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Review

Autism Pathoetiology and Pathophysiology: Roles of STAT3 and NF-κB Dimer Interactions in Regulating the Mitochondrial Melatonergic Pathway in Placental, CNS, and Systemic Cells

George Anderson[1,*]

[1]CRC Scotland & London, SW1V 1PG London, UK
*Correspondence: anderson.george@rocketmail.com (George Anderson)
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Abstract

People with autism spectrum disorders (ASD) show a relative suppression of the melatonergic pathway across CNS and systemic cells. The differential regulation of the mitochondrial melatonergic pathway may therefore be an important core aspect of ASD pathophysiology in all its manifestations. Recent data across diverse human cells show that the melatonergic pathway is powerfully regulated by interactions between signal transducer and activator of transcription 3 (STAT3) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), with the composition of the NF-κB dimer determining whether the melatonergic pathway is upregulated or downregulated. Diverse aspects of ASD pathoetiology and pathophysiology, including the aryl hydrocarbon receptor (AhR), microRNAs, suboptimal mitochondrial function, pro-inflammatory cytokines, glucocorticoid receptor, vagal nerve, and oxytocin, are all intimately linked to pineal and/or local melatonin regulation, indicating the relevance of the mitochondrial melatonergic pathway regulation in the pathoetiology and pathophysiology of ASD. This article reviews and integrates diverse aspects of ASD pathoetiology and pathophysiology, with implications for future research and treatment.

Keywords: autism; melatonin; aryl hydrocarbon receptor; NF-κB; STAT3; mitochondria; preeclampsia; vagal nerve; glucocorticoid receptor; treatment

1. Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder currently characterized by alterations in social interaction and communication, concurrent to restricted interests and verbal or behavioral stereotypies. The presence of raised circulating serotonin levels has long been appreciated to be evident in ASD [1] in many but not all people classed on this spectrum [2]. Although this may arise from increased antibodies against monoamine oxidase A (MAO-A) [3], a number of investigators have proposed that raised circulatory serotonin levels may occur due to a decreased capacity to use serotonin as a necessary precursor to initiate the melatonergic pathway, for example from a decrease in chaperone protein, 14-3-3, stabilization of the first melatonergic pathway enzyme, Aralkylamine N-acetyltransferase (AANAT) [4]. Decreased 14-3-3 availability can arise from increased microRNAs (miRNAs) such as miR-451 [5] and miR-375 [6]. This is supported by data showing decreased circadian/pineal [7] and systemic melatonergic pathway induction in ASD [5] as well as the clinical utility of nighttime melatonin treatment in management of sleep and wider ASD symptomatology [8]. Recent work indicates that suppressed pineal and local melatonergic pathway induction may be a core aspect of ASD, as with many other diverse medical conditions [9,10]. Suppressed mitochondrial melatonin may therefore be intimately linked data showing suboptimal mitochondrial function in ASD [11,12] with wider downstream developmental and ongoing consequences.

Numerous factors and processes are associated with ASD pathoetiology and pathophysiology, including increased phosphorylation and activation of signal transducer and activator of transcription 3 (STAT3) [13–15] and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) [16–18] as well as related increases in interleukin (IL)-6 [19–21]. Recent work indicates that the IL-6/Janus Kinase (JAK)/STAT3 pathway interacts with the specific dimer composition of NF-κB in the nucleus to either up-regulate or down-regulate the mitochondrial melatonergic pathway across diverse cell types, with NF-κB dimer component effects specific to particular cells [22]. These authors showed that the anti-inflammatory effect of IL-10 in pineal, bone marrow, spleen and peritoneal cells is determined by the interactions of STAT3 and NF-κB dimer composition in the regulation of the melatonergic pathway [22]. As the suppression of the melatonergic pathway across CNS and systemic cells has long been recognized as an aspect of ASD pathophysiology [5,23,24] the regulation of STAT3 interactions with NF-κB dimer composition in the modulation of the melatonergic pathway is likely to constitute core aspects of ASD pathoetiology and pathophysiology, including via alterations in mitochondrial function that are evident in ASD [25].

Alterations in the circadian rhythm [26–28] and cortisol activation of the glucocorticoid receptor (GR)-α in the course of circadian regulation and hypothalamic-pituitary-adrenal (HPA) axis activation during stress have long been linked to ASD pathophysiology [29–31]. The suppression of pineal melatonin [7], and systemic melatonin [5] as well as gut microbiome-derived short-chain fatty acid, butyrate [32] in ASD therefore disinhibits the GR-α, thereby modulating the circadian rhythm and stress response effects of cortisol. This has relevance across a range of diverse medical conditions linked to decreased pineal melatonin and increased gut dysbiosis, including Alzheimer's disease [33], cancer [34], and diabetes associated conditions, including ASD [35] as well as for ASD pathoetiology driven by gestational diabetes [36]. Circadian and stress/cortisol dysregulation arises from a decrease in both pineal melatonin and gut derived butyrate. Both melatonin and butyrate inhibit GR-α nuclear translocation from the cytoplasm to the nucleus [37,38], leading to a dysregulated circadian and stress linked HPA axis activation in ASD pathoetiology and pathophysiology [39,40]. As melatonin can inhibit STAT3 and NF-κB activation, the suppression of pineal melatonin in ASD contributes to alterations in STAT3 interactions with NF-κB dimer composition, thereby altering the modulation of the systemic melatonergic pathway in ASD. As local melatonin upregulation is a key aspect of the resolution of local inflammation, including as mediated by vagal nerve activation [41], the suppression of the local melatonergic pathway in ASD has significant implications for attaining resolution of inflammation systemically. Decreased vagal nerve activation is common in ASD [42], which may therefore be confounded by a decreased capacity to induce local melatonin in ASD across body organs/tissues [5]. Similarly, the suppression of pineal melatonin increases gut dysbiosis and gut permeability [43], which are typically associated with decreased gut microbiome-derived butyrate, linking the classical gut associated changes in ASD with alterations in circadian (pineal melatonin) and systemic (vagal) processes associated with inflammation resolution.

This article reviews data on circadian and systemic changes in the pathoetiology and pathophysiology of ASD. It is proposed that alterations in circadian and systemic processes are strongly determined by variations in the regulation of the local mitochondrial melatonergic pathway. The mitochondrial melatonergic pathway is regulated by alterations in the canonical and non-canonical STAT3 interactions with NF-κB dimer composition [22]. This has prevention, treatment and future research implications including by integrating data showing increased hyperglycemia inducing methylglyoxal and advanced glycation end-products in ASD pathophysiology [44], thereby providing a context for the association of diabetes/hyperglycemia with ASD [35].

The next two sections briefly review the alterations in circadian and local melatonin regulation. The first section highlights the interactions of pineal melatonin and cortisol in the course of night-time dampening and resetting in preparation for the coming day.

2. Night-Time Dampening and Resetting

Altered night-time dampening and resetting may be an aspect of the pathoetiology and pathophysiology of an array of diverse medical conditions, including Alzheimer's disease [33] and cancer [45,46]. Changes in night-time melatonin and cortisol interactions may also be core aspects of conditions driving accelerated aging, such as type 2 diabetes mellitus (T2DM) [47]. T2DM is more common in ASD and is proposed to contribute to ASD pathophysiology [48]. The overlaps of ASD and T2DM may therefore arise from suppressed pineal melatonin in ASD [49] and in T2DM [50]. Suppressed pineal melatonin may arise from a number of factors and processes that act to increase STAT3 and thereby attenuate AANAT enzymatic activity that initiates the melatonergic pathway [49,51]. Approximately 65% of people with ASD, vs controls, have less than 50% of pineal melatonin levels [52], highlighting the importance of incorporating pineal melatonin in ASD pathophysiology. The role of the melatonergic pathway in the pathophysiological overlaps of ASD and T2DM is highlighted by data showing melatonin and melatonin receptor levels and allele variants to modulate T2DM [50]. Consequently, any suppression of pineal and/or local melatonin in ASD [5] would be expected to increase T2DM risk/symptomatology, with T2DM then contributing to the circadian and systemic underpinnings of ASD via the attenuation of the capacity of pineal and systemic cells to induce the melatonergic pathway. Night-time changes in pineal melatonin and cortisol in ASD, T2DM and aging are shown in Fig. 1 (Ref. [22,53–57]).

Night-Time Melatonin and Cortisol Modulation of Oxytocin and Vagal Nerve

The loss of pineal and local melatonin is typically modelled as a loss of melatonin's antioxidant and anti-inflammatory capacity. However, pineal melatonin can act on a number of systemic processes and body systems to influence processes of dampening and resolution of inflammation. For example, melatonin directly, and via oxytocin upregulation [58–60], can activate the vagal nerve, which dampens inflammatory activity across different organs and tissues via the release of acetylcholine (ACh) that activates a number of ACh receptors, especially the alpha 7 nicotinic acetylcholine receptor (α7nAChR), to suppress immune driven inflammation. This seems mediated via specialized proresolving mediators (SPMs) upregulation [61], which changes the NF-κB dimer composition allowing different NF-κB dimer composition to interact with nuclear pSTAT3 to upregulate (or down regulate) local melatonin production [22,62]. Pineal melatonin also interacts with this set of processes by increasing α7nAChR levels at night

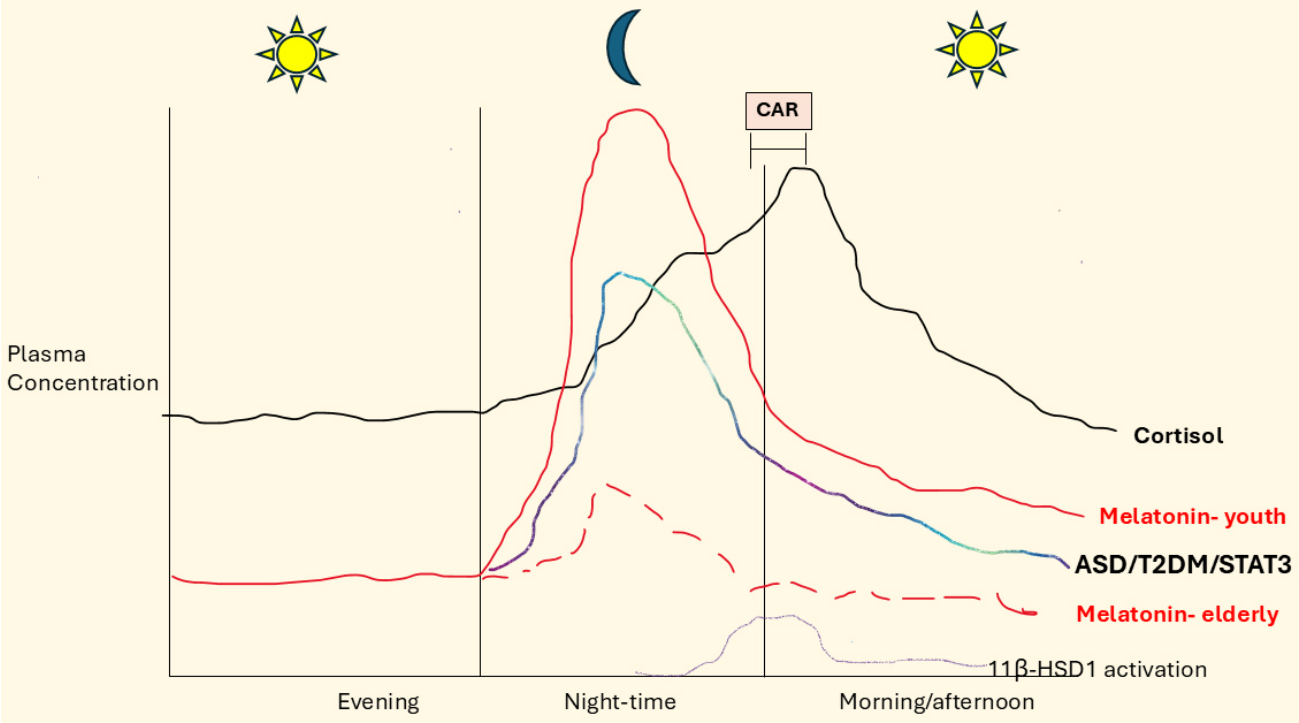

Fig. 1. Melatonin and cortisol circadian variations in ASD, T2DM and over age. Pineal melatonin dramatically decreases over aging as indicated by 'elderly' vs 'youth' comparison. ASD, including as influenced by increased T2DM, suppresses pineal melatonin levels, thereby enhancing the likelihood of accelerated aging driven changes. Pineal melatonin suppression in ASD may be mediated by increased pSTAT3 in pinealocytes thereby suppressing AANAT activation and consequent induction of the melatonergic pathway. Pineal melatonin suppression in ASD can be driven by the same processes that suppress local melatonin production across body cells and systems [22], namely the interactions of heightened levels and activation STAT3 and NF-κB, which are determined by the specific NF-κB dimer composition. Night-time and morning cortisol awakening response (CAR) cortisol levels tend to remain stable over aging, although in some conditions cortisol levels may remain enhanced during the day following their morning CAR peak. Melatonin and cortisol are highly interactive. Melatonin acts on the adrenal cortex to decrease cortisol release [53,54] whilst melatonin also suppresses glucocorticoid receptor (GR)-α nuclear translocation from its complex in the cytoplasm [55]. Although other GR exist, including GR-β, and GR locations can be plasma membrane, mitochondrial membrane and mitochondrial matrix [56], most data on cortisol effects have been restricted to the cytoplasmic GR-α. The suppression of pineal melatonin in ASD, T2DM and over aging may therefore disinhibit night-time cortisol influence across body cells and systems and therefore alter how cells, their microenvironments and body systems are prepared for the coming day. Enhanced GR-α activation, as with raised pro-inflammatory cytokines, increases local cellular cortisol production by 11 beta hydroxysteroid dehydrogenase 1 (11β-HSD1) [57], thereby increasing local cortisol's influence on cell function and intercellular, homeostatic interactions in the microenvironment in which all cells exist. Other factors pertinent to ASD (and T2DM), including gut microbiome-derived butyrate and B cell lymphoma-2 (Bcl-2)-associated athanogene 1 (BAG-1), which also inhibit GR-α nuclear translocation but are not included for clarity. Abbreviations: 11β-HSD1, 11 beta hydroxysteroid dehydrogenase; BAG-1, bcl2-associated athanogene 1; CAR, cortisol awakening response; GR, glucocorticoid receptor; T2DM, type 2 diabetes mellitus; ASD, autism spectrum disorders; STAT3, signal transducer and activator of transcription 3; AANAT, Aralkylamine N-acetyltransferase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells.

[63], thereby upregulating the capacity of ACh and vagal nerve activation to dampen inflammatory activity. See Fig. 2 (Ref. [5,63]).

In contrast to the effects of melatonin and oxytocin, GR-α activation by cortisol has complex effects on the vagal nerve, including its suppression [64]. Heightened cortisol effects in ASD are likely to be confounded by disinhibited GR-α activation and consequent alterations in the levels of GR-β and the GR localization site (cytoplasm, plasma membrane, mitochondrial membrane and mitochondrial matrix), and 11β-HSD1 induction [65,66]. Consequently, cortisol may have heightened and differential effects in the absence of raised cortisol levels per se that will be importantly determined by suppressed pineal and/or local melatonin production. This also applies to the interactions of cortisol with oxytocin, with cortisol having a rapid negative feedback on oxytocin induction of adrenocorticotropic hormone (ACTH) and the HPA axis [67], whilst

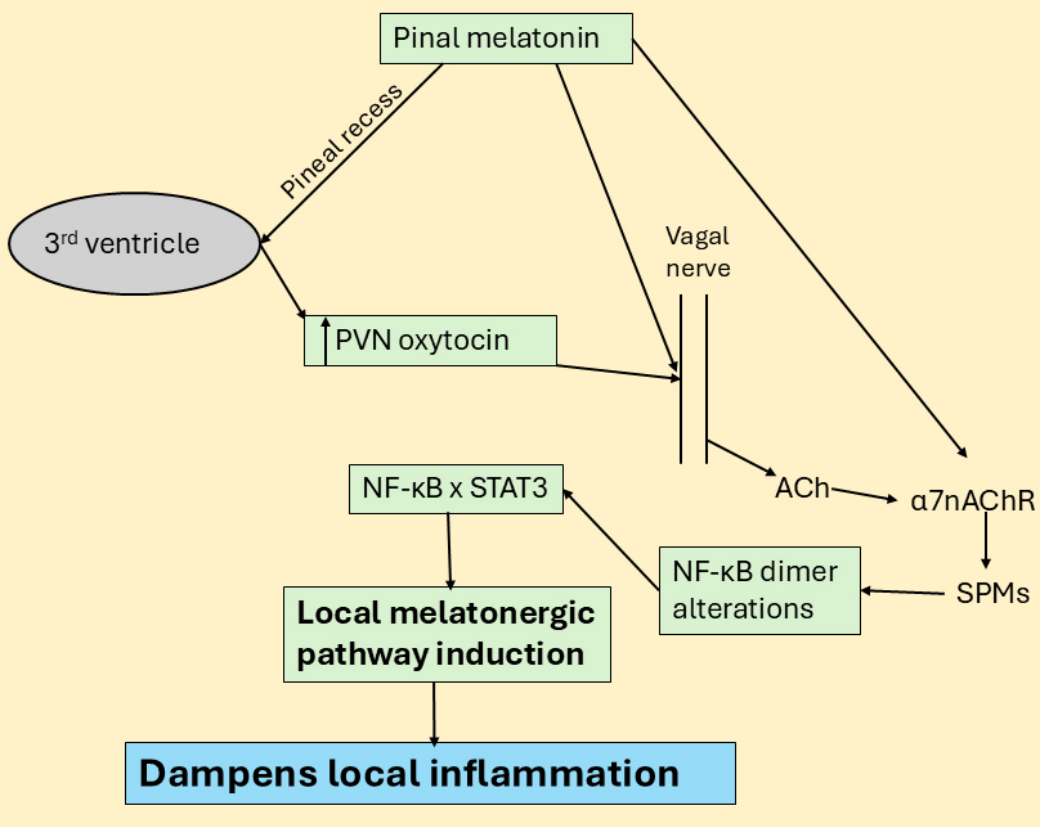

Fig. 2. Pineal melatonin, including via oxytocin, regulates the vagal nerve. Pineal melatonin directly and via oxytocin induction can activate the vagal nerve to release acetylcholine (ACh) on to the α7nAChR, which induces specialized proresolving mediators (SPMs). As pineal melatonin increases the α7nAChR [63], this may be another route whereby suppressed pineal melatonin modulates wider processes of dampening and resetting, including by the vagal nerve. SPMs can alter the NF-κB dimer composition by switching from a pro-inflammatory dimer composition (typically p65/p50) to a resolution inducing NF-κB composition (typically c-Rel/p50) via the upregulation of the local melatonergic pathway. The suppressed vagal activity and decreased oxytocin in ASD may therefore be intimately linked to alterations in the circadian rhythm and the attenuated capacity to upregulate the local melatonergic pathway in any given organ/tissue [5]. The suppression of pineal and local melatonin production may therefore be core aspects of ASD pathophysiology, including from decreased pineal melatonin induction of hypothalamic paraventricular nucleus (PVN) oxytocin. Abbreviations: α7nAChR, alpha 7 nicotinic acetylcholine receptor; Ach, acetylcholine; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PVN, paraventricular nucleus; SPMs, specialized pro-resolving mediators; STAT3, signal transducer and activator of transcription 3.

electroacupuncture suppresses enhanced HPA axis activity via oxytocin upregulation [68]. The suppression of pineal melatonin and melatonin's induction of oxytocin is therefore a significant contributor to alterations in circadian and stress induced HPA axis activation and regulation. Early life stressors epigenetically regulate the methylation of the GR and oxytocin receptors to alter the nature of social interactions, as shown in preclinical models [69]. The capacity of pineal melatonin to upregulate oxytocin as well as suppress GR-α nuclear translocation and adrenal cortex cortisol production would indicate that suppressed pineal (and possibly local) melatonin in ASD will modulate the interactions of the HPA axis with oxytocin and therefore vagal nerve activation, and that this will interact with early stress induced epigenetic changes in the GR and oxytocin receptors.

The amygdala [6,70], hippocampus [71] and ventral tegmental area (VTA)/nucleus accumbens (N.Acc) [72] show alterations in ASD linked to affect, cognition and motivation, respectively. Cortisol significantly modulates these three sites and their associated functions, exemplified by cortisol activation of the GR-α in the central amygdala (CeA), which increases local corticotropin releasing hormone (CRH) that upregulates the κ-opioid receptor and its ligand, dynorphin, in the basolateral amygdala (BLA), leading to feelings of dysphoria, as shown in preclinical models [73]. This change in affective state can be prevented by PVN oxytocin projections to CeA astrocytes that suppress CRH induction by cortisol at the CeA GR-α [74]. Such data indicate that the suppression of pineal and local melatonin induction of oxytocin may allow cortisol/stress to induce a dysregulated affective state (dysphoria) that is

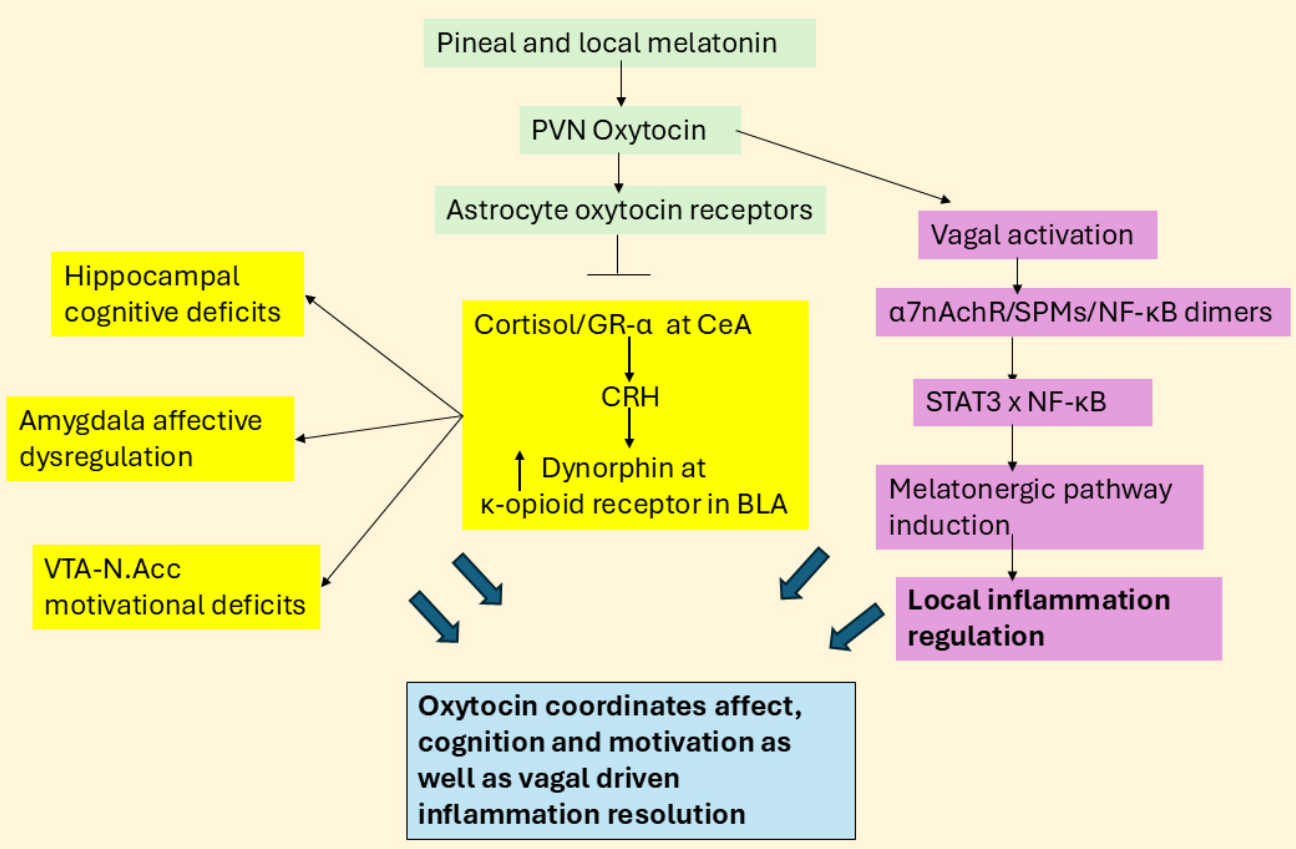

Fig. 3. Melatonin, oxytocin and vagal nerve modulate cognition, affect and motivation. Pineal and local melatonin may increase oxytocin activation of the vagal nerve, with vagal ACh driving the α7nAChR/SPMs/NF-κB dimers pathway (purple shading) whilst also coordinating the effects of cortisol by inhibiting GR-α induced CRH in the central amygdala (CeA) thereby suppressing dynorphin and κ-opioid receptor activation in the basolateral amygdala (BLA) with parallel effects in the hippocampus and VTA/N.Acc in the regulation of cognition and motivation, respectively (mechanisms not shown for clarity). The changes in the BLA and CeA will also modulate hippocampal and VTA/N.Acc function, with consequences for wider brain interarea connectivity. The suppression of pineal and local melatonin in ASD, including by attenuating oxytocin effects, will therefore have a wide range of CNS and systemic consequences relevant to classical ASD pathoetiology and ongoing pathophysiology. Abbreviations: α7nAChR, alpha 7 nicotinic acetylcholine receptor; BLA, basolateral amygdala; CeA, central amygdala; CRH, corticotrophin releasing hormone; GR, glucocorticoid receptor; N.Acc, nucleus accumbens; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PVN, paraventricular nucleus; SPMs, specialized pro-resolving mediators; STAT3, signal transducer and activator of transcription 3; VTA, ventral tegmental area; CNS, central nervous system.

not uncommon in ASD [75]. Similar factors and processes also regulate hippocampal cognition and VTA/N.Acc motivation. As indicated above, the suppression of pineal and local melatonin as well as oxytocin in ASD will modulate the influence of the vagal nerve and cortisol/stress on affect, cognition and motivation, as shown in Fig. 3.

3. Autism, the Opioidergic System, Borderline Personality and Perceived Social Rejection

There is a growing appreciation of the pathophysiological overlaps of autism with borderline personality disorder (BPD) [76,77], with both showing significant alterations in the opioidergic system. Perceived rejection sensitivity is a key aspect of BPD pathophysiology [73] and may be an unrecognized aspect of ASD affective dysregulation [78]. BPD [79], like ASD [80,81], is associated with very high levels of non-suicidal self-injury, which may arise from alexithymia and difficulties in emotion recognition/expression [82] or from white matter disruption [83] and/or from perceived social rejection induced dysphoria [73] driven by increased dynorphin in the CeA arising from suppressed oxytocin, as shown in Fig. 3.

Alterations in the opioidergic system have long been associated with ASD pathophysiology, with μ-opioid receptor knockout rodents being a preclinical ASD model that shows improved social interactions following intranasal oxytocin administration [84]. BPD pathophysiology is in-

timately associated with decreased μ-opioid receptor activation coupled with increased κ-opioid receptor activation, with some treatment efficacy being derived from ultra-low dose buprenorphine, a partial μ-opioid receptor agonist and κ-opioid receptor antagonist [85,86]. In different preclinical ASD models (prenatal valproate and Fmr1-knockout) buprenorphine increased social behaviors that correlated with increased neuronal activity in the VTA/N.Acc and medial prefrontal cortex (PFC) [87], with medial PFC activation negatively feeding back on amygdala activity [88]. Alterations in the μ-/κ-opioid receptor ratio across brain regions can therefore have significant impacts on social behaviors and interarea brain patterned activity, as indicated in preclinical models, with links to how early developmental trauma/stress may modulate the pathophysiological overlaps of ASD and BPD [89–91].

The regulation of the opioidergic system may be intimately linked to alterations in pineal melatonin, with melatonin acting on the pituitary to increase the μ-opioid receptor endogenous ligand, beta-endorphin [92], whilst a specific fragment of beta-endorphin, called des-tyrosine-gamma-endorphin (DTγE), dramatically increases pineal melatonin, as shown in rodents [93]. In contrast, melatonin inhibits the sleep disturbing effect of the κ-opioid receptor [94,95]. Acute stress induced CRH increases dynorphin that activates the κ-opioid receptor to suppress dopamine release [96,97], which is proposed to suppress the reward system and increase anhedonia, whilst chronic stress can drive dysphoria and low mood via dynorphin activation of the κ-opioid receptor [98]. Alterations in nociception are common in ASD, including hypersensitivity and hyposensitivity [99], with affective aspects of nociception significantly regulated by right amygdala κ-opioid receptor activation [100] and the alterations in the μ-, κ-and δ-opioidergic receptors arising from early developmental stress [101]. This also has pathophysiological relevance in BPD [73] and may be significantly modulated by suppression of pineal and/or local melatonin availability [102]. Decreased melatonergic pathway availability may therefore regulate the opioidergic system to modulate diverse aspects of symptomatology in ASD and BPD. This may have relevance to wider bodies of data showing increased amygdala κ-opioid receptor to correlate with poor self-reported social status [103], indicating that the amygdala μ/κ-opioid receptor ratio may regulate our perceived connectedness to others more widely, implicating roles for pineal and/or local melatonergic pathway regulation in the modulation of wider affective aspects of social connectedness. Current classification of ASD, in the absence of any physiological indices, highlights the importance of social interaction and connectedness, suggesting a significant role for alterations in the opioidergic system and its regulation in the defining characteristics of ASD.

Alterations in the opioidergic system in ASD and BPD may be partly mediated by increased gut permeability and gut dysbiosis in ASD [104] as well as in BPD [105]. Gut permeability/dysbiosis are typically associated with decreases in the short-chain fatty acid, butyrate. Butyrate is a histone deacetylase inhibitor (HDACi) and epigenetic regulator that is also used as a metabolic substrate to increase the melatonergic pathway, as shown in intestinal epithelial cells [106]. Butyrate also epigenetically regulates the μ- and κ-opioid receptors [107, 108]. Some of the consequences of stress/cortisol induced gut permeability/dysbiosis on the opioidergic system may therefore be mediated via decreased butyrate and its regulation of the melatonergic pathway and/or opioidergic system. Factors influencing the availability of tryptophan for the initiation of the tryptophan-serotonin-N-acetylserotonin-melatonin pathway will also have consequences for butyrate's effects. As well as increasing gut dysbiosis/permeability, chronic stress increases κ-opioid receptor levels, which are major contributors to sleep disruption, indicating that suppressed pineal and local melatonin production in ASD will alter the consequences of chronic stress, including decreasing the μ-/κ-opioid receptor ratio that will negatively regulate sleep to further contribute to circadian and pineal melatonin dysregulation [94].

Suppressed pineal and local melatonin in ASD may therefore be intimately linked to alterations in the opioidergic system, with significant consequences for development of interarea brain connectivity, affective regulation, perceived social rejection and non-suicidal self-injury, with significant overlaps to BPD symptomatology and pathophysiology.

This begs the question as to how the opioidergic system interacts with canonical and non-canonical pSTAT3 and NF-κB dimer composition in the modulation of the mitochondrial melatonergic pathway.

Opioidergic System Interactions With STAT3, NF-κB and miRNAs

Activation of the κ-opioid receptor increases STAT3, with diverse effects across different body cells and organs [109], including upregulating mitochondrial function in challenged cardiomyocytes [110]. In other cell types, κ-opioid receptor decreases pSTAT3 by sequestering pSTAT3 to the plasma membrane, as shown in chondrocytes [111]. It is unknown as to how κ-opioid receptor activation modulates amygdala pSTAT3, including whether it differentially impacts on the canonical, nuclear translocating $STAT3^{Tyr705}$ and/or non-canonical, mitochondria translocating $STAT3^{Ser727}$. Canonical, nuclear translocating pSTAT3 is mediated by Tyrosine705 phosphorylation of STAT3, whilst non-canonical, mitochondria translocating STAT3 is mediated by Serine727 phosphorylation. How these different sites of STAT3 phosphorylation interact with NF-κB dimer composition in regulating the melatonergic pathway and how this then acts to modulate the opioidergic system requires investigation, see Fig. 4 (Ref.

[22,112]). This will be important to clarify in future research, especially as κ-opioid receptor activation in the basolateral amygdala drives dysphoria that is commonly evident in ASD [75]. The capacity of melatonin to increase the μ-opioid receptor ligand, beta endorphin, indicates that pineal and/or local melatonin will increase the μ-/κ-opioid receptor ratio, thereby paralleling the beneficial effects of buprenorphine on social processes in ASD preclinical models [85–91].

Activation of the μ-opioid receptor typically increases pSTAT3 [113] and has differential effects on NF-κB that seem dependent upon cell type and phenotypic state [114]. NF-κB activation also increases the μ-opioid receptor [115]. Both μ- and κ-opioid receptor interact with the chaperone protein, 14-3-3ζ, [116], with 14-3-3ζ significantly interacting with mitochondrial STAT3^{Ser727} to regulate 14-3-3ζ availability [62,117]. This may be important given the role of 14-3-3ζ in the stabilization of AANAT in the initiation of the melatonergic pathway [5,6]. As indicated, ASD may be associated with an increase in microRNA (miR)-451 [5], which, like miR-375 and miR-7 can attenuate the initiation of the melatonergic pathway by AANAT by decreasing 14-3-3ζ availability [118]. The regulation of 14-3-3ζ may therefore be of importance in the coordination of the opioidergic system and mitochondrial melatonergic pathway, including as arising from mitochondrial, non-canonical STAT3^{Ser727} binding and regulating 14-3-3ζ availability [62]. This is supported by data showing miR-451 to regulate STAT3 [119,120] and NF-κB [121,122], as does miR-375 [123,124] and miR-7 [125,126]. Whether the regulation of 14-3-3ζ by STAT3^{Ser727} is coordinated by these miRNAs with consequences for opioidergic system regulation will be important to determine. The interactions of canonical and non-canonical pSTAT3 with NF-κB dimer composition in the modulation of the melatonergic pathway are shown in Fig. 4.

Overall, the data linking canonical and non-canonical pSTAT3 interactions with NF-κB dimer composition in the modulation of the melatonergic pathway requires extensive further investigation to determine whether this is intimately linked to alterations in the opioidergic system and opioid receptors at key sites, as well as the regulation of oxytocin, vagal nerve and gut microbiome.

4. Aryl Hydrocarbon Receptor, STAT3, NF-κB, Opioidergic System and Melatonergic Pathway

The aryl hydrocarbon receptor (AhR) significantly modulates ASD pathophysiology [127,128]. The AhR has a number of complex effects that are dependent upon specific ligands and cell types as well as its site of expression, namely within the cytoplasm and/or on the mitochondrial membrane [129]. The AhR can be activated by many ligands including endogenous (FICZ) and induced (kynurenine) as well as environmental toxins, such as air pollutants and cigarette smoke products [130]. The AhR also regulates the melatonergic pathway via AhR activation induction of cytochrome P450 (CYP)1B1 and CYP1A2, which can hydroxylate melatonin as well as O-demethylate melatonin 'backwards' to its immediate precursor, N-acetylserotonin (NAS) [131]. The association of the AhR with ASD may therefore be via direct suppression of melatonin availability, whilst the complexity of AhR effects may arise from cell conditions that determine whether the melatonergic pathway is available or not. Consequently, AhR effects may be dependent upon STAT3 interactions with NF-κB dimer composition [22].

This is further complicated by the AhR also regulating STAT3 across diverse cell types and medical conditions, including cancer [132] and cardiovascular diseases [133]. The raised levels of pro-inflammatory cytokines (IFN-γ, IL-1β, IL-6, and TNF-α) in ASD [134] induce indoleamine 2,3-dioxygenase (IDO) that converts tryptophan to kynurenine to reduce tryptophan availability for the tryptophan-melatonin pathway, with kynurenine activating the AhR, to further reduce melatonin availability [135]. Raised kynurenine and kynurenic acid levels are evident in ASD children, vs controls, with both of these kynurenine pathway products activating the AhR [136], Such data indicates an enhanced ligand availability for AhR activation in ASD that concurrently decreases tryptophan-melatonin pathway availability. Diabetes linked hyperglycemia increases glucose glycation thereby increasing methylglyoxal levels, which dramatically suppress tryptophan availability via protein-protein interactions [137]. This not only decreases tryptophan availability for the tryptophan-melatonin pathway, thereby limiting tryptophan availability for conversion to kynurenine and AhR activation. This is likely to contribute to variations in kynurenine pathway products and therefore AhR activation in ASD [138]. This requires further investigation as it indicates that AhR complexity and contrasting effects may arise from an uninvestigated tryptophan-melatonin pathway availability, including as arising from raised methylglyoxal in prediabetes, type 1 dianbetes mellitus (T1DM) and T2DM suppressing tryptophan availability. Such interactions highlight the interconnected nature of ASD with diabetic pathophysiology and how this may contribute to contrasting results across studies.

As pro-inflammatory cytokine-induced IDO drives the kynurenine activation of the AhR, the AhR is intimately associated with a pro-inflammatory NF-κB dimer composition. The AhR and NF-κB are classically thought to have negative reciprocal interactions [139], with the AhR able to bind the pro-inflammatory component of NF-κB, p65, both in the cytoplasm and nucleus [139]. The AhR can therefore modulate mitochondrial pSTAT3^{Ser727} effects, given that the mitochondrial translocation of pSTAT3^{Ser727} also drives NF-κB, p65 and the NLRP3 inflammasome to mitochondria [140] (see Fig. 4), Mitochondrial NF-κB and p65 directly modulate mitochondrial

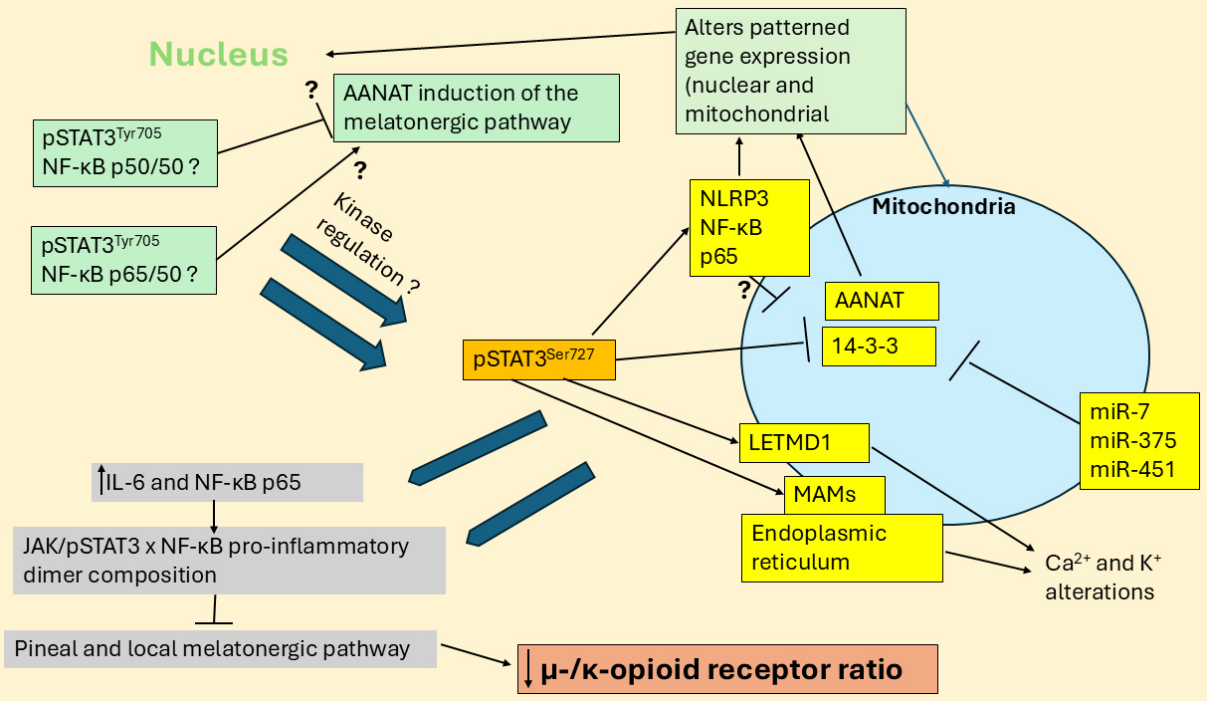

Fig. 4. STAT3 interaction with NF-κB dimers modulates melatonergic and opioidergic pathways. Canonical pSTAT3^{Tyr705} interacts with NF-κB dimer composition in the nucleus to modulate the cellular melatonergic pathway, which may be present in the nucleus although more likely in mitochondria. Nuclear (green shade) translocated STAT3^{Tyr705} interacts with NF-κB dimer components (such as p65/50 and p50/p50) to stimulate or inhibit the melatonergic pathway, with specific effects partly dependent upon cell type [22]. Nuclear STAT3^{Tyr705} interactions with NF-κB dimer components may also modulate non-canonical, mitochondria translocating pSTAT3^{Ser727}, including from alterations in specific kinases that phosphorylate and activate pSTAT3^{Ser727}. At mitochondria, pSTAT3^{Ser727} can regulate many core aspects of mitochondrial function, including: (1) regulates mitochondria-associated membranes (MAMs), thereby modulating endoplasmic reticulum Ca^{2+} mitochondrial influx, a key driver of alterations in mitochondrial function; (2) pSTAT3^{Ser727} can bind and regulate mitochondrial 14-3-3 availability. As 14-3-3 is required to stabilize AANAT stabilization to initiate the melatonergic pathway any suppression of 14-3-3 availability, including by miR-7, miR-375 and miR-451, will attenuate melatonergic pathway availability; (3) In some cells, mitochondrial pSTAT3^{Ser727} can form a positive reciprocal feedback loop with LETM1 domain-containing protein 1 (LETMD1), thereby regulating mitochondrial Ca^{2+} and K^{+} flux; and (4) Mitochondrial translocation of pSTAT3^{Ser727} enhances the mitochondrial translocation of the NACHT, LRR and PYD domains-containing protein 3 (NLRP3) inflammasome, NF-κB and p65 with consequences for patterned gene expression in both the nucleus and mitochondria, as shown in different cell types. Interestingly, LETM1/LETMD1 has a 14-3-3 like matrix motif [112] that may bind AANAT and/or form a 'dimer' with 14-3-3, indicating a possibly wider complexity to mitochondrial melatonergic pathway regulation. Importantly, pro-inflammatory processes (IL-6, NF-κB p65, NLRP3) in a given cell will have consequences for adjacent cells of the local microenvironment, via increased IL-6 and NLRP3 inflammasome induced IL-1β and IL-18 release driving inflammatory processes in neighboring cells, including via released IL-6 activating JAK/pSTAT3/NF-κB to stimulate or suppress the melatonergic pathway in cells of the local microenvironment. The suppressed capacity to induce the melatonergic pathway in a given cell therefore has implication for the regulation of the melatonergic pathway in neighboring cells and inflammatory responses within its local microenvironment. The suppression of pineal and/or local melatonin will have consequences for μ-/κ-opioid receptor ratio and therefore the role of the opioidergic system in ASD, including in the regulation of affect, cognition and motivation, as highlighted in Fig. 3. The specifics of pSTAT3 interactions with NF-κB dimer composition in ASD cells over the course of development will be important to determine. Abbreviations: AANAT, aralkylamine N-acetyltransferase; JAK, Janus kinase; LETM1, Leucine Zipper EF-hand containing Transmembrane protein 1; MAMs, mitochondria-associated membranes; miR, microRNA; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3: NACHT, LRR and PYD domains-containing protein 3; STAT3, signal transducer and activator of transcription 3; LETMD1: LETM1 domain-containing protein 1; IL, interleukin.

transcription and function, whilst the NLRP3 inflammasome locates adjacent to the outer mitochondrial membrane, thereby increasing access to mitochondrial caspases that cleave pro-IL-1β and pro-IL-18 into their active forms. By suppressing NF-κB and p65 the AhR may therefore change pSTAT3^{Ser727} regulation of mitochondrial function.

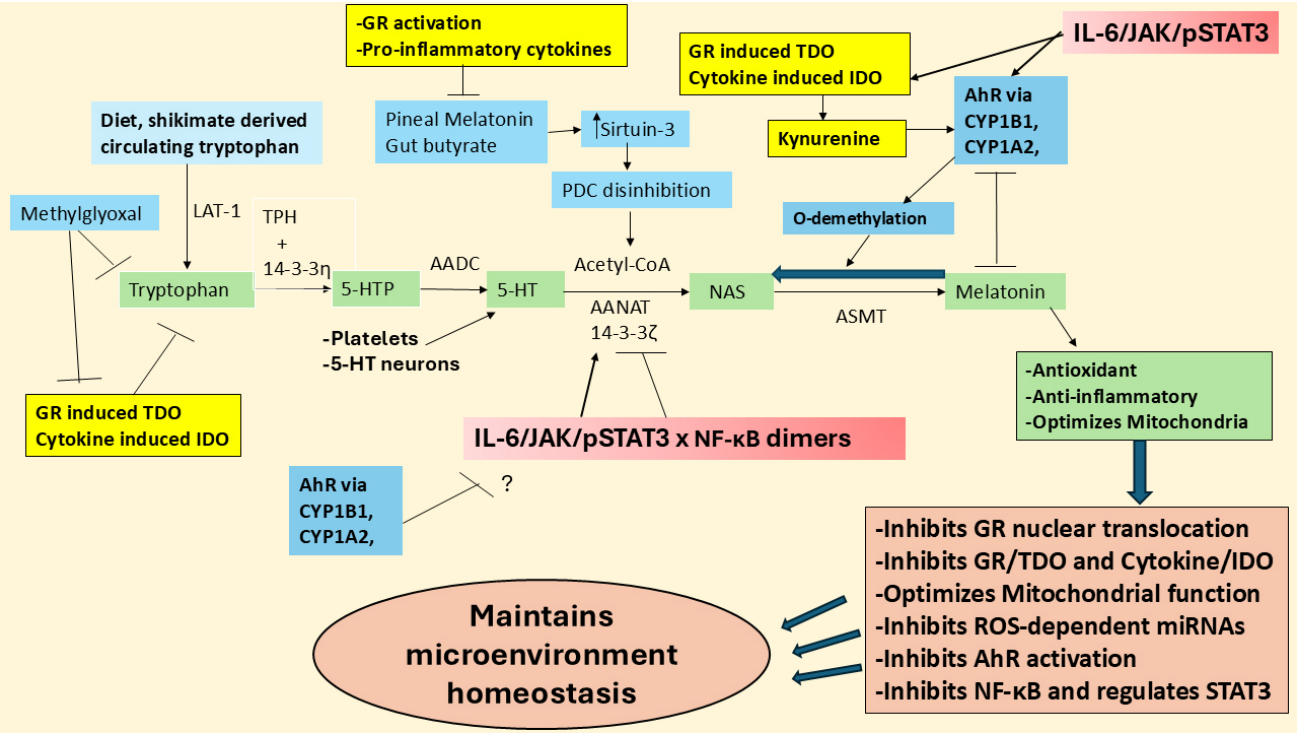

Fig. 5. A diversity of factors can modulate the tryptophan-melatonin pathway. The mitochondrial melatonergic pathway of the tryptophan-melatonin pathway (green shade) is evident in all cells where it has been investigated. Methylglyoxal, via protein-protein interactions with tryptophan, not only suppresses tryptophan but also tryptophan derived kynurenine pathway products that can activate the AhR, thereby changing the consequence of AhR activation as well as GR-induced TDO and cytokine induced IDO by limiting tryptophan availability. As the AhR can modulate STAT3 and inhibit NF-κB p65, the suppression of tryptophan conversion to kynurenine can change the influence of the AhR on the regulation of the melatonergic pathway. The AhR induction of CYP1B1 and CYP1A2 leads to the hydroxylation and/or 'O-demethylation' of melatonin, with both processes decreasing melatonin availability and effects. As IL-6 not only induces the JAK/pSTAT3 pathway but also IDO, IL-6 may therefore initiate the IDO/kynurenine/AhR/CYP1B1/CYP1A2 to suppress the tryptophan-melatonin pathway, although this would be dependent upon tryptophan availability for conversion to kynurenine, and therefore subject to suppression by methylglyoxal. Alterations in T2DM/hyperglycemia/methylglyoxal and AhR activation may therefore act on core aspects of ASD pathophysiology by modulating mitochondrial function, including the mitochondrial melatonergic pathway, with consequences for cellular function and homeostatic intercellular interactions. Abbreviations: 5-HT, serotonin; 5-HTP, 5-hydroxytryptophan; AADC, aromatic-L-amino acid decarboxylase; AANAT, aralkylamine N-acetyltransferase; AhR, aryl hydrocarbon receptor; ASMT, acetylserotonin methyltransferase; CYP, cytochrome P450; GR, glucocorticoid receptor; IDO, indoleamine 2,3-dioxygenase; JAK, Janus kinase; LAT-1, large amino acid transporter 1; NAS, N-acetylserotonin; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PDC, pyruvate dehydrogenase complex; ROS, reactive oxygen species; STAT3, signal transducer and activator of transcription 3; TDO, tryptophan 2,3-dioxygenase; TPH, tryptophan hydroxylase.

Heightened NLRP3 inflammasome and IL-1β are evident in ASD, as shown in ASD fibroblasts [141], with mitochondrial ROS driving NLRP3 inflammasome activation. This suggests that the suppression of the mitochondrial melatonergic pathway in ASD may be a significant determinant of NLRP3 activation, which may be modulated by AhR suppression of NF-κB and p65 to therefore shape the consequences of pSTAT3^{Ser727} mitochondrial translocation [142]. As methylglyoxal suppresses tryptophan to decrease kynurenine availability for AhR activation, diabetes/hyperglycemia/methylglyoxal and the AhR may therefore interact with STAT3/NF-κB to modulate core aspects of mitochondrial dysfunction, including the mitochondrial melatonergic pathway, in ASD. Whether the suppression of the AhR by methylglyoxal decreasing tryptophan availability for conversion to kynurenine upregulates NF-κB p65 induced pro-inflammatory cytokines will be important to determine. Overall, factors that modulate STAT3 interactions with NF-κB in the modulation of mitochondrial function and the melatonergic pathway, including genetic, epigenetic and early developmental stressors, as well as methylglyoxal and the AhR, may be intimate aspects of mitochondrial dysfunction in ASD. The interactions of the AhR and methylglyoxal with the tryptophan-melatonin pathway are shown in Fig. 5.

Overall, the AhR has complex effects on many aspects of ASD pathophysiology, including interactions of STAT3 and NF-κB, with consequences for mitochondrial function and NLRP3 inflammasome activation. These effects are intimately intertwined with modulation of the mitochondrial melatonergic pathway, as shown in Figs. 4,5.

5. Autism Pathoetiology Implications

As indicated above the relative suppression of the melatonergic pathway across CNS and systemic cells may be an important aspect of ASD pathophysiology in all its manifestations [5], which include a range of severe learning difficulties to high-functioning ASD. Melatonergic pathway suppression is intimately associated with STAT3 and its interactions with NF-κB dimer composition, as well as other regulatory factors such as diabetes/methylglyoxal, the AhR and miRNAs, as indicated above. As ASD is classically conceptualized as a neurodevelopmental disorder [143], when and how does such mitochondrial melatonergic pathway dysregulation occur?

Early developmental risk factors for ASD include preeclampsia [144], which is associated with a decrease in placental melatonin production [145] and may exemplify the importance of prenatal melatonergic pathway modulation in ASD pathoetiology. Many of the melatonergic pathway regulatory factors highlighted above are also important to placental regulation, including miRNAs [146–148], STAT3 [149] and NF-κB [150]. Preeclampsia increases cortisol transfer over the placenta via 11β-HSD2 suppression [151]. This suggests parallels to the alterations in night-time dampening and resetting arising from suppressed pineal melatonin and associated disinhibition of the wider cortisol system, as indicated in Fig. 1. Do such placental alterations establish an early developmental pattern of microenvironment interactions in the developing fetus leading to a subtle change in optimal homeostatic interactions occurring, with consequences for differential stress responses, arising from a decreased melatonin/cortisol ratio prenatally? Another prenatal conditions, intrauterine growth restriction (IUGR), is also associated with increased cortisol transfer over the placenta [152] and enhanced ASD risk in the offspring [153]. It should be noted that this does not necessarily indicate that placental melatonin replicates circadian, pineal melatonin suppression in ASD as the placental release of melatonin is not circadian [154]. However, a decrease in the placental melatonin/cortisol ratio may change the nature of cellular and intercellular homeostasis in the developing fetus within a crucial temporal window.

The AhR is highly expressed in the placenta and modulates many aspects of placental function, including trophoblast cell proliferation, migration and apoptosis, as well as energy metabolism [155]. As noted, the AhR via CYP1B1 and CYP1A2 can hydroxylate melatonin and 'backward' convert melatonin to N-acetylserotonin (NAS) via O-demethylation [131], with NAS being a brain-derived neurotrophic factor (BDNF) mimic via its activation of the BDNF receptor, tyrosine receptor kinase (Trk)B [156]. This may suggest an increase in placental and fetal NAS that not only suppresses melatonin availability but increases TrkB activation, which in ASD models is associated with ASD pathophysiology via alterations in α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor activation [157]. As NAS can also increase hippocampal BDNF [158], alterations in the placental NAS/melatonin pathway may contribute to the diverse effects of BDNF and TrkB in ASD pathoetiology, as shown in diverse preclinical models [159,160], with relevance to brain overgrowth (macrocephaly) that is evident in a subset of people with ASD [161].

At least 8 isoforms of the GR-α are evident in the placenta and can vary by fetal sex and birthweight [162], being proposed as an important interface with the maternal environment and fetal growth [163]. GR-α isoforms also influence nutrient regulation [164]. Preclinical data indicates that prenatal stress leads to hypermethylation of glucocorticoid-related genes that disrupts the placental glucocorticoid barrier, with significant consequences for fetal development [165]. The GR-β is present in the human placenta and is classically modelled as a dominant negative regulator of GR-α, although recent work shows the GR-β to have transcriptional consequences that are independent of its inhibition of GR-α [166]. The raised pro-inflammatory cytokines evident in ASD increase the GR-β/GR-α ratio to suppress the capacity of cortisol and corticosteroids to dampen inflammatory activity [167], including by GR-β attenuating the capacity of GR-α to suppress NF-κB [166]. How the GR-β/GR-α ratio modulates NF-κB dimer components and their interactions with pSTAT3 in the regulation of the placental, fetal and post-natal melatonergic pathway will be important to determine, including as to the consequences that this has for night-time dampening and resetting mediated by the interactions of pineal melatonin and cortisol following the establishment of the circadian rhythm in the developing infant. As melatonin attenuates GR-α nuclear translocation, the suppression of melatonin will decrease the threshold for GR-β induction and alterations in NF-κB regulation and therefore in the regulation of the melatonergic pathway. This is one route whereby alterations in the placenta may shift the influence of melatonin and cortisol in the developing fetus and infant.

The plasma membrane GR is also evident in the placenta, perhaps especially in syncytiotrophoblasts [168]. However, the presence and regulation of the mitochondrial membrane GR and mitochondrial matrix GR in the placenta awaits investigation and the role of placental bcl2-associaited athanogene (BAG)-1 [169] in the transport of GR to the mitochondrial matrix, as in other cell types [170], requires further investigation. As melatonin, like gut microbiome derived butyrate, suppresses GR-α nuclear translo-

cation, presumably the suppression of placental melatonin in ASD prenatal risk conditions (e.g., preeclampsia and IUGR) will have consequences for wider cortisol receptors and their effects in both the placenta and developing fetus, with later developmental consequences.

As in any cell the increased glycolysis in preeclamptic trophoblasts leads to glycation induced methylglyoxal [171]. These authors showed that preeclamptic trophoblasts increase methylglyoxal and methylglyoxal induced advanced glycation end products (N(6)-(carboxymethyl)lysine [CML], and N^{ε}-(carboxyethyl)lysine [CEL], as well as methylglyoxal-derived hydroimidazolone [MG-H]), coupled to a decrease in glyoxalase (Glo)1 that metabolizes methylglyoxal [171]. Maternal plasma concentrations of methylglyoxal, CML and MG-H1 increase as early as the 12th week of gestation indicating that these products may be potential early biomarkers of preeclampsia [171]. Notably, mitoQ (a mitochondrial oxidant quencher) prevented these preeclamptic methylglyoxal driven changes when the data was replicated in a trophoblast cell line. This data readily links to the decreased placental melatonin in preeclampsia and how its loss in mitochondria can prevent melatonin from offsetting the consequences of suboptimal mitochondrial function as indicated by raised mitochondria oxidant production and its influence on patterned gene expression via ROS-dependent miRNAs. This also has implications for intercellular fluxes and therefore for alterations in the homeostatic interactions of the local microenvironment.

Melatonin increases mitochondria located sirtuin-3 [172] which suppresses oxidant production at three points of the electron transport chain [173]. Consequently, the detrimental effects of suppressed placental melatonin may, at least partly, arise from a decrease in melatonin induction of trophoblast sirtuin-3. Decreased trophoblast sirtuin-3 and associated increase in the acetylation, and inhibition, of the antioxidant enzyme, manganese superoxide dismutase (MnSOD), are evident in preeclampsia and contribute to increased mitochondrial ROS driven alterations in patterned gene expression [174]. The suppression of the placental melatonergic pathway therefore modulates mitochondrial function, at least partly via a decrease in mitochondrial sirtuin-3 and endogenous antioxidants.

As noted above, methylglyoxal can directly downregulate tryptophan availability by protein-protein interactions [137], indicating that the necessity to upregulate methylglyoxal in the course of glycolysis may be intimately linked across diverse cell types to the suppression of the melatonergic pathway. In many circumstances, this would seem to arise from the increased glycolysis and methylglyoxal suppression of the tryptophan-melatonin pathway as an indicant of the need for chemoattracted immune cells to deal with the changes/challenges occurring, a situation where the local production of melatonin would suppress immune cell efficacy. Whether this is pertinent in preeclampsia and how it associates with ASD pathoetiology will be important to determine. As the glucocorticoid receptor (GR) can be glycated by methylglyoxal to alter its function [174], the raised levels of methylglyoxal in preeclampsia may not only suppress melatonin but also alter the nature of the wider cortisol system response, including GR subtypes and sites of localization. This requires future investigation.

The above would indicate that the understanding of ASD etiology may require a fuller investigation of processes and conditions, such as preeclampsia, and how they may contribute to the alterations in the mitochondrial melatonergic pathway that are proposed to be a core factor in ASD pathophysiology. Given the importance of melatonin and cortisol (and their interactions) in the night-time dampening and resetting of body cells, microenvironments and systems across the life-span, it would not seem incongruous that factors influencing melatonin and cortisol levels and effects as well as their interactions will be important in determining the consequences of environmental sampling that occurs over the course of pregnancy. This also provides a framework for understanding ASD genetic susceptibility factors and the processes on which they act in ASD etiology. See Fig. 6.

6. Future Research Implications

(1) Does suppressed pineal melatonin in ASD initially disinhibit GR-α activation with consequent alterations in the wider cortisol 'system', including the levels of GR-β and the GR localization site (cytoplasm, plasma membrane, mitochondrial membrane and mitochondrial matrix), as well as 11β-HSD1 induction [65,66]. Would such dysregulation of melatonin and cortisol at night modulate oxytocin levels as well as the interactions of cortisol with oxytocin, such as cortisol's rapid negative feedback on the oxytocin induction of adrenocorticotropic hormone (ACTH) and the HPA axis [67]? Does suppressed pineal and/or local (PVN) melatonin decrease oxytocin and therefore vagal nerve stimulation that dampens local inflammatory activity?

(2) As early life stressors epigenetically regulate the methylation of the GR and oxytocin receptors to alter the nature of social interactions in preclinical models [69], would the suppressed capacity to induce pineal and local melatonin in ASD modulate the impact of early life stressors via melatonin's capacity to induce oxytocin and suppress GR-α nuclear translocation? Is this also modulated by the loss of pineal melatonin's suppression of gut permeability/dysbiosis and potentiation of butyrate production, given that butyrate also suppresses GR-α nuclear translocation?

(3) Does μ-, vs κ-, opioid receptor activation differentially modulate amygdala, especially basolateral amygdala (BLA), pSTAT3 either via canonical $STAT3^{Tyr705}$ and/or non-canonical $STAT3^{Ser727}$, thereby impacting on the regulation of the local melatonergic pathway in BLA neurons and/or astrocytes?

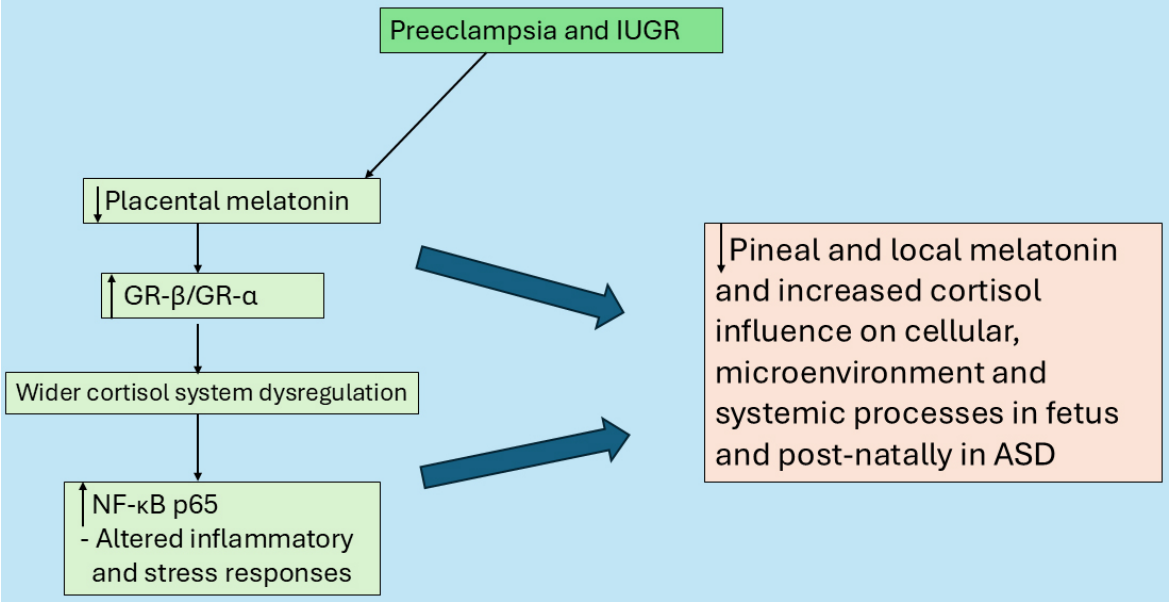

Fig. 6. Preeclampsia and IUGR suppress placental melatonin to change cortisol fetal effects. Suppressed placental melatonin may disinhibit the GR-α, which increases GR-β, thereby enhancing NF-κB p65 activation to dysregulate stress responses. These changes in the placenta drive alterations in the developing fetus in a crucial temporal window that shapes homeostatic interactions in local microenvironments and later postnatal development. Abbreviations: GR, glucocorticoid receptor; IUGR, intrauterine growth restriction; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells.

(4) Are the interactions of the opioidergic system and receptors with the melatonergic pathway dependent upon 14-3-3 regulation and availability, including as a consequence of mitochondria located STAT3^{Ser727} interacting with, and regulating, 14-3-3ζ availability? Is the availability of 14-3-3ζ also determined by the miRNAs, miR-451, miR-375 and miR-7 [5]?

(5) Is 14-3-3ζ regulation by STAT3^{Ser727} coordinated with miR-451, miR-375 and/or miR-7 levels and their regulation, with consequences for opioidergic system/receptor levels?

(6) Does the increase in methylglyoxal levels in ASD, by decreasing tryptophan availability [137], contribute to the variability of increased serotonin and kynurenine pathway products in ASD. Would methylglyoxal, by decreasing tryptophan availability for conversion to kynurenine, therefore attenuate AhR activation, including in the modulation of the melatonergic pathway as well as the AhR suppression of NF-κB? This would indicate specific consequences for AhR activation in the presence or suppression of the tryptophan-melatonin pathway? Is this an unrecognized aspect of the complexity and mixed results linked to AhR activation?

(7) Are the complexity of AhR effects determined by whether the melatonergic pathway is present or not in a given cell, with consequences not only for a given cell but for its interactions with other cells in its local microenvironment?

(8) Does the association of preeclampsia and IUGR with ASD risk arise from a decrease in placental melatonin/cortisol ratio to alter cellular, microenvironment and systemic melatonergic pathway availability across body cells? Does this arise from an early developmental 'crucial window'? Is this 'crucial window' determined by alterations in the homeostatic interactions of cells in their given microenvironment?

(9) How do variations in the GR-β/GR-α ratio modulate placental NF-κB dimer composition and therefore the regulation of the melatonergic pathway via interactions with STAT3? Does this have consequences for subsequent post-natal night-time dampening and resetting mediated by the interactions of pineal melatonin and cortisol, suggesting that non-circadian variations in placental/fetal melatonin and cortisol modulate their subsequent post-natal levels and effects? How does an increased GR-β/GR-α ratio and decreased 11β-HSD2 in the placenta and post-natal cells modulate pSTAT3^{Tyr705} and pSTAT3^{Ser727}? Does an increase in the GR-β/GR-α ratio, via increased NF-κB, drive a maintained inflammation that enhances immune cell chemoattraction to resolve inflammation and therefore coupled to suppression of the melatonergic pathway? This could indicate that 'glucocorticoid resistance' acts to signal the necessity of immune system chemoattraction and activation by minimizing the effects of cortisol and melatonin.

(10) As the glucocorticoid receptor (GR) can be glycated by methylglyoxal to alter its function [175], the raised levels of methylglyoxal in preeclampsia may not only sup-

press melatonin via protein-protein interactions [137] but also alter the nature of the wider cortisol system response, including GR subtypes, GR-β/GR-α ratio and sites of GR localization. This requires future investigation.

(11) Do alterations in the regulation of the melatonergic pathway and its interactions with cortisol occur prior to placenta formation? The melatonergic pathway is evident in oocytes and the granulosa immune cells that regulate oocyte selection and development. Would this have relevance to intercellular interactions in blastocysts and the subsequent interface with the endometrial wall and maternal immune cells in the course of shallow placentation?

(12) Hyperserotonemia in ASD is associated with learning difficulties [176]. It requires investigation whether this arises from decreased conversion of hippocampal serotonin to melatonin given the importance of melatonin in long-term potentiation (LTP) regulation [177,178]. Does the wide range of cognitive capacity in people classed with ASD arise from factors regulating mitochondrial melatonergic pathway availability in the hippocampus?

(13) ASD is associated with an increased risk of cancer and COVID-19 fatality [179,180]. This may be especially evident in people with ASD and learning difficulties, with ASD linked to a decreased cytotoxicity of natural killer (NK) cells [181,182]. Is the suppressed capacity to induce the melatonergic pathway in ASD across diverse cell types [5] also evident in NK cells? Exogenous melatonin increases NK cell cytotoxicity, which is also powerfully regulated by melatonin over the circadian rhythm [183], suggesting that the suppression of endogenous NK cell tryptophan-melatonin pathway by canonical and non-canonical STAT3 interactions with NF-κB dimer composition may modulate the NK cell melatonergic pathway and associated cytotoxicity. This will be important to determine in ASD, given the capacity of melatonin to increase NK cell elimination of tumor cells and viral infected cells. Alternatively, is the increased risk of cancer and COVID-19 fatality in ASD linked to increased concurrent T2DM and raised methylglyoxal levels that bind tryptophan to attenuate the initiation of the tryptophan-melatonin pathway [137]?

7. Treatment Implications

(1) Although the above clearly provides future research that should shape prevention and treatment, it is clear that the utilization of melatonin in ASD will provide some circadian and systemic benefits to decrease symptomatology.

(2) Given the overlapping pathophysiology of ASD with Borderline personality, there may be some utility of ultra-low dose buprenorphine, with possible particular relevance to stress-induced by social rejection and associated emotional dysregulation [184]. It is also important to note that low dose buprenorphine has also shown clinical utility in single case studies of people with ASD, with improvement in social interaction processes [185].

(3) As hyperglycemia driven methylglyoxal modulates tryptophan availability for the tryptophan-melatonin pathway, quercetin may have some utility in ASD due to its quenching of methylglyoxal [186]. Preclinical models would indicate that quercetin and its derivatives have utility in ASD [187].

(4) Other dietary factors/nutriceuticals, such as the polyphenol, epigallocatechin gallate (EGCG), have some clinical utility in ASD, which is typically modelled as being mediated via sealing the gut barrier, decreasing dysbiosis and increasing butyrate [188]. However, EGCG is also a monoamine oxidase inhibitor and therefore may increase serotonin availability for the melatonergic pathway in people with ASD without hyperserotonemia [189]. EGCG also inhibits the AhR [190], which as indicated above may be intimately linked to the regulation of core ASD pathophysiology.

(5) Another nutriceutical, resveratrol, which inhibits the AhR and increases sirtuins [191], is also proposed to have benefits in offsetting the effects of prenatal stress/valproate induction of ASD-like characteristics in preclinical models [192]. Whether resveratrol regulates the STAT3 interaction with NF-κB in the modulation of the melatonergic pathway will be important to determine in regard to its potential clinical efficacy.

(6) Recent work has highlighted the potential of repetitive transcranial magnetic stimulation (rTMS) in the treatment of neurodevelopmental disorders, including ASD [193]. Interestingly, rTMS decreases systemic cortisol [194] and increases pineal melatonin [195] indicating that rTMS will have significant impacts on how CNS and systemic processes are dampened and reset at night. Whether the rTMS upregulation of pineal melatonin increases oxytocin and oxytocin activation of the vagal nerve, as indicated above in Fig. 3, will be important to determine in clinical investigations. It will be important to clarify whether rTMS effects, both at the site of direct application and systemically, involve alterations in canonical and noncanonical STAT3 and its interactions with NF-κB dimer composition, as some data may suggest [196,197]. The association of rTMS with the regulation of fear processing and post-traumatic stress disorder (PTSD) [198,199] may underpin and reshape the conceptualization of an altered stress response in ASD, as previously indicated for another neurodevelopmental disorder [200]. The extent to which the effects of rTMS are mediated via pineal melatonin, including in the regulation of the gut barrier/permeability [201] and/or oxytocin stimulation of the vagal nerve having efficacy as consequence of melatonin availability in gut cells will be interesting to determine.

8. Conclusions

The above highlights the potential relevance of alterations in the melatonergic pathway in ASD with pathoetiological and ongoing pathophysiological implications. It

is proposed that the interactions of canonical and non-canonical STAT3 with NF-κB dimer composition may be an important, under-explored aspect of ASD biological underpinnings. This provides a perspective of core processes on to which many previously disparate bodies of data on ASD can be incorporated and integrated. The understanding of the role of the mitochondrial melatonergic pathway in early developmental processes, as exemplified by preeclampsia, should provide a body of knowledge that will allow the monitoring and targeting of early developmental processes in the pathoetiology of ASD.

Abbreviations

11β-HSD1, 11β-hydroxysteroid dehydrogenase type 1; 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; ASMT, N-acetylserotonin O-methyltransferase; BAG-1, bcl-2 associated athanogene 1; BDNF, brain-derived neurotrophic factor; BLA, basolateral amygdala; CAR, cortisol awakening response; CeA, central amygdala; CRH, corticotrophin releasing hormone; CSF, cerebrospinal fluid; CYP, cytochrome P450; FKBP4, FKBP prolyl isomerase 4; GR, glucocorticoid receptor; GRE, glucocorticoid receptor element; HDAC, histone deacetylase; HPA, hypothalamic-pituitary-adrenal; hsp, heat shock protein; IDO, indoleamine 2,3-dioxygenase; IUGR, intrauterine growth restriction; LETM1, Leucine Zipper EF-hand containing Transmembrane protein 1; lnc, long non-coding; LAT-1, large amino acid transporter 1; MAMs, mitochondria-associated membranes; MHC, major histocompatibility complex; N.Acc, nucleus accumbens; NAS, N acetylserotonin; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NK, natural killer; NLRP3, NACHT, LRR and PYD domains-containing protein 3; OXPHOS, oxidative phosphorylation; PDC, pyruvate dehydrogenase complex; PVN, paraventricular nucleus; SPMs, specialized pro-resolving mediators; STAT3, signal transducer and activator of transcription 3; T2DM, type 2 diabetes mellitus; TCA, tricarboxylic acid; TDO, tryptophan 2,3 dioxygenase; TPH, tryptophan hydroxylase; VTA, ventral tegmental area.

Author Contributions

GA confirms sole responsibility for the following: study conception and design and manuscript writing. GA read and approved the final manuscript.

Ethics Approval and Consent to Participate

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Conflict of Interest

The author declares no conflict of interest.

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