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

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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, 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 melatonin 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/glial 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 pathoetiologial 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], neurotism [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), 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-acetylseryotonin (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 chemotraction 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 metalloprotease 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-κB 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 pathophysiology, including: (1) Stress/HPA axis activity drives GR activation and GR/TDO-kyurenine/AhR induction. Stress/GR drives gut-derived LPS and other TLR2/4 activators that upregulate the transcription factors, NF-κB 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 dishibit 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). 14-3-3ζ stabilized AANAT metabolizes 5-HT to N-acetylsertotonin (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 disinhbition allowing the induction of the mitochondrial melatonergic pathway to be intimately linked to mitochondrial metabolic function. Pinacel melatonin and the gut microbiome-derived short-chain fatty acid, butyrate, induce sirtuin-3, which deacetylates and dishibits 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-kyurenine 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-κB 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-acetylsertotonin O-methyltransferase; BACE1, β-site amyloid precursoer 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-acetylsertotonin; NF-κB, 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 dis-inhibition 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 promoter.

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 translocate 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 systematically [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 pathoetiopathology 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 (HMGBox). 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 nico- tinic 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 Ca2+ 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 down-regulation 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 manner 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 pathophysiologicals 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 pathophysiology 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-κB/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-κB/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 daytime, 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 (ARTNT), thereafter inducing genes with the xenobiotic response element (XRE) in their promoter. The AhR can also be expressed on the mitochondrial membrane where it regulates Ca2+ influx via the voltage dependent anion channel (VDAC1) [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 kynurene 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, arylhydrocarbon 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 tied 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 phagocyte 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 (Tyr3, 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 presenlin (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 pathoetiopathology 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 pathoetiopathology 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 chemotraction may be driven by decreased melatonin regulation of PINK1/parkin-mediated mitophagy [133] and associated upregulation of major histocompatibility complex (MHC)-I [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 chemoaattraction (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 pathobiology 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 chemoaattraction 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 pathobiology 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 tanyocytes 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 mitochondrial 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\(\text{NTR}\), 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 chemotacttract 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-acetylseryltonin; 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.
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 p75NTR 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 (EAAT2), 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/acyt-el-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 hyperphosphorlated tau driven tangles are downstream consequences of dysregulated glia mitochondrial melatonergic pathway dysregulation. Amyloid-β and hyperphosphorlated 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-I, 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 PVNCRH neuronal regulation and the CAR/HPA axis. Notably, PVNCRH 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’ (plagues 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 by 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 Xc−. It will be important to determine the relative influences of such processes, including heightened glutamatergic activity induction of pro-BDNF, TrkB-T1 and the p75NTR 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 Xc− 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 mitochondrial 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 chemottracts CD8+ t cells, implicating ‘autoimmune’/免疫-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, bel-2 associated anathogene 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-dioxigenase; LAT-1, large amino acid transporter 1; MAO, monoamine oxidase; MERTK, MER Proto-Oncogene, Tyrosine Kinase; MHC, major histocompatibility complex; NAS, N-acetylserotonin;
NF-κB, 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; TIM, mitochondrial import receptor subunit; TrkB-FL, tyrosine receptor tryptophan 2,3-dioxygenase; TIM, mitochondrial import inner membrane translocase subunit; TOM, mitochondrial import outer receptor subunit; TrkB-T1, tyrosine receptor kinase B full length; TrkB-T1, tyrosine receptor kinase B truncated; VIP, vasoactive intestinal peptide; WAT, white adipocyte.

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