329. doi: 10.1194/jlr.M080374.

[98]. Li S, Yin J, Nielsen M, et al. (2019). Sirtuin 3 Mediates Tau Deacetylation. J Alzheimers Dis. **69(2),** 355-362. doi: 10.3233/JAD-190014.

[99]. Das, R., Balmik, A.A., Chinnathambi, S. (2020). Effect of Melatonin on Tau aggregation and Tau-mediated cell surface morphology. Int J Biol Macromol. **2020**, pii: S0141-8130(19)39787-9. doi: 10.1016/j.ijbiomac.2020.01.296.

[100]. Pozuelo-Rubio, M. (2010). Proteomic and biochemical analysis of 14-3-3-binding proteins during C2-ceramide-induced apoptosis. FEBS J **277(16)**, 3321-42. doi: 10.1111/j.1742-4658.2010.07730.x.

[101]. Barupal, D.K., Baillie, R., Fan, S., et al. (2019). Sets of coregulated serum lipids are associated with Alzheimer's disease pathophysiology. Alzheimers Dement (Amst) **11**, 619-627. doi: 10.1016/j.dadm.2019.07.002.

[102]. Zhang, Y., Cui, G., Wang, Y., Gong, Y., Wang, Y. (2019). SIRT1 activation alleviates brain microvascular endothelial dysfunction in peroxisomal disorders. Int J Mol Med **44(3)**, 995-1005. doi: 10.3892/ijmm.2019.4250.

[103]. Yao, B., He, J., Yin, X., et al. (2019). The protective effect of lithocholic acid on the intestinal epithelial barrier is mediated by the vitamin D receptor via a SIRT1/Nrf2 and NF-κB dependent mechanism in Caco-2 cells. Toxicol Lett **316**, 109-118. doi: 10.1016/j.toxlet.2019.08.024.

[104]. Fu, C., Hao, S., Xu, X., et al. (2019). Activation of SIRT1 ameliorates LPS-induced lung injury in mice via decreasing endothelial tight junction permeability. Acta Pharmacol Sin **40(5),** 630-641. doi: 10.1038/s41401-018-0045-3.

[105]. Cao, S., Zhang, Q., Wang, C., et al. (2018). LPS challenge increased intestinal permeability, disrupted mitochondrial function and triggered mitophagy of piglets.
Innate Immun **24(4)**, 221-230. doi: 10.1177/1753425918769372.

[106]. Landfield, P.W., Blalock, E.M., Chen, K.C., Porter, N.M. A new glucocorticoid hypothesis of brain aging: implications for Alzheimer's disease. Curr Alzheimer Res **4(2)**, 205-12.

[107]. Vanuytsel T, van Wanrooy S, Vanheel H, et al. (2014). Psychological stress and corticotropin-releasing hormone increase intestinal permeability in humans by a mast cell-dependent mechanism. Gut **63(8)**, 1293-9. doi: 10.1136/gutjnl-2013-305690.

[108]. Gałecki, P., Talarowska, M., Anderson, G., Berk, M., Maes, M. (2015). Mechanisms underlying neurocognitive dysfunctions in recurrent major depression. Med Sci Monit **21**, 1535-47. doi: 10.12659/MSM.893176.

[109]. Morton, R.E., St John, P.D., Tyas, S.L. (2019). Migraine and the risk of all-cause dementia, Alzheimer's disease, and vascular dementia: A prospective cohort study in community-dwelling older adults. Int J Geriatr Psychiatry **34(11),** 1667-1676. doi: 10.1002/gps.5180.

[110]. Anderson, G. (2019). Integrating Pathophysiology in Migraine: Role of the Gut Microbiome and Melatonin. Curr Pharm Des **25(33)**, 3550-3562. doi: 10.2174/1381612825666190920114611.

[111]. Maity, S., Muhamed, J., Sarikhani, M., et al. (2020). Sirtuin 6 deficiency transcriptionally up-regulates TGF-β signaling and induces fibrosis in mice. J Biol Chem **295(2**), 415-434. doi: 10.1074/jbc.RA118.007212.

[112]. Shen J, Li Y, Qu C, et al. (2019). The enriched environment ameliorates chronic unpredictable mild stress-induced depressive-like behaviors and cognitive impairment by activating the SIRT1/miR-134 signaling pathway in hippocampus. J Affect Disord **248**, 81-90. doi: 10.1016/j.jad.2019.01.031.

[113]. Spadari, R.C., Cavadas, C., de Carvalho, A.E.T.S., et al. (2018). Role of Beta-adrenergic Receptors and Sirtuin Signaling in the Heart During Aging, Heart Failure, and Adaptation to Stress. Cell Mol Neurobiol **38(1)**, 109-120. doi: 10.1007/s10571-017-0557-2.

[114]. Muñoz-Cobo, I., Belloch, F.B., Díaz-Perdigón, T., Puerta, E., Tordera, R.M. (2017). SIRT2 inhibition reverses anhedonia in the VGLUT1+/- depression model. Behav Brain Res **335**, 128-131. doi: 10.1016/j.bbr.2017.07.045.

[115]. Xie, X., Shen, Q., Cao, L., et al. (2019). Depression caused by long-term stress regulates premature aging and is possibly associated with disruption of circadian rhythms in mice. Physiol Behav **199**, 100-110. doi: 10.1016/j.physbeh.2018.11.011.

[116]. Pluta, R., Ułamek-Kozioł, M. (2019). Lymphocytes, Platelets, Erythrocytes, and Exosomes as Possible Biomarkers for Alzheimer's Disease Clinical Diagnosis. Adv Exp Med Biol **1118**, 71-82. doi: 10.1007/978-3-030-05542-4_4.

[117]. Inyushin, M., Zayas-Santiago, A., Rojas, L., Kucheryavykh, Y., Kucheryavykh, L. (2019). Platelet-generated amyloid beta peptides in Alzheimer's disease and glaucoma. Histol Histopathol **34(8)**, 843-856. doi: 10.14670/HH-18-111.

[118]. Kniewallner, K.M., Foidl, B.M., Humpel, C. (2018). Platelets isolated from an Alzheimer mouse damage healthy cortical vessels and cause inflammation in an organotypic ex vivo brain slice model. Sci Rep **8(1),** 15483. doi: 10.1038/s41598-018-33768-2.

[119]. Münzer, P., Borst, O., Walker, B., et al. (2014). Acid sphingomyelinase regulates platelet cell membrane scrambling, secretion, and thrombus formation. Arterioscler Thromb Vasc Biol **34(1)**, 61-71. doi: 10.1161/ATVBAHA.112.300210.

[120]. McVey, M.J., Kim, M., Tabuchi, A., et al. (2017). Acid sphingomyelinase mediates murine acute lung injury following transfusion of aged platelets. Am J Physiol Lung Cell Mol Physiol **312(5),** L625-L637. doi: 10.1152/ajplung.00317.2016.

[121]. Carestia, A., Mena, H.A., Olexen, C.M., et al. (2019). Platelets Promote Macrophage Polarization toward Pro-inflammatory Phenotype and Increase Survival of Septic Mice. Cell Rep **28(4)**, 896-908.e5. doi: 10.1016/j.celrep.2019.06.062.

[122]. Wang, Z., Zhang, X., Zhu, L., et al. (2019). Inulin alleviates inflammation of alcoholic liver disease via SCFAs-inducing suppression of M1 and facilitation of M2 macrophages in mice. Int Immunopharmacol **78**, 106062. doi: 10.1016/j.intimp.2019.106062.

[123]. Hally, K.E., La Flamme, A.C., Harding, S.A., Larsen, P.D.(2018). Platelets regulate leucocyte responses to Toll-like receptor stimulation. Clin Transl Immunology **7(7),** e1036. doi: 10.1002/cti2.1036.

[124]. Sun, J., Zhang, M., Chen, K., et al. (2018). Suppression of TLR4 activation by resveratrol is associated with STAT3 and Akt inhibition in oxidized low-density lipoprotein-activated platelets. Eur J Pharmacol **836**, 1-10. doi: 10.1016/j.ejphar.2018.08.014.

[125]. Bacchetti, T., Vignini, A., Giulietti, A., et al. (2015). Higher Levels of Oxidized Low Density Lipoproteins in Alzheimer's Disease Patients: Roles for Platelet Activating Factor Acetyl Hydrolase and Paraoxonase-1. J Alzheimers Dis **46(1)**, 179-86. doi: 10.3233/JAD-143096.

[126]. Wu, H., Li, R., Pei, L.G., et al. (2018). Emerging Role of High Mobility Group Box-1 in Thrombosis-Related Diseases. Cell Physiol Biochem **47(4)**, 1319-1337. doi: 10.1159/000490818.

[127]. Wiest, I., Wiemers, T., Kraus, M.J., et al. (2019). Multivariate Platelet Analysis Differentiates Between Patients with Alzheimer's Disease and Healthy Controls at First Clinical Diagnosis. J Alzheimers Dis **71(3**), 993-1004. doi: 10.3233/JAD-190574.

[128]. Gergalova, G., Lykhmus, O., Kalashnyk, O., et al. (2012). Mitochondria express α7 nicotinic acetylcholine receptors to regulate Ca2+ accumulation and cytochrome c release: study on isolated mitochondria. PLoS One **7(2),** e31361. doi: 10.1371/journal.pone.0031361.

[129]. Fišar, Z., Hansíková, H., Křížová, J., et al. (2019). Activities of mitochondrial respiratory chain complexes in platelets of patients with Alzheimer's disease and depressive disorder. Mitochondrion. **48,** 67-77. doi: 10.1016/j.mito.2019.07.013.

[130]. Hayashi, H., Cherpokova, D., Martinod, K., et al. (2017). Sirt3 deficiency does not affect venous thrombosis or NETosis despite mild elevation of intracellular ROS in platelets and neutrophils in mice. PLoS One **12(12)**, e0188341. doi: 10.1371/journal.pone.0188341.

[131]. Moscardó, A., Vallés, J., Latorre, A., Jover, R., Santos, M.T. (2015). The histone deacetylase sirtuin 2 is a new player in the regulation of platelet function. J Thromb Haemost **13(7)**, 1335-44. doi: 10.1111/jth.13004.

[132]. Latorre, A., Moscardó, A.(2016). Regulation of Platelet Function by Acetylation/Deacetylation Mechanisms. Curr Med Chem **23(35)**, 3966-3974.

[133]. Kumari, S., Chaurasia, S.N., Nayak, M.K., Mallick, R.L., Dash, D.(2015). Sirtuin Inhibition Induces Apoptosis-like Changes in Platelets and Thrombocytopenia. J Biol Chem **290(19),** 12290-9. doi: 10.1074/jbc.M114.615948.

[134]. Granzotto A, Bomba M, Castelli V, et al. (2019). Inhibition of de novo ceramide biosynthesis affects aging phenotype in an in vitro model of neuronal senescence. Aging (Albany NY) **11(16)**, 6336-6357. doi: 10.18632/aging.102191.

[135]. Silva, D.F., Selfridge, J.E., Lu, J., et al. (2013). Bioenergetic flux, mitochondrial mass and mitochondrial morphology dynamics in AD and MCI cybrid cell lines. Hum Mol Genet **22(19),** 3931-46. doi: 10.1093/hmg/ddt247.

[136]. Huo, X., Wang, C., Yu, Z., et al. (2017). Human transporters, PEPT1/2, facilitate melatonin

transportation into mitochondria of cancer cells: An implication of the therapeutic potential. J Pineal Res 62(4). doi: 10.1111/jpi.12390.

[137]. Anderson, G. (2019). Endometriosis Pathoetiology and Pathophysiology: Roles of Vitamin A, Estrogen, Immunity, Adipocytes, Gut Microbiome and Melatonergic Pathway on Mitochondria Regulation. Biomol Concepts **10(1)**, 133-149. doi: 10.1515/bmc-2019-0017.

[138]. Pontes, G.N., Cardoso, E.C., Carneiro-Sampaio, M.M., Markus, R.P. (2007). Pineal melatonin and the innate immune response: the TNF-alpha increase after cesarean section suppresses nocturnal melatonin production. J Pineal Res **43(4),** 365-71.

[139]. Kirsz, K., Szczęsna, M., Biernat, W., Molik, E., Zięba, D.A. (2019). Involvement of orexin A in nocturnal melatonin secretion into the cerebrospinal fluid and the blood plasma in seasonal sheep. Gen Comp Endocrinol 113304. doi: 10.1016/j.ygcen.2019.113304.

[140]. Brunkhorst, R., Pfeilschifter, W., Rajkovic, N., et al. (2019). Diurnal regulation of sphingolipids in blood. Biochim Biophys Acta Mol Cell Biol Lipids **1864(3)**, 304-311. doi: 10.1016/j.bbalip.2018.12.001.

[141]. Manni, R., Cremascoli, R., Perretti, C., et al. (2019). Evening melatonin timing secretion in real life conditions in patients with Alzheimer disease of mild to moderate severity. Sleep Med **63**, 122-126. doi: 10.1016/j.sleep.2019.04.018.

[142]. Nayak, M.K., Dhanesha, N., Doddapattar, P., et al. (2018). Dichloroacetate, an inhibitor of pyruvate dehydrogenase kinases, inhibits platelet aggregation and arterial thrombosis. Blood Adv **2(15)**, 2029-2038. doi: 10.1182/bloodadvances.2018022392.

[143]. Schoenwaelder SM, Darbousset R, Cranmer SL, et al. (2016). 14-3-3ζ regulates the mitochondrial respiratory reserve linked to platelet phosphatidylserine exposure and procoagulant function. Nat Commun **7**, 12862. doi: 10.1038/ncomms12862.

[144]. Xu, J., Jackson, C.W., Khoury, N., Escobar, I., Perez-Pinzon, M.A. (2018). Brain SIRT1 Mediates Metabolic Homeostasis and Neuroprotection. Front Endocrinol (Lausanne) **9,** 702. doi: 10.3389/fendo.2018.00702.

[145]. Wang, R.H., Zhao, T., Cui, K., et al. (2016). Negative reciprocal regulation between Sirt1 and Per2 modulates the circadian clock and aging. Sci Rep **6,** 28633. doi: 10.1038/srep28633.

[146]. Meng, H., Yan, W.Y., Lei, Y.H., et al. (2019). SIRT3 Regulation of Mitochondrial Quality Control in Neurodegenerative Diseases. Front Aging Neurosci **11**, 313. doi: 10.3389/fnagi.2019.00313.

[147]. Peek, C.B., Affinati, A.H., Ramsey, K.M., et al. (2013). Circadian clock NAD+ cycle drives mitochondrial oxidative metabolism in mice. Science **342(6158)**, 1243417. doi: 10.1126/science.1243417.

[148]. Ramsey, K.M., Yoshino, J., Brace, C.S., et al. (2009). Circadian clock feedback cycle through NAMPT-mediated NAD+ biosynthesis. Science **324(5927)**, 651-4. doi: 10.1126/science.1171641.

[149]. Averill, L.A., Abdallah, C.G., Levey, D.F., et al. (2019). Apolipoprotein E gene polymorphism, posttraumatic stress disorder, and cognitive function in older U.S. veterans: Results from the National Health and Resilience in Veterans Study. Depress Anxiety **36(9),** 834-845. doi:

10.1002/da.22912.

[150]. Fernando, W.M.A.D.B., Martins, I.J., Morici, M., et al., (In press). Sodium Butyrate Reduces Brain Amyloid-β Levels and Improves Cognitive Memory Performance in an Alzheimer's Disease Transgenic Mouse Model at an Early Disease Stage. J Alzheimers Dis doi: 10.3233/JAD-190120.

[151]. Sun, J., Xu, J., Yang, B., et al., (2020). Effect of Clostridium butyricum against Microglia-Mediated Neuroinflammation in Alzheimer's Disease via Regulating Gut Microbiota and Metabolites Butyrate. Mol Nutr Food Res **64(2)**, e1900636. doi: 10.1002/mnfr.201900636.

[152]. Cui, B., Su, D., Li, W., et al., (2018). Effects of chronic noise exposure on the microbiome-gut-brain axis in senescence-accelerated prone mice: implications for Alzheimer's disease. J Neuroinflammation **15(1)**, 190. doi: 10.1186/s12974-018-1223-4.

[153]. Panagia, M., He, H., Baka, T., et al., (2020). Increasing mitochondrial ATP synthesis with butyrate normalizes ADP and contractile function in metabolic heart disease. NMR Biomed e4258. doi: 10.1002/nbm.4258.

[154]. Chriett, S., Dąbek, A., Wojtala, M., et al., (2019). Prominent action of butyrate over β-hydroxybutyrate as histone deacetylase inhibitor, transcriptional modulator and anti-inflammatory molecule. Sci Rep **9(1)**, 742. doi: 10.1038/s41598-018-36941-9.

[155]. Neth, B.J., Mintz. A., Whitlow, C., et al., (2020). Modified ketogenic diet is associated with improved cerebrospinal fluid biomarker profile, cerebral perfusion, and cerebral ketone body uptake in older adults at risk for Alzheimer's disease: a pilot study. Neurobiol Aging **86,** 54-63. doi: 10.1016/j.neurobiolaging.2019.09.015.

[156]. Morrill, S.J., Gibas, K.J. (2019). Ketogenic diet rescues cognition in ApoE4+ patient with mild Alzheimer's disease: A case study. Diabetes Metab Syndr **13(2)**, 1187-1191. doi: 10.1016/j.dsx.2019.01.035.

[157]. Hasan-Olive, M.M., Lauritzen, K.H., Ali, M., et al., (2019). A Ketogenic Diet Improves Mitochondrial Biogenesis and Bioenergetics via the PGC1α-SIRT3-UCP2 Axis. Neurochem Res **44(1)**, 22-37. doi: 10.1007/s11064-018-2588-6.

[158]. Elamin, M., Ruskin, D.N., Masino, S.A., Sacchetti, P. (2018). Ketogenic Diet Modulates NAD+-Dependent Enzymes and Reduces DNA Damage in Hippocampus. Front Cell Neurosci **12,** 263. doi: 10.3389/fncel.2018.00263.

[159]. Mendes, P.F.S., Varela, E.L.P., Monteiro, M.C., et al. (2018). Neuroprotective Mechanisms of Resveratrol in Alzheimer's Disease: Role of SIRT1. Oxid Med Cell Longev **2018**, 8152373. doi: 10.1155/2018/8152373.

[160]. Cosín-Tomàs, M., Senserrich, J., Arumí-Planas, M., et al. (2019). Role of Resveratrol and Selenium on Oxidative Stress and Expression of Antioxidant and Anti-Aging Genes in Immortalized Lymphocytes from Alzheimer's Disease Patients. Nutrients **11(8)**, pii: E1764. doi: 10.3390/nu11081764.

[161]. Gabandé-Rodríguez, E., Gómez de Las Heras, M., Mittelbrunn, M. (2019). Control of Inflammation by Calorie Restriction Mimetics: On the Crossroad of Autophagy and Mitochondria. Cells **9(1)**, pii: E82. doi: 10.3390/cells9010082.

[162]. Khoury, N., Xu, J., Stegelmann, S.D., et al., (2019). Resveratrol Preconditioning Induces Genomic and Metabolic Adaptations within the Long-Term Window of Cerebral Ischemic Tolerance Leading to Bioenergetic Efficiency. Mol Neurobiol **56(6)**, 4549-4565. doi: 10.1007/s12035-018-1380-6.

[163]. Hu, Y., Chen, D., Zheng, P., et al., (2019). The Bidirectional Interactions between Resveratrol and Gut Microbiota: An Insight into Oxidative Stress and Inflammatory Bowel Disease Therapy. Biomed Res Int **2019**, 5403761. doi: 10.1155/2019/5403761.

[164]. Alrafas, H.R., Busbee, P.B., Nagarkatti, M., Nagarkatti, P.S. (2019). Resveratrol modulates the gut microbiota to prevent murine colitis development through induction of Tregs and suppression of Th17 cells. J Leukoc Biol **106(2)**, 467-480. doi: 10.1002/JLB.3A1218-476RR.

[165]. Anderson, G., Mae,s M. (2015). Pharmaceutical and nutrition benefits in Alzheimer's disease via convergence on the Melatoninergic Pathways. *In "Frontiers in Clinical Drug Research-Alzheimer Disorder"* (Atta-Ur-Rahmanr, Ed..), Vol 78, pp.50-127. Bentham Press e-books

[166]. Ozansoy, M., Ozansoy, M.B., Yulug, B., et al., (In press). Melatonin affects the release of exosomes and tau-content in in vitro amyloid-beta toxicity model. J Clin Neurosci pii: S0967-5868(19)31646-7. doi: 10.1016/j.jocn.2019.11.046.

[167]. Song, J. (2019). Pineal gland dysfunction in Alzheimer's disease: relationship with the immune-pineal axis, sleep disturbance, and neurogenesis. Mol Neurodegener **14(1)**, 28. doi: 10.1186/s13024-019-0330-8.

[168]. Wade AG, Farmer M, Harari G, et al., (2014). Add-on prolonged-release melatonin for cognitive function and sleep in mild to moderate Alzheimer's disease: a 6-month, randomized, placebo-controlled, multicenter trial. Clin Interv Aging **9,** 947-61. doi: 10.2147/CIA.S65625.

[169]. Jang H, Lee S, Choi SL, et al. (2017). Taurine Directly Binds to Oligomeric Amyloid-β and Recovers Cognitive Deficits in Alzheimer Model Mice. Adv Exp Med Biol **975(1)**, 233-241. doi: 10.1007/978-94-024-1079-2_21.

[170]. Sun Q, Hu H, Wang W, et al. (2014). Taurine attenuates amyloid β 1-42-induced mitochondrial dysfunction by activating of SIRT1 in SK-N-SH cells. Biochem Biophys Res Commun **447(3),** 485-9. doi: 10.1016/j.bbrc.2014.04.019.

[171]. Fang H, Meng F, Piao F, et al, (2019). Effect of Taurine on Intestinal Microbiota and Immune Cells in Peyer's Patches of Immunosuppressive Mice. Adv Exp Med Biol **1155**, 13-24. doi: 10.1007/978-981-13-8023-5_2.

[172]. Anderson, G., Maes, M. (2015). Pharmaceutical and Nutritional Benefits in Alzheimer's Disease via Convergence on the Melatoninergic Pathways. "*In FCDR-Alzheimer Disorder*" ((Atta-Ur-Rahmanr, Ed.), Vol. 4, pp. 50-127. Bentham Science Publications.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 27 February 2020 doi:10.20944/preprints202002.0396.v1

LEGEND Fig 1

Stress, ApoE4, diet and lifestyle can all increase gut dysbiosis/permeability, leading to an increase in ceramide and decreased pineal melatonin, thereby negatively regulating Bmal1-sirtuins-PDC interactions and therefore mitochondrial OXPHOS. This is especially important in reactive glia and immune cells, where the circadian rhythm acts to reset cells to a quiescent phenotype via mitochondrial OXPHOS. This provides a model of AD as a common end-point to a heterogenous series of genetic, epigenetic, diet and lifestyle interactions over the lifespan.