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THEORETICAL REVIEW

Sleep in autism: A biomolecular approach to aetiology and treatment

P. Ballester [a, b, *], A.L. Richdale [c], E.K. Baker [d, e, f], A.M. Peiró [a, b]

[a] Neuropharmacology on Pain and Functional Diversity (NED) Research Group, Alicante Institute of Sanitary and Biomedical Research (ISABIAL), Alicante, Spain
[b] Department of Clinical Pharmacology, Organic Chemistry and Pediatrics, Miguel Hernández University of Elche, Elche, Spain
[c] Olga Tennison Autism Research Centre, School of Psychology & Public Health, La Trobe University, Melbourne, Australia
[d] Diagnosis and Development, Murdoch Children's Research Institute, Parkville, Australia
[e] Department of Paediatrics, University of Melbourne, Parkville, Australia
[f] School of Psychology and Public Health, La Trobe University, Melbourne, Australia

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SUMMARY

People with autism spectrum disorder (ASD) commonly experience other comorbidities. Studies indicate that between 50% and 83% of individuals with ASD have sleep problems or disorders. The most commonly reported sleep problems are: (a) insomnia symptoms including the inability to get to sleep or stay asleep; and (b) circadian rhythm sleep-wake disorders, defined as a misalignment between the timing of endogenous circadian rhythms and the external environment. The circadian system provides timing information for the sleep-wake cycle that is regulated by the interaction of an endogenous processes (circadian - Process C, and homeostatic - Process S) and synchronizing agents (neurohormones and neurotransmitters), which produce somnogenic activity. A clinical priority in ASD is understanding the cause of these sleep problems in order to improve treatment outcomes. This review approaches sleep in autism from several perspectives: Sleep-wake mechanisms and problems, and brain areas and molecules controlling sleep (e.g., GABA and melatonin) and wake maintenance (e.g., serotonin, acetylcholine and glutamate). Specifically, this review examines how altered sleep structure could be related to neurobiological alterations or genetic mutations and the implications this may have for potential pharmacological treatments in individuals with ASD.

Sleep problems are commonly reported in autism spectrum disorder (ASD) across the lifespan, with as many as 80% of children [1] and over 50% of adults reporting poor sleep [2,3]. Sleep-related problems can have significant mental and physical health impacts and these effects can be more severe in ASD [4]. However, sleep problems are often under-recognised and consequently under-treated in those on the autism spectrum. The majority of sleep treatment research has targeted children with ASD, with poor treatment responses commonly reported for some autistic children; pharmacological treatments for sleep in autistic individuals remains under researched [5]. Poor treatment responses in children may be attributed to treatments failing to address and target the specific underlying causes of sleep difficulties in ASD [6,7]. Furthermore, there is evidence that autistic individuals have abnormalities and dysregulation in the brain areas and neurotransmitters/hormones that regulate sleep [8,9]. Thus, understanding the relationships between the specific sleep disturbances experienced by those on the autism spectrum, and these brain areas and neurotransmitters may provide insights into potential targeted pharmaceutical treatments. Understanding the genesis of sleep difficulties in autism may also provide insights into the aetiology of autism itself [10,11].

This review explores how altered sleep structure could be related to brain neurobiological alterations, and/or genetic mutations in ASD. Consideration of potential alterations in the neurotransmitters associated with sleep-wake states may lead to improved pharmacological approaches to treating sleep problems in the autism population.

* Corresponding author. Neuropharmacology on Pain and Functional Diversity (NED) research group. Institute of Sanitary and Biomedical Research (ISABIAL). c/ Pintor Baeza, 12, 03010, Alicante, Spain.
E-mail address: maria.ballester04@umh.es (P. Ballester).

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Abbreviations

AA-NAT	arylalkylamine N-acetyltransferase
ASMT	acetylserotonin O-Methyltransferase
ACh	acetylcholine
ACM	ambulatory circadian monitoring
ASD	autism spectrum disorder
BZDs	benzodiazepines
CAP	cyclic alternation patterns
CSWRD	Circadian sleep-wake rhythm disorders
EEG	electroencephalography
GABA	γ-aminobutyric acid
GluK2	kainate receptor subunit
ICSD-3	International classification of sleep disorders 3rd Edition
ID	intellectual disability
mGlu8	metabotropic glutamate receptor 8
NMDAR	N-methyl-D-aspartic acid receptor
NREM	sleep and non-rapid eye movement
PSG	polysomnography
RCTs	randomized controlled trials
REM	rapid eye movement
SCN	suprachiasmatic nuclei
SE	sleep efficiency
SoL	sleep onset latency
SSRIs	selective serotonin re-uptake inhibitors
SWS	Slow Wave Sleep
TAP	(variable that combines) wrist Temperature, motor Activity and body Position
TCAs	tricyclic antidepressants
TST	total sleep time
VLPO	ventrolateral preoptic
W	Wakefulness
WASO	wake after sleep onset
5-HT	serotonin, 5-hydroxytryptamine

The sleep-wake mechanism

The human body typically works on time loops or rhythms, and the most evident expression of this is the sleep-wake cycle [12]. The sleep-wake cycle is expressed by different brain states that change from one to another over a 24-h period: Wakefulness, NREM Stage 1–3 (deep sleep) and REM sleep. Each sleep state is characterized by a singular stage of brain activity and physiological functions, alternating in a rhythmic fashion, known as the NREM–REM cycle, that generally repeats itself every 90–120 min throughout the night (Figs. 1 and 2) [13].

Being awake is a state of consciousness accompanied by heightened perception, environmental responsiveness and physical activity and is defined by the presence of an alpha and beta rhythm (trains of sinusoidal EEG power between 8 and 13 Hz activity over the occipital regions). In contrast, sleep is a behavioural state of relatively low responsiveness to the environment and physical inactivity or rest. Humans enter sleep through NREM1, which is characterized by alpha brain waves associated with relaxation and wakefulness [14]. NREM2 is a deeper stage and is characterized by K-complexes and sleep spindles and bursts of neural oscillatory activity in a frequency of 10–12 Hz for at least 0.5 s [15]. These components of NREM2 sleep prevent sensory input getting to the cortex, and thus aid sleep maintenance [16]. Although a high frequency of spindles are prevalent in the initial stages of NREM3 [17,18], this final stage is predominantly characterized by delta waves of 0.1–4 Hz (Slow Wave Sleep [SWS]). This is the most restorative stage of sleep and is closely associated with sleep quality [19]. REM sleep is characterized by darting eye movements, motor inhibition of non-ocular muscles and an increase in autonomic activity [20]. REM sleep is less prominent in the first half of the sleep phase, but gradually increases in the second half of the night. Of note, all sleep stages have been implicated in cognitive functions, memory consolidation and the coordination of neural network activity [21].

The two-process model of sleep: process C and S

Two processes interact across the 24-h day to regulate sleep and wakefulness: a sleep dependent homeostatic process (Process S), which represents the build-up of sleepiness across the day, and a sleep independent circadian process or rhythm (Process C). The combined action of these two processes determines sleep propensity, sleep duration, and the timing of sleep [22,23] (Fig. 3). The homeostatic Process S increases during wakefulness, is closely associated with sleep debt, and influences sleep through sleep-inducing substances (somnogens i.e., interleukin-1, TNF-alpha, prostaglandin D2 and GH-releasing factor) [24], which are positively correlated with sleep pressure and negatively correlated with spontaneous and prolonged wakefulness [25,26]. In contrast, the circadian Process C is related to light, hormonal rhythms, social cues, temperature and genetic information from *clock genes* [27,28].

Evidence for disruption of the sleep-wake cycle in autism spectrum disorder

In autism, polysomnography (PSG) studies have shown a reduction of REM sleep, NREM2 and SWS spindles, and an increase in NREM1 sleep [29,30]. Moreover, REM sleep period bands that typically disappear after 8 months of age, have been described in autistic children, suggesting a less mature sleep pattern [31] (see Fig. 3b). Sleep microstructure, using cyclic alternating patterns (CAP) has been explored in ASD samples. The first study described some alterations of NREM sleep in autistic children, as evidenced by a lower CAP rate during SWS when compared to controls [32]. A second study comparing three groups of children (autism, Asperger syndrome and controls) aged 7–15 years, demonstrated similar results. This study also described a lower CAP rate in NREM stages 1 and 2, but not SWS in the Asperger syndrome group [33]. A larger study that compared regressive (understood as the loss of previously acquired spoken language) and non-regressive ASD and typically developing children concluded that regressive autistic children showed lower CAP rates than the other two comparison groups [34], indicating a disrupted sleep pattern in these individuals.

Sleep problems and disorders

Further evidence for disrupted sleep-wake rhythms is demonstrated by the high frequency of sleep problems experienced by those on the autism spectrum, see Table 1. The causes are numerous, and include neurodegenerative processes, which can disrupt sleep-wake cycle networks and deplete sleep-related cerebral neurotransmitters [35]. Sleep problems or disorders frequently impact the individual's ability to get enough sleep or good sleep quality. The most frequently reported sleep problems in

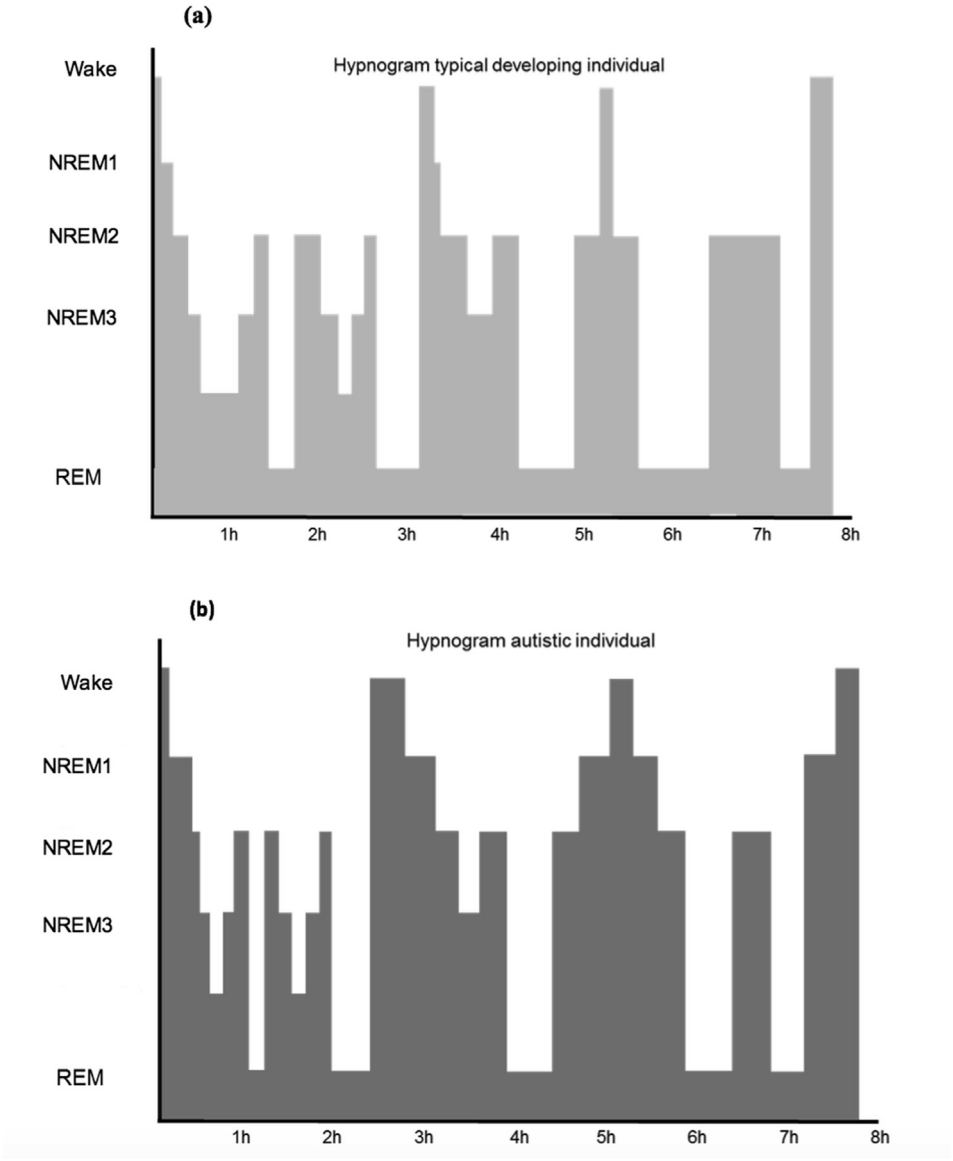

Fig. 1. Hypnograms from (a) a person without sleep problems and; (b) a person on the autism spectrum.

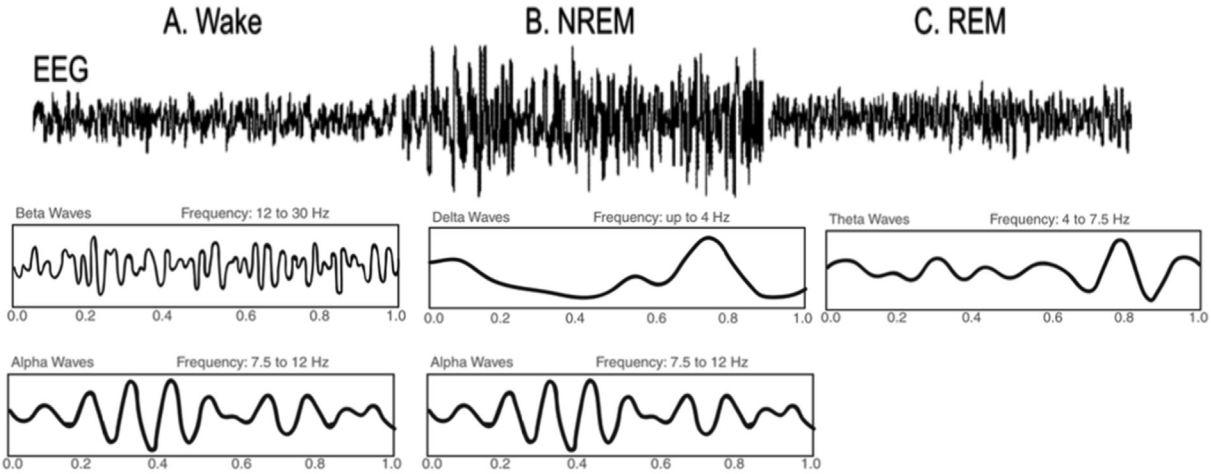

Fig. 2. Examples of sleep/wake states. (A) Awake state showing low-amplitude electroencephalogram (EEG). (B) Non-rapid eye movement (NREM) sleep state showing a high amplitude of EEG. (C) REM sleep states showing a low-amplitude.

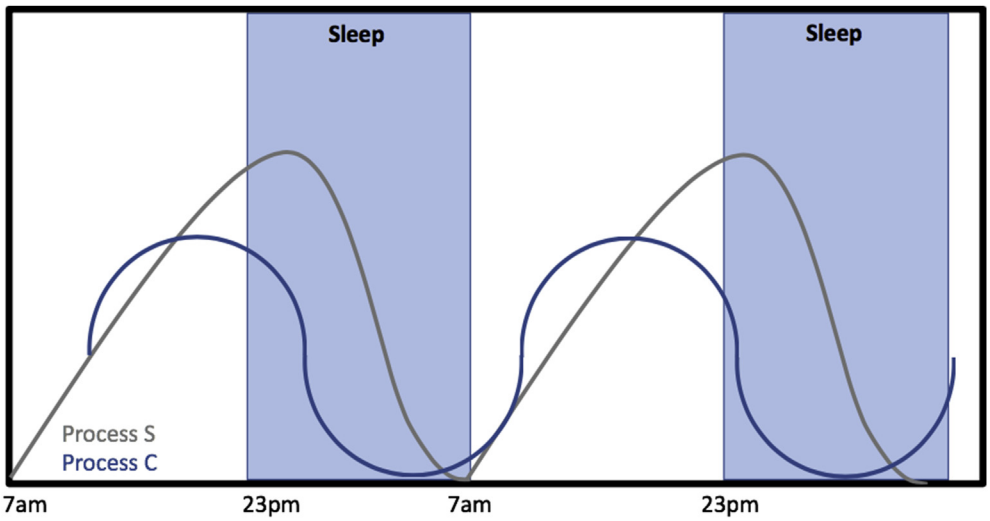

Fig. 3. An adaptation of the two-process model from Borbély.

the autistic population are insomnia and circadian rhythm sleep wake disorders [36].

Insomnia

Insomnia symptomatology is the most frequently reported sleep problem for those on the autism spectrum. It is defined as a report of sleep initiation or maintenance problems despite adequate opportunity and circumstances to sleep, with resulting daytime consequences (e.g., fatigue, memory consolidation problems). Increased sleep onset latency (SoL), prolonged wake after sleep onset (WASO), reduced total sleep time (TST), and reduced sleep efficiency (SE) are frequently reported [37]. These symptoms must be present three or more times per week for at least three months [38]. It is not well understood why autistic individuals are more susceptible to insomnia symptoms, though several theories have been proposed. These theories include: 1) disruption of a consolidated sleep routine (e.g., co-sleeping, needing to wear a particular item of sleepwear [39]); 2) abnormal cortisol and/or melatonin profiles [40,41]; and/or, 3) a coexisting psychiatric disorder which is often reported for both children [42,43] and adults [30] on the autism spectrum.

Circadian rhythm sleep-wake disorders (CRSWDs)

CRSWDs are closely related with Process C, and include conditions in which sleep timing is out of alignment across the 24-h day; shifted forward (phase advance), backward (phase delay), or having a sleep-wake cycle duration that does not fit into a 24-h period [44,45]. When these sleep problems are suspected the Dim Light Melatonin Onset (DLMO) should be assessed [46]. About 40% of autistic adults (with no intellectual impairment) have a CRSWD [47,48], predominantly a phase delay [47–49]. However, recent findings in autistic adults with intellectual disability (ID) have described advanced phase disorder [50], which is also seen in a small number of adults with no ID [47,51]. CRSWDs may arise due to *clock* and *melatonin pathway* gene variations [52,53], abnormal melatonin profiles [54], inappropriate light exposure patterns [55], anomalies in the timing of brain development processes [8,9,56] and/or social-communication difficulties that may result in misinterpretation/failure to understand social cues associated with sleep timing [57,58]. Some CRSWDs can be treated with external melatonin, and treatment is guided by the circadian timing assessed by the DLMO [59].

Brain areas and molecules promoting sleep/wake transition and sleep maintenance

Once the opportunity for sleep arises a transition from wake to sleep can occur via sleep- and wake-promoting groups of cells which exert mutually inhibitory activity [60]. Recent research shows that neurons in the ventrolateral preoptic (VLPO) nucleus are crucial for sleep as they inhibit wake-promoting systems, but the process that triggers their activation at sleep onset remains to be established [61,62] (see Figs. 3 and 4). The main neurotransmitters and hormones involved in sleep promotion include γ-aminobutyric acid (GABA) and melatonin, while serotonin, acetylcholine and glutamate are predominantly involved in promoting wakefulness.

Sleep promotion

γ-aminobutyric acid (GABA)

GABA is an inhibitory neurotransmitter, mainly through the activation of the GABA-A receptor, which causes an increase in NREM spindles [63,64] and the muscle inhibition described in REM sleep [65]. GABA is found in the suprachiasmatic nuclei (SCN) and VLPO circuits, which are responsible for modulating sleep [66] and circadian rhythmicity [67]. Furthermore, melatonin and benzodiazepines can bind to GABA-A receptors with some GABA projections stimulating melatonin production via Acetylserotonin O-Methyltransferase (ASMT) [68].

This system is critical to cortical development and has been strongly implicated in ASD [69]. Specifically, reductions of GABA-A receptors in frontal cortical areas have been shown [70] with a reduction in GABAergic inhibition [71], and an aberrant functioning of the enzyme for GABA synthesis [72,73]. Furthermore, the decreased levels of melatonin at night and increased levels of serotonin and its intermediate metabolites reported in some ASD studies [74,75] could be influenced by GABA, as its projections can impact the last steps of melatonin synthesis [76]. This is supported by the increase of GABA in the hypothalamus and pineal gland seen after the administration of exogenous melatonin [77].

Melatonin

Melatonin is synthesized from serotonin in the pineal gland and has soporific, anxiolytic and chronobiotic effects that assist in sleep

Table 1
Summary of research papers assessing sleep in ASD.

Authors (Year)	*n*	Age (yrs)	Assessment Methods	Key Findings	Limitations
Baker and Richdale (2015) [163]	36 ASD 36 controls	$M = 34.41$ $M = 32.66$	Questionnaire Diary Actigraphy	ASD Adults had more general sleep disturbances (higher scores on questionnaires, longer SoL and poorer SE).	Effect of psychopathology and medication on sleep
Ballester et al. (2018) [50]	41 ASD 51 controls	$M = 33$ $M = 33$	Ambulatory Circadian Monitoring	ASD had low SE, prolonged SoL and increased number and length of night awakenings. Also, advanced sleep-wake phase disorder.	Control sample is healthy and unmedicated Intellectual disability may worsen the results
Benson et al. (2019) [164]	15 ASD 17 controls	$M = 22.8$ $M = 23.7$	Questionnaire Actigraphy	ASD slept longer on average per night but took longer to fall asleep.	Small sample size Ongoing medications effect
Hare et al. (2006) [48]	10 ASD 19 Controls	$M = 30.8$ $M = 46.89$	Actigraphy	Increased SoL, and poorer SE%	Control group significantly older
Hare et al. (2006) [165]	14 ASD + ID 17 ID Controls	$M = 28.50$ $M = 38.52$	Actigraphy	No differences between the two groups	Control group significantly older Wide age range used
Limoges et al. (2005) [51]	27 ASD 78 Controls	$M = 21.1$ $M = 24.18$	Questionnaire PSG ($n = 16$)	Increased SoL, WASO and poorer SE%	Sample included adolescents
Matson et al. (2008) [166]	168 ASD + ID 166 Controls (ID only)	$M = 48.42$ $M = 54.73$	Questionnaire	44.7% of individuals with ASD + ID experienced a sleep problem compared to only 13.7% of the ID only group	Sample included adolescents
Øyane & Bjorvatn (2005) [167]	15 ASD	$M = 19.6$	Questionnaire Diary Actigraphy ($n = 10$)	80% had a sleep problem (actigraphy). Only minor sleep problems on questionnaire	No control group
Tani et al. (2003) [168]	20 ASD 10 Controls	$M = 27.2$ $M = 26.5$	Questionnaire Diary Free description	Higher proportion of adults with ASD reported insomnia compared to control participants across all three measures	Groups not matched on size Small control group
Tani et al. (2004) [169]	20 ASD 10 Controls	$M = 27.2$ $M = 26.5$	PSG	A greater proportion of individuals with ASD had WASO $\geq$ 30 min compared to controls	Groups not matched on size Small control group
Tani et al. (2005) [170]	20 ASD 10 Controls	$M = 27.2$ $M = 26.5$	Actigraphy	No differences	Groups not matched on size Small control group
Tessier et al. (2018) [171]	17 ASD 16 control 13 ASD 13 control	$M = 22.0$ $M = 21.1$ $M = 10.2$ $M = 10.5$	EEG	ASD adults had lower parasympathetic activity in the morning than controls, and adults had higher sympathetic/parasympathetic balance than children during REM sleep, regardless of their clinical status.	Small sample size

Mean (M), Polysomnography (PSG), Electroencephalogram (EEG), Sleep onset latency (SoL), wake after sleep onset (WASO), total sleep time (TST), sleep efficiency (SE).

onset and timing [78]. There are two rate limiting enzymes for melatonin synthesis, arylalkylamine N-acetyltransferase (AA-NAT) and ASMT [79], and their gene variations are associated with a dramatic decrease in melatonin activity [80].

Several studies have indicated that some autistic individuals do not show the normal night-time increases in melatonin levels (references for abnormal levels), but normal night-time levels have also been noted [81,82]. This imbalance described in ASD could be associated with carrying the allele for a loss of function in *ASMT* or *CYP1A2* (melatonin high-affinity enzyme involved in its metabolism) [83] or to genetic alterations in the rate limiting enzymes AA-NAT [84] and ASMT [83,85]. Additionally, melatonin deficits in ASD may result in a reduction of sleep spindles leading to increases in WASO. In contrast, elevated melatonin levels during the day may suggest atypical rhythm timing, in particular a delayed CRSWD [47].

Promotion of wakefulness

Wakefulness is maintained by cortical glutamatergic activation through centres located in the brainstem, serotoninergic raphe nuclei [86], cholinergic pontine reticular formation [87], orexine containing cells [88] and neurotransmitters such as dopamine [89].

Serotonin (5-hydroxytryptamine, 5-HT)

Dorsal and medial raphe nuclei contain many 5-HT neurons that promote wakefulness [90]. 5-HT inactivity correlates with REM sleep [91], and the raphe nuclei have been shown to be permissive structures for the appearance of REM sleep [92]. Neuronal damage that produces a reduction in 5-HT activity generates a phase advancement of the sleep-wake rhythm [93].

Individuals on the autism spectrum have reduced functional connectivity in the cortex [94], and arousal projections from the raphe nuclei could be damaged [95]. Furthermore, increased whole-blood serotonin levels have been described in children with ASD, and in their unaffected relatives [96], but evidence of alterations in brain 5-HT transportation is equivocal with both increased and decreased concentrations being reported [97,98]. In addition, the intermediate product in the transformation of 5-HT into melatonin, N-acetyl serotonin, is higher than in controls [98]. These findings could be associated with abnormal functioning of both enzymes (AANAT and ASMT) seen in postmortem brains and platelets [85,99].

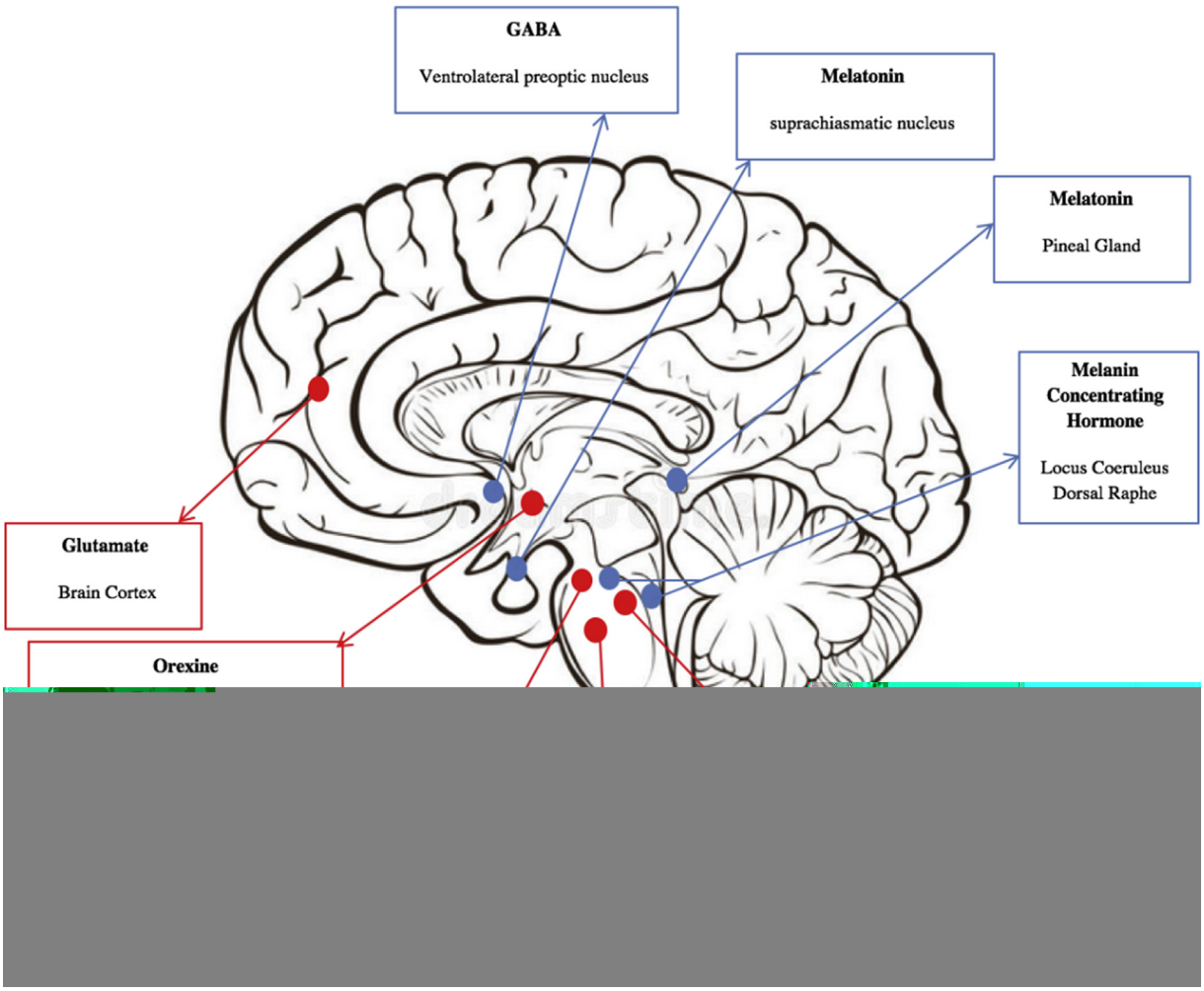

Fig. 4. Brain areas and molecules in charge of sleep (blue) and wake (red) transition and maintenance. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Acetylcholine (ACh)

The regulation of sleep by ACh is focused on the M2 (muscarinic) subtype which plays a role in REM sleep [100]. In fact, cholinergic projections from the cerebral cortex to limbic structures and the lateral hypothalamus achieve maximal activity rates during wakefulness [101].

A wealth of evidence associates the cholinergic system with ASD. Decreased concentrations of choline, a precursor of ACh and a cholinergic receptor agonist [102], and cytosol levels of ACh [103] have been correlated with the severity of autistic behaviour. Some post-mortem studies in autism have described the reduction of several subunits of ACh muscarinic receptors, which could be related to reductions in REM sleep [104]. In autistic adults, the binding of ACh to one of the cholinergic receptors and also to both nicotinic receptors was diminished in the parietal and frontal cortices, however, any relationship with sleep disturbances has not yet been studied [105].

Glutamate

Glutamate, together with GABA, is critical to the brain's excitatory-inhibitory balance. Thus, it can be assumed that both molecules may play a role in the regulation of the sleep-wake cycle [106]. For example, glutamate levels in the rat cortex show increases in concentration during wakefulness and REM sleep, and decreases during NREM sleep [107]. Additionally, glutamatergic neurons stimulate the cortex [66] when the thalamus is activated during wakefulness [108].

A hyperarousal hypothesis of insomnia has been proposed for individuals with ASD [109–111], and the link between glutamate and hyperarousal is that the antagonism of glutamate receptors has reduced hyperarousal [112]. In line with this, ASD has been genetically associated with several polymorphisms in glutamate receptors. The kainate receptor subunit (GluK2) [113], the metabotropic glutamate receptor 8 (mGlu8) [114], the N-methyl-D-aspartic acid receptor (NMDAR, subunit GluN2A [115] and GluN2B) [116] have all been potentially associated with ASD, and are highly implicated in synaptic plasticity. Studies have reported increased plasma levels of glutamate in a sample of children with high-functioning autism [117], together with abnormalities in the glutamate neurotransmitter system in post-mortem autistic brains [118].

Pharmacological treatment of sleep problems

Given the involvement of the neurotransmitters and neurohormones described above in sleep-wake regulation and their potential dysregulation in autistic individuals, treatments that target these systems could be efficacious in treating sleep problems in

ASD. However, there are only two drugs (aripiprazole and risperidone) approved to treat ASD symptoms (irritability and disruptive behavioural symptoms, respectively) and none for the highly prevalent sleep problems that are experienced. Thus, drugs are often used off-label to treat sleep, with some concerning potential side-effects (e.g., metabolic syndrome, dyskinesias, hyperactivity) [119].

Furthermore, the use of pharmacological treatments off-label may lead to multiple medications being prescribed (even though there is a lack of consensus about the definition of polypharmacy [120]; we defined it as $\geq$5 medications [121]) being taken by an individual. This is considered a risk factor for adverse effects, and drug–drug or drug–disease interactions [122]. Treatment research, including usual multiple drug prescription patterns, in randomized controlled trials (RCTs) is strongly needed across the lifespan. The efficacy of such treatments on sleep problems or disorders must be assessed using objective examination of any REM and non-REM changes on PSG, as well as change in sleep quality parameters and quality of life.

1. Melatonin

Melatonin is the most common pharmacological treatment prescribed for insomnia and CRSWDs in ASD [90]. Melatonin has purportedly demonstrated anti-anxiolytic effects [123,124] and consequently may also improve wellbeing [125]. Furthermore, it may mitigate hyperarousal-related insomnia through its effects on the hypothalamic–pituitary–adrenal axis, as demonstrated in animal models [126]. However, no studies have analysed melatonin effects on arousal or anxiety in autism.

The general agreement is that melatonin reduces SoL, advances the sleep phase [40,81,127,128] and increases TST [129]. However, significant improvements in WASO are generally not reported which is likely due to the short half-life of melatonin [54]. In line with this, a reduced number of awakenings has been shown when a prolonged release form is used [130]. Other limitations in melatonin studies include [1]: small sample size [2]; inclusion criteria not being restricted to ASD; and [3] no screening for other comorbidities that could affect sleep or predictors of response (e.g., endogenous melatonin, age, anxiety) [131–133]. However, in the past three years some research groups have targeted the first limitation, assessing the efficacy of a prolonged release form of melatonin in larger samples. First, a 13-week RCT performed in 125 children and adolescents demonstrated that melatonin increased TST and decreased SoL when compared to placebo [129]. Thirty participants did not finished the RCT; withdrawal of parent consent and loss to follow-up were the main reasons, and most participants belonged to the placebo group. Subsequently, a 39 week open label study of melatonin with the 95 participants who finished the RCT, confirmed the results previously obtained [134]. Recent studies have explored the side effects of long-term use of melatonin (104 weeks) in 80 children and adolescents; melatonin was shown to be safe with minor side effects (e.g., 6.3% fatigue, 6.3% daytime somnolence and 4.2% mood swings) [135]. Nonetheless, beneficial effects were also shown in both the participant's behaviour and caregivers quality of life [136]. Further attention should also be paid to metabolic phenotypes and possible drug–drug interactions that could predispose autistic individuals to side-effects [137], for example, the clearance rate of melatonin when it is combined with anticonvulsants can be altered [138].

Recent attention has been paid to some melatonin agonists drugs, such as agomelatine, a molecule that has demonstrated efficacy in a 3-month RCT compared to placebo. The results demonstrated increases in TST and sleep stability in a small sample of autistic adults with ID [139].

Other drugs promoting sleep

Nowadays, there is a lack of research on other drugs and their clinical efficacy and safety profile for targeting sleep problems. However, diverse studies have shown that across the life span more psychotropic drugs are being prescribed to the autistic population for a range of indications. Hence, in most cases, the outcome to evaluate the effectiveness of a treatment for sleep is a couple of items from a questionnaire in a clinical study that was not even designed to assess sleep improvements.

Antipsychotics

Antipsychotics, such as risperidone and quetiapine, are used to control some behavioural symptoms in autism, though effects on sleep have also been described. A six-month open-label extension study in 56 children and adolescents on the spectrum (5–17 years old), described that participants on the higher doses of risperidone experienced major sleep improvements according to a sleep visual analogue scale reported by the participants [140]. An eight-week open-label study, carried out in 11 adolescents on the spectrum demonstrated that a low-dose of quetiapine improved sleep outcomes measured using the Children's Sleep Habits Questionnaire [141], and also a positive relationship between reduced aggressive behaviours and improved sleep was found [142].

Benzodiazepines and hypnotics

Benzodiazepines (BZDs) act on the α and γ subunits of the GABA chloride receptor, prompting a conformational change in the receptor complex, and facilitating GABA inhibitory action. Their inhibitory action on GABA promotes sedation and muscle relaxation [143]. A review of clonazepam use in children with developmental disabilities, showed some effectiveness in reducing nightmares and abnormal motor behaviours during the sleep phase [144]. A small case series of 11 autistic children showed that clonazepam improved some sleep disturbances, with several adverse events reported (e.g., paradoxical response with agitation and increased activity) [145]. There are other examples including single dose temazepam (20 mg) in adults with autism, which increased daytime sleep duration, but did not improve propensity for nighttime sleepiness or aggressive behaviour [146].

On the other hand, the non-BZDs, zaleplon, zolpidem and eszopiclone, act at the BZD-1 subtype in the GABA receptor complex. They have a shorter half-life and fewer side effects compared to BZDs [147]. However, currently there are no clinical trials available for their use in autism.

Alpha-2-adrenergic agonists

The use of alpha agonists as an off-label prescription has increased over the time in ASD. A review showed that 12% of US children (4–18 years) received them for diagnoses of sleep and anxiety disorders without any evidence for efficacy from RCTs [148].

Clonidine is one of the primary alpha agonists used to treat sleep disorders in autism [149]. There is some evidence for efficacy from two open-label, retrospective studies in non-autistic children and adolescents which demonstrated improved sleep initiation and maintenance, with good tolerability and few adverse events [150].

A recent trial with guanfacine, in children with ID and/or autism, demonstrated that 45% of trial participants had a reduction of at least 50% in hyperactivity on the Aberrant Behavior Checklist-hyperactivity subscale [151]; however, several side effects, including drowsiness and irritability were noted [152]. Although

immediate release guanfacine is used off-label for sleep disturbances, there is no scientific evidence of its effectiveness [148]. The only RCT of extended release guanfacine did not significantly improve sleep in those with autism [153], and in fact decreased the amount of TST [154].

Cholinergic agents

An open label study in a small number of autistic children showed that donezepil, a reversible inhibitor of acetylcholinesterase which increases cholinergic transmission, was effective in increasing REM sleep [155], and in improving behavioural and attention issues in autism, and decreased REM latency [156]. However, side-effects which could negatively affect sleep should be considered given the beneficial effects of donezepil on sleep have only been shown in one small study of autistic children [157].

Antidepressants, anticonvulsants and antihistamines

There is a lack of studies regarding the use and efficacy of sedating antidepressants, selective serotonin re-uptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs), for treating sleep disturbances in autistic adults. The SSRI, Trazodone, frequently used due to its morning hangover effect could be beneficial for the phase advance in sleep described for autistic adults. Amongst the TCAs, amitriptyline, imipramine and doxepin are commonly used for insomnia treatment in neurotypical adults [158]. A one month open-label study of mirtazapine in 26 autistic adults found improvements in some co-morbid symptoms including irritability, anxiety, and insomnia in one third of the participants [159]. Also, there is limited evidence about the use of anticonvulsants (e.g., gabapentin) for insomnia treatment in ASD, with contradictory outcomes ranging from insomnia to sedation [160]. Moreover, antihistamines are the main non-prescription medication for childhood sleep disorders [161], but potential adverse events range from sedation to serious anticholinergic effects, including fever, constipation, urinary retention and tachycardia [162].

Conclusions

The impact of sleep problems or disorders in ASD is likely greater than estimated in terms of limited recognition, misdiagnosis and associated health consequences. Currently, there are limited practice guidelines. Best evidence suggests that melatonin can be an effective treatment for insomnia symptoms in autistic children. However, its mechanism of action remains unknown. Melatonin would be indicated when a CRSWD is present, however it is only recently that CRSWDs have gained research interest in ASD, with very limited consideration of CRSWDs in autistic children. Nonetheless, identifying the specific sleep problem/disorder first and its underlying cause is critical for treatment planning. Clinicians should also consider the role of each patient's current medication regime in relation to the presenting sleep problem, especially polypharmacy, and the potential for drug–drug interactions, particularly when an off-label treatment is being considered/used. Understanding the neurobiological mechanisms that may underlie poor sleep in autism, as described above, is in its infancy, as is the use of medications that may match particular neurobiological profiles that underly poor sleep. Thus, there is an urgent need to both understand the genesis of poor sleep in autism, which likely has multiple aetiologies. RCTs in autistic populations with sleep problems are highly warranted to determine the efficacy, safety, tolerability and long-term effects of potential behavioural and pharmacological therapies, either alone or in combination.

Research agenda

- Increasing knowledge about sleep disorders and insomnia symptom aetiology from both a behavioural and neurobiological perspective in ASD is needed to improved diagnosis and ultimately, treatment. Two prominent hypotheses for which there is some support are 1) melatonin and clock genes variants, and 2) hyperarousal.
- Co-morbid psychiatric conditions may play a prominent role in sleep problems in ASD and their role requires investigation.
- Treatment research, including RCTs, is sorely needed across the lifespan.
- Testing the efficacy of pharmacological treatments based on the neurobiological control of the sleep/wake cycle and known neurobiological abnormalities in ASD is required. This should include examination of any REM and non-REM changes on PSG, as well as change in sleep quality parameters.

Practice Points

- Clinicians need to carefully evaluate presenting sleep problems, including a detailed history of the sleep problems. Sleep questionnaire(s) and a prospective 2-week sleep diary (actigraphy if possible) should also be utilised. If a CRSWD is suspected, DLMO should be measured where feasible. In some cases, referral to a tertiary sleep centre and PSG may be required.
- The role or presence of co-morbid psychopathology must be considered.
- The role of current medications in the presenting sleep problem should be considered, including polypharmacy, and the potential for any prescribed sleep medication to interact with current medications.
- Medications should be based on presenting symptomatology and the diagnosed sleep disorder and/or co-morbid condition(s) that may affect sleep. Medications should be carefully monitored, especially in children, where they are generally off-label.

Conflicts of interest

The authors do not have any conflicts of interest to disclose.

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