Review

# Physiological processes underpinning the ubiquitous benefits and interactions of melatonin, butyrate and green tea in neurodegenerative conditions

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## ABSTRACT

There is a growing dissatisfaction at the lack of progress in treating neurodegenerative conditions, such as Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis. No current pharmaceuticals have any significant impact on the pathophysiological changes occurring in such neurodegenerative conditions. More promising has been the utilization of nutraceuticals, a number of which show preventative and treatment benefits. This article reviews the beneficial effects of melatonin, sodium butyrate and epigallocatechin gallate (EGCG) in the management of the pathophysiological changes underpinning neurodegenerative conditions. It is proposed that all three nutraceuticals upregulate the tryptophan-melatonin pathway, which may be particularly important in astrocytes given astrocyte regulation of neuronal energy supply and antioxidants, including released melatonin. Alterations in the tryptophan-melatonin pathway are intimately intertwined with changes in the kynurenine pathway and its neuroregulatory products, including kynurenic acid and quinolinic acid. This article places these changes in the tryptophan-melatonin pathways within a novel circadian-systemic interaction, involving the regulation of the night-time rise in cortisol culminating in the morning cortisol awakening response that mediates effects via glucocorticoid receptor (GR) activation. The night-time and morning GR activation is suppressed by melatonin, gut microbiome derived butyrate and bcl2-associated athanogene (BAG)-1. As melatonin, butyrate and BAG-1 decrease over age, there is a heightened level of GR nuclear translocation with age at night and early morning. This is exemplified by the 10-fold decrease in pineal melatonin in people in their 9$^{th}$, versus 2$^{nd}$, decade of life. The 'battle' of melatonin/butyrate/EGCG versus cortisol/GR for influence on cellular function, microenvironment homeostasis and systemic system (immune) regulation at night and early morning shapes how the body and brain are prepared for the coming day and drives the emergence of aging associated neurodegenerative conditions. It is upon such processes that melatonin, butyrate and EGCG have their impacts.

**Key words:** Butyrate, melatonin, green tea, *N*-acetylserotonin, aryl hydrocarbon receptor, cortisol awakening response, hypothalamus-pituitary-adrenal axis, B cell lymphoma-2-associated anthanogene 1, mitochondria.

## 1. INTRODUCTION

Accumulating evidence has highlighted the utility of various natural products (nutraceuticals) in decreasing the risk and attenuating symptoms across a host of diverse medical conditions, including neurodegenerative disorders (1, 2). Beneficial nutraceuticals in neurodegenerative disorders include melatonin (3, 4), sodium butyrate (5) and the green tea polyphenol, epigallocatechin gallate (EGCG) (6). As all three nutraceuticals show beneficial effects on diverse neurodegenerative conditions, including Alzheimer's disease (7-9), Parkinson's disease (7,8,10), amyotrophic lateral sclerosis (1,8) and multiple sclerosis (11,12) as well as in various neuropsychiatric conditions (13-15), cancer (16-18) and cardiovascular disorders (19, 20), it would seem likely that these natural products act on core physiological processes, including mitochondrial function, relevant across health, disease and aging.

All medical conditions show evidence of alterations in mitochondrial function, not always limited to a particular organ/tissue that classically defines a given medical condition. For example, dysregulated platelet mitochondrial function is evident in schizophrenia (21), Alzheimer's disease, amyotrophic lateral sclerosis and cancer (1). Changes in mitochondrial function across body cells and systems highlight the importance of systemic processes in the pathoetiology and pathophysiology of diverse medical conditions (4).

This article reviews the roles of melatonin, butyrate and EGCG in the regulation of the biological underpinnings of neurodegenerative conditions, highlighting their impact on central nervous system (CNS) and systemic processes via their modulation of the tryptophan-melatonin pathway and the impact of this pathway on mitochondrial function. This is placed within the context of recent data on the pathogenesis of medical conditions, including cancer (22, 23) and neurodegenerative conditions (4), as arising at night during sleep (24). First, data is briefly reviewed on the processes proposed to underpin the efficacy of melatonin, butyrate and EGCG in neurodegenerative conditions.

## 2. PROCESSES REGULATED BY MELATONIN, BUTRYRATE AND EGCG

Melatonin effects are generally attributed to its release by the pineal gland at night, with benefits mediated via its capacity as an antioxidant, anti-inflammatory and optimizer of mitochondrial function (25). This is parsimonious with classical views as to the pathophysiological relevance of increased oxidants, pro-inflammatory cytokines and suboptimal mitochondrial function in disease processes (26). The effects of exogenous and pineal melatonin are classically attributed to the activation of the melatonin receptors (MT)1 and MT2, with associated intracellular signaling pathways that drive transcription factors to induce genes in the nucleus (27). However, as well as melatonin having receptor-independent effects (28), a growing body of data shows melatonin to being taken up into, and produced within, the mitochondria of all systemic and CNS cells, including astrocytes (29), microglia (30) and macrophages (31). Exogenous and pineal melatonin, including via Brain and muscle arnt-like (Bmal1), can upregulate the mitochondrial melatonergic pathway across body and CNS cells (32). As mitochondria are the major oxidant-producing organelles in cells, the optimization of mitochondrial function by melatonin suppresses oxidant production as well as oxidant-induced microRNAs (miRNAs) that shape patterned gene expression (1). The regulation of mitochondrial function is therefore a core process in determining the raised levels of oxidants, inflammation and alterations in intercellular interactions that are ubiquitous aspects of disease pathophysiology, including in neurodegenerative diseases (1, 24).

Butyrate, like acetate and propionate, is a short-chain fatty acid produced by the gut microbiome. Butyrate mediates many of the beneficial effects of the gut microbiome (33, 34), via a number of different processes. Butyrate is a histone deacetylase inhibitor (HDACi) and

therefore epigenetic regulator, as well as activating the G-protein coupled receptors (GPR)-41, GPR-43 and GPR-109. However, like melatonin (35), many of the beneficial effects of butyrate seem mediated by its capacity to increase the mitochondria-located sirtuin-3 (36). Sirtuin-3 deacetylates the pyruvate dehydrogenase complex (PDC), thereby increasing the conversion of pyruvate to acetyl-coenzyme A (acetyl-CoA), with raised acetyl-CoA and sirtuin-3 enhancing mitochondrial ATP production by the tricarboxylic acid (TCA) cycle and oxidative phosphorylation (OXPHOS), whilst decreasing mitochondrial oxidant production by Complex I and II (37-39). Butyrate, like melatonin, can therefore better optimize mitochondrial energy production coupled with a decrease in oxidants and upregulation of the mitochondrial melatonergic pathway (33). As noted, mitochondria are the major producers of cellular oxidants, with raised levels of mitochondrial superoxide and its rapid conversion to hydrogen peroxide, allowing mitochondrial 'reactive oxygen species' (ROS) to change patterned gene expression via ROS-driven miRNAs (40), such as miR-21 that alters glia-neuronal interactions in Alzheimer's disease (41). By increasing sirtuin-3 induced acetyl-CoA, butyrate provides the necessary cosubstrate for the initiation of the mitochondrial melatonergic pathway (33), thereby allowing the induction of the mitochondrial melatonergic pathway to contribute to limiting mitochondrial ROS and changing patterned gene expression.

As with melatonin and butyrate, green tea affords protection against a diverse range of medical conditions, including severe acute respiratory syndrome, coronavirus 2 (SARS-CoV-2) infection that drove the COVID-19 pandemic (42, 43). The most investigated beneficial product in green tea is the polyphenol, EGCG. EGCG is proposed to act via diverse pathways in the modulation of cellular function including direct interactions with plasma membrane proteins and phospholipids with consequences for a wide array of transcription factors, signal transduction pathways, mitochondrial function, mitophagy, autophagy, and epigenetic processes, including DNA methylation and miRNAs, as well modulating the gut microbiome (44-48). However, EGCG also regulates the tryptophan-melatonin pathway including via 14-3-3 upregulation (49) and the inhibition of monoamine oxidase (50), whilst also increasing sirtuin-3 (51), thereby paralleling the effects of melatonin and butyrate in upregulating the mitochondrial melatonergic pathway and mitochondrial function across diverse systemic and CNS cell types.

As the capacity to induce the tryptophan-melatonin pathway determines the availability of the mitochondrial melatonergic pathway, and is a significant commonality of melatonin, butyrate and EGCG physiological effects, the tryptophan-melatonin pathway is briefly described next.

## 3. THE TRYPTOPHAN-MELATONIN AND KYNURENINE PATHWAYS

The mitochondrial melatonergic pathway, driven mainly by the tryptophan-melatonin pathway, is proposed to be evident in all mitochondria-containing human cells as well as in the mitochondria of all eukaryotic life (animals, plants, and fungi) on planet Earth (52). The melatonergic pathway refers to the last two enzymatic reactions of the tryptophan-melatonin pathway, as shown in Figure 1.

The initiation of the tryptophan-melatonin pathway requires dietary (and perhaps gut microbiome shikimate pathway) derived tryptophan, which enters the circulation. Circulating tryptophan is taken up and transported into cells by the large amino acid transporters (LATs), including by astrocyte LAT-1, into the CNS. Tryptophan is then converted by tryptophan hydroxylase (TPH) to 5-hydroxytryptophan (5-HTP) that is further converted to 5-hydroxytryptamine (serotonin; 5-HT) by aromatic-L-amino acid decarboxylase (AADC). To initiate the conversion of tryptophan, TPH (body TPH1and brain TPH2) require stabilization by 14-3-3, including the 14-3-3ε isoform (53). Aralkylamine *N*-acetyltransferase (AANAT)

then converts serotonin to *N*-acetylserotonin (NAS), with AANAT also requiring stabilization by 14-3-3 (including the 14-3-3ζ isoform) (54). To achieve the conversion of serotonin to NAS, AANAT also requires the presence of acetyl-CoA. Acetylserotonin methyltransferase (ASMT) converts NAS to melatonin. As acetyl-CoA is primarily derived from the PDC conversion of pyruvate to acetyl-CoA, this allows the initiation of the mitochondrial melatonergic pathway to be intimately linked to, and dependent upon, the mitochondrial initiation of optimized OXPHOS. The mitochondrial melatonergic pathway is therefore intimately linked to mitochondrial metabolism. The tryptophan-melatonin pathway and some of its regulatory factors are shown in Figure 1.

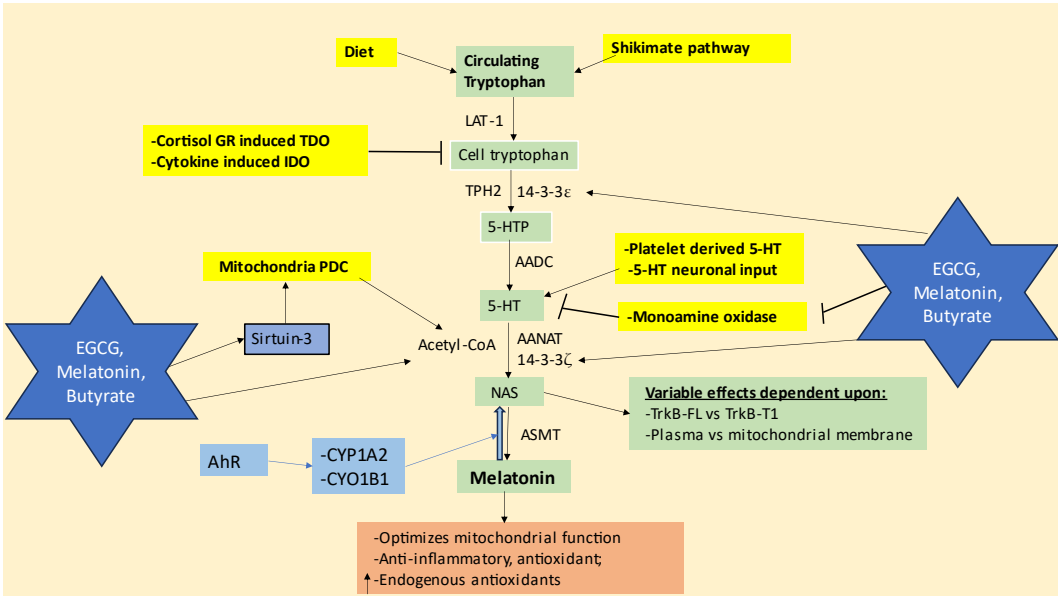


**Fig. 1. The tryptophan-melatonin pathway and its regulation**.

The figure *shows the cellular tryptophan-melatonin pathway (green shade). A number of factors can regulate the tryptophan-melatonin pathway (yellow shade), including dietary intake of tryptophan, whilst gut microbiome shikimate pathway activation also provides another tryptophan source. Circulating tryptophan is taken into cells by the LAT-1. Cortisol activation of the GR induces TDO, which converts tryptophan to kynurenine, as does pro-inflammatory cytokine induced IDO, both of which will deplete tryptophan availability. Tryptophan is converted to 5-HTP by 14-3-3 stabilized TPH2 in astrocytes. 5-HTP is then converted to serotonin (5-HT) by AADC. Serotonin may also be provided to cells from efflux by circulating platelets or serotonergic neurons. Serotonin availability may be suppressed by raised levels of monoamine oxidase. The AhR induced CYP1A2 and CYP1B1 (blue shade) can O-demethylate melatonin to NAS, thereby increasing the NAS/melatonin ratio. NAS can have diverse effects via TrkB activation, including as arising from the differential consequences of TrkB-FL vs TrkB-T1 and mitochondrial vs plasma membrane TrkB localization. EGCG, melatonin and butyrate inhibit monoamine oxidase, as well as increasing sirtuin-3 to disinhibit PDC, with both effects enhancing the mitochondrial melatonergic pathway, thereby increasing the mitochondria optimizing, antioxidant and anti-inflammatory effects of melatonin. Melatonin, butyrate and EGCG can also increase 14-3-3 proteins to increase the tryptophan-melatonin pathway. Abbreviations: 5-HT: serotonin; 5-HTTP: 5-hydroxytryptophan; AADC: aromatic-L-amino acid decarboxylase; AANAT: aralkylamine N-acetyltransferase; acetyl-CoA: acetyl-coenzyme A; AhR: aryl hydrocarbon receptor; ASMT: N-acetylserotonin O-methyltransferase; CYP: cytochrome P450: EGCG: epigallocatechin gallate; GR: glucocorticoid receptor; IDO: indoleamine 2,3-dioxygenase; LAT-1: large amino acid*

*transporter 1; NAS: N-acetylserotonin; TDO: tryptophan 2,3-dioxygenase; TPH: tryptophan hydroxylase; TrkB-FL: tyrosine receptor kinase B-full length; TrkB-T1: tyrosine receptor kinase B-truncated.*

Factors, including intercellular, epigenetic, genetic, and circadian that modulate tryptophan availability/uptake, TPH, 14-3-3 isoforms, AANAT, acetyl-CoA, and ASMT will therefore influence the capacity of mitochondria to upregulate the mitochondrial melatonergic pathway (1). Numerous factors can regulate the tryptophan-melatonin pathway, including stress/cortisol activation and nuclear translocation of the glucocorticoid receptor (GR), which induces tryptophan 2,3-dioxygenase (TDO), as well as pro-inflammatory cytokine induced indoleamine 2,3-dioxygenase (IDO). The induction of IDO and TDO lead to tryptophan being converted to kynurenine (2). Kynurenine is converted to a number of kynurenine pathway products that can dramatically regulate neuronal function and survival, such as the excitatory picolinic acid and excitotoxic quinolinic acid, both via effects at the n-methyl-d-aspartate receptor (NMDAr) (2). In contrast, kynurenic acid is inhibitory at the NMDAr (2). The suppression of the tryptophan-melatonin pathway by IDO and TDO is therefore associated with significant alterations in the regulation of neuronal activity by different products of the kynurenine pathway. The kynurenine pathway is shown in Figure 2 and is also regulated by butyrate, melatonin and EGCG.

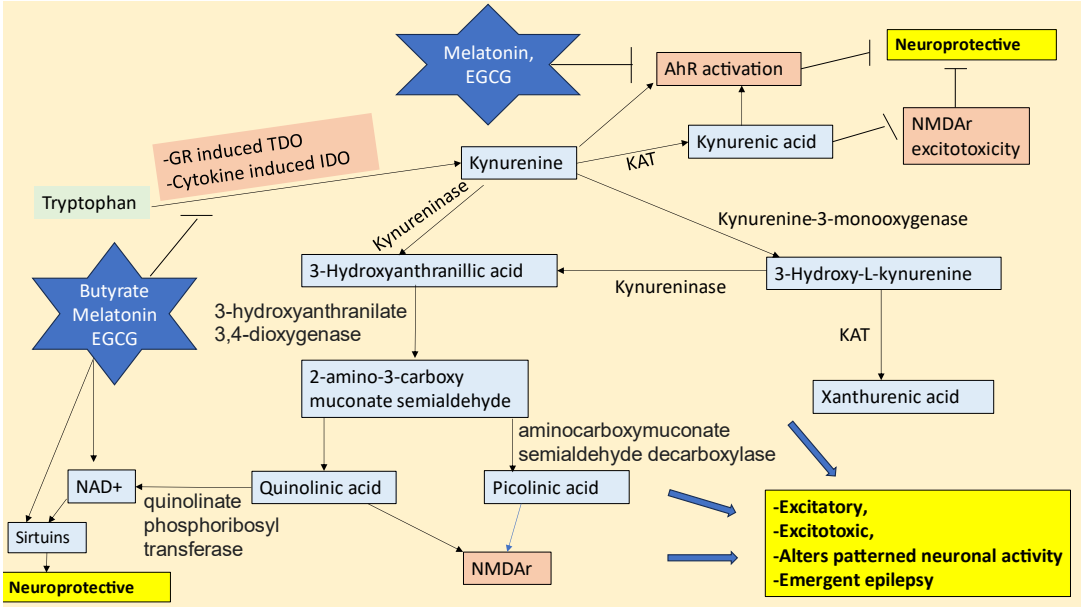


**Fig. 2. Kynurenine pathway in neuronal regulation.**

The figure *shows the kynurenine pathway (light blue shade). Cortisol activation of the GR induces TDO which, like pro-inflammatory cytokine induction of IDO convert tryptophan to kynurenine. Kynurenine can be converted to kynurenic acid by kynurenine aminotransferase (KAT-I, II, III). Both kynurenine and kynurenic acid activate the aryl hydrocarbon receptor (AhR), whilst kynurenic acid can also inhibit the n-methyl-d-aspartate receptor (NMDAr), where it affords protection in neurodegenerative conditions, in contrast to the kynurenine and kynurenic acid effects at the AhR, which typically accelerate aging and neuronal loss. Kynurenine can also lead to the induction of picolinic acid and quinolinic acid, which are excitatory and excitotoxic, respectively at the NMDAr. However, quinolinic acid can also be metabolized to NAD+, which can afford protection via sirtuin upregulation. Melatonin and EGCG inhibit the AhR, with melatonin, EGCG and butyrate inhibiting the GR induction of TDO and the cytokine induction of IDO, thereby increasing tryptophan availability. The driving*

*of tryptophan down the kynurenine pathway alters patterned neuronal activity, with raised picolinic acid and quinolinic acid contributing to the emergence of epilepsy in neurodegenerative conditions. Melatonin, butyrate and EGCG can increase NAD+ induced sirtuins, thereby enhancing the neuroprotective effects of the kynurenine pathway. The specific patterning of the kynurenine pathway products can therefore have contrasting effects on neuronal survival and patterned neuronal activity. Abbreviations: AhR: aryl hydrocarbon receptor; GR: glucocorticoid receptor; IDO: indoleamine 2,3-dioxygenase; KAT: kynurenine aminotransferase; NAD: nicotinamide; NMDAr: n-methyl-d-aspartate receptor; TDO: tryptophan 2,3-dioxygenase.*

Both kynurenine and kynurenic acid can activate the aryl hydrocarbon receptor (AhR). The AhR has diverse and complex effects, being intimately associated with aging (55, 56) and neurodegenerative conditions such as Alzheimer's disease (57) and Parkinson's disease (58), as well as being a crucial target for inhibition in cancer treatment (59). The AhR may also further deplete melatonin via the AhR induction of the cytochrome P450 (CYP)1A2 and CYP1B1, which O-demethylate melatonin, thereby 'backward' converting melatonin to NAS (60, 61), and increasing the NAS/melatonin ratio (62), as shown in Figure 1. Although NAS and melatonin have similar antioxidant and anti-inflammatory effects, NAS is distinct by being a brain-derived neurotrophic factor (BDNF) mimic, and BDNF inducer (63), via the activation of the BDNF receptor, tyrosine receptor kinase B (TrkB) (64). NAS and BDNF effects are further complicated by various TrkB isoforms, predominantly TrkB-full length (TrkB-FL) and TrkB truncated (TrkB-T1), with TrkB-T1 negating the beneficial effects of TrkB-FL. TrkB effects are further complicated by expression of TrkB on the mitochondrial, and/or plasma, membrane (65), (see Figure 1). Melatonin at physiological levels has mutual inhibitory interactions with the AhR, whilst EGCG is an AhR antagonist, as are other commonly used nutraceuticals such as resveratrol, curcumin, folate, and vitamin B12 (66). Although butyrate can enhance AhR activation on intestinal epithelial cells to maintain the gut barrier (67), butyrate has diverse effects on the AhR in other organs and tissues (68, 69). Such data highlights how the tryptophan-melatonin pathway allows cells to have considerable plasticity in their responses, as well as highlighting how melatonin, butyrate and EGCG can modulate the tryptophan-melatonin pathway and its interactions with the kynurenine pathway. Generally, melatonin, butyrate and EGCG not only limit kynurenine pathway induction but also shape the nature of the kynurenine pathway to provide neuroprotective products, as shown in Figure 2.

## 4. MITOCHONDRIAL MELATONERGIC PATHWAY: CORE HUB FOR NUTRICEUTICALS

A growing body of data indicate that the dysregulation of the tryptophan-melatonin pathway, including factors suppressing serotonin availability from serotonergic neurons and platelets (1), has pathophysiological consequences mediated by the suppressed capacity to induce the mitochondrial melatonergic pathway. As pineal and exogenous melatonin, butyrate and EGCG can regulate the tryptophan-melatonin pathway (see figure 1), the mitochondrial melatonergic pathway may be a core hub for the ubiquitous benefits of melatonin, butyrate and EGCG across diverse medical conditions, including cancer and neurodegenerative disorders (1, 4, 5, 22). This may be mediated by the impacts of these nutraceuticals in the suppression of aging-associated processes (70), including via sirtuin-3 upregulation (71), as shown in Figure 2.

As noted, the capacity of melatonin, butyrate and EGCG to increase sirtuin-3 (33, 36, 51), allows these nutraceuticals to optimize mitochondrial function via the dampening of oxidant production by Complex I and II, thereby attenuating ROS-induced miRNAs and their impact on patterned gene transcription. As the induction of sirtuin-3 deacetylates and disinhibits the

PDC, mitochondrial ATP production levels are increased, which is coupled to an increased availability of acetyl-CoA as a necessary cosubstrate for the initiation of the mitochondrial melatonergic pathway by 14-3-3 stabilized AANAT. Butyrate increases the mitochondrial melatonergic pathway, as shown in intestinal epithelial cells (72), thereby maintaining the gut barrier and preventing circulating lipopolysaccharide (LPS) from contributing to neurodegenerative processes as well as dysregulating immune and glia cell responses. Butyrate prevents gut barrier permeability, as do melatonin (73) and EGCG (74), highlighting the gut barrier and the prevention of gut dysbiosis as important commonalities of melatonin, butyrate and EGCG. Gut permeability and gut dysbiosis have major implications for the systemic tryptophan-melatonin pathway across all body and brain cells. Increased gut permeability/dysbiosis is invariably associated with heightened pro-inflammatory immune activation, thereby driving raised levels of pro-inflammatory cytokines, which induce IDO to deplete tryptophan by increasing its conversion to kynurenine. As 60% of CNS kynurenine is derived from systemic processes (75), systemic kynurenine can significantly change neuronal and astrocyte function following the induction of various kynurenine pathway products, as indicated in Figure 2. The protection afforded by melatonin, butyrate and EGCG in neurodegenerative conditions is therefore intimately linked to the regulation and interactions of the tryptophan-melatonin pathway, the kynurenine pathway and immune/glia regulation of neuronal activity and patterned interarea communication across the CNS.

As well as tryptophan availability, other aspects of the tryptophan-melatonin pathway are regulated by these nutraceuticals. In some neurodegenerative conditions, various 14-3-3 isoforms are decreased, most notably in Parkinson's disease (76), although also in wider neurodegenerative conditions (77). As noted, 14-3-3 is crucial to the stabilization of TPH and AANAT, and therefore to the functioning of the tryptophan-melatonin pathway and mitochondrial melatonergic pathway, with the latter also being importantly regulated by the conversion of serotonin provided by platelets and serotonergic neuronal inputs to cells (see Figure 1). EGCG increases 14-3-3 levels (78, 79), whilst butyrate via its capacity as a pan-HDACi also regulates 14-3-3 levels (80), as does melatonin (81). In medical conditions associated with decreased cellular 14-3-3 proteins, such as autism (82), cellular capacity to produce melatonin is significantly reduced, highlighting the importance of 14-3-3 regulation by these nutraceuticals in the regulation of the mitochondrial melatonergic pathway.

Suppressed serotonin levels are often evident in neurodegenerative conditions in proximity to lost neurons, including in Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis (1, 66). The lost serotonergic input attenuates the capacity of neurons and glia to initiate the mitochondrial melatonergic pathway. This suppressed serotonergic availability is also contributed to by the raised levels of monoamine oxidase (MAO), which degrades serotonin and other monoamines. Increased MAO is evident across neurodegenerative conditions, with MAO inhibitors being significant treatment targets for Alzheimer's disease (83), Parkinson's disease (84), and amyotrophic lateral sclerosis (85). EGCG (50, 86), butyrate (87), melatonin and its analogs (88) all inhibit MAO, thereby contributing to increased serotonin availability for the initiation of the mitochondrial melatonergic pathway and the optimization of mitochondrial function.

As noted (1), platelets are increasingly appreciated to play a role in diverse medical conditions, including cancer, Alzheimer's disease and amyotrophic lateral sclerosis (1). Platelets can significantly uptake and efflux serotonin, as well as expressing TPH for serotonin synthesis, reviewed in (1). As well as serotonin, thrombin and fibrin(ogen), platelets also efflux other factors relevant to neuronal survival and neurogenesis, including melatonin and sphingosine-1-phosphate (89). The damaging effects of activated platelets are typically driven by thrombin release and the associated increased clot risk. Platelet activation is significantly decreased by melatonin (90), EGCG (91), and the pan-HDACi effects of butyrate (1, 92). The

role of nutraceutical effects in platelets in the pathoetiology and pathophysiology of neurodegenerative conditions will be important to determine, especially as platelets are also significant regulators of gut permeability and gut dysbiosis, forming a gut-platelet axis (1). Overall, platelets are another aspect of the pathophysiology of neurodegenerative conditions, with effects that include the regulation of the mitochondrial melatonergic pathway, both directly via serotonin and melatonin efflux, as well as indirectly via the gut microbiome/permeability and associated butyrate regulation.

AhR activation, via increased CYP1A2 and CYP1B1, O-demethylates melatonin to its precursor NAS, thereby suppressing local cell melatonin availability (see Figure 1). EGCG inhibits the AhR (93), with melatonin having mutual inhibitory interactions with the AhR at physiological levels (94), although perhaps not at supraphysiological levels (95). Butyrate has specific interactions with the AhR in intestinal epithelial cells, where the AhR maintains the gut barrier, with the AhR typically activated by tryptamine derived from the conversion of tryptophan by tryptophan decarboxylase (96). How butyrate regulates the AhR in other cell types will be important to determine. The AhR induced CYP1A1, CYP1B1 and CYP1A2, also increase the hydroxylation of melatonin, further depleting melatonin levels (60, 61). Overall, melatonin, EGCG and butyrate regulate the AhR, with consequences for mitochondrial melatonin availability.

Stress/cortisol activation of the glucocorticoid receptor (GR) induces TDO, thereby increasing the kynurenine/tryptophan ratio, as does the pro-inflammatory cytokine induction of IDO (see Figure 1). There is a long-standing association of stress-induced cortisol and HPA axis activation in the pathoetiology and pathophysiology of neurodegenerative conditions (97-99). Cortisol activation of the GR leads to its nuclear translocation from the cytoplasmic complex with heat shock protein (hsp)90 and p23, with the GR binding to the glucocorticoid response element in thousands of genes, as well as interacting with other transcription factors to modulate their transcriptional effects. Both melatonin and butyrate prevent the GR from being translocated to the nucleus. Butyrate mediates this via GR acetylation with melatonin effects possibly involving the induction of bcl2-associated athanogene (BAG)-1 by epigenetic mechanisms, reviewed in (24). It is unknown if EGCG has any such direct effects on GR nuclear translocation. However, EGCG does inhibit 11β-hydroxysteroid dehydrogenase (HSD)1, thereby attenuating local cortisol production by the 11β-HSD1 conversion of cortisone to cortisol. The role of cortisol, the GR, HPA axis, the night-time cortisol level rise culminating in the morning cortisol awakening response (CAR) have recently been proposed to be intimately intertwined with the levels of pineal melatonin and gut microbiome-derived butyrate. Such work indicates that the pathogenesis of neurodegenerative conditions (and other medical conditions) may be importantly determined by the interactions of circadian and systemic processes during sleep (24).

## 5. NIGHT-TIME PATHOETIOLOGY TO NEURODEGENERATIVE CONDITIONS

There is a growing appreciation that the pathoetiology of many medical conditions, including cancer and neurodegenerative conditions may be importantly determined by night-time processes (100). Recent work indicates that the physiological processes underpinning this are mediated, at least partly, by the night-time availability of pineal and local melatonin and gut microbiome derived butyrate as well as the availability of bcl2-associated athanogene (BAG)-1 (100). The changes in the levels of melatonin and cortisol over the circadian rhythm are shown in Figure 3. HPA axis derived cortisol levels do not dramatically change over aging, with heightened cortisol levels being importantly determined by higher GR activation and pro-inflammatory cytokines induction of local 11β-hydroxysteroid dehydrogenase (11β-HSD)1 in cells (101). In contrast, pineal melatonin shows a dramatic10-fold decrease between the 2$^{nd}$ and

9th decade of life (102). Such dramatic decreases in melatonin have significant implications due to the attenuation of melatonin's antioxidant, anti-inflammatory and mitochondrial optimizing effects over the course of aging. Suppressed pineal melatonin has significant implications for the regulation of cortisol levels and GR activation over the course of the night and during the morning cortisol awakening response (CAR).

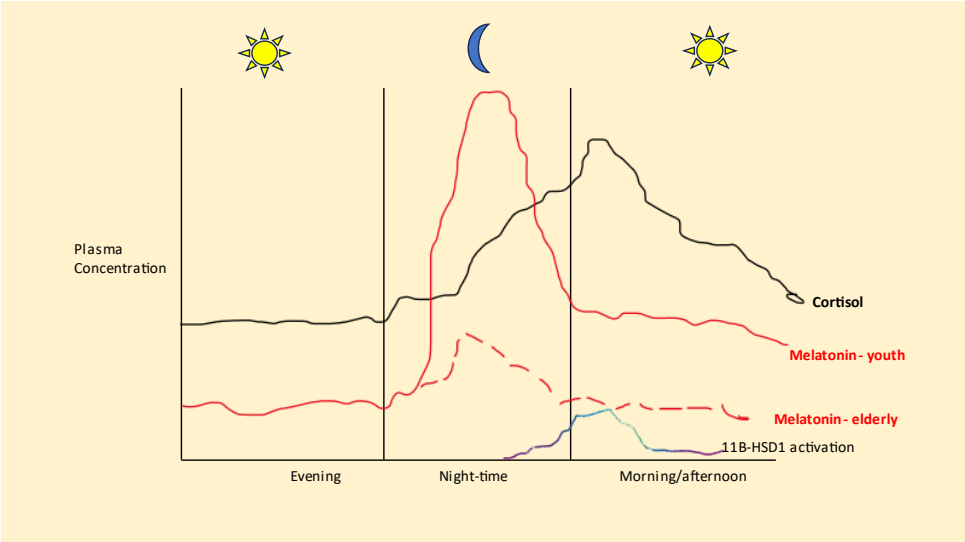


**Fig. 3. Circadian variations in cortisol and melatonin over age.**

*The figure shows typical cortisol and melatonin variations over the evening, night (sleep) and morning/afternoon periods, with melatonin levels shown for young adults and the elderly. In young adults, plasma melatonin rapidly rises in the absence of light at night, subsequently decreasing slowly over the night and morning periods. Between adolescence and the 9th decade of life there is a 10-fold decrease in melatonin production at night, as indicated by comparison of melatonin levels in youths and the elderly. As this dramatic decrease in pineal melatonin over age is not replicated in the cortisol rhythm and morning CAR, the attenuated availability of melatonin in the elderly will heighten nuclear translocation of the GR following cortisol binding to the GR in its cytoplasmic complex with hsp90 and p23. Consequently, there is an elevated GR induction of genes with a glucocorticoid response element in their promotor in the elderly, with significant consequences for the induction of thousands of genes in almost all body cells and systems, including glia and immune cells. The loss of melatonin's dampening of pro-inflammatory cytokines, coupled to raised cortisol levels activating the GR, increase local cortisol production by 11β-HSD1. Elevated 11β-HSD1 levels therefore make a significant contribution to heightened cellular cortisol levels and associated GR activation, which may act locally to suppress pro-inflammatory cytokines. The suppression of pineal melatonin over aging and in the course of diverse medical conditions, as with the suppression of gut microbiome derived butyrate, not only increases 11β-HSD1 and GR activation but also increases GR nuclear translocation, thereby enhancing GR driven gene induction across all body and brain cells, even if only transiently before negative feedback from heightened GR activation. Abbreviations: 11β-HSD1: 11 beta hydroxysteroid dehydrogenase; CAR: cortisol awakening response; GR: glucocorticoid receptor; hsp: heat shock protein.*

The attenuation of pineal melatonin production over aging, as well as the association of suppressed pineal melatonin with diverse medical conditions, such as type 2 diabetes mellitus (103), increases GR nuclear translocation. The suppression of pineal melatonin has a number of consequences that modulates GR nuclear translocation, including: 1) attenuating the

melatonin induction of BAG-1, which prevents GR nuclear translocation and can increase GR translocation to mitochondria (24); 2) increasing gut permeability/dysbiosis, thereby decreasing circulating butyrate and the butyrate suppression of GR nuclear translocation (104); 3) suppressing the capacity of melatonin to dampen residual night-time inflammatory activity (105), thereby leading to the maintenance of low level inflammatory activity at night that can increase 11β-HSD1 and GR activation; and 4) direct effects of melatonin on the suppression of GR nuclear translocation, as well as indirect effects via long noncoding (lnc)RNAs and miRNAs (4, 100). As noted, the heightened GR nuclear translocation and raised levels of pro-inflammatory cytokines at night contribute to raised cortisol levels via the induction of 11β-HSD1, with the raised local cortisol levels induced negatively feeding back on local pro-inflammatory cytokine production (101). 11β-HSD1 has long been appreciated to contribute to cognitive loss over aging, although not clearly understood how this occurs (101). The above would suggest that 11β-HSD1 effects are mediated at night in the course of the raised cortisol levels over the night, culminating in the morning CAR. The morning CAR is of some importance as cortisol effects at the GR impact on all body cells, including reactive cells/systems, such as glia and immune cells, [see Table 1] (100). Although clearly under-investigated, the rising levels of cortisol over the night and during the morning CAR are classically thought to prepare the body for the coming day (106), possibly by increasing respiration and blood pressure. However, the above would suggest that variations in the GR nuclear translocation over the course of the night and during the morning CAR will have significant consequences for body cells and systems, with significant etiological impacts on neurodegenerative disorders.

Most medical conditions show evidence of gut dysbiosis, with an associated increase in gut permeability (33). Gut dysbiosis is invariably associated with a decrease in the production of the short-chain fatty acid, butyrate (33, 34), whilst an increase in gut permeability allows LPS to enter the circulation where it can contribute to neurodegenerative processes, primarily via alterations in the regulation of glia and immune cells (107). LPS, as well as other endogenous toll-like receptor (TLR)4 ligands, induces nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) and yin yang (YY)1, which drive the induction of β-site amyloid precursor protein-cleaving enzyme (BACE)1. BACE1 increase the amyloid-β that is classically associated with Alzheimer's disease, although elevations in amyloid-β are also evident in Parkinson's disease and amyotrophic lateral sclerosis (1, 66, 97). Amyloid-β induction seems primarily as a consequence of its evolved role as an anti-microbial and is therefore induced following indications of microbial signalling when TLR4 is activated by gut derived LPS and an array of endogenous ligands. However clearly not all instances of gut permeability lead to dementia. Rather, there is a suppressed capacity of astrocytes to produce melatonin over aging, with astrocyte melatonin production/efflux expected to occur following NF-kB and YY1 induction, as shown in other cell types (31, 108). The suppressed capacity of astrocytes to sequentially link BACE1 and amyloid-β production with the upregulation of the astrocyte melatonergic pathway, prevents the autocrine and paracrine effects of melatonin that time-limits amyloid-β production and negative consequences (109). Factors acting to suppress the tryptophan-melatonin pathway in CNS cells, including via the suppression of pineal melatonin and gut microbiome derived butyrate, contribute to maintained amyloid-β production, making amyloid-β "too much of a good thing" (107).

Notably, amyloid-β is increased across diverse medical conditions, including breast cancer and glioblastoma (110, 111), indicating amyloid-β is not defining of Alzheimer's disease or cognitive loss across other neurodegenerative conditions. Rather, BACE1 and amyloid-β production indicate an absence of synchronized melatonin/amyloid-β induction (107, 109). The suppression of astrocyte melatonin efflux, not only leads to the loss of melatonin's autocrine effects on the TLR4/NF-kB/YY1/BACE1/amyloid-β pathway but also prevents the melatonin

suppression of hyperphosphorylated tau in neurons, reviewed in (107). Exogenous α-synuclein in Parkinson's disease also activates astrocyte TLR4/NF-kB leading to release of a number of neuronal damaging factors, including proinflammatory cytokines and oxidants (112), with α-synuclein similarly suppressed by melatonin (112). The gut is intimately linked to this via gut permeability derived LPS and the suppression of butyrate, with butyrate not only contributing to gut barrier maintenance, but also increasing the astrocyte mitochondrial melatonergic pathway (4, 107). Overall, the lost capacity to induce pineal and local melatonin prevents its time-limiting suppression of amyloid-β and α-synuclein levels and effects that are classically linked to the pathophysiology of dementia and synucleinopathies. The suppression of pineal melatonin potentiates the capacity of 11β-HSD1 derived cortisol to activate the GR over the course of the night and the morning CAR, thereby changing the microenvironment homeostatic interactions of astrocytes, neurons, microglia, pericytes, endothelial cells and extravasating immune cells in the pathoetiology of neurodegenerative conditions (see Figure 4).

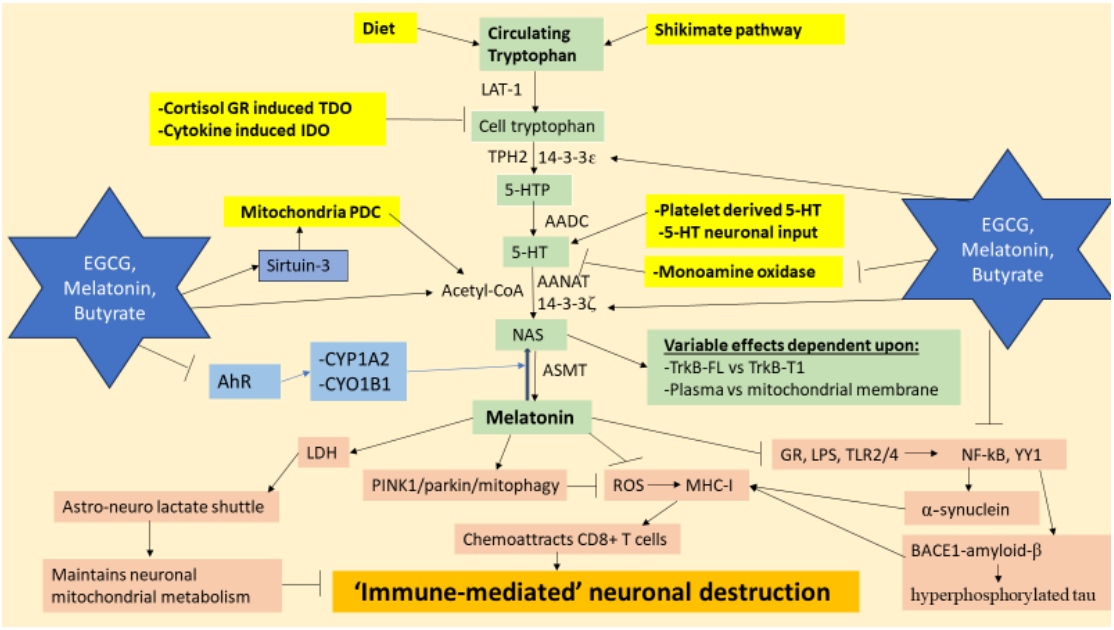


**Fig. 4. Nutraceuticals and tryptophan-melatonin pathway in neurodegenerative processes**.

*The figure summarizes how melatonin, butyrate and EGCG may act on the astrocyte tryptophan-melatonin pathway, as described in Figure 1 (green shade). Neuronal loss in neurodegenerative conditions is ultimately mediated via 'immune-mediated' processes, predominantly via the chemoattraction of $CD8^+$ T cells, as shown in Alzheimer's disease and Parkinson's disease. The loss of astrocyte melatonin prevents its induction of lactate dehydrogenase (LDH), which is necessary for the provision of lactate to neurons in the astrocyte-neuronal lactate shuttle, thereby compromising neuronal metabolism and survival. As neurons utilize lactate to produce pyruvate for the pyruvate dehydrogenase complex, thereby increasing acetyl-CoA, there will be a decreased capacity of neurons to initiate the mitochondrial melatonergic pathway, making neurons susceptible to elimination. The consequent rise in neuronal ROS and oxidative stress increase MHC-I, which chemoattracts $CD8^+$ T cells that mediate neuronal destruction. Neuronal loss in classical neurodegenerative conditions is therefore an 'immune-mediated' process, thereby overlapping neurodegenerative conditions with some classical autoimmune disorders involving cell elimination. Melatonin can also suppress such destruction via PINK1/parkin upregulation of mitophagy. However, in the absence of melatonin, mitophagy is suppressed contributing to dysregulated metabolism and*

*increased oxidative stress. By suppressing the GR, LPS and TLR2/4 induction of NF-kB and YY1, astrocyte melatonin, pineal melatonin, EGCG and butyrate suppress the induction of BACE1/amyloid-β, hyperphosphorylated tau and α-synuclein and the contribution of these peptide inclusions to ROS induced MHC-1. The night-time interactions of melatonin, butyrate and BAG-1 with the GR significantly modulate the astrocyte-neuronal interactions, likely mediated via the suppression of the astrocyte tryptophan-melatonin pathway over aging that enhances GR impacts, which butyrate, EGCG and melatonin would suppress. Alterations in the astrocyte-neuronal interactions are one example of how the suppression of pineal melatonin and butyrate over aging upregulates the night-time cortisol rise and morning CAR influence on the homeostatic interactions of cells in microenvironments across the brain and body. Abbreviations: 5-HT: serotonin; 5-HTTP: 5-hydroxytryptophan; AADC: aromatic-L-amino acid decarboxylase; AANAT: acetyl-CoA: acetyl-coenzyme A; aralkylamine N-acetyltransferase; AhR: aryl hydrocarbon receptor; ASMT: N-acetylserotonin O-methyltransferase; BACE1: β-site amyloid precursor protein-cleaving enzyme; BAG-1: bcl2-associated athanogene 1; CAR: cortisol awakening response; CYP: cytochrome P450: EGCG: epigallocatechin gallate; GR: glucocorticoid receptor; IDO: indoleamine 2,3-dioxygenase; LAT-1: large amino acid transporter 1; LDH: lactate dehydrogenase; LPS: lipopolysaccharide; MHC-I: major histocompatibility factor-class 1; 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; TPH: tryptophan hydroxylase; TrkB-FL: tyrosine receptor kinase B-full length; TrkB-T1: tyrosine receptor kinase B-truncated; YY1: yin yang 1.*

As well as modulating classical neurodegenerative processes, butyrate also significantly suppresses the night-time GR and morning CAR GR activation by inhibiting GR nuclear translocation. This is mediated by butyrate's acetylation of the GR and its cytoplasmic partner, heat shock protein (hsp)90, preventing GR nuclear translocation (113). Butyrate production in the gut peaks during periods of 'fasting' (114), suggesting relevant, if not heightened, levels of butyrate production during the night when peristaltic movement in the gut is slowed, thereby providing an optimum environment for butyrate production. Circulating butyrate levels over the circadian rhythm in humans clearly requires investigation, including the influence of nocturnal eating disorder, which associates with diverse medical conditions (115). Overall, butyrate is likely to be a relevant regulator of night-time processes regulating cortisol and morning CAR effects at the GR in close association with the levels and effects of pineal and local melatonin production.

The suppression of butyrate, melatonin and BAG-1 over aging are proposed to initiate the pathogenesis of diverse medical conditions, including Alzheimer's disease (4), Parkinson's disease (116) and cancer (24). This seems mediated, at least partly, via alterations in how GR nuclear (vs mitochondrial and cytoplasmic) localization impacts on the homeostatic interactions of a given cell with its local microenvironment, such as astrocytes, microglia, neurons, pericytes and endothelial cells in CNS conditions. Cell interactions in microenvironments have been most extensively investigated in cancer, where the tumor conducts the 'orchestra of the tumor microenvironment' by various fluxes, including kynurenine activation of the AhR on natural killer (NK) cells and $CD8^+$ T cells (117). Recent work indicates other microenvironments may also have similar dynamics, with cells in a given microenvironment being prone to elimination by how a neighbouring cell influences their capacity to initiate the tryptophan-melatonin pathway and optimize mitochondrial function (118). For example, the suppression of the astrocyte tryptophan-melatonin pathway not only decreases melatonin efflux to dampen inflammation in the microenvironment, but also suppresses lactate efflux from a decrease in melatonin's induction of lactate dehydrogenase, as

shown in other cell types (119). The loss of astrocyte melatonin and lactate makes neurons vulnerable and increases mitochondrial ROS levels to drive miRNAs that act to suppress the melatonergic pathway in neurons. This highlights how neuronal loss in neurodegenerative conditions can arise from the dysregulation of systemic and circadian processes, being at least partly mediated via GR nuclear translocation during the night-time cortisol rise and morning CAR. Heightened GR nuclear translocation alters the homeostatic interactions in a given microenvironment, as exemplified by changes in astrocytes. Given that neurons are highly dependent upon astrocytes for energy, antioxidants and neurotransmitter regulation, any negative impact on astrocyte function will make neurons more susceptible to challenge, as highlighted in Figure 4.

The suppression of the neuronal capacity to induce the tryptophan-melatonin pathway is driven by the loss of astrocyte lactate provision due to decreased pineal and astrocyte melatonin, which induces lactate via the upregulation of lactate dehydrogenase (LDH), see Figure 4. Neuronal mitochondria require astrocyte lactate to function, with lactate being readily converted to pyruvate in neurons. Neuronal pyruvate is then utilized by the pyruvate dehydrogenase complex (PDC) to produce acetyl-CoA, which is a necessary cosubstrate to initiate the neuronal mitochondrial melatonergic pathway. The suppression of the astrocyte-neuronal lactate shuttle, coupled to the suppression of the neuronal mitochondrial melatonergic pathway, increases neuronal ROS and oxidative stress, which suppresses Pten-induced kinase (PINK)1/parkin mediated mitophagy, thereby further enhancing oxidative and metabolic stress that induce the major histocompatibility complex (MHC)-I. MHC-I leads to the chemoattraction of $CD8^+$ T cells, which destroy neurons, as shown in Parkinson's disease (116) and Alzheimer's disease (4). Such neurodegenerative conditions may therefore be more accurately classified as etiologically 'mitochondrial interactive disorders,' which culminate in cell death driven by 'immune-mediated' processes that are variants of 'autoimmune' disorders. It is upon such diverse, dynamic, and continually developing processes that melatonin, butyrate and EGCG act.

As noted, the etiology of neurodegenerative disorders may be importantly determined by night-time processes that regulate how cortisol activation of GR 'prepares the body for the coming day.' Notably, the raised cortisol levels that can drive excessive GR nuclear translocation seem, at least partly, mediated via cortisol/GR and pro-inflammatory cytokine upregulation of 11β-hydroxysteroid dehydrogenase (11β-HSD)1 (101). 11β-HSD1 therefore has to be integrated into the circadian and systemic interactions regulating cortisol effects at the GR, as well as how melatonin, EGCG and butyrate will modulate 11β-HSD1. As noted, melatonin and butyrate suppress GR nuclear translocation and therefore the cortisol/GR upregulation of 11β-HSD1, with both melatonin and butyrate also acting to suppress the pro-inflammatory cytokine induction of 11β-HSD1. However, EGCG has more distinct effects in the regulation of the enhanced local cortisol production by 11β-HSD1.

EGCG is a potent inhibitor of 11β-HSD1 by directly binding to the active catalytic site of 11β-HSD1 where it forms a hydrogen bond with Lys187 of the catalytic triade of 11β-HSD1 (120). As well as increasing melatonin availability via monoamine oxidase inhibition (50) to increase the melatonin suppression of 11β-HSD1 (121-123) and melatonin's suppression of GR nuclear translocation, the green tea polyphenol, EGCG, also directly inhibits 11β-HSD1, as shown in preclinical models (124). The efficacy of EGCG to suppress 11β-HSD1 will be optimized when EGCG is available in the late night and early morning period when cortisol levels peak, including during the morning CAR (124). Morning availability of EGCG will therefore afford benefits in conditions exacerbated by raised 11β-HSD1 driven cortisol activation of the GR, including CNS and neurodegenerative conditions (8, 125). Notably, preclinical data shows increased forebrain 11β-HSD1 associates with a decreased hippocampal BDNF (126), with suppressed BDNF levels often associated with neurodegenerative

conditions (127) and decreased neurogenesis, with the latter intimately linked to heightened stress levels (128).

EGCG suppression of 11β-HSD1 may also have indirect consequences for neurodegenerative conditions, including via EGCG suppression of 11β-HSD1 in adipocytes and in the course of metabolic syndrome (129). Metabolic syndrome is a significant risk factor for dementia (130), with EGCG affording protection (131), whilst 11β-HSD1 exacerbates metabolic syndrome driven dementia (132). EGCG also offsets the impacts of aging-linked heightened 11β-HSD1 and cortisol/GR activation in driving other systemic processes linked to neurodegenerative conditions, including sarcopenia (133), osteoporosis (134), and suppressed brown adipocyte (BAT) mitochondrial function and thermogenesis (135).

Although both melatonin and EGCG decrease gut permeability and gut dysbiosis to increase butyrate availability (136), and butyrate increases the mitochondrial melatonergic pathway (72), there is no direct data linking butyrate (or HDACi) to 11β-HSD1 regulation. The effects of butyrate on 11β-HSD1 will be important to determine in systemic and CNS cells, especially as GR activation increases gut permeability/dysbiosis (104) and 11β-HSD1 significantly regulates the gut microbiome and bile acids (137).

By highlighting the role of circadian and systemic processes in the pathophysiology of neurodegenerative conditions, the impacts of ubiquitously beneficial nutraceuticals, such as melatonin, butyrate and EGCG may be important in diverse organs and processes. The benefits of green tea/EGCG, like melatonin and butyrate, are intimately linked to the modulation of wider circadian and systemic processes relevant to optimized mitochondrial function, and driven, at least partly, via the night-time and early morning suppression of adrenal and 11β-HSD1 derived cortisol activation of the GR. As pro-inflammatory cytokines, such as tumor necrosis factor (TNF)α and interleukin (IL)-1B, increase 11β-HSD1 (138), the dampening effects of melatonin, butyrate and EGCG on immune-inflammatory activation will also contribute to a decrease in 11β-HSD1 induction (139-141), as shown in Figure 4. This has a number of future research, treatment and wider implications.

## 6. FUTURE RESEARCH IMPLICATIONS

- Does butyrate modulate 11β-HSD1 in systemic and CNS cells, including directly and/or via mitochondrial melatonergic pathway upregulation?
- How does circulating butyrate vary over the night in humans? Would butyrate production at night be modulated by 'night-time eating disorder', which has links to polycystic ovary syndrome (142), another disorder showing evidence of circadian dysregulation of cortisol and melatonin interactions (143)?
- How does butyrate modulate the AhR in brain and systemic cells?
- Do melatonin, butyrate and/or EGCG increase the gut microbiome shikimate pathway, thereby increasing the production of the aromatic amino acids, including tryptophan, phenylalanine and tyrosine? Would this be mediated via alterations in the composition of the gut microbiome, including *Akkermansia muciniphila* upregulation, as previous work would indicate (66)?
- Do melatonin, butyrate and/or EGCG directly modulate BAG-1 and increase the mitochondrial translocation of the glucocorticoid receptor (GR)?
- Do melatonin, butyrate and/or EGCG modulate the mitochondrial melatonergic pathway in platelets, thereby impacting on the role of platelets in neurodegenerative disorders (1)?
- Is melatonin production suppressed in astrocytes of preclinical models as well as in patients with neurodegenerative disorders? If so, would this be modulated by nutraceuticals that impact on how systemic and circadian processes interact to modulate how night-time and morning cortisol at the GR primes the body and brain microenvironments for the coming day?

## 7. TREATMENT IMPLICATIONS

- It will be important to determine the timing and interaction effects of melatonin, butyrate and EGCG within the context of a night-time pathoetiology of neurodegenerative conditions, as detailed throughout.
- It requires investigation in preclinical trials as to the importance of the astrocyte tryptophan-melatonin pathway in neurodegenerative conditions, and how this is impacted by melatonin, butyrate and/or EGCG.

## 8. WIDER IMPLICATIONS

The above may also provide a framework for integrating the effects of other nutraceuticals, including many used in treatment by traditional Chinese and Indian medicine. A number of traditional phytotherapies are known to regulate the tryptophan-melatonergic pathway and/or the gut microbiome, including Ciwujia tablet (144), Armillaria mellea (Vahl) P. Kumm (145), Sesamol (146) and curcumin (147). Investigations as to the impacts of traditional medicines/nutraceuticals on the night-time processes highlighted above should better clarify the means of their efficacy and give directions as to how this can be improved.

Aging-associated conditions, such as sarcopenia (133) and osteoporosis (134), which are upregulated in classically defined neurodegenerative disorders, such as Alzheimer's disease, may be intimately related via the interactions of circadian and systemic processes, including gut microbiome derived butyrate. Rather than being comorbidities of a classically defined Alzheimer's disease pathophysiology, such 'comorbidities' of dementia reflect changes in real-life physiological processes that can have a number of detrimental outcomes in different organs and tissues. This is a significant challenge to current classification systems of 'endpoint catastrophes', such as Alzheimer's disease and osteoporosis, and has a number of future research and treatment implications.

## 9. CONCLUSIONS

The treatment of neurodegenerative conditions, including current classifications of the 'endpoint catastrophes' that are Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis, is widely regarded as very poor. This stems from an inadequate understanding of the pathophysiological changes occurring over time that culminate in these endpoint catastrophic conditions. Such a situation clearly demands a different way of conceptualizing the pathophysiological changes driving such neurodegenerative conditions. The above provides a perspective that highlights the importance of circadian and systemic processes interacting at night in the pathoetiology of neurodegenerative conditions, suggesting that melatonin, butyrate and BAG-1 'battle' with cortisol effects at the glucocorticoid receptor (GR) in shaping how body cells, microenvironments and body systems are 'prepared for the coming day'. This provides a novel conceptualization of neurodegenerative conditions into which the effects of various nutraceuticals may be understood. The current article has highlighted the roles of melatonin, butyrate and EGCG and how these nutraceuticals can modulate the night-time pathoetiology of neurodegenerative conditions, with an emphasis on the tryptophan-melatonin pathway and associated altered regulation of the kynurenine pathway. Clearly, astrocytes are a crucial hub given their fundamental role in the regulation of neuronal metabolism, function and survival. The inability of astrocytes and microglia to regulate the changes occurring in neurodegenerative conditions necessitates the extravasation of cytolytic cells, primarily CD8+ T cells that ultimately drive neuronal destruction. The more refined use of nutraceuticals within the frame of reference provided in this article should better clarify

relevant preventative and treatment targets for these poorly conceptualized conditions. The common 'comorbidities' of neurodegenerative disease, such as sarcopenia and osteoporosis, would seem intimately linked to the night-time circadian and systemic interactions highlighted throughout, allowing for concurrent improvements in their prevention and management.

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**AUTHORSHIP**

GA: Conceptualization, Writing—original draft, Writing—review & editing.

**CONFLICTS OF INTEREST**

The author declares no conflicts of interest.

**ABBREVIATIONS**

11β-HSD1: 11β-Hydroxysteroid-Dehydrogenase Type 1
5-HT: serotonin
5-HTP: 5-hydroxytryptophan
α7nAChR: alpha 7 nicotinic acetylcholine receptor
AADC: amino acid decarboxylase
AANAT: aralkylamine *N*-acetyltransferase
acetyl-CoA: acetyl-coenzyme A
AhR: aryl hydrocarbon receptor
ASMT: acetylserotonin methyltransferase
BAG-1: B cell lymphoma-2-associated anthanogene 1
Bcl-2: B cell lymphoma-2
BDNF: brain-derived neurotrophic factor
CAR: cortisol awakening response
CRH: corticotropin-releasing hormone
CYP1A2: cytochrome P450 enzyme 1A2
DCs: dendritic cells
DNMT1: DNA methyltransferase 1
FKBP4: FKBP prolyl isomerase 4
GnRH: gonadotrophin releasing hormone
GR: glucocorticoid receptor
GRE: glucocorticoid response element
HPA: hypothalamus-pituitary-adrenal
Hsp90: heat shock protein 90
IDO: indoleamine 2,3-dioxygenase
LATs: large amino acid transporters
lncRNA: long non-coding RNA
LPS: lipopolysaccharide
miRNAs: microRNAs
NAS: *N*-acetylserotonin
NF-kB: nuclear factor kappa-light-chain-enhancer of activated B cells

NK: natural killer
Nrf2: nuclear factor erythroid 2–related factor 2
OXPHOS: oxidative phosphorylation
PDC: pyruvate dehydrogenase complex
PINK1: PTEN-associated kinase 1
ROS: reactive oxygen species
T2DM: type 2 diabetes mellitus
TCA: tricarboxylic acid
TDO: tryptophan 2,3-dioxygenase
Th17: T helper type 17
TPH: tryptophan hydroxylase
Treg: regulatory T cell
TrkB: tyrosine receptor kinase B
TrkB-FL: tyrosine receptor kinase B-full length
TrkB-T1: tyrosine receptor kinase B-truncated
YY1: yin yang 1

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