Frontiers in Bioscience Landmark

Front. Biosci. (Landmark Ed) **2023**; 28(12): 355
https://doi.org/10.31083/j.fbl2812355

Review

A More Holistic Perspective of Alzheimer's Disease: Roles of Gut Microbiome, Adipocytes, HPA Axis, Melatonergic Pathway and Astrocyte Mitochondria in the Emergence of Autoimmunity

George Anderson[1,*]

[1]CRC Scotland & London, SW1V 1PG London, UK
*Correspondence: anderson.george@rocketmail.com (George Anderson)
Academic Editors: Simone Battaglia and Masaru Tanaka
Submitted: 30 August 2023 Revised: 14 October 2023 Accepted: 27 October 2023 Published: 28 December 2023

Abstract

Alzheimer's disease is widely regarded as poorly treated due to poor conceptualization. For 40 years, Alzheimer's disease pathophysiology has focused on two culprits, amyloid-β induced plaques and hyperphosphorylated tau associated tangles, with no significant treatment advance. This is confounded by data showing amyloid-β to be an endogenous antimicrobial that is increased in a wide array of diverse medical conditions associated with heightened inflammation. This article reviews the wider bodies of data pertaining to Alzheimer's disease pathophysiology, highlighting the role of suppressed astrocyte mitochondrial function and mitochondrial melatonergic pathway as a core hub in driving neuronal loss in dementia. It is proposed that astrocyte function over aging becomes dysregulated, at least partly mediated by systemic processes involving the 10-fold decrease in pineal melatonin leading to the attenuated capacity of night-time melatonin to dampen residual daytime inflammation. Suppressed pineal melatonin also attenuates melatonin's inhibition of glucocorticoid receptor nuclear translocation, thereby changing not only stress/hypothalamus-pituitary-adrenal (HPA) axis consequences but also the consequences of the cortisol awakening response, which 'primes the body for the coming day'. Gut microbiome-derived butyrate also inhibits glucocorticoid receptor nuclear translocation, as well as inducing the mitochondrial melatonergic pathway. It is proposed that the loss of astrocyte melatonin prevents the autocrine and paracrine effects of melatonin in limiting amyloid-β levels and effects. Suppressed astrocyte melatonin production also attenuates the melatonin induction of astrocyte lactate, thereby decreasing neuronal mitochondrial metabolism and the neuronal mitochondrial melatonergic pathway. The loss of astrocyte lactate and melatonin, coupled to the suppression of neuronal mitochondrial metabolism and melatonin production decreases mitophagy, leading to the induction of the major histocompatibility complex (MHC)-1. MHC-1 initiates the chemoattraction of $CD8^+$ t cells, leading to neuronal destruction in Alzheimer's disease being driven by 'autoimmune'/'immune-mediated' processes. Alzheimer's disease may therefore be conceptualized as being initiated by systemic processes that act on astrocytes as a core hub, with the suppression of the astrocyte melatonergic pathway leaving neurons deplete of appropriate metabolic substrates and co-ordinated antioxidants. This culminates in an 'immune-mediated' cell death. Future research and treatment/prevention implications are indicated.

Keywords: Alzheimer's disease; gut microbiome; melatonin; N-acetylserotonin; aryl hydrocarbon receptor; kynurenine; HPA axis; glucocorticoid receptor; adipocytes; treatment

1. Introduction

There is a growing dissatisfaction with the lack of progress in the treatment and prevention of Alzheimer's disease [1]. This is widely accepted as arising from a poor conceptualization of the relevant processes forming the biological underpinnings of neuronal and cognitive loss in the course of dementia. For 40 years, research and targeted treatment in Alzheimer's disease have focused on the overproduction of amyloid-β plaques and hyperphosphorylated tau tangles [2]. A plethora of wider pathophysiological processes have data supporting their role in Alzheimer's disease, including alterations driven by immune/glia inflammation, circadian disruption, obesity, diet, stress, sub-optimal mitochondrial function and gut microbiome-derived products [3–8]. The amyloid hypothesis is also significantly challenged by amyloid-β being an endogenous antimicrobial, suggesting that its overproduction may be 'too much of a good thing' in the course of heightened inflammation and toll-like receptor (TLR)2/4 signaling [1,9]. This is further supported by the high amyloid-β levels evident in other diverse medical conditions, including glioblastoma [10], breast cancer [11], type 1 diabetes mellitus (T1DM) [12], Parkinson's disease [13] and amyotrophic lateral sclerosis [14]. The heightened amyloid-β levels in Parkinson's disease and Lewy Body diseases can drive the increased α-synuclein aggregation classically defining these diseases [13], indicating a role for excessive amyloid-β production in upregulating other pathophysiological processes. Such data, coupled to the role of systemic processes in neurodegeneration has formed the underpinnings of a growing consensus that a more holistic perspective of Alzheimer's disease is required, including the incorporation of the heightened levels of amyloid-β and

hyperphosphorylated tau. This is laced with the hope that a systemic conceptualization not only embraces the complexity of data highlighted above but will also provide more feasible and achievable targets for treatment and prevention.

This article highlights the wide array of systemic processes, including gut microbiome and white adipocyte products as well as the hypothalamus-pituitary-adrenal (HPA) axis and pineal/local melatonergic pathway in the regulation of astrocyte modulation of neuronal activity and survival. Classical central nervous system (CNS) areas associated with neuronal and cognitive loss, such as the cortex and hippocampus, are highlighted as well as non-classically associated brain areas, such as the hypothalamus. This provides a pathoetiological model allowing systemic processes to alter CNS function, with an important hub being the interface of astrocytes and neurons. Such a systemic perspective also incorporates how other currently classified conditions, such as polycystic ovary syndrome (PCOS) [15,16], major depressive disorder (MDD) [17], bipolar disorder [17], neuroticism [18], obesity [19,20], stress/post-traumatic stress disorder (PTSD) [21], discrimination stress [22], migraine [23] and type 2 diabetes mellitus (T2DM) [24] are associated with an increased risk of dementia. Such wide arrays of data highlight the problems of a current classification system that is based on endpoint 'catastrophes' and the importance of investigating, assessing and seeking biomarkers for physiological processes across current medical classifications.

The pineal and local mitochondrial melatonergic pathway is an important aspect of Alzheimer's disease pathoetiology and is briefly reviewed next.

2. Tryptophan-Melatonin Pathway

There is a gradual decrease in pineal melatonin over aging culminating in a dramatic 10-fold lower level at night in people in their ninth decade of life, compared to adolescence [25]. As night-time melatonin is credited with dampening any residual low-level inflammatory activity and optimizing mitochondrial function, the suppressed capacity of melatonin at night over aging has consequences for the pathoetiology of most medical conditions, including cancer [26] and cardiovascular disorders [27], as well as dementia [28]. The relevance of melatonin is highlighted by its powerful efficacy in preventing dementia in preclinical models [29–31].

Notably, melatonin seems produced in all body cells, primarily within mitochondria [32], where its synthesis is intimately associated with the capacity of mitochondria to upregulate the pyruvate dehydrogenase complex (PDC), which increases the conversion of pyruvate to acetyl-CoA, thereby increasing adenosine triphosphate (ATP) production by the tricarboxylic acid (TCA) cycle and oxidative phosphorylation (OXPHOS). As acetyl-CoA is a necessary cosubstrate for the conversion of serotonin to N-acetylserotonin (NAS) in the initiation of the melatonergic pathway, the mitochondrial melatonergic pathway is intimately linked to mitochondrial function. The capacity of cells to upregulate the melatonergic pathway seems important to their capacity to resist challenge, either environmental/systemic and/or from within the microenvironment in which they reside [33]. Many medical conditions, including 'autoimmune'/'immune-mediated' disorders may arise from the suppressed capacity of a given cell to upregulate melatonin, thereby preventing melatonin from regulating PINK1/parkin mediated mitophagy. Dysregulated mitophagy leads to major histocompatibility complex (MHC)-1 induction and the MHC-1 driven chemoattraction of $CD8^+$ t cells that drive the 'autoimmune' destruction of cells, including substantia nigra pars compact dopamine neurons in Parkinson's disease [33,34]. The tryptophan-melatonin pathway, and how it links to processes driving plaques and tangles, is shown in Fig. 1.

The melatonergic pathway is evident in all mitochondria-containing cells, where it is induced by two transcription factors that drive amyloid-β production, namely Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and yin yang 1 (YY1), via β-site amyloid precursor protein-cleaving enzyme (BACE)1 induction [35,36]. The suppressed capacity of NF-κB and YY1 to synchronize melatonin production and release in association with BACE1 and amyloid-β, will prolong amyloid-β production whilst maintaining astrocyte and microglia reactivity, thereby driving microbial/alarmin signalling and associated heightened local inflammation [1]. The loss of synchronized glia autocrine and paracrine melatonin will contribute to ongoing CNS inflammation. The elimination of amyloid-β by anti-amyloid antibodies would not be expected to impact on such dysregulated inflammatory processes, which data on the poor efficacy of anti-amyloid antibodies pharmaceuticals would seem to indicate [37]. Melatonin also stimulates the expression of the non-amyloidogenic alpha-secretase activities of A disintegrin and metalloproteinase domain-containing protein (ADAM) 10 and ADAM17 [38] whilst inhibiting the expression of the amyloidogenic beta- and gamma-secretases [39].

The above provides a framework (Fig. 1) to link a wide array of diverse bodies of data on dementia pathophysiology, by highlighting the importance of the astrocyte melatonergic pathway and how it can become desynchronized from NF-kB and YY1 induced BACE1/amyloid-β, resulting in excessive amyloid-β production and the maintenance of inflammatory interactions of astrocytes, neurons, and microglia in the course of dementia pathophysiology.

3. Circadian Rhythm and Dementia

Recent data implicates decreased pineal melatonin coupled to sleep/circadian disruption in Alzheimer's disease pathoetiology, which is supported by data showing a dramatic 10-fold decrease in pineal melatonin between

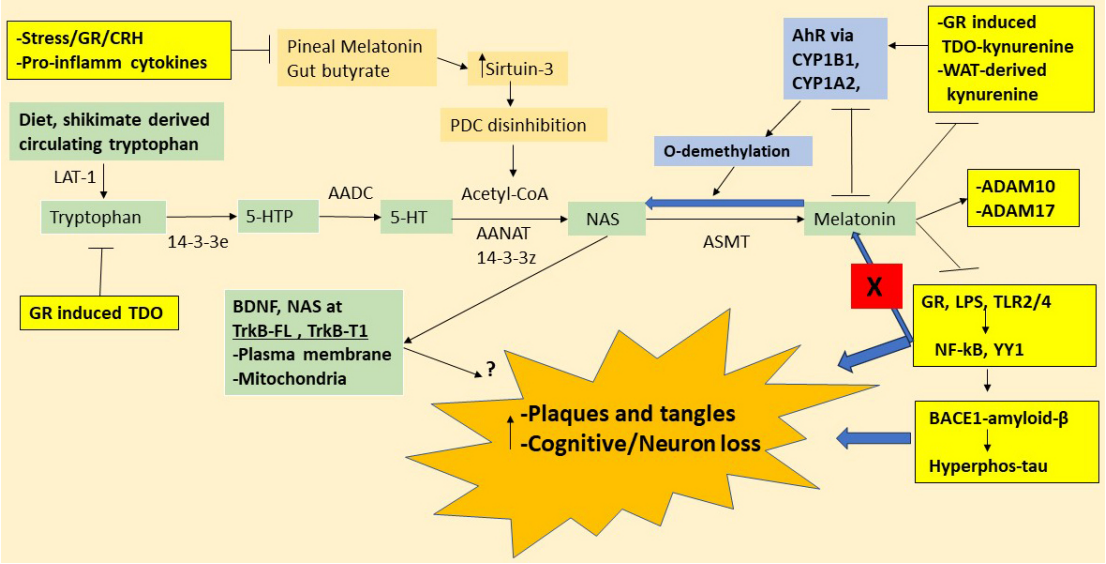

Fig. 1. Tryptophan-melatonin pathway interactions. Shows the tryptophan-melatonin pathway (green shade) and how it is intimately linked to key systemic processes relevant to dementia pathoetiology, including: (1) Stress/HPA axis activity drives GR activation and GR/TDO-kynurenine/AhR induction. Stress/GR drives gut-derived LPS and other TLR2/4 activators that upregulate the transcription factors, NF-kB and YY1, thereby inducing-BACE1-amyloid-β and hyperphosphorylated tau; (2) white adipocyte (WAT)-derived kynurenine activates the AhR as well as inducing neurotoxic kynurenine pathway products; and (3) gut microbiome-derived butyrate and circadian melatonin upregulates sirtuin-3 to disinhibit PDC, thereby optimizing mitochondrial function, whilst also providing acetyl-CoA as a necessary cosubstrate for the conversion of serotonin to NAS in the initiation of the melatonergic pathway. Tryptophan is mainly diet-derived but is also produced by the shikimate pathway of the gut microbiome. The large amino acid transporter (LAT)-1 takes circulating tryptophan into cells, including astrocytes, with TPH1 and TPH2 needing to be stabilized by 14-3-3e to allow tryptophan to be converted to 5-HTP. AADC then converts 5-HTP to 5-HT (serotonin). 14-3-3z stabilized AANAT metabolizes 5-HT to N-acetylserotonin (NAS), in the presence of acetyl-CoA as a necessary cosubstrate. NAS is converted to melatonin by ASMT. Acetyl-CoA levels are highly dependent upon optimized mitochondrial function arising from PDC disinhibition allowing the induction of the mitochondrial melatonergic pathway to be intimately linked to mitochondrial metabolic function. Pineal melatonin and the gut microbiome-derived short-chain fatty acid, butyrate, induce sirtuin-3, which deacetylates and disinhibits PDC, thereby enhancing the conversion of pyruvate to acetyl-CoA. Stress/CRH/GR activation and pro-inflammatory cytokines suppress pineal melatonin and increase gut permeability/dysbiosis, thereby lowering butyrate levels. The AhR, via CYP1A2 and CYP1B1, can O-demethylates melatonin to NAS, with AhR induced CYP1B1/CYP1A2/CYP1A1 also able to hydroxylate melatonin to 6-hydroxymelatonin via modifiable protein-protein interactions. The AhR can therefore suppress melatonin by a couple of processes as well as raising the CYP1NAS/melatonin ratio. NAS and melatonin have many common but important differential effects given that NAS activates the BDNF receptor, TrkB, as well as inducing BDNF, being a couple of means whereby NAS enhances TrkB activation. TrkB activation may be beneficial in dementia, although this may be dependent upon the full-length (TrkB-FL) isoform as the truncated isoform (TrkB-T1) can contribute to apoptosis. Notably, TrkB-FL and TrkB-T1 effects will be dependent upon location on the mitochondrial and/or plasma membranes. Melatonin affords powerful protection in dementia models, partly mediated by its suppression of the gut-permeability associated LPS and GR nuclear translocation, thereby preventing the GR from inducing TDO-kynurenine and BACE1-amyloid-β. Melatonin also suppresses hyperphosphorylated-tau both directly and via decreased amyloid-β. Melatonin also stimulates the non-amyloidogenic α-secretase activities of ADAM10 and ADAM17, whilst inhibiting the expression of the amyloidogenic β- and γ-secretases. The melatonergic pathway is therefore in intimate interactions with systemic processes linked to dementia, with the incapacity of NF-kB and YY1 to induce melatonin from the melatonergic pathway (red shade X) being crucial to dementia pathophysiology. Abbreviations: 5-HT, serotonin; 5-HTTP, 5-hydroxytryptophan; AADC, aromatic-L-amino acid decarboxylase; acetyl-CoA, acetyl-coenzyme A; AANAT, aralkylamine N-acetyltransferase; AhR, aryl hydrocarbon receptor; ASMT, N-acetylserotonin O-methyltransferase; BACE1, β-site amyloid precursor protein-cleaving enzyme 1; BDNF, brain-derived neurotrophic factor; CRH, corticotrophin releasing hormone; CYP, cytochrome P450; GR, glucocorticoid receptor; HPA, hypothalamus-pituitary-adrenal; LAT-1, large amino acid transporter 1; LPS, lipopolysaccharide; NAS, N-acetylserotonin; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; TLR, toll-like receptor; TrkB-FL, tyrosine receptor kinase B-full length; TrkB-T1, tyrosine receptor kinase B-truncated; TDO, tryptophan 2,3-dioxygenase; PDC, pyruvate dehydrogenase complex; ADAM, A disintegrin and metalloproteinase domain-containing protein; YY, yin yang.

adolescence and the ninth decade of life [25], with consequences that include the suppression of melatonin's anti-inflammatory, antioxidant and mitochondrial optimizing effects at night in dampening the consequences of day-time stressors and challenges, including immune and glial cell reactivity [26]. The relevance of night-time/sleep linked systemic processes is also indicated by the circadian role of the gut microbiome. Butyrate is primarily produced during fasting [40], which has important implications for the regulation of the glucocorticoid receptor (GR) in the course of not only stress/HPA axis activation but also for the cortisol awakening response (CAR). CAR is a dramatic and important, although under-investigated, circadian rhythm, typically described 'as preparing the body for the coming day'. Gut microbiome-derived butyrate and CAR may be significantly regulated by variations in circadian and local melatonin availability, which butyrate and melatonin prevent GR nuclear translocation, with relevance to a host of diverse medical conditions including cancer [41].

3.1 Circadian Rhythm and Gut Microbiome

A plethora of medical conditions are associated with alterations in the gut microbiome, invariably involving decreases in the short-chain fatty acid, butyrate [42]. As noted, butyrate is primarily induced during fasting, including when asleep [40]. Pineal melatonin effects include the suppression of gut permeability and associated decrease in gut dysbiosis, concurrently elevating butyrate levels [43]. Melatonin is also very highly produced in the gut, especially after feeding where is seems to increase the swarming of gut bacteria in the presence of food [44,45]. The gut microbiome and the timing of food intake are integral aspects of the circadian rhythm.

The benefits of butyrate are mediated via a number of processes, including: (1) activation of the G-protein coupled receptors (GPR), GPR-41, -43 and -109 [46]; (2) via histone deacetylase inhibition (HDACi) thereby allowing butyrate to epigenetically regulate systemic and CNS cells [47]; (3) by optimizing mitochondrial function, involving the upregulation of sirtuin-3 and the deacetylation and disinhibition of PDC, thereby increasing ATP from OXPHOS and the TCA cycle, coupled to decreased mitochondrial oxidant production [48,49]. As the upregulation of the mitochondrial melatonergic pathway is intimately linked to mitochondrial optimization, as shown in intestinal epithelial cells [50], butyrate upregulates the mitochondrial melatonergic pathway [50]. Factors influencing the tryptophan-melatonin pathway in a given cell will therefore have consequence for how the gut microbiome regulates that cell.

Stress/GR activation and proinflammatory cytokines can suppress pineal melatonin [51], whilst increasing gut permeability/dysbiosis, thereby lowering butyrate levels [52,53]. Such data highlights the dynamic two-way interactions of systemic processes and CNS processes over the circadian rhythm (see Fig. 1). Variations in pineal melatonin, local tryptophan-melatonin pathway regulation and gut microbiome-derived butyrate also interact to modulate the consequence of HPA axis activation, including in the course of the cortisol awakening response (CAR).

3.2 HPA Axis and Cortisol Awakening Response

The HPA axis has been extensively investigated following its induction by stress, including in Alzheimer's disease pathoetiology, where heightened levels of circulating cortisol are evident, as shown in a recent meta-analysis [54]. However, although of unknown physiological relevance, morning CAR does not seem significantly altered in Alzheimer's disease patients [54]. CAR drives a large surge in cortisol release starting just before the end of sleep and lasting for the first 30 minutes following awakening. The role of CAR is generally placed in the vague context of 'preparing the body for the coming day', with hope that its relevance may be better clarified by more rigorous methodology [55]. The effects of CAR, and indeed stress driven HPA axis activation, is considerably complicated by the diverse ways that glucocorticoid receptor (GR) can influence cell processes. The GR is the main mediator of HPA axis and CAR effects, with the GR being predominantly expressed in the cytoplasm in a complex with heat shock protein (hsp)90 and p23. Upon activation, the GR is transported to the nucleus where it induces genes containing the glucocorticoid receptor element (GRE) in their promotor.

The availability of pineal and/or local melatonin is relevant to CAR effects, with melatonin preventing GR nuclear translocation [56], including possibly via the upregulation of bcl2-associated athanogene (BAG)1 [41]. Butyrate, via its capacity as a HDACi, also suppresses GR nuclear translocation, involving increased acetylation of the GR and hsp90 [57,58]. Consequently, variations in pineal and local melatonin as well as butyrate availability over the course of sleep not only regulate inflammation, antioxidant status and mitochondrial function, but also have direct impacts on GR nuclear effects during CAR. This may be of some importance given the dramatic effects that cortisol can have on the function of all immune and glial cells, in contrast to melatonin and butyrate (see Table 1 in [41]), and therefore on patterned immune/glia responses for the coming day. This would indicate that although CAR level/slope may not be significantly different in Alzheimer's disease [54], the dramatic decrease in pineal melatonin and gut microbiome-derived butyrate will significantly regulate CAR consequences in Alzheimer's disease. As the different cells in a given local microenvironment, including the tumor microenvironment [59], may have their tryptophan-melatonin pathway differentially regulated, GR activation can have distinct effects in the cells of a given microenvironment. This alters the nature of the homeostatic interactions that occur in the course of CAR 'preparing the body for the coming day'. Such homeostatic alterations are proposed to contribute to the pathoetiology

of 'autoimmune'/'immune-mediated' disorders [33], which recent data indicates to include Alzheimer's disease [60].

Notably, this is complicated by the diverse effects of GR activation. The GR has a number of genomic and non-genomic effects, including via the induction of intracellular signaling pathways following plasma membrane GR activation [61]. The GR may also interact with other transcription factors in the nucleus to modulate diverse genes with no GRE in their promoter. GR effects, both in CAR and stress/HPA axis activation, may also be further complicated by factors upregulating BAG-1, as recently proposed for melatonin [62]. BAG-1 can not only prevent nuclear translocation but can also chaperone the GR to mitochondria [63], where it can be translocated over the inner and outer mitochondrial membranes (by mitochondrial import inner membrane translocase subunit (TIM) 23 and mitochondrial import outer receptor subunit (TOM) 20) allowing the GR to interact with PDC and hsp60, with consequences for mitochondrial metabolism, including the regulation of the mitochondrial melatonergic pathway [41].

3.3 Butyrate, Melatonin, ApoE4 and CAR Interactions in Mitochondria Regulation

Importantly, the consequences of CAR/GR, butyrate and pineal/local melatonin interactions are crucially determined by how they interact to regulate mitochondrial function. This involves both the dampening of residual inflammation and mitochondrial oxidant production, as well as how CAR may prime systemic and CNS cells for the coming day. It is widely recognized that suboptimal mitochondrial function is an integral aspect of dementia, both systemically [64] and in brain cells [65,66], with mitochondrial dysfunction evident in many of dementia's currently conceptualized 'comorbidities', such as obesity [67], T2DM [68] and depression [69]. Mitochondrial function may be especially relevant in reactive cells, namely immune and glial cells, including astrocytes, which have a powerful role in the regulation of neuronal activity and survival [69].

There is a growing appreciation of the importance of astrocytes in the regulation of a wide array of neuropsychiatric and neurodegenerative conditions that have been classically conceptualized as 'neuronal' disorders, including depression [69], Parkinson's disease [70], amyotrophic lateral sclerosis (ALS) [14], and multiple sclerosis [71]. The role of astrocytes in such conditions is attributed to a wide array of processes including by astrocyte AhR nuclear translocator (ARNT)-like 1 and BAG3 determining levels of α-synuclein and hyperphosphorylated tau, implicating the circadian rhythm and BAG regulation in the modulation of neurodegenerative processes [3]. It is proposed here that dysregulation of the astrocyte tryptophan-melatonin pathway is an early change in the pathoetiology of Alzheimer's disease.

Astrocyte Mitochondrial Tryptophan-Melatonin Pathway

TLR2/4 can be activated by numerous ligands, including LPS, hsp60, hsp90, amyloid-β, α-synuclein, fibrinogen and high-mobility group box (HMGB)1. Astrocyte TLR2/4 signaling increases NF-kB and YY1, thereby increasing BACE1 and amyloid-β production [72,73]. This is parsimonious with amyloid-β as an endogenous antimicrobial [9]. As both NF-kB and YY1 upregulate the melatonergic pathway, as shown in other cell types [35,36], the concurrent/sequential release of melatonin following TLR2/4 activation will have autocrine and paracrine effects that dampen and time-limit inflammatory responses and raised oxidants. As cytokines and oxidants can induce further TLR2/4 ligands as well as the nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3 (NLRP3) inflammasome [74], the autocrine and intracrine effects of astrocyte melatonin will prevent prolonged signaling via TLR2/4. Melatonin suppresses the NF-kB and reactive oxygen species (ROS)-driven NLRP3 inflammasome [74], which may be partly mediated over the circadian rhythm by pineal melatonin upregulating the α7 nicotinic acetylcholine receptor (α7nAChR) [75], which suppresses immune inflammation and is a significant treatment target in Alzheimer's disease [76]. As to whether local paracrine melatonin release from astrocytes regulates local α7nAChR levels will be important to determine. Such data highlights the potentially important role of pineal and local astrocyte melatonin in the regulation of an Alzheimer's disease pathophysiological factor (NLRP3) [77] and protective factor (α7nAChR) [78]. As stress/GR activation can regulate α7nAChR [79], the interactions of pineal melatonin's circadian induction of the α7nAChR [80] with the wider night-time changes in morning CAR modulation will be important to determine. Notably, the α7nAChR is also expressed on the mitochondrial outer membrane where its binding by agonists suppresses Ca^{2+} influx and decreases cytochrome c release [81], suggesting that it may linked to optimizing mitochondrial resilience under challenge [82] as well as wider cellular and mitochondrial plasticity.

Astrocyte melatonin release has been long established [83], being regulated by the main Alzheimer's disease susceptibility gene, apolipoprotein (Apo)E4 [84]. ApoE4 is the major susceptibility gene for Alzheimer's disease, with carriers of two ApoE4 alleles having an 8-15-fold increase in Alzheimer's disease susceptibility [85]. ApoE is predominantly expressed in astrocytes in the brain, where it regulates lipid metabolism, with ApoE4 increasing the unsaturated fatty acid chains on triglycerides [86]. Whether the ApoE4 upregulation of astrocyte mitochondrial melatonergic pathway is relevant to neuronal loss in dementia will be important to determine, including whether there is any role for a heightened dependence of astrocyte melatonin in ApoE4 carriers. ApoE4 effects include the downregulation of astrocyte monoamine oxidase (MAO)-A and MAO-B, thereby increasing the availability of serotonin as

a precursor for the melatonergic pathway [85]. This is one means by which astrocyte ApoE4 can increase astrocyte melatonin production [85], thereby contributing to a role for enhanced astrocyte melatonin in the maintenance of homeostatic interactions of astrocytes with neurons and other brain cells. The suppressed capacity to induce astrocyte melatonin over aging may therefore have more significant impacts on ApoE4 carriers, thereby indicating a more significant role for the greater drop in local melatonin dampening of local inflammation in ApoE4 carriers.

As noted, heightened amyloid-β levels are evident in other classical neurodegenerative conditions, including glioblastoma [10], Parkinson's disease with Lewy bodies [13], tauopathies [87] and ALS [14]. The pathophysiologies of all of these conditions implicate a significant astrocyte role [14,88–90], including via regulation by ApoE alleles [91–94]. Clearly, it will be important to clarify the nature of astrocyte ApoE in the regulation of the astrocyte tryptophan-melatonin pathway over aging in the pathoetiology of dementia and associated neurodegenerative conditions.

The loss of serotonergic neurons is intimately linked to the suppression of the astrocyte tryptophan-melatonin pathway in dementia, with serotonergic neuronal loss being a relatively early event in Alzheimer's disease [95]. Decreased serotonin levels are also evident in Alzheimer's disease platelets, with platelet serotonin inversely correlating with cerebrospinal fluid (CSF) hyperphosphorylated-tau and amyloid-β [96]. Such systemic suppression of serotonin availability may be linked to decreased gut microbiome-derived butyrate, which downregulates MAO-B, thereby increasing serotonin availability [97]. Butyrate's suppression of MAO-B, thereby enhancing serotonin availability may be another route whereby butyrate upregulates the melatonergic pathway [50] in astrocytes and other cells as well as modulating the capacity of pineal melatonin at night to also upregulate the astrocyte melatonergic pathway. The regulation of serotonin availability may therefore be another aspect of gut-pineal interactions in the modulation of morning CAR activation of the GR. Inflammation driven indoleamine 2,3-dioxygenase (IDO) and GR induced tryptophan 2,3-dioxygenase (TDO), by converting tryptophan to kynurenine decrease tryptophan availability and thereby will also suppress serotonin availability.

Whether the role of autocrine melatonin in switching from an inflammatory M1-like phenotype in macrophages [35] and microglia [80] to a quiescent, pro-phagocytic M2-like phenotype is paralleled in astrocytes will be important to determine. This would seem not unlikely, given the role of exogenous melatonin in dampening astrocyte reactivity [98,99]. The maintenance of astrocyte reactivity is an important driver of microglia reactivity, which is also dampened by autocrine and paracrine melatonin [100]. Such data highlights the importance of maintained astrocyte reactivity in regulation of the wider CNS inflammatory activity in dementia, as well as the role of astrocyte TLR2-4/NF-kB/YY1/BACE1/amyloid-β in driving the maintained amyloid-β production that further contributes to inflammation and neuronal loss in the course of dementia. However, although previous data is highly suggestive of a role of such processes, clearly the astrocyte mitochondrial melatonergic pathway requires investigation. The proposed sequential release of melatonin following TLR2/TLR4/NF-kB/YY1/BACE1/amyloid-β pathway in astrocytes (as well as microglia and neurons) will dampen the maintained heightened inflammation that is widely thought to underpin neuronal loss in dementia and across other neurogenerative conditions, as indicated by the effects of exogenous melatonin across diverse preclinical models [101–103]. Such studies also indicate that in the course of dampening inflammatory signaling melatonin will have autocrine and paracrine effects that optimize mitochondrial function, thereby acting on core process that underpin the complex and dynamic flurry of cell fluxes that are typical of the chaos of 'endpoint' disorders, such as the current classification of later stage Alzheimer's disease. The beneficial effects of pineal melatonin and gut microbiome-derived butyrate may then be intimately linked to their night-time capacity to induce the astrocyte mitochondrial melatonergic pathway, thereby optimizing astrocytes in their regulation of neuronal activity and survival. This would suggest that dementia, like cancer [26], may be importantly determined by night-time, sleep linked processes, upon which the morning CAR activation of the GR will act to regulate local microenvironment homeostasis. See Fig. 2.

3.4 The Aryl Hydrocarbon Receptor and Circadian Rhythm

Raised aryl hydrocarbon receptor (AhR) levels and activation are closely linked to aging [104], including via disruption to the circadian rhythm [105]. As highlighted in Fig. 1, AhR activation induces cytochrome P450 (CYP)1A2 and CYP1B1, thereby O-demethylating melatonin to NAS as well as increasing melatonin hydroxylation [106,107]. The AhR is typically held in a cytoplasmic complex with hsp90 and when activated by an AhR ligand translocates to the nucleus where it forms a dimer with the AhR nuclear translocator (ARNT), thereafter inducing genes with the xenobiotic response element (XRE) in their promotor. The AhR can also be expressed on the mitochondrial membrane where it regulates Ca^{2+} influx via the voltage dependent anion channel (VDAC)1 [108] and interacts with the mitochondria-located translocator protein kDa18 (TSPO) [109]. The diverse and sometimes contrasting effects of the AhR may be partly determined by site of translocation as well as by other alternatively sited mitochondria receptors, such as the α7nAChR, TrkB and GR [110].

The AhR has numerous endogenous and exogenous ligands, including kynurenine derived from pro-

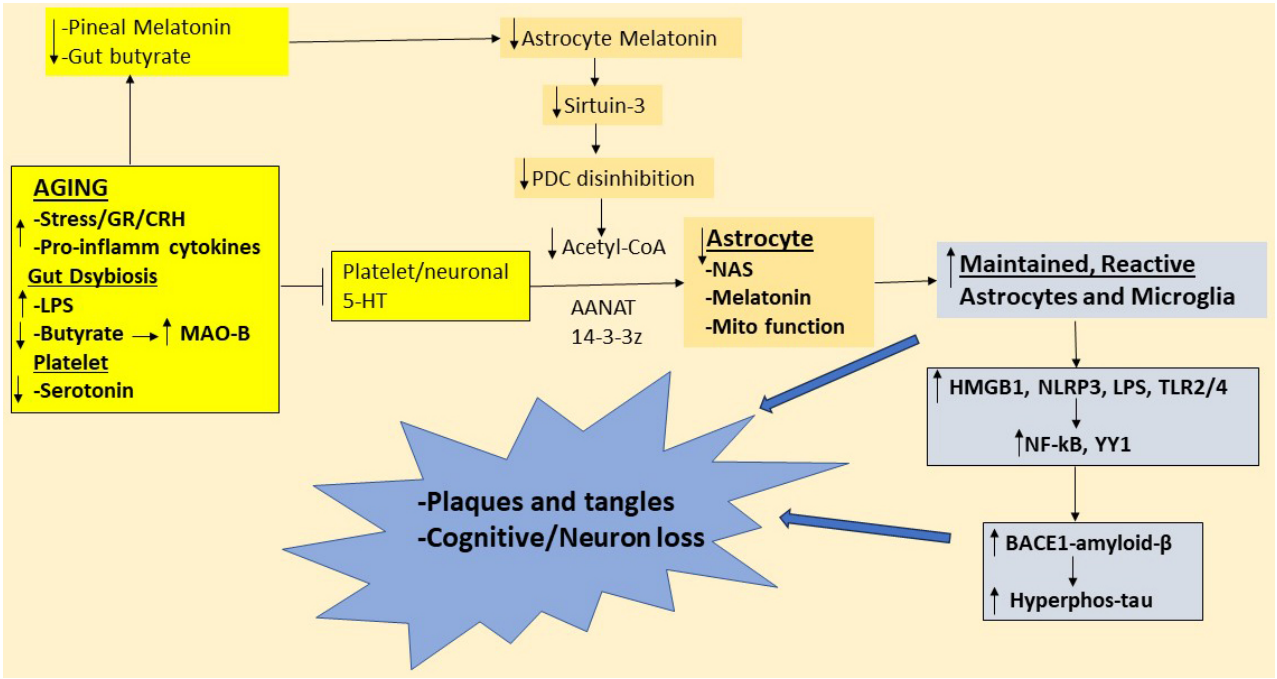

Fig. 2. Shows how changes over aging suppress pineal melatonin and gut microbiome-derived butyrate as well as platelet and neuronal serotonin (yellow shade), which all contribute to suppress astrocyte (gold shade) melatonin and NAS availability. This contributes to astrocyte mitochondrial dysfunction, with enhanced astrocyte reactivity increasing microglia reactivity, thereby contributing to maintained, raised levels of HMGB1 and LPS activation of TLR2/4 and increased NLRP3 inflammasome induced IL-1β and IL-18, further contributing to the inflammatory milieu that enhance BACE1/amyloid-β and associated increase in hyperphosphorylated tau. The emergent plaques and tangles in the 'end-point chaos' of later stage Alzheimer's disease may therefore be powerfully determined by factors, including systemic, that regulate the availability of the astrocyte tryptophan-melatonin pathway. Abbreviations: 5-HT, serotonin; acetyl-CoA, acetyl-coenzyme A; AANAT, aralkylamine N-acetyltransferase; AhR, aryl hydrocarbon receptor; BACE1, β-site amyloid precursor protein-cleaving enzyme 1; CRH, corticotrophin-releasing hormone; GR, glucocorticoid receptor; HMGB1, high-mobility group box; Hyperphos, hyperphosphorylated; LPS, lipopolysaccharide; MAO-B, monoamine oxidase-B; Mito, mitochondrial; NAS, N-acetylserotonin; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3; PDC, pyruvate dehydrogenase complex; TLR, toll-like receptor; YY1, yin yang 1.

inflammatory cytokine induction of indoleamine 2,3-dioxygenase (IDO) and cortisol/GR induction of tryptophan 2,3-dioxygenase (TDO). The array of AhR ligands, site of expression, and the AhR regulation of the mitochondrial melatonergic pathway allows AhR activation to have a complexity of consequences. Such plasticity of AhR activation considerably complicates its role in aging [111], whilst also highlighting the adaptability of the AhR in the regulation of core cellular processes as determined over the course of evolution. As the conversion of tryptophan to kynurenine by IDO and TDO also increases other kynurenine pathway products, including neuroregulatory kynurenic acid and quinolinic acid, AhR activation by kynurenine will be coupled to concomitant AhR-independent effects of kynurenine pathway products on neuronal activity and interarea communication across the brain. Given that 60% of brain kynurenine is derived from the periphery [112], systemic processes that drive large kynurenine increases, such as from white adipocyte (WAT) in obesity [113], can drive significant changes in the CNS relevant to dementia pathophysiology, including depriving tryptophan for the tryptophan-melatonin pathway, and kynurenic acid/quinolinic acid neuroregulation as well as AhR activation.

By O-demethylating melatonin to NAS, thereby increasing TrkB activation, the AhR is a significant contributor to Alzheimer's disease pathophysiology. As noted, NAS is a brain-derived neurotrophic factor (BDNF) mimic via its activation of the BDNF receptor, TrkB [114]. TrkB activation of the TrkB-FL is a treatment target for Alzheimer's disease, given its trophic and metabolic benefits [115]. However, in the presence of amyloid-β the truncated TrkB-T1 is markedly increased and significantly contributes to neuronal loss, as shown in Alzheimer's disease preclinical models [116,117]. By increasing the NAS/melatonin ratio and associated TrkB-T1 activation, the AhR and its ligands can contribute to Alzheimer's disease pathophysiology by a number of mechanisms. The loss of

pineal melatonin's suppression of pro-inflammatory cytokines/IDO/kynurenine and cortisol/GR/TDO/kynurenine will contribute to heightened AhR activation, thereby increasing the NAS/melatonin ratio and heightened TrkB-T1 activation-linked neuronal loss, especially in the presence of raised amyloid-β levels. The suppression of gut microbiome butyrate will also contribute to this via decreased HDACi, thereby increasing GR nuclear translocation and TDO induction. As noted, the marked suppression of pineal melatonin and gut derived butyrate will enhance GR nuclear translocation, thereby modulating not only the HPA axis stress response, but also the consequence of CAR as it 'prepares the body for the coming day'. Such processes allow the AhR to be intimately linked to the circadian rhythm in the regulation of Alzheimer's disease pathophysiology. See Fig. 1.

3.5 GR, MERTK, TrkB-T1, Melatonergic Pathway and Autoimmunity in Alzheimer's Disease

Interestingly, stress/GR activation of astrocytes induces MER proto-oncogene, tyrosine kinase (MERTK), thereby driving astrocytes to phagocytose excitatory synapses on to GABAergic neurons, which is mediated by the GR acting as a nuclear transcription factor [118]. MERTK is one of the TAM receptors (Tyro3, Axl, and Mertk), which are linked to immune regulation, cell differentiation and apoptotic cell/debris clearance [119], with MERTK alleles associated with Alzheimer's disease risk, especially in females [120]. As to whether stress/GR-driven increase in astrocyte MERTK, by driving astrocyte phagocytosis of excitatory synapses onto GABAergic neurons, contributes to the increased glutamatergic excitotoxicity in Alzheimer's disease [121] requires investigation. As heightened glutamatergic N-methyl-D-aspartate receptor (NMDAr) activation, including by amyloid-β, contributes to the raised TrkB-T1 levels in Alzheimer's disease [122], the loss of melatonin and butyrate suppression of GR nuclear translocation will enhance GR-induced MERTK and GABAergic suppression and heightened glutamatergic NMDAr activation, thereby increasing TrkB-T1 levels. This indicates a role for circadian and systemic factors in the modulation of substantial changes in how astrocytes regulate neuronal interactions and activation. Notably, the GR can also increase BACE1 and amyloid-β via plasma membrane GR activation [123] as well as by regulating presenilin (PSEN)1 assembly on the endoplasmic reticulum (ER), thereby inducing amyloid-β accumulation on the ER mitochondrial associated membrane (MAM) [124]. The roles of melatonin and butyrate in the modulation of these other routes of BACE1 and amyloid-β induction by stress/CAR activation of the GR have still to be determined.

Whether the loss of night-time pineal melatonin and gut microbiome-derived butyrate increases the morning CAR activation of astrocyte GR to not only increase BACE1 and amyloid-β but also contribute to MERTK induction and heightened TrkB-T1 levels, especially in the presence of amyloid-β, will be interesting to determine. When this is coupled to an AhR-driven increase in the NAS/melatonin ratio, thereby enhancing NAS activation of TrkB-T1 (on the plasma and/or mitochondrial membranes), neuronal loss will be potentiated [116,117]. Overall, the circadian loss of night-time melatonin and gut microbiome-derived butyrate will also be relevant to later stages of neuronal loss in dementia, where heightened amyloid-β and TrkB-T1 levels are evident, as well as in the pathoetiology of dementia.

However, it is important to note the widespread mitochondrial dysfunction in dementia cannot be simply understood as a consequence of various fluxes and challenges, but rather mitochondrial function is a dynamic core aspect of intercellular homeostatic interactions, with the suppression of the mitochondrial melatonergic pathway a target for other cells in a given microenvironment when the products of a challenged cell drive a prolonged maladaptive dyshomeostasis. Such intercellular dyshomeostasis drives the pathoetiology of 'autoimmune'/'immune-mediated' disorders [12,33], where the regulation of the mitochondrial melatonergic pathway in a 'targeted' cell (such as in pancreatic β-cells in T1DM [12]) is dynamically shaped by other cells in the local microenvironment. This is most evident in the tumor microenvironment, where cancers release kynurenine to activate the AhR to shape the metabolic function of other tumor microenvironment cells in the course of generating 'immune tolerance' and shaping intercellular fluxes [59,125].

The dynamic intercellular fluxes within a given microenvironment modulate processes that shape mitochondrial function, including ROS production, thereby driving ROS-dependent microRNAs (miRNAs) [126] that shape patterned gene expression in an ever-changing dynamic over the circadian rhythm. Whether such systemic and microenvironment determined mitochondrial ROS-driven miRNAs underpin the increased TrkB-T1, especially in the presence of amyloid-β, will be important to determine over the course of dementia progression. How this is coordinated with melatonergic pathway suppressing miRNAs, such as miR-7, miR-375 and miR-451 [127–129], may be of particular importance, given the use of streptozotocin (a known melatonergic pathway inhibitor [130]) in preclinical models of dementia [131] and autoimmune disorders [132]. Such suppression of mitochondrial melatonin would overlap neuronal loss in Alzheimer's disease with that of Parkinson's disease, where 'autoimmune'/'immune-mediated' processes involving $CD8^+$ t cell chemoattraction may be driven by decreased melatonin regulation of PINK1/parkin-mediated mitophagy [133] and associated upregulation of major histocompatibility complex (MHC)-1 [33], driving neuronal [134,135] and possibly microglia [136] destruction. This is supported by data showing

the presence of heightened $CD8^+$ t cells levels in the Alzheimer's disease brain in proximity to amyloid plaques [137,138], which is strengthened further by data showing $CD8^+$ t cells to drive neuronal loss in Alzheimer's disease models [134].

Such data indicates that the suppression of the mitochondrial melatonergic pathway is a significant driver of dysregulated mitophagy via the loss of melatonin's regulation of PINK1/parkin/mitophagy [133], arising from systemic (pineal melatonin, gut butyrate, CAR/GR, WAT kynurenine) changing the dynamic interactions in a given microenvironment where prolonged inflammation and microbial/viral-type signaling (TLR2/4/9) drives a dyshomeostasis that cannot be dealt with by the immediately responding immune cells (astrocytes and microglia), leading to the chemoattraction (via MHC-1) of $CD8^+$ t cells that drives cell destruction (predominantly neurons but also glia). This has parallels to the course of acute viral infection, as evident in the COVID-19 pandemic [139], where the immune response is initially determined by 'first responders' (such as neutrophils, macrophages and mast cells) but is taken over by the immune system 'second wave' ($CD8^+$ t cells and natural killer cells). Neuronal loss in Alzheimer's disease therefore has significant 'autoimmune'/'immune-mediated' overlaps with neuronal loss in the Parkinson's disease substantia nigra pars compacta [33,140].

Overall, the suppressed capacity to maintain the mitochondrial melatonergic pathway in astrocytes may be an important initiator of dementia pathoetiology with the subsequent protracted pathophysiology involving alterations in dynamic mitochondrial homeostatic interactions in a given microenvironment. Systemic and local microenvironment processes interact to suppress the mitochondrial melatonergic pathway, thereby initiating the chemoattraction of $CD8^+$ t cells and the 'autoimmune'/'immune-mediated' destruction of neurons that underpin the progressive cognitive loss in dementia. The above suggests changes in the nature of Alzheimer's disease pathophysiology over time, including in the nature of immune involvement, rather than a static progression of the same pathophysiological processes. This may be more akin to concepts of 'staging' in neuropsychiatric conditions, such as bipolar disorder [141], likely in association with distinct treatments at different physiologically determined 'stages' [142]. Such ever-changing processes ultimately culminate in the 'end-point chaos' of the currently defined late-stage Alzheimer's disease. See Fig. 3.

4. Hypothalamic Interactions with Circadian Rhythm and Systemic Processes

As well as the gut microbiome, pineal melatonin, and CAR/HPA axis, conceptualizing Alzheimer's disease as a systemic disorder may require the incorporation of wider regulators of circadian and systemic processes, including the hypothalamus. The hypothalamus is classically determined by variations in neuronal release of various peptides that regulate 'basic animal' processes, such as reproduction, aggression, sex drive, appetite, thirst, and social bonding. Although alterations in hypothalamic function have long been identified in Alzheimer's disease [143,144], the relative paucity of amyloid-β levels and effects have led to this brain regulator of core systemic processes being relatively little investigated out-with the hypothalamic role in initiating the HPA axis [145]. However, hypothalamic cells, including tanycytes and astrocytes are important regulators of many systemic processes linked to Alzheimer's disease risk, including obesity, T2DM and glycemic dysregulation [146]. Integrating alterations in wider hypothalamic function may therefore be an overlooked aspect of Alzheimer's disease pathoetiology.

The most investigated nucleus of the hypothalamus is the paraventricular nucleus (PVN), primarily due to PVN^{CRH} neurons initiating CAR and the HPA axis/stress response linked to Alzheimer's disease pathophysiology [147]. The cortisol awakening response (CAR) is regulated by suprachiasmatic nucleus (SCN) derived vasoactive intestinal peptide (VIP) projections to the PVN^{CRH} neurons, with VIP increasing CRH release to initiate the stress/CAR circadian rhythm [148]. The circadian timing of SCN^{VIP} release is determined by the day, vs night, GABA uptake by the astrocyte GABA transporter (GAT)3, allowing increased extracellular GABA at night to suppress VIP levels [149]. Such astrocyte regulation of VIP may be of some importance, given preclinical data showing chronic VIP administration from an early age to significantly decrease amyloid-β plaques and preserve susceptible brain areas against atrophy in an Alzheimer's disease preclinical model [150]. As well as being regulated by astrocytes, VIP also regulates astrocyte function by increasing glycolysis-driven lactate provision as an energy source for neurons where lactate is converted to pyruvate [151]. The conversion of glucose to pyruvate in astrocytes is proposed to favor the conversion of pyruvate to lactate and the relatively suppressed utilization of pyruvate in the production of acetyl-CoA by the astrocyte PDC under conditions of neuronal activity/challenge and hypoxia [151]. Whether this is dependent upon the availability of the astrocyte mitochondrial melatonergic pathway, including in the course of aging when the astrocyte mitochondrial melatonergic pathway may be suppressed will be important to determine. Preclinical data indicates that the genetic downregulation of astrocyte lactate dehydrogenase generates memory deficits that are only evident in the aged [152]. Are variations in the astrocyte mitochondrial melatonergic pathway significant regulators of the astrocyte-neuron lactate shuttle? This is indirectly supported by data in Sertoli cells where melatonin increases lactate dehydrogenase mRNA and protein levels [153], suggesting that lost astrocyte (and perhaps pineal) melatonin suppresses pyruvate conversion to

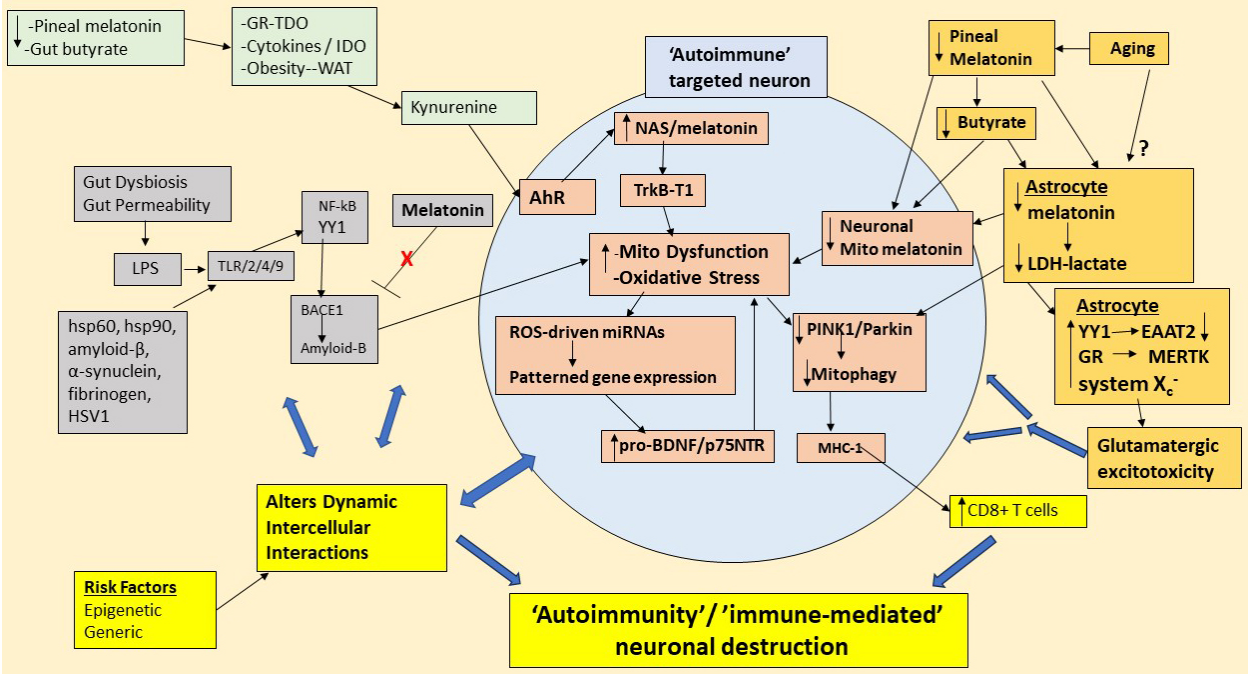

Fig. 3. Shows how gut dysbiosis, gut permeability, pro-inflammatory cytokines, GR, AhR, NAS/melatonin ratio, and decreased pineal melatonin act primarily on astrocytes to decrease astrocyte melatonin release, thereby suppressing the anti-inflammatory and mitochondria optimizing effects of autocrine and paracrine melatonin. Consequently, astrocyte and neuronal BACE1 and amyloid-β continue to be produced in association with raised tau hyperphosphorylation, thereby driving the endpoint 'chaos' of plaques and tangles that classically define Alzheimer's disease. The decreased astrocyte mitochondrial melatonin at night is at least partly mediated via a decrease in pineal melatonin and gut microbiome-derived butyrate, although there may be more aging-associated factors that also suppress the astrocyte tryptophan-melatonin pathway (top right-hand, gold shade). The loss of pineal and astrocyte melatonin suppresses lactate dehydrogenase (LDH) and therefore lactate production by astrocytes, thereby depriving energy for neuronal mitochondria and decreasing neuronal mitochondria melatonergic pathway induction. The suppression of astrocyte melatonin maintains the NF-kB induction of YY1, thereby decreasing EAAT2, which, like the increased System X_c^- and MERTK, enhances glutamatergic excitotoxicity that raises neuronal apoptotic susceptibility and contributes to spreading apoptotic susceptibility (gold shade). Gut derived LPS, as well as other TLR2/4/9 ligands (grey shade) induce NF-kB and YY1 to increase BACE1 and amyloid-β, which in the absence of melatonin leads to prolonged amyloid-β production that exacerbates neuronal mitochondrial function. Decreased pineal melatonin and gut butyrate will heighten the GR-TDO, pro-inflammatory cytokine-IDO and white adipocyte (WAT) derived kynurenine to activate the AhR. By increasing NAS and suppressing melatonin, the AhR will contribute to neuronal susceptibility via oxidative stress induced TrkB-T1, which NAS activates. Oxidative stress and neuronal mitochondrial dysfunction also increase pro-BDNF and its ligand, $p75^{NTR}$, which also contributes to neuronal vulnerability as well as dysregulating patterned immune responses. The neuronal mitochondrial dysfunction and suppressed melatonin decrease PINK1/parkin/mitophagy, and increase MHC-1, which chemoattracts $CD8^+$ t cells that drive neuronal destruction (yellow shade). Such immune-mediated processes will be contributed to, if not initiated by, alterations in the homeostatic interactions in the neuronal microenvironment, which will be subject to epigenetic and genetic risk factors (yellow shade). Abbreviations: AhR, aryl hydrocarbon receptor; BACE1, β-site amyloid precursor protein-cleaving enzyme; BDNF, brain-derived neurotrophic factor; EAAT, excitatory amino acid transporter; GR, glucocorticoid receptor; hsp, heat shock protein; HSV1, herpes simplex virus; IDO, indoleamine 2,3-dioxygenase; LDH, lactate dehydrogenase; LPS, lipopolysaccharide; MERTK, MER proto-oncogene, tyrosine kinase; MHC-1, major histocompatibility complex-class 1; Mito, mitochondria; NAS, N-acetylserotonin; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; PINK1, PTEN-induced kinase 1; ROS, reactive oxygen species; TDO, tryptophan 2,3-dioxygenase; TLR, toll-like receptor; TrkB-T1, tyrosine kinase receptor B-truncated; WAT, white adipocyte; YY1, yin yang 1.

lactate, thereby depriving neurons of their major source of metabolism. Is suppressed astrocyte melatonin (and/or pineal melatonin) over aging thereby intimately linked to a decrease in astrocyte lactate dehydrogenase, thereby increasing the availability of pyruvate for PDC conversion to acetyl-CoA? Would this suggest that the maintenance of the astrocyte mitochondrial melatonergic pathway carries precedence of astrocyte lactate production for neurons?

Is suppressed astrocyte mitochondrial melatonergic pathway over aging associated with a compensatory in-

crease in the activity of the cystine-glutamate antiporter (system X_c^-)? If so, the need for astrocytes to compensate melatonergic pathway suppression by system X_c^- upregulation would be expected to associate with heightened glutamatergic excitotoxicity in neurons. System X_c^- is upregulated in many neurodegenerative disorders, including ALS, Parkinson's disease and Alzheimer's disease [154]. These authors showed that TLR4 signaling by LPS increases system X_c^- in glia [154], which would seem not unlikely to be further increased under prolonged TLR2/4 signaling that fails to induce the NF-kB/YY1 induction of the astrocyte melatonergic pathway. In such circumstances, the astrocyte GSH production would preserve astrocytes but would not provide the autocrine and paracrine anti-inflammatory effects of melatonin.

As indicated above, heightened glutamatergic activity contributes to an excitotoxicity driven neuronal loss in Alzheimer's disease [121], with enhanced glutamatergic NMDAr activation contributing to heightened TrkB-T1 levels, decreased BDNF, and increased neurotoxic pro-BDNF release to activate heightened $p75^{NTR}$ receptors in Alzheimer's disease [122,155], thereby accelerating amyloid-β production and cognitive loss, as shown in preclinical models [156]. Such glutamatergic processes contribute to the emergence of seizures in Alzheimer's disease [7] and well as linking depression pathophysiology to dementia [157]. Raised circulating pro-BDNF levels also alter immune cell function, contributing to the immune dysregulation in Alzheimer's disease and how this overlaps depression with dementia [69,158]. The suppression of the astrocyte melatonergic pathway and associated system X_c^- upregulation will further contribute to raised glutamatergic signaling, thereby spreading excitotoxic signaling to other regions and layers within the cortex and limbic system. YY1 upregulation will also exacerbate glutamatergic excitotoxicity via the YY1 suppression of the astrocyte excitatory amino acid transporter (EAAT)2, thereby increasing glutamate availability at the synapse [159]. As YY1 is highly regulated by HDAC effects at the promotor of YY1 induced genes [160], the loss of the HDACi capacity of gut microbiome-derived butyrate would be expected to contribute to further EAAT2 suppression.

Although classically conceptualized as providers of lactate and trophic support to neurons, it is important to note that astrocytes are functional immune cells. As in any condition when immune cells become dysregulated, their homeostatic interactions with other cells can dramatically change, as shown in COVID-19 fatalities that were primarily mediated by immune cell responses [161]. The above would indicate that the suppressed mitochondrial melatonergic pathway (as well as suppressed pineal melatonin) in Alzheimer's disease drives compensatory processes in astrocytes (such as system X_c^- upregulation and increased glutamate release) that compromises neuronal survival. This seems driven by suppressed astrocyte mitochondrial function inhibiting neuronal mitochondrial function via decreased neuronal lactate availability for conversion to pyruvate and thereby suppressing PDC/acetyl-CoA and mitochondrial melatonergic pathway induction in neurons. As noted, the autocrine and paracrine effects of astrocyte melatonin would suppress TLR2/4-BACE1-amyloid-β as well as the hyperphosphorylation of tau, thereby being the major driver of classically defined Alzheimer's disease pathophysiology. The above would suggest that amyloid-β derived plaques and hyperphosphorylated tau driven tangles are downstream consequences of dysregulated glia mitochondrial melatonergic pathway dysregulation. Amyloid-β and hyperphosphorylated tau are therefore not useful treatment targets but are simply downstream consequence of a dysregulated astrocyte mitochondrial melatonergic pathway that contributes to wider pathophysiological processes as regulated by alterations in the circadian rhythm and gut microbiome (including suppressed EAAT2 and enhanced system X_c^-). Such dysregulation may be passed on to other neurons via heightened glutamatergic activity, in the presence of a suppressed astrocyte melatonergic pathway at sites to which such overly excited neurons project. As in Parkinson's disease, the suppression of the melatonergic pathway will enhance mitophagy dysregulation, driving an increase in oxidant-induced MHC-1, leading to 'autoimmune'/'immune-mediated' destruction of neurons by infiltrating $CD8^+$ t cells [33,34,140]. See Fig. 3.

The above provides a framework for linking and investigating wider pathophysiological processes. The dramatic suppression of pineal melatonin in the circulation and third ventricle over the course of aging is relevant to SCN regulation, including the SCN^{VIP} regulation [162], and thereby to PVN^{CRH} neuronal regulation and the CAR/HPA axis. Notably, PVN^{CRH} neuronal activation is significantly suppressed by PVN oxytocin neurons, which seems likely to be mediated by the release of oxytocin in dense core vesicles that act to on oxytocin receptors on PVN astrocytes. This would parallel the effects of PVN oxytocin neuronal projections to the central amygdala where oxytocin acts on astrocyte oxytocin neurons to suppress CRH release and the consequent CRH induction of the dynorphin/kappa-opioid receptor activation that seems to underpin the dysphoria evident in mood and affective disorders as well as in PCOS [163,164].

This may have relevance to Alzheimer's disease. Data shows melatonin, SCN melatonin receptor (MT1r) and VIP to be significantly decreased in later stages of dementia [165], implicating suppression of pineal melatonin with not only alterations in GR nuclear translocation but also in the timing and amplitude of the CAR/HPA axis. Oxytocin is popularly associated with social processes/bonding/cognition [166], with social isolation being a susceptibility and accelerating factor in Alzheimer's disease [167]. Notably, the oxytocin receptor is significantly

regulated by HDAC [168], indicating that the loss of gut microbiome-derived butyrate will impact on the level and influence of astrocyte oxytocin receptors in the modulation of CRH.

5. Future Research and Treatment Implications

It is becoming increasingly clear in recent decades that understanding neuronal loss in dementia has to progress from a conception of 'good' (BDNF) and 'bad' (plaques and tangles) to a conception that embraces and incorporates the complexity of data pertaining to Alzheimer's disease. The above goes some way to incorporate most of the detailed data on Alzheimer's disease pathophysiology. A number of future research directions and treatment/prevention implications are detailed below.

5.1 Future Research Implications

Whether local paracrine melatonin release from astrocytes regulates local α7nAChR levels, thereby impacting on immune/glia inflammation and associated consequences on cognition will be important to determine.

Whether the suppressed capacity to induce astrocyte melatonin over aging has heightened consequences for ApoE4 carriers will be important to clarify.

There is a growing appreciation of the role of platelets, and their regulation by gut microbiome-circadian interactions, in the pathophysiology of an array of diverse medical conditions, including Alzheimer's disease, amyotrophic lateral sclerosis, and cancer [169]. The role of gut microbiome-circadian interactions in the modulation of Alzheimer's disease pathophysiology will be important to determine, including via the regulation of platelet serotonin as a precursor for the mitochondrial melatonergic pathway.

The importance of the gut microbiome in Alzheimer's disease is indicated by clinical and preclinical data indicating that the increased risk of Alzheimer's disease in the partners of Alzheimer's disease patients may be mediated cohabitation linked similarities in their gut microbiomes [170].

Whether the role of autocrine melatonin in switching from an inflammatory M1-like phenotype in macrophages [35] and microglia [80] to a quiescent, pro-phagocytic M2-like phenotype is paralleled in astrocytes will be important to determine.

A number of processes may contribute to the increased glutamate/GABA ratio in Alzheimer's disease, including MERTK phagocytosis of excitatory inputs to GABA neurons, YY1 suppression of EAAT2, and increased System X_C^-. It will be important to determine the relative influences of such processes, including heightened glutamatergic activity induction of pro-BDNF, TrkB-T1 and the $p75^{NTR}$ in driving neuronal loss and Alzheimer's disease pathophysiology.

Whether the loss of night-time pineal melatonin and gut microbiome-derived butyrate increases the morning CAR activation of astrocyte GR to not only increase BACE1 and amyloid-β but also contribute to MERTK induction and heightened TrkB-T1 levels, perhaps especially in the presence of amyloid-β, will be important to determine.

The conversion of glucose to pyruvate in astrocytes favors the conversion of pyruvate to lactate, with relatively little pyruvate utilized by the astrocyte mitochondrial PDC, as evident in neurons under challenge, during neuronal activity and in conditions of hypoxia [151]. Whether this is dependent upon the availability of the astrocyte mitochondrial melatonergic pathway, including in the course of aging when the astrocyte mitochondrial melatonergic pathway may be suppressed will be important to determine.

Whether a suppressed astrocyte mitochondrial melatonergic pathway underpins System X_C^- upregulation in a quest to regulate astrocyte antioxidant status by GSH provision will be important to determine. Whether the loss of astrocyte (and/or pineal) melatonin decreases astrocyte lactate dehydrogenase, thereby decreasing the conversion of pyruvate to lactate will be important to determine. As astrocyte lactate is converted to pyruvate in neurons, thereby enhancing neuronal mitochondrial function, acetyl-CoA and neuronal mitochondrial melatonergic pathway induction, the suppression of astrocyte melatonin may have dramatic consequences for neuronal function, as well as the loss of astrocyte and neuronal melatonin increasing levels of hyperphosphorylated tau. This is important for future research to determine.

5.2 Treatment Implications

The above systemic conceptualization of Alzheimer's disease and its emphasis on astrocytes and the astrocyte melatonergic pathway as a crucial hub has a number of treatment implications that will be better clarified when the astrocyte melatonergic pathway is more extensively investigated. However, a number of treatment targets are readily apparent.

(1) The utilization of melatonin and monitoring of the gut microbiome to optimize butyrate production is likely to suppress Alzheimer's disease pathoetiology for those genetically at risk and in the early stages of mild cognitive impairment. The utility of melatonin and butyrate is likely to wane as dementia progresses, although this has still to be systematically investigated.

(2) A number of factors may act to suppress the astrocyte tryptophan-melatonin pathway, including suppressed 14-3-3 isoforms, serotonin and acetyl-CoA. Whether the adjunctive use of tryptophan supplements with melatonin and butyrate affords any added protection will be important to determine, given their safety profiles and ready availability.

(3) A number of AhR inhibitors show utility in Alzheimer's disease preclinical models, including green tea's epigallocatechin gallate [171], curcumin [172] and resveratrol [173], with efficacy often being modelled on diverse physiological processes, such as the induction of sirtuin-1 [174], although all dampen inflammatory processes in astrocytes [172,175,176], whilst also inhibiting and regulating the AhR [177–179]. As well as helping to preserve melatonin levels via AhR inhibition, these nutriceuticals can increase the tryptophan-melatonin pathway via other mechanisms, including via the inhibition of MAO, thereby increasing serotonin availability [180–182]. Increasing serotonin availability from dorsal raphe neurons as well as platelets is likely to have utility under conditions when the AhR is relatively suppressed [169].

(4) Although requiring more technical development, the utilization of mesenchymal stem cell exosomes that target the astrocyte and/or pinealocyte tryptophan-melatonin pathway would allow a more precise treatment focus on key hubs in Alzheimer's disease pathophysiology.

(5) It is important to mention that social processes and physical contact can have important physiological consequences that can modulate Alzheimer's disease pathophysiology, as highlighted by the acceleration of dementia by loneliness, with effects at least partly mediated via the regulation of the HPA axis [183].

(6) Some of the physiological consequences of social interaction may be mediated via the upregulation of hypothalamic and amygdala oxytocin and the oxytocin suppression of stress/dysphoria associated CRH via hypothalamic and amygdala astrocytes [163,164]. Recent work indicates that oxytocin intranasal administration has a number of benefits, including cognitive in Alzheimer's disease patients [166].

6. Conclusions

There is a growing dissatisfaction with lack of progress in understanding Alzheimer's disease pathophysiology, and the consequent lack of any plausible treatment. It seems clear that there is more to Alzheimer's disease than amyloid-β and its annihilation by anti-amyloid antibodies [1]. Given the increases in amyloid-β in numerous other medical conditions and data showing amyloid-β to be an endogenous antimicrobial, it is clear that amyloid-β is part of a dysregulated inflammatory process. The data reviewed above highlight the role of systemic processes, including the circadian rhythm (pineal melatonin and cortisol awakening response), gut microbiome/permeability (LPS and butyrate) and white adipocytes (kynurenine activation of the AhR) that interact to modulate astrocyte function. As brain 'immune type' cells, astrocytes have a powerful role in the regulation of neuronal survival and function, including by the provision of energy (lactate) and antioxidants. Astrocyte dysregulation is therefore a major problem for neuronal survival and function. Over the course of aging, there is a 10-fold decrease in pineal melatonin, leading to the loss of its antioxidant, anti-inflammatory and mitochondria optimizing effects, which has significant CNS and systemic consequences. Astrocytes have long been known to constitutively produce and release melatonin. Whether astrocyte melatonin is decreased, as in the pineal gland, over aging is surprisingly unknown, especially as exogenous melatonin has been extensively shown to prevent amyloid-β induced neuronal loss in preclinical models. The two transcription factors that upregulate BACE1 and amyloid-β production, NF-kB and YY1, have been shown in other cell types to induce melatonin, suggesting that it may be the loss of concurrent/sequential melatonin in astrocytes that underpins the prolonged amyloid-β production. Suppressed astrocyte melatonin would be compatible with the System X_c^- upregulation in astrocytes to acquire antioxidant support by glutathione synthesis, which has the unfortunate consequence of increasing glutamatergic excitotoxicity, further contributing to a spreading neuronal loss. The terminal process in neuronal death seems to arise as a consequence of decreased astrocyte lactate provision and the incapacity of neurons to optimize mitochondrial function, including the mitochondrial melatonergic pathway. The loss of neuronal melatonin drives an oxidant-driven decrease in mitophagy and increase in MHC-1, which chemoattracts $CD8^+$ t cells, implicating 'autoimmune'/'immune-mediated' processes as a final stage of neuronal death in Alzheimer's disease. This provides a number of viable research and treatment targets, the investigation of which should clarify more appropriate management that is targeted to core pathophysiological processes in both the prevention and treatment of dementia.

Abbreviations

5-HT, serotonin; 5-HTTP, 5-hydroxytryptophan; α7nAChR, alpha 7nicotinic acetylcholine receptor; AADC, aromatic-L-amino acid decarboxylase; AANAT, aralkylamine N-acetyltransferase; acetyl-CoA, acetyl-coenzyme A; ACTH, adrenocorticotropic hormone; AhR, aryl hydrocarbon receptor; ALS, amyotrophic lateral sclerosis; AMPK, AMP-activated protein kinase; Apo, apolipoprotein; ASMT, N-acetylserotonin O-methyltransferase; BAG-1, bcl-2 associated athanogene 1; BAT, brown adipocyte; BDNF, brain-derived neurotrophic factor; CAR, cortisol awakening response; CRH, corticotrophin releasing hormone; CSF, cerebrospinal fluid; CYP, cytochrome P450; EAAT, excitatory amino acid; GPR, G-protein coupled receptors; GR, glucocorticoid receptor; GRE, glucocorticoid receptor element; HDAC, histone deacetylase; HMGB, high-mobility group box; HPA, hypothalamic-pituitary-adrenal; hsp, heat shock protein; IDO, indoleamine 2,3-dioxygenase; LAT-1, large amino acid transporter 1; MAO, monoamine oxidase; MERTK, MER Proto-Oncogene, Tyrosine Kinase; MHC, major histocompatibility complex; NAS, N-acetylserotonin;

NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP, nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-; OXPHOS, oxidative phosphorylation; PCOS, polycystic ovary syndrome; PDC, pyruvate dehydrogenase complex; PINK1, PTEN-associated kinase 1; PVN, paraventricular nucleus; SCN, suprachiasmatic nucleus; T1DM, type 1 diabetes mellitus; TCA, tricarboxylic acid; TDO, tryptophan 2,3-dioxygenase; TIM, mitochondrial import inner membrane translocase subunit; TOM, mitochondrial import outer receptor subunit; TrkB-FL, tyrosine receptor kinase B-full length; TrkB-T1, tyrosine receptor kinase B-truncated; VIP, vasoactive intestinal peptide; WAT, white adipocyte.

Author Contributions

GA was responsible for the entire preparation of this manuscript.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The author declares no conflict of interest.

References

[1] Anderson G. Why do anti-amyloid beta antibodies not work? Time to reconceptualize dementia pathophysiology by incorporating astrocyte melatonergic pathway desynchronization from amyloid-beta production. Revista Brasileira de Psiquiatria. 2023; 45: 89–92.

[2] Glenner GG, Wong CW. Alzheimer's disease: initial report of the purification and characterization of a novel cerebrovascular amyloid protein. Biochemical and Biophysical Research Communications. 1984; 120: 885–890.

[3] Sheehan PW, Nadarajah CJ, Kanan MF, Patterson JN, Novotny B, Lawrence JH, *et al*. An astrocyte BMAL1-BAG3 axis protects against alpha-synuclein and tau pathology. Neuron. 2023; 111: 2383–2398.e7.

[4] Ellouze I, Sheffler J, Nagpal R, Arjmandi B. Dietary Patterns and Alzheimer's Disease: An Updated Review Linking Nutrition to Neuroscience. Nutrients. 2023; 15: 3204.

[5] Johnson GA, Krishnamoorthy RR, Stankowska DL. Modulating mitochondrial calcium channels (TRPM2/MCU/NCX) as a therapeutic strategy for neurodegenerative disorders. Frontiers in neuroscience. 2023; 17: 1202167.

[6] Ticinesi A, Mancabelli L, Carnevali L, Nouvenne A, Meschi T, Del Rio D, *et al*. Interaction Between Diet and Microbiota in the Pathophysiology of Alzheimer's Disease: Focus on Polyphenols and Dietary Fibers. Journal of Alzheimer's Disease. 2022; 86: 961–982.

[7] Anderson G, Ojala J. Alzheimer's and seizures: interleukin-18, indoleamine 2,3-dioxygenase and quinolinic Acid. International Journal of Tryptophan Research. 2010; 3: 169–173.

[8] Anderson G, Maes M. Local melatonin regulates inflammation resolution: a common factor in neurodegenerative, psychiatric and systemic inflammatory disorders. CNS & Neurological Disorders Drug Targets. 2014; 13: 817–827.

[9] Vojtechova I, Machacek T, Kristofikova Z, Stuchlik A, Petrasek T. Infectious origin of Alzheimer's disease: Amyloid beta as a component of brain antimicrobial immunity. PLoS Pathogens. 2022; 18: e1010929.

[10] Zayas-Santiago A, Díaz-García A, Nuñez-Rodríguez R, Inyushin M. Accumulation of amyloid beta in human glioblastomas. Clinical and Experimental Immunology. 2020; 202: 325–334.

[11] Zayas-Santiago A, Martínez-Montemayor MM, Colón-Vázquez J, Ortiz-Soto G, Cirino-Simonet JG, Inyushin M. Accumulation of amyloid beta (Aβ) and amyloid precursor protein (APP) in tumors formed by a mouse xenograft model of inflammatory breast cancer. FEBS Open Bio. 2022; 12: 95–105.

[12] Anderson G. Type I Diabetes Pathoetiology and Pathophysiology: Roles of the Gut Microbiome, Pancreatic Cellular Interactions, and the 'Bystander' Activation of Memory CD8$^+$ T Cells. International Journal of Molecular Sciences. 2023; 24: 3300.

[13] Vadukul DM, Papp M, Thrush RJ, Wang J, Jin Y, Arosio P, *et al*. α-Synuclein Aggregation Is Triggered by Oligomeric Amyloid-β 42 via Heterogeneous Primary Nucleation. Journal of the American Chemical Society. 2023; 145: 18276–18285.

[14] Anderson G. Amyotrophic Lateral Sclerosis Pathoetiology and Pathophysiology: Roles of Astrocytes, Gut Microbiome, and Muscle Interactions via the Mitochondrial Melatonergic Pathway, with Disruption by Glyphosate-Based Herbicides. International Journal of Molecular Sciences. 2022; 24: 587.

[15] Sarahian N, Sarvazad H, Sajadi E, Rahnejat N, Eskandari Roozbahani N. Investigation of common risk factors between polycystic ovary syndrome and Alzheimer's disease: a narrative review. Reproductive Health. 2021; 18: 156.

[16] Sabayan B, Foroughinia F, Borhani Haghighi A, Mowla A. Are women with polycystic ovary syndrome (PCOS) at higher risk for development of Alzheimer disease? Alzheimer Disease and Associated Disorders. 2007; 21: 265.

[17] Chang WH, Su CC, Chen KC, Hsiao YY, Chen PS, Yang YK. Which Severe Mental Illnesses Most Increase the Risk of Developing Dementia? Comparing the Risk of Dementia in Patients with Schizophrenia, Major Depressive Disorder and Bipolar Disorder. Clinical Psychopharmacology and Neuroscience. 2023; 21: 478–487.

[18] Terracciano A, Cenatus B, Zhu X, Karakose S, Stephan Y, Marcolini S, *et al*. Neuroticism and white matter hyperintensities. Journal of Psychiatric Research. 2023; 165: 174–179.

[19] Boccara E, Golan S, Beeri MS. The association between regional adiposity, cognitive function, and dementia-related brain changes: a systematic review. Frontiers in Medicine. 2023; 10: 1160426.

[20] Pino JMV, Silva VF, Mônico-Neto M, Seva DC, Kato MY, Alves JN, *et al*. Severe Obesity in Women Can Lead to Worse Memory Function and Iron Dyshomeostasis Compared to Lower Grade Obesity. International Journal of Endocrinology. 2023; 2023: 7625720.

[21] Prieto S, Nolan KE, Moody JN, Hayes SM, Hayes JP, Department of Defense Alzheimer's Disease Neuroimaging Initiative. Posttraumatic stress symptom severity predicts cognitive decline beyond the effect of Alzheimer's disease biomarkers in Veterans. Translational Psychiatry. 2023; 13: 102.

[22] Misiura MB, Butts B, Hammerschlag B, Munkombwe C, Bird A, Fyffe M, *et al*. Intersectionality in Alzheimer's Disease: The Role of Female Sex and Black American Race in the Development and Prevalence of Alzheimer's Disease. Neurotherapeutics. 2023; 20: 1019–1036.

[23] Kim J, Ha WS, Park SH, Han K, Baek MS. Association between migraine and Alzheimer's disease: a nationwide cohort study. Frontiers in Aging Neuroscience. 2023; 15: 1196185.
[24] Litkowski EM, Logue MW, Zhang R, Charest BR, Lange EM, Hokanson JE, *et al*. Mendelian randomization study of diabetes and dementia in the Million Veteran Program. Alzheimer's & Dementia. 2002; 23: 14–16.
[25] Karasek M, Reiter R J. Melatonin and aging. Neuroendocrinology Letters. 2002; 23: 14–16.
[26] Anderson G. Daytime orexin and night-time melatonin regulation of mitochondria melatonin: roles in circadian oscillations systemically and centrally in breast cancer symptomatology. Melatonin Research. 2019; 2: 1–8.
[27] Tobeiha M, Jafari A, Fadaei S, Mirazimi SMA, Dashti F, Amiri A, *et al*. Evidence for the Benefits of Melatonin in Cardiovascular Disease. Frontiers in Cardiovascular Medicine. 2022; 9: 888319.
[28] Ahmad F, Sachdeva P, Sarkar J, Izhaar R. Circadian dysfunction and Alzheimer's disease - An updated review. Aging Medicine (Milton (N.S.W)). 2022; 6: 71–81.
[29] Mihardja M, Roy J, Wong KY, Aquili L, Heng BC, Chan YS, *et al*. Therapeutic potential of neurogenesis and melatonin regulation in Alzheimer's disease. Annals of the New York Academy of Sciences. 2020; 1478: 43–62.
[30] Park H, Kim J. Activation of melatonin receptor 1 by CRISPR-Cas9 activator ameliorates cognitive deficits in an Alzheimer's disease mouse model. Journal of Pineal Research. 2022; 72: e12787.
[31] Chen C, Yang C, Wang J, Huang X, Yu H, Li S, *et al*. Melatonin ameliorates cognitive deficits through improving mitophagy in a mouse model of Alzheimer's disease. Journal of Pineal Research. 2021; 71: e12774.
[32] Tan DX, Manchester LC, Liu X, Rosales-Corral SA, Acuna-Castroviejo D, Reiter RJ. Mitochondria and chloroplasts as the original sites of melatonin synthesis: a hypothesis related to melatonin's primary function and evolution in eukaryotes. Journal of Pineal Research. 2013; 54: 127–138.
[33] Anderson G, Almulla AF, Reiter RJ, Maes M. Redefining Autoimmune Disorders' Pathoetiology: Implications for Mood and Psychotic Disorders' Association with Neurodegenerative and Classical Autoimmune Disorders. Cells. 2023; 12: 1237.
[34] Wang BY, Ye YY, Qian C, Zhang HB, Mao HX, Yao LP, *et al*. Stress increases MHC-I expression in dopaminergic neurons and induces autoimmune activation in Parkinson's disease. Neural Regeneration Research. 2021; 16: 2521–2527.
[35] Muxel SM, Pires-Lapa MA, Monteiro AWA, Cecon E, Tamura EK, Floeter-Winter LM, *et al*. 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. 2012; 7: e52010.
[36] Bernard M, Voisin P. Photoreceptor-specific expression, light-dependent localization, and transcriptional targets of the zinc-finger protein Yin Yang 1 in the chicken retina. Journal of Neurochemistry. 2008; 105: 595–604.
[37] Ebell MH, Barry HC. Why Physicians Should Not Prescribe Aducanumab for Alzheimer Disease. American Family Physician. 2022; 105: 353–354.
[38] Shukla M, Htoo HH, Wintachai P, Hernandez JF, Dubois C, Postina R, *et al*. Melatonin stimulates the nonamyloidogenic processing of βAPP through the positive transcriptional regulation of ADAM10 and ADAM17. Journal of Pineal Research. 2015; 58: 151–165.
[39] Panmanee J, Nopparat C, Chavanich N, Shukla M, Mukda S, Song W, *et al*. Melatonin regulates the transcription of βAPP-cleaving secretases mediated through melatonin receptors in human neuroblastoma SH-SY5Y cells. Journal of Pineal Research. 2015; 59: 308–320.
[40] Leone V, Gibbons SM, Martinez K, Hutchison AL, Huang EY, Cham CM, *et al*. Effects of diurnal variation of gut microbes and high-fat feeding on host circadian clock function and metabolism. Cell Host & Microbe. 2015; 17: 681–689.
[41] Anderson G. Melatonin, BAG-1 and cortisol circadian interactions in tumor pathogenesis. Roles of glucocorticoid receptor translocation site and mitochondrial melatonergic pathway. Exploration of Targeted Anti-tumor Therapy. 2023; 4: 962–993.
[42] Anderson G, Maes M. Gut Dysbiosis Dysregulates Central and Systemic Homeostasis via Suboptimal Mitochondrial Function: Assessment, Treatment and Classification Implications. Current Topics in Medicinal Chemistry. 2020; 20: 524–539.
[43] Gao T, Wang Z, Dong Y, Cao J, Lin R, Wang X, *et al*. Role of melatonin in sleep deprivation-induced intestinal barrier dysfunction in mice. Journal of Pineal Research. 2019; 67: e12574.
[44] Paulose JK, Cassone VM. The melatonin-sensitive circadian clock of the enteric bacterium Enterobacter aerogenes. Gut Microbes. 2016; 7: 424–427.
[45] Graniczkowska KB, Shaffer CL, Cassone VM. Transcriptional effects of melatonin on the gut commensal bacterium Klebsiella aerogenes. Genomics. 2022; 114: 110321.
[46] Huang M, Yu Y, Tang X, Dong R, Li X, Li F, *et al*. 3-Hydroxybutyrate ameliorates sepsis-associated acute lung injury by promoting autophagy through the activation of GPR109α in macrophages. Biochemical Pharmacology. 2023; 213: 115632.
[47] Patnala R, Arumugam TV, Gupta N, Dheen ST. HDAC Inhibitor Sodium Butyrate-Mediated Epigenetic Regulation Enhances Neuroprotective Function of Microglia During Ischemic Stroke. Molecular Neurobiology. 2017; 54: 6391–6411.
[48] Chen M, Hui S, Lang H, Zhou M, Zhang Y, Kang C, *et al*. SIRT3 Deficiency Promotes High-Fat Diet-Induced Nonalcoholic Fatty Liver Disease in Correlation with Impaired Intestinal Permeability through Gut Microbial Dysbiosis. Molecular Nutrition & Food Research. 2019; 63: e1800612.
[49] Aleshin VA, Artiukhov AV, Kaehne T, Graf AV, Bunik VI. Daytime Dependence of the Activity of the Rat Brain Pyruvate Dehydrogenase Corresponds to the Mitochondrial Sirtuin 3 Level and Acetylation of Brain Proteins, All Regulated by Thiamine Administration Decreasing Phosphorylation of PDHA Ser293. International Journal of Molecular Sciences. 2021; 22: 8006.
[50] Jin CJ, Engstler AJ, Sellmann C, Ziegenhardt D, Landmann M, Kanuri G, *et al*. Sodium butyrate protects mice from the development of the early signs of non-alcoholic fatty liver disease: role of melatonin and lipid peroxidation. The British Journal of Nutrition. 2016; 116: 1682–1693.
[51] Fernandes PA, Tamura EK, D'Argenio-Garcia L, Muxel SM, da Silveira Cruz-Machado S, Marçola M, *et al*. Dual Effect of Catecholamines and Corticosterone Crosstalk on Pineal Gland Melatonin Synthesis. Neuroendocrinology. 2017; 104: 126–134.
[52] Vanuytsel T, van Wanrooy S, Vanheel H, Vanormelingen C, Verschueren S, Houben E, *et al*. Psychological stress and corticotropin-releasing hormone increase intestinal permeability in humans by a mast cell-dependent mechanism. Gut. 2014; 63: 1293–1299.
[53] Shukla PK, Meena AS, Pierre JF, Rao R. Central role of intestinal epithelial glucocorticoid receptor in alcohol- and corticosterone-induced gut permeability and systemic response. FASEB Journal. 2022; 36: e22061.
[54] Saelzler UG, Verhaeghen P, Panizzon MS, Moffat SD. Intact circadian rhythm despite cortisol hypersecretion in Alzheimer's disease: A meta-analysis. Psychoneuroendocrinology. 2021; 132: 105367.
[55] Stalder T, Lupien SJ, Kudielka BM, Adam EK, Pruessner JC, Wüst S, *et al*. Evaluation and update of the expert consensus guidelines for the assessment of the cortisol awakening response (CAR). Psychoneuroendocrinology. 2022; 146: 105946.
[56] Quiros I, Mayo JC, Garcia-Suarez O, Hevia D, Martin V, Rodríguez C, *et al*. Melatonin prevents glucocorticoid inhibition

of cell proliferation and toxicity in hippocampal cells by reducing glucocorticoid receptor nuclear translocation. The Journal of Steroid Biochemistry and Molecular Biology. 2008; 110: 116–124.

[57] Kim M, Lee HA, Cho HM, Kang SH, Lee E, Kim IK. Histone deacetylase inhibition attenuates hepatic steatosis in rats with experimental Cushing's syndrome. The Korean Journal of Physiology & Pharmacology. 2018; 22: 23–33.

[58] Zhu K, Zhang Y, Zhang J, Zhou F, Zhang L, Wang S, *et al*. Acetylation of Hsp90 reverses dexamethasone-mediated inhibition of insulin secretion. Toxicology Letters. 2020; 320: 19–27.

[59] Anderson G. Tumor Microenvironment and Metabolism: Role of the Mitochondrial Melatonergic Pathway in Determining Intercellular Interactions in a New Dynamic Homeostasis. International Journal of Molecular Sciences. 2022; 24: 311.

[60] Weaver DF. The Immunopathy of Alzheimer's Disease: Innate or Adaptive? Current Alzheimer Research. 2023; 20: 63–70.

[61] Jia WY, Zhang JJ. Effects of glucocorticoids on leukocytes: Genomic and non-genomic mechanisms. World Journal of Clinical Cases. 2022; 10: 7187–7194.

[62] Anderson G. Why are aging and stress associated with dementia, cancer, and other diverse medical conditions? Role of pineal melatonin interactions with the HPA axis in mitochondrial regulation via BAG-1. Melatonin Research. 2023; 6: 345–371.

[63] Luo S, Hou Y, Zhang Y, Feng L, Hunter RG, Yuan P, *et al*. Bag-1 mediates glucocorticoid receptor trafficking to mitochondria after corticosterone stimulation: Potential role in regulating affective resilience. Journal of Neurochemistry. 2021; 158: 358–372.

[64] Sultana MA, Hia RA, Akinsiku O, Hegde V. Peripheral Mitochondrial Dysfunction: A Potential Contributor to the Development of Metabolic Disorders and Alzheimer's Disease. Biology. 2023; 12: 1019.

[65] Zyśk M, Beretta C, Naia L, Dakhel A, Påvénius L, Brismar H, *et al*. Amyloid-β accumulation in human astrocytes induces mitochondrial disruption and changed energy metabolism. Journal of Neuroinflammation. 2023; 20: 43.

[66] Fairley LH, Lai KO, Wong JH, Chong WJ, Vincent AS, D'Agostino G, *et al*. Mitochondrial control of microglial phagocytosis by the translocator protein and hexokinase 2 in Alzheimer's disease. Proceedings of the National Academy of Sciences of the United States of America. 2023; 120: e2209177120.

[67] Todosenko N, Khaziakhmatova O, Malashchenko V, Yurova K, Bograya M, Beletskaya M, *et al*. Mitochondrial Dysfunction Associated with mtDNA in Metabolic Syndrome and Obesity. International Journal of Molecular Sciences. 2023; 24: 12012.

[68] Luo M, Santulli G. Editorial: The link between obesity, type 2 diabetes, and mitochondria. Frontiers in Endocrinology. 2023; 14: 1229935.

[69] Anderson G. Depression Pathophysiology: Astrocyte Mitochondrial Melatonergic Pathway as Crucial Hub. International Journal of Molecular Sciences. 2022; 24: 350.

[70] Liu T, Zuo H, Ma D, Song D, Zhao Y, Cheng O. Cerebrospinal fluid GFAP is a predictive biomarker for conversion to dementia and Alzheimer's disease-associated biomarkers alterations among de novo Parkinson's disease patients: a prospective cohort study. Journal of Neuroinflammation. 2023; 20: 167.

[71] Milicevic KD, Bataveljic DB, Bogdanovic Pristov JJ, Andjus PR, Nikolic LM. Astroglial Cell-to-Cell Interaction with Autoreactive Immune Cells in Experimental Autoimmune Encephalomyelitis Involves P2X7 Receptor, β_3-Integrin, and Connexin-43. Cells. 2023; 12: 1786.

[72] Gong CY, Zhou AL, Mao JH, Hu YE, Geng JS. The role of Toll-like receptor 4 on inflammation and Aβ formation in cortex astrocytes. Sheng Li Xue Bao. 2014; 66: 631–638.

[73] Nowak K, Lange-Dohna C, Zeitschel U, Günther A, Lüscher B, Robitzki A, *et al*. The transcription factor Yin Yang 1 is an activator of BACE1 expression. Journal of Neurochemistry. 2006; 96: 1696–1707.

[74] Shao A, Gao S, Wu H, Xu W, Pan Y, Fang Y, *et al*. Melatonin Ameliorates Hemorrhagic Transformation via Suppression of ROS-Induced NLRP3 Activation after Cerebral Ischemia in Hyperglycemic Rats. Oxidative Medicine and Cellular Longevity. 2021; 2021: 6659282.

[75] Farré-Alins V, Narros-Fernández P, Palomino-Antolín A, Decouty-Pérez C, Lopez-Rodriguez AB, Parada E, *et al*. Melatonin Reduces NLRP3 Inflammasome Activation by Increasing α7 nAChR-Mediated Autophagic Flux. Antioxidants (Basel, Switzerland). 2020; 9: 1299.

[76] Wang X, Bell IM, Uslaner JM. Activators of α7 nAChR as Potential Therapeutics for Cognitive Impairment. Current Topics in Behavioral Neurosciences. 2020; 45: 209–245.

[77] Xia X, He X, Zhao T, Yang J, Bi Z, Fu Q, *et al*. Inhibiting mtDNA-STING-NLRP3/IL-1β axis-mediated neutrophil infiltration protects neurons in Alzheimer's disease. Cell Proliferation. 2023; e13529.

[78] Singh S, Agrawal N, Goyal A. Role of Alpha-7-Nicotinic Acetylcholine Receptor in Alzheimer's Disease. CNS & Neurological Disorders Drug Targets. 2023. (online ahead of print)

[79] Hunter RG, Bloss EB, McCarthy KJ, McEwen BS. Regulation of the nicotinic receptor alpha7 subunit by chronic stress and corticosteroids. Brain Research. 2010; 1325: 141–146.

[80] Markus RP, Silva CLM, Franco DG, Barbosa EM, Jr, Ferreira ZS. Is modulation of nicotinic acetylcholine receptors by melatonin relevant for therapy with cholinergic drugs? Pharmacology & Therapeutics. 2010; 126: 251–262.

[81] Gergalova G, Lykhmus O, Kalashnyk O, Koval L, Chernyshov V, Kryukova E, *et al*. Mitochondria express α7 nicotinic acetylcholine receptors to regulate Ca2+ accumulation and cytochrome c release: study on isolated mitochondria. PLoS ONE. 2012; 7: e31361.

[82] Lv G, Wang W, Sun M, Wang F, Ma Y, Li C. Inhibiting specificity protein 1 attenuated sevoflurane-induced mitochondrial stress and promoted autophagy in hippocampal neurons through PI3K/Akt/mTOR and α7-nAChR signaling. Neuroscience Letters. 2023; 794: 136995.

[83] Liu YJ, Zhuang J, Zhu HY, Shen YX, Tan ZL, Zhou JN. Cultured rat cortical astrocytes synthesize melatonin: absence of a diurnal rhythm. Journal of Pineal Research. 2007; 43: 232–238.

[84] Liu YJ, Meng FT, Wang LL, Zhang LF, Cheng XP, Zhou JN. Apolipoprotein E influences melatonin biosynthesis by regulating NAT and MAOA expression in C6 cells. Journal of Pineal Research. 2012; 52: 397–402.

[85] Strittmatter WJ, Saunders AM, Schmechel D, Pericak-Vance M, Enghild J, Salvesen GS, *et al*. Apolipoprotein E: high-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. Proceedings of the National Academy of Sciences of the United States of America. 1993; 90: 1977–1981.

[86] Sienski G, Narayan P, Bonner JM, Kory N, Boland S, Arczewska AA, *et al*. *APOE4* disrupts intracellular lipid homeostasis in human iPSC-derived glia. Science Translational Medicine. 2021; 13: eaaz4564.

[87] Sorrentino F, Arighi A, Serpente M, Arosio B, Arcaro M, Visconte C, *et al*. Niemann-Pick Type C 1 (NPC1) and NPC2 Gene Variability in Demented Patients with Evidence of Brain Amyloid Deposition. Journal of Alzheimer's Disease. 2021; 83: 1313–1323.

[88] Diep YN, Park HJ, Kwon JH, Tran M, Ko HY, Jo H, *et al*. Astrocytic scar restricting glioblastoma via glutamate-MAO-B activity in glioblastoma-microglia assembloid. Biomaterials Research. 2023; 27: 71.

[89] Chang NP, DaPrano EM, Evans WR, Nissenbaum M, McCourt M, Alzate D, *et al*. Neuronal DAMPs exacerbate neurodegener-

ation via astrocytic RIPK3 signaling. bioRxiv. 2023. (preprint)
[90] Fiock KL, Hook J, Hefti MM. Determinants of Astrocytic Pathology in Stem Cell Models of Primary Tauopathies. bioRxiv. 2023. (preprint)
[91] Miao G, Zhuo D, Han X, Yao W, Liu C, Liu H, *et al*. From degenerative disease to malignant tumors: Insight to the function of ApoE. Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie. 2023; 158: 114127.
[92] Liu JY, Ma LZ, Wang J, Cui XJ, Sheng ZH, Fu Y, *et al*. Age-Related Association Between APOE ε4 and Cognitive Progression in de novo Parkinson's Disease. Journal of Alzheimer's Disease. 2023; 91: 1121–1132.
[93] Palmer JM, Huentelman M, Ryan L. More than just risk for Alzheimer's disease: APOE ε4's impact on the aging brain. Trends in Neurosciences. 2023; 46: 750–763.
[94] He D, Shang L, Liu Q, Shen D, Sun X, Cai Z, *et al*. Association of apolipoprotein E ε4 allele and amyotrophic lateral sclerosis in Chinese population. Amyotrophic Lateral Sclerosis & Frontotemporal Degeneration. 2022; 23: 399–406.
[95] Smith GS, Protas H, Kuwabara H, Savonenko A, Nassery N, Gould NF, *et al*. Molecular imaging of the association between serotonin degeneration and beta-amyloid deposition in mild cognitive impairment. NeuroImage. Clinical. 2023; 37: 103322.
[96] Tajeddinn W, Fereshtehnejad SM, Seed Ahmed M, Yoshitake T, Kehr J, Shahnaz T, *et al*. Association of Platelet Serotonin Levels in Alzheimer's Disease with Clinical and Cerebrospinal Fluid Markers. Journal of Alzheimer's Disease. 2016; 53: 621–630.
[97] Srivastav S, Neupane S, Bhurtel S, Katila N, Maharjan S, Choi H, *et al*. Probiotics mixture increases butyrate, and subsequently rescues the nigral dopaminergic neurons from MPTP and rotenone-induced neurotoxicity. The Journal of Nutritional Biochemistry. 2019; 69: 73–86.
[98] Babaee A, Vaghefi SHE, Dehghani Soltani S, Asadi Shekaari M, Shahrokhi N, Basiri M. Hippocampal Astrocyte Response to Melatonin Following Neural Damage Induction in Rats. Basic and Clinical Neuroscience. 2021; 12: 177–186.
[99] Yawoot N, Sengking J, Wicha P, Govitrapong P, Tocharus C, Tocharus J. Melatonin attenuates reactive astrogliosis and glial scar formation following cerebral ischemia and reperfusion injury mediated by GSK-3β and RIP1K. Journal of Cellular Physiology. 2022; 237: 1818–1832.
[100] Yang J, Wang T, Jin X, Wang G, Zhao F, Jin Y. Roles of Crosstalk between Astrocytes and Microglia in Triggering Neuroinflammation and Brain Edema Formation in 1,2-Dichloroethane-Intoxicated Mice. Cells. 2021; 10: 2647.
[101] Mukda S, Panmanee J, Boontem P, Govitrapong P. Melatonin administration reverses the alteration of amyloid precursor protein-cleaving secretases expression in aged mouse hippocampus. Neuroscience Letters. 2016; 621: 39–46.
[102] Chinchalongporn V, Shukla M, Govitrapong P. Melatonin ameliorates Aβ_42 -induced alteration of βAPP-processing secretases via the melatonin receptor through the Pin1/GSK3β/NF-κB pathway in SH-SY5Y cells. Journal of Pineal Research. 2018; 64: e12470.
[103] Guo YL, Wei XJ, Zhang T, Sun T. Molecular mechanisms of melatonin-induced alleviation of synaptic dysfunction and neuroinflammation in Parkinson's disease: a review. European Review for Medical and Pharmacological Sciences. 2023; 27: 5070–5082.
[104] Eckers A, Jakob S, Heiss C, Haarmann-Stemmann T, Goy C, Brinkmann V, *et al*. The aryl hydrocarbon receptor promotes aging phenotypes across species. Scientific Reports. 2016; 6: 19618.
[105] Salminen A. Aryl hydrocarbon receptor (AhR) impairs circadian regulation: Impact on the aging process. Ageing Research Reviews. 2023; 87: 101928.
[106] Mokkawes T, de Visser SP. Melatonin Activation by Cytochrome P450 Isozymes: How Does CYP1A2 Compare to CYP1A1? International Journal of Molecular Sciences. 2023; 24: 3651.
[107] Ma X, Idle JR, Krausz KW, Gonzalez FJ. Metabolism of melatonin by human cytochromes p450. Drug Metabolism and Disposition: the Biological Fate of Chemicals. 2005; 33: 489–494.
[108] Hwang HJ, Dornbos P, Steidemann M, Dunivin TK, Rizzo M, LaPres JJ. Mitochondrial-targeted aryl hydrocarbon receptor and the impact of 2,3,7,8-tetrachlorodibenzo-p-dioxin on cellular respiration and the mitochondrial proteome. Toxicology and Applied Pharmacology. 2016; 304: 121–132.
[109] Steidemann MM, Liu J, Bayes K, Castro LP, Ferguson-Miller S, LaPres JJ. Evidence for crosstalk between the aryl hydrocarbon receptor and the translocator protein in mouse lung epithelial cells. Experimental Cell Research. 2023; 429: 113617.
[110] Anderson G, Maes M. Interactions of Tryptophan and Its Catabolites With Melatonin and the Alpha 7 Nicotinic Receptor in Central Nervous System and Psychiatric Disorders: Role of the Aryl Hydrocarbon Receptor and Direct Mitochondria Regulation. International Journal of Tryptophan Research. 2017; 10: 1178646917691738.
[111] Ojo ES, Tischkau SA. The Role of AhR in the Hallmarks of Brain Aging: Friend and Foe. Cells. 2021; 10: 2729.
[112] Németh H, Toldi J, Vécsei L. Role of kynurenines in the central and peripheral nervous systems. Current Neurovascular Research. 2005; 2: 249–260.
[113] Alemán JO, Iyengar NM, Walker JM, Milne GL, Da Rosa JC, Liang Y, *et al*. Effects of Rapid Weight Loss on Systemic and Adipose Tissue Inflammation and Metabolism in Obese Postmenopausal Women. Journal of the Endocrine Society. 2017; 1: 625–637.
[114] Jang SW, Liu X, Pradoldej S, Tosini G, Chang Q, Iuvone PM, *et al*. N-acetylserotonin activates TrkB receptor in a circadian rhythm. Proceedings of the National Academy of Sciences of the United States of America. 2010; 107: 3876–3881.
[115] Povarnina PY, Volkova AA, Vorontsova ON, Kamensky AA, Gudasheva TA, Seredenin SB. A Low-Molecular-Weight BDNF Mimetic, Dipeptide GSB-214, Prevents Memory Impairment in Rat Models of Alzheimer's Disease. Acta Naturae. 2022; 14: 94–100.
[116] Kemppainen S, Rantamäki T, Jerónimo-Santos A, Lavasseur G, Autio H, Karpova N, *et al*. Impaired TrkB receptor signaling contributes to memory impairment in APP/PS1 mice. Neurobiology of Aging. 2012; 33: 1122.e23-39.
[117] Tessarollo L, Yanpallewar S. TrkB Truncated Isoform Receptors as Transducers and Determinants of BDNF Functions. Frontiers in Neuroscience. 2022; 16: 847572.
[118] Byun YG, Kim NS, Kim G, Jeon YS, Choi JB, Park CW, *et al*. Stress induces behavioral abnormalities by increasing expression of phagocytic receptor MERTK in astrocytes to promote synapse phagocytosis. Immunity. 2023; 56: 2105–2120.e13.
[119] Zhou S, Li Y, Zhang Z, Yuan Y. An insight into the TAM system in Alzheimer's disease. International Immunopharmacology. 2023; 116: 109791.
[120] Zhang L, He CH, Coffey S, Yin D, Hsu IU, Su C, *et al*. Single-cell transcriptomic atlas of Alzheimer's disease middle temporal gyrus reveals region, cell type and sex specificity of gene expression with novel genetic risk for MERTK in female. medRxiv. 2023. (preprint)
[121] Yu SP, Jiang MQ, Shim SS, Pourkhodadad S, Wei L. Extrasynaptic NMDA receptors in acute and chronic excitotoxicity: implications for preventive treatments of ischemic stroke and late-onset Alzheimer's disease. Molecular Neurodegeneration. 2023; 18: 43.
[122] Tanqueiro SR, Ramalho RM, Rodrigues TM, Lopes LV, Sebastião AM, Diógenes MJ. Inhibition of NMDA Receptors Prevents the Loss of BDNF Function Induced by Amyloid β. Frontiers in Pharmacology. 2018; 9: 237.

[123] Choi GE, Lee SJ, Lee HJ, Ko SH, Chae CW, Han HJ. Membrane-Associated Effects of Glucocorticoid on BACE1 Upregulation and Aβ Generation: Involvement of Lipid Raft-Mediated CREB Activation. The Journal of Neuroscience. 2017; 37: 8459–8476.
[124] Choi GE, Park JY, Park MR, Yoon JH, Han HJ. Glucocorticoid enhances presenilin1-dependent Aβ production at ER's mitochondrial-associated membrane by downregulating Rer1 in neuronal cells. Redox Biology. 2023; 65: 102821.
[125] Anderson G. Tumour Microenvironment: Roles of the Aryl Hydrocarbon Receptor, O-GlcNAcylation, Acetyl-CoA and Melatonergic Pathway in Regulating Dynamic Metabolic Interactions across Cell Types-Tumour Microenvironment and Metabolism. International Journal of Molecular Sciences. 2020; 22: 141.
[126] Kang LL, Zhang DM, Jiao RQ, Pan SM, Zhao XJ, Zheng YJ, *et al*. Pterostilbene Attenuates Fructose-Induced Myocardial Fibrosis by Inhibiting ROS-Driven Pitx2c/miR-15b Pathway. Oxidative Medicine and Cellular Longevity. 2019; 2019: 1243215.
[127] Qiu J, Zhang J, Zhou Y, Li X, Li H, Liu J, *et al*. MicroRNA-7 inhibits melatonin synthesis by acting as a linking molecule between leptin and norepinephrine signaling pathways in pig pineal gland. Journal of Pineal Research. 2019; 66: e12552.
[128] Xu L, Li G, Tang X, Feng C, Li M, Jiang X, *et al*. MiR-375-3p mediates reduced pineal function in hypoxia-ischemia brain damage. Experimental Neurology. 2021; 344: 113814.
[129] Pagan C, Goubran-Botros H, Delorme R, Benabou M, Lemière N, Murray K, *et al*. Disruption of melatonin synthesis is associated with impaired 14-3-3 and miR-451 levels in patients with autism spectrum disorders. Scientific Reports. 2017; 7: 2096.
[130] do Carmo Buonfiglio D, Peliciari-Garcia RA, do Amaral FG, Peres R, Nogueira TCA, Afeche SC, *et al*. Early-stage retinal melatonin synthesis impairment in streptozotocin-induced diabetic wistar rats. Investigative Ophthalmology & Visual Science. 2011; 52: 7416–7422.
[131] Andrade MK, Souza LC, Azevedo EM, Bail EL, Zanata SM, Andreatini R, *et al*. Melatonin reduces β-amyloid accumulation and improves short-term memory in streptozotocin-induced sporadic Alzheimer's disease model. IBRO Neuroscience Reports. 2023; 14: 264–272.
[132] Patel R, Parmar N, Rathwa N, Palit SP, Li Y, Garcia-Ocaña A, *et al*. A novel therapeutic combination of sitagliptin and melatonin regenerates pancreatic β-cells in mouse and human islets. Biochimica et Biophysica Acta. Molecular Cell Research. 2022; 1869: 119263.
[133] Sun C, Qiu X, Wang Y, Liu J, Li Q, Jiang H, *et al*. Long-term oral melatonin alleviates memory deficits, reduces amyloid-β deposition associated with downregulation of BACE1 and mitophagy in APP/PS1 transgenic mice. Neuroscience Letters. 2020; 735: 135192.
[134] Fernando N, Gopalakrishnan J, Behensky A, Reich L, Liu C, Bass V, *et al*. Single-cell multiomic analysis reveals the involvement of Type I interferon-responsive CD8+ T cells in amyloid beta-associated memory loss. bioRxiv. 2023. (preprint)
[135] Wang C, Zou Q, Pu Y, Cai Z, Tang Y. Berberine Rescues D-Ribose-Induced Alzheimer's Pathology via Promoting Mitophagy. International Journal of Molecular Sciences. 2023; 24: 5896.
[136] Kellogg CM, Pham K, Machalinski AH, Porter HL, Blankenship HE, Tooley KB, *et al*. Microglial MHC-I induction with aging and Alzheimer's is conserved in mouse models and humans. GeroScience. 2023. (online ahead of print)
[137] Heming M, Börsch AL, Wiendl H, Meyer Zu Hörste G. High-dimensional investigation of the cerebrospinal fluid to explore and monitor CNS immune responses. Genome Medicine. 2022; 14: 94.
[138] Altendorfer B, Unger MS, Poupardin R, Hoog A, Asslaber D, Gratz IK, *et al*. Transcriptomic Profiling Identifies CD8$^+$ T Cells in the Brain of Aged and Alzheimer's Disease Transgenic Mice as Tissue-Resident Memory T Cells. Journal of Immunology (Baltimore, Md.: 1950). 2022; 209: 1272–1285.
[139] Anderson G, Carbone A, Mazzoccoli G. Tryptophan Metabolites and Aryl Hydrocarbon Receptor in Severe Acute Respiratory Syndrome, Coronavirus-2 (SARS-CoV-2) Pathophysiology. International Journal of Molecular Sciences. 2021; 22: 1597.
[140] Chen C, McDonald D, Blain A, Mossman E, Atkin K, Marusich MF, *et al*. Parkinson's disease neurons exhibit alterations in mitochondrial quality control proteins. NPJ Parkinson's Disease. 2023; 9: 120.
[141] Kupka R, Duffy A, Scott J, Almeida J, Balanzá-Martínez V, Birmaher B, *et al*. Consensus on nomenclature for clinical staging models in bipolar disorder: A narrative review from the International Society for Bipolar Disorders (ISBD) Staging Task Force. Bipolar Disorders. 2021; 23: 659–678.
[142] Anderson G, Jacob A, Bellivier F, Geoffroy PA. Bipolar Disorder: The Role of the Kynurenine and Melatonergic Pathways. Current Pharmaceutical Design. 2016; 22: 987–1012.
[143] Martignoni E, Petraglia F, Costa A, Bono G, Genazzani AR, Nappi G. Dementia of the Alzheimer type and hypothalamus-pituitary-adrenocortical axis: changes in cerebrospinal fluid corticotropin releasing factor and plasma cortisol levels. Acta Neurologica Scandinavica. 1990; 81: 452–456.
[144] Chaudhary S, Zhornitsky S, Chao HH, van Dyck CH, Li CSR. Hypothalamic Functional Connectivity and Apathy in People with Alzheimer's Disease and Cognitively Normal Healthy Controls. Journal of Alzheimer's Disease. 2022; 90: 1615–1628.
[145] Tsui KC, Roy J, Chau SC, Wong KH, Shi L, Poon CH, *et al*. Distribution and inter-regional relationship of amyloid-beta plaque deposition in a 5xFAD mouse model of Alzheimer's disease. Frontiers in Aging Neuroscience. 2022; 14: 964336.
[146] Hayden MR, Banks WA. Deficient Leptin Cellular Signaling Plays a Key Role in Brain Ultrastructural Remodeling in Obesity and Type 2 Diabetes Mellitus. International Journal of Molecular Sciences. 2021; 22: 5427.
[147] Ouanes S, Clark C, Richiardi J, Maréchal B, Lewczuk P, Kornhuber J, *et al*. Cerebrospinal Fluid Cortisol and Dehydroepiandrosterone Sulfate, Alzheimer's Disease Pathology, and Cognitive Decline. Frontiers in Aging Neuroscience. 2022; 14: 892754.
[148] Jones JR, Chaturvedi S, Granados-Fuentes D, Herzog ED. Circadian neurons in the paraventricular nucleus entrain and sustain daily rhythms in glucocorticoids. Nature Communications. 2021; 12: 5763.
[149] Patton AP, Morris EL, McManus D, Wang H, Li Y, Chin JW, *et al*. Astrocytic control of extracellular GABA drives circadian timekeeping in the suprachiasmatic nucleus. Proceedings of the National Academy of Sciences of the United States of America. 2023; 120: e2301330120.
[150] Korkmaz OT, Ay H, Aytan N, Carreras I, Kowall NW, Dedeoglu A, *et al*. Vasoactive Intestinal Peptide Decreases β-Amyloid Accumulation and Prevents Brain Atrophy in the 5xFAD Mouse Model of Alzheimer's Disease. Journal of Molecular Neuroscience. 2019; 68: 389–396.
[151] Beard E, Lengacher S, Dias S, Magistretti PJ, Finsterwald C. Astrocytes as Key Regulators of Brain Energy Metabolism: New Therapeutic Perspectives. Frontiers in Physiology. 2022; 12: 825816.
[152] Frame AK, Robinson JW, Mahmoudzadeh NH, Tennessen JM, Simon AF, Cumming RC. Aging and memory are altered by genetically manipulating lactate dehydrogenase in the neurons or glia of flies. Aging. 2023; 15: 947–981.
[153] Rossi SP, Matzkin ME, Riviere E, Martinez G, Ponzio R, Levalle O, *et al*. Melatonin improves oxidative state and lactate metabolism in rodent Sertoli cells. Molecular and Cellular En-

docrinology. 2023; 576: 112034.
[154] Figuera-Losada M, Thomas AG, Stathis M, Stockwell BR, Rojas C, Slusher BS. Development of a primary microglia screening assay and its use to characterize inhibition of system x_c^- by erastin and its analogs. Biochemistry and Biophysics Reports. 2017; 9: 266–272.
[155] Song C, Wu YS, Yang ZY, Kalueff AV, Tsao YY, Dong Y, *et al*. Astrocyte-Conditioned Medium Protects Prefrontal Cortical Neurons from Glutamate-Induced Cell Death by Inhibiting TNF-α Expression. Neuroimmunomodulation. 2019; 26: 33–42.
[156] Chen J, Zhang T, Jiao S, Zhou X, Zhong J, Wang Y, *et al*. proBDNF Accelerates Brain Amyloid-β Deposition and Learning and Memory Impairment in APPswePS1dE9 Transgenic Mice. Journal of Alzheimer's Disease. 2017; 59: 941–949.
[157] Hu YT, Tan ZL, Hirjak D, Northoff G. Brain-wide changes in excitation-inhibition balance of major depressive disorder: a systematic review of topographic patterns of GABA- and glutamatergic alterations. Molecular Psychiatry. 2023. (online ahead of print)
[158] Zhao XP, Li H, Dai RP. Neuroimmune crosstalk through brain-derived neurotrophic factor and its precursor pro-BDNF: New insights into mood disorders. World Journal of Psychiatry. 2022; 12: 379–392.
[159] Karki P, Webb A, Smith K, Johnson J, Jr, Lee K, Son DS, *et al*. Yin Yang 1 is a repressor of glutamate transporter EAAT2, and it mediates manganese-induced decrease of EAAT2 expression in astrocytes. Molecular and Cellular Biology. 2014; 34: 1280–1289.
[160] Rizor A, Pajarillo E, Son DS, Aschner M, Lee E. Manganese phosphorylates Yin Yang 1 at serine residues to repress EAAT2 in human H4 astrocytes. Toxicology Letters. 2022; 355: 41–46.
[161] Anderson G, Carbone A, Mazzoccoli G. Aryl Hydrocarbon Receptor Role in Co-Ordinating SARS-CoV-2 Entry and Symptomatology: Linking Cytotoxicity Changes in COVID-19 and Cancers; Modulation by Racial Discrimination Stress. Biology. 2020; 9: 249.
[162] Reiter RJ, Sharma R, Cucielo MS, Tan DX, Rosales-Corral S, Gancitano G, *et al*. Brain washing and neural health: role of age, sleep, and the cerebrospinal fluid melatonin rhythm. Cellular and Molecular Life Sciences. 2023; 80: 88.
[163] Wahis J, Baudon A, Althammer F, Kerspern D, Goyon S, Hagiwara D, *et al*. Astrocytes mediate the effect of oxytocin in the central amygdala on neuronal activity and affective states in rodents. Nature Neuroscience. 2021; 24: 529–541.
[164] Bruchas MR, Land BB, Lemos JC, Chavkin C. CRF1-R activation of the dynorphin/kappa opioid system in the mouse basolateral amygdala mediates anxiety-like behavior. PLoS ONE. 2009; 4: e8528.
[165] Wu YH, Zhou JN, Van Heerikhuize J, Jockers R, Swaab DF. Decreased MT1 melatonin receptor expression in the suprachiasmatic nucleus in aging and Alzheimer's disease. Neurobiology of Aging. 2007; 28: 1239–1247.
[166] Michaelian JC, McCade D, Hoyos CM, Brodaty H, Harrison F, Henry JD, *et al*. Pilot Randomized, Double-Blind, Placebo-Controlled Crossover Trial Evaluating the Feasibility of an Intranasal Oxytocin in Improving Social Cognition in Individuals Living with Alzheimer's Disease. Journal of Alzheimer's Disease Reports. 2023; 7: 715–729.
[167] Guarnera J, Yuen E, Macpherson H. The Impact of Loneliness and Social Isolation on Cognitive Aging: A Narrative Review. Journal of Alzheimer's Disease Reports. 2023; 7: 699–714.
[168] Wang H, Duclot F, Liu Y, Wang Z, Kabbaj M. Histone deacetylase inhibitors facilitate partner preference formation in female prairie voles. Nature Neuroscience. 2013; 16: 919–924.
[169] Anderson G. Gut Microbiome and Circadian Interactions with Platelets Across Human Diseases, including Alzheimer's Disease, Amyotrophic Lateral Sclerosis, and Cancer. Current Topics in Medicinal Chemistry. 2023. (online ahead of print)
[170] Zhang Y, Shen Y, Liufu N, Liu L, Li W, Shi Z, *et al*. Transmission of Alzheimer's disease-associated microbiota dysbiosis and its impact on cognitive function: evidence from mice and patients. Molecular Psychiatry. 2023. (online ahead of print)
[171] Valverde-Salazar V, Ruiz-Gabarre D, García-Escudero V. Alzheimer's Disease and Green Tea: Epigallocatechin-3-Gallate as a Modulator of Inflammation and Oxidative Stress. Antioxidants (Basel, Switzerland). 2023; 12: 1460.
[172] Seady M, Fróes FT, Gonçalves CA, Leite MC. Curcumin modulates astrocyte function under basal and inflammatory conditions. Brain Research. 2023; 1818: 148519.
[173] Zhang Y, Chen D, Tian R, Yan X, Zhou Y. Resveratrol alleviates amyloid β-induced neuronal apoptosis, inflammation, and oxidative and endoplasmic reticulum stress by circ_0050263/miR-361-3p/PDE4A axis during Alzheimer's disease. Chemical Biology & Drug Design. 2023; 102: 1121–1132.
[174] Razick DI, Akhtar M, Wen J, Alam M, Dean N, Karabala M, *et al*. The Role of Sirtuin 1 (SIRT1) in Neurodegeneration. Cureus. 2023; 15: e40463.
[175] Kan Z, Wang Y, Chen Q, Tang X, Thompson HJ, Huang J, *et al*. Green Tea Suppresses Amyloid β Levels and Alleviates Cognitive Impairment by Inhibiting APP Cleavage and Preventing Neurotoxicity in 5XFAD Mice. Molecular Nutrition & Food Research. 2021; 65: e2100626.
[176] Rao YL, Ganaraja B, Suresh PK, Joy T, Ullal SD, Manjrekar PA, *et al*. Effect of resveratrol and combination of resveratrol and donepezil on the expression of microglial cells and astrocytes in *Wistar* albino rats of colchicine-induced Alzheimer's disease. 3 Biotech. 2023; 13: 319.
[177] Han SG, Han SS, Toborek M, Hennig B. EGCG protects endothelial cells against PCB 126-induced inflammation through inhibition of AhR and induction of Nrf2-regulated genes. Toxicology and Applied Pharmacology. 2012; 261: 181–188.
[178] Mohammadi-Bardbori A, Akbarizadeh AR, Delju F, Rannug A. Chromatin remodeling by curcumin alters endogenous aryl hydrocarbon receptor signaling. Chemico-biological Interactions. 2016; 252: 19–27.
[179] Cheng J, Wang S, Lv SQ, Song Y, Guo NH. Resveratrol inhibits AhR/Notch axis and reverses Th17/Treg imbalance in purpura by activating Foxp3. Toxicology Research. 2023; 12: 381–391.
[180] Lin SM, Wang SW, Ho SC, Tang YL. Protective effect of green tea (-)-epigallocatechin-3-gallate against the monoamine oxidase B enzyme activity increase in adult rat brains. Nutrition. 2010; 26: 1195–1200.
[181] Bester E, Petzer A, Petzer JP. Coumarin derivatives as inhibitors of d-amino acid oxidase and monoamine oxidase. Bioorganic Chemistry. 2022; 123: 105791.
[182] Lan JS, Liu Y, Hou JW, Yang J, Zhang XY, Zhao Y, *et al*. Design, synthesis and evaluation of resveratrol-indazole hybrids as novel monoamine oxidases inhibitors with amyloid-β aggregation inhibition. Bioorganic Chemistry. 2018; 76: 130–139.
[183] van der Velpen IF, de Feijter M, Raina R, Özel F, Perry M, Ikram MA, *et al*. Psychosocial health modifies associations between HPA-axis function and brain structure in older age. Psychoneuroendocrinology. 2023; 153: 106106.