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Neural hyperexcitability in Angelman syndrome: Genetic factors and pharmacologic treatment approaches

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ABSTRACT

Angelman syndrome (AS) is a rare neurodevelopmental disorder that is typically caused by deletion or a loss-of-function mutation of the maternal copy of the ubiquitin ligase E3A (*UBE3A*) gene. The disorder is characterized by severe intellectual disability, deficits in speech, motor abnormalities, altered electroencephalography (EEG) activity, spontaneous epileptic seizures, sleep disturbances, and a happy demeanor with frequent laughter. Regarding electrophysiologic abnormalities in particular, enhanced delta oscillatory power and an elevated excitatory/inhibitory (E/I) ratio have been documented in AS, with E/I ratio especially studied in rodent models. These electrophysiologic characteristics appear to relate with the greatly elevated rates of epilepsy in individuals with AS, and associated hypersynchronous neural activity. Here we briefly review findings on EEG, E/I ratio, and epileptic seizures in AS, including data from rodent models of the disorder. We summarize pharmacologic approaches that have been used to treat behavioral aspects of AS, including neuropsychiatric phenomena and sleep disturbances, as well as seizures in the context of the disorder. Antidepressants such as SSRIs and atypical antipsychotics are among the medications that have been used behaviorally, whereas anticonvulsant drugs such as valproic acid and lamotrigine have frequently been used to control seizures in AS. We end by suggesting novel uses for some existing pharmacologic agents in AS, including noradrenergic transmission reducing drugs (alpha2 agonists, beta blockers, alpha1 antagonists) and cholinesterase inhibitors, where these various classes of drugs may have the ability to ameliorate both behavioral disturbances and seizures.

1. Introduction

In 1965, British physician Harry Angelman reported in a publication his observations of three children who exhibited characteristic physical and behavioral features, including pronounced intellectual disability and "puppet-like" movement patterns (Angelman, 1965). This disorder eventually came to be known as Angelman syndrome (AS), a rare neurodevelopmental disorder that occurs in roughly one in ten thousand to forty thousand births (Kyllerman, 2013; Leyser et al., 2014). It was later found to be typically caused by deletion or a loss-of-function mutation of the maternal copy of the ubiquitin ligase E3A (*UBE3A*) gene (Born et al., 2017; Colas et al., 2005). Three papers from Beaudet and colleagues in 1997 first established this single gene as the underlying cause of AS in humans, and also developed the first mouse model of the disorder (Albrecht et al., 1997; Matsuura et al., 1997; Sutcliffe et al., 1997). Since AS was already known to be associated with deletions within chromosome 15q11–13, and *UBE3A* is located within this region of the genome, this group of researchers sought to determine if molecular defects were present in *UBE3A* of 11 individuals with AS (Matsuura et al., 1997). They found that de novo truncating mutations there indicate that *UBE3A* underlies AS possibly due to alterations in the maternally-expressed gene product (Matsuura et al., 1997). They further explored this topic in the mouse, showing that the homolog of *UBE3A* in mice (*Ube3a*) is highly conserved at both the nucleotide and protein levels (Sutcliffe et al., 1997). This research resulted in the development of a mouse model of AS, where implementation of *paternal* uniparental disomy encompassing *Ube3a* in these animals caused strongly reduced expression of *Ube3a* in Purkinje cells, hippocampal neurons, and mitral cells of the olfactory bulb (Albrecht et al., 1997; Sutcliffe et al., 1997). These findings in the mouse helped establish that loss of *maternal* expression of *Ube3a* in these key brain regions is a prominent phenotype of the disorder (Albrecht et al., 1997; Sutcliffe et al., 1997).

Individuals with AS exhibit a range of characteristics, including: marked intellectual impairment, reduction or absence of speech, motor abnormalities such as ataxia, altered electroencephalography (EEG) activity including increased power of delta oscillations, spontaneous epileptic seizures of various types, sleep disturbances, and a happy demeanor with frequent laughter (Dooley et al., 1981; Hanzlik et al.,

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2020; Hipp et al., 2021; Levin et al., 2022). While more prominent delta oscillations are the most widely reported EEG abnormality in AS, changes in the beta, theta, and gamma bands have also been described in the literature, in some instances during wakefulness as well as during sleep (den Bakker et al., 2018; Frohlich et al., 2019; Levin et al., 2022). These alterations in the EEG may relate with changes in the excitatory/inhibitory (E/I) ratio reported in AS, where some publications in rodent models describe an increase in E/I ratio mediated by changes in glutamatergic and/or GABAergic signaling (Antoine, 2022; Rotaru et al., 2018; Wallace et al., 2012). This putative increase in neural excitability in AS may be accompanied by the greatly elevated rate of epilepsy observed in AS, with various types of seizures occurring in up to eighty percent or more of individuals at some point during childhood (Cassater et al., 2021; Fiumara et al., 2010; Liu et al., 2022; Pelc et al., 2008a).

In the current publication, we briefly examine the literature on EEG, E/I ratio, and epileptic seizures in AS, and this includes data from rodent models of the disorder (Yang, 2020). While electrophysiologic disturbances appear to play a critical role in the disorder, their pharmacologic (or non-pharmacologic) management is not very effective in many cases (Blackmer and Feinstein, 2016; Gu et al., 2019b; Riday et al., 2012). We summarize pharmacologic approaches that have been used to treat behavioral aspects of AS, such as anxiety, hyperactivity, or sleep disturbances, as well as seizures in the context of the disorder. Antidepressants (including SSRIs and mirtazapine) and antipsychotics are among the medications that have been used for neuropsychiatric phenomena and for sleep disturbances (Ferdousy et al., 2011; Hanzlik et al., 2020), whereas anticonvulsant drugs such as valproic acid and phenytoin have often been used to control various types of seizures in AS (Dion et al., 2007; Thibert et al., 2009), although newer agents may have similar efficacy but fewer side effects (Shaaya et al., 2016). After reviewing these currently used pharmacologic approaches, we suggest novel uses for some other existing pharmacologic agents in AS, including noradrenergic transmission reducing drugs (alpha2 agonists, beta blockers, alpha1 antagonists) and cholinesterase inhibitors, where these various classes of drugs may have the ability to ameliorate both behavioral disturbances and seizures. Regarding the data on rodent models of AS presented in this publication, it should be noted that there are significant limitations to modeling a complex human neurodevelopmental disorder such as AS in a rodent. While humans (*UBE3A*) and mice (*Ube3a*) share marked similarities for this gene (Rotaru et al., 2020; Sutcliffe et al., 1997), and maternal disruption or deletion of this gene in a mouse or a rat can result in AS-like symptomatology such as recurrent epileptic seizures, observations in a rodent model are not always analogous to those in a human.

2. Relationship to epileptic seizures

Epilepsy is very common in individuals with AS, and can be difficult to treat. Epileptic seizures in AS are indeed often resistant to or not well controlled by traditional antiepileptic drugs (Pelc et al., 2008a; Wang et al., 2020), and there is currently no FDA approved antiepileptic treatment or therapy specifically for AS. Epilepsy in AS tends to predominate in childhood, but can still remain or reappear in adulthood (Pelc et al., 2008a). Seizures may be present in 85% of individuals with AS within the first three years of life, although fewer than 25% exhibit seizures during the first year (Fiumara et al., 2010). More than 95% of individuals with epilepsy in AS have daily seizures for at least a limited time during early childhood, and two-thirds develop disabling seizures (Samanta, 2021). The most common types of seizures include generalized tonic-clonic, atonic or myoclonic, atypical absences, and non-convulsive status epilepticus, with more than one seizure type occurring in about 50% of individuals with the *UBE3A* deletion phenotype (Fiumara et al., 2010; Samanta, 2021; Thibert et al., 2013).

There are indeed differences in the clinical expression of seizures in AS based on the underlying genotype, with earlier onset and more severe epilepsy in individuals with maternal *UBE3A* gene deletion within chromosome 15q11–13 (Cassater et al., 2021). Individuals with the deletion phenotype also tend to have more severe AS symptoms, exhibiting both more severe seizures and more severe intellectual impairment and motor abnormalities (Fiumara et al., 2010). In a sample of 265 children with AS, epilepsy was present in 91% of individuals with the deletion phenotype, and 61% of those with the non-deletion phenotype (Cassater et al., 2021). In a study of 39 children with AS, all of those with the deletion phenotype had epilepsy, whereas three of four children with a mutation within *UBE3A* had epilepsy (Mertz et al., 2016). In that study, epilepsy also occurred earlier in deletion cases than in those with *UBE3A* mutations (Mertz et al., 2016). (It should be noted that in the previous two studies, they are referring to Class I and Class II deletions of portions of chromosome 15 that include *UBE3A* along with multiple other genes, where these other genes may also contribute to the phenotype (Cassater et al., 2021; Mertz et al., 2016)). In sum, epilepsy is very common in individuals with AS, manifesting in a variety of seizure types that can be difficult to treat, where the deletion phenotype tends to result in more severe cases.

Mouse models of AS, many of which have the maternal copy of *Ube3a* either constitutively deleted or conditionally silenced during different time periods either prenatally or postnatally, lend insight into epileptogenesis and treatment of epilepsy in human subjects with AS. These studies have established that deletion of *Ube3a* can result in greater susceptibility to inducible seizures in mouse models, as well as various other behavioral abnormalities such as motor impairments or learning and memory deficits (Ciarlone et al., 2016; Jiang et al., 1998; Mandel-Brehm et al., 2015). They have also shown that various pharmacologic or dietary interventions, such as lovastatin, levetiracetam, insulin-like growth factor 2 (IGF-2), the GABAergic modulator ganaxolone, or ketone ester supplementation, can diminish the occurrence of seizures (Chung et al., 2018; Ciarlone et al., 2017, 2016; Cruz et al., 2021; Sonzogni et al., 2018). Mutating the inhibitory phosphorylation site of alphaCaMKII, reducing expression of the protein Arc, or intracerebroventricular infusion of the microRNA miR-134 inhibitor Ant-134, can also reduce seizures in AS model mice, providing insight into the molecular pathways underlying AS (Campbell et al., 2022; Mandel-Brehm et al., 2015; Van Woerden et al., 2007). Murine model studies have also helped elucidate the neural circuits underlying AS (Mandel-Brehm et al., 2015), and have shown for example that deletion of *Ube3a* in GABAergic but not glutamatergic neurons has a proconvulsant phenotype (Gu et al., 2019a). An important additional point addressed in some of these studies is whether maternal loss of *Ube3a* in embryogenesis and/or early postnatal life is sufficient to reproduce a spectrum of abnormalities present in AS, including epilepsy or other behavioral symptoms, or instead whether loss of expression of this gene in adulthood is important for AS-like abnormalities. Some of these data indeed emphasize the importance of embryonic or early life disruption of *Ube3a* in producing symptoms resembling AS (Silva-Santos et al., 2015; Sonzogni et al., 2019).

3. EEG findings

It has been suggested that irregularities in delta oscillations are characteristic of AS and distinguish it from other developmental syndromes, whereas theta band irregularities may be shared with a range of other disorders (Valente et al., 2003). In a retrospective analysis of EEG data from 12 overnight sleep studies, individuals with AS exhibited increased delta (2–4 Hz) power during all stages of sleep, as well as during wakefulness (Levin et al., 2022). Delta oscillations in children and adults with AS are characterized by high amplitude 2–3 Hz activity (in some cases, with a triphasic waveform) principally over frontal regions, with superimposed interictal epileptiform discharges, although irregularities at slightly higher frequencies (4–6 Hz) have also been observed (Laan et al., 1997; Laan and Vein, 2005; Leyser et al., 2014; Wang et al., 2005, 2020). These EEG patterns are similar across individuals with AS, independent of whether they have seizures (Laan and

Vein, 2005). Increased amplitude of delta activity can be accompanied by intermittent spike and slow-wave discharges, maximal in the occipital region (Rubin et al., 1997). In a study of 160 subjects with AS where 115 had complete data, their EEG recordings exhibited intermittent rhythmic delta waves (83.5% of subjects), interictal epileptiform discharges (74.2%), intermittent rhythmic theta waves (43.5%), and posterior rhythm slowing (43.5%) (Vendrame et al., 2012). Classification tree analysis suggested that these EEG patterns may relate to the different underlying genetic variants of AS (Vendrame et al., 2012). In a study of AS children and adolescents with the deletion phenotype, individuals with more prominent EEG delta frequency abnormality had earlier onset of epilepsy and greater impairment in cognitive, motor, and communication domains (Hipp et al., 2021). Delta power, as measured in a cohort of 82 subjects with AS, can indeed be used to predict cognitive function (Ostrowski et al., 2021). These data, along with those from other studies, support the use of the delta band, measured by quantitative EEG, as a biomarker for the development of treatments for AS (Hipp et al., 2021; Martinez et al., 2023). Martinez et al. (2023), for example, found that treatment with the drug minocycline modulated both epileptiform activity and EEG spectral power in individuals with AS (Martinez et al., 2023), and mouse model studies described below have begun using EEG measures to monitor the effects of antisense oligonucleotide therapy (Lee et al., 2023; Spencer et al., 2022).

EEG signaling other than delta band power can also be altered in individuals with AS. EEG patterns in AS can be characterized by notched delta and rhythmic theta activity, accompanied by epileptiform discharges (Thibert et al., 2013). In a study of children with AS, they exhibited enhanced long-range EEG coherence across a range of frequencies during wakefulness, whereas this increased coherence was specific to the gamma band during sleep (den Bakker et al., 2018). Children with AS, compared to neurotypical controls, also showed fewer sleep spindles that were shorter in duration (den Bakker et al., 2018). EEG activity also varies as a function of *UBE3A* phenotype in AS, with elevated theta power and decreased beta power in the deletion relative to the non-deletion phenotype (Frohlich et al., 2019). In that study, there was also an excess of broadband EEG power (1–32 Hz) that peaked in the delta band, which was shared by both genotypes, but was stronger in the deletion phenotype at younger ages (Frohlich et al., 2019). That study also suggested that several other genes, located near *UBE3A* and that encode $GABA_A$ receptor subunits, may also play a role in AS (Frohlich et al., 2019).

Rodent models also lend insight into electrophysiologic abnormalities underlying AS. Mouse models of AS created on 129S and C57BL/6 strain backgrounds, with deletion of the maternal *Ube3a* gene in each case, exhibited broadly-increased delta power, relative to wild type littermates (Sidorov et al., 2017). In an additional study, mice on a C57BL/6J background in which exon 2 of the *Ube3a* gene was deleted, exhibited increased EEG delta power as well as epileptiform spiking activity (Copping and Silverman, 2021). With maternal deletion of *Ube3a*, C57BL/6J mice exhibited spontaneous EEG polyspikes, increased hippocampal and cortical power in the delta and theta bands, as well as marked behavioral impairments (Born et al., 2017). In the same study, *Ube3a* deletion 129S mice showed motor irregularities, abnormal contextual fear conditioning, a lower audiogenic seizure threshold, and altered EEG spectral power (Born et al., 2017). It should also be noted that in that study, AS model mice on a 129S background were more susceptible to audiogenic and kainate-induced seizures than those on a C57BL/6J background, suggesting the importance of considering strain differences in neural circuitry (and possibly neurochemistry) underlying seizure induction in these models (Born et al., 2017). In mouse models of AS, delta power (and possibly other frequency bands) can also be used to predict the therapeutic effectiveness of antisense oligonucleotide treatment aimed at modulating *Ube3a* expression (Lee et al., 2023; Spencer et al., 2022). Lastly, in a *rat* model that was CRISPR engineered to have a complete maternal deletion of *only* the *Ube3a* gene, animals were tested at various ages for EEG power and seizure phenotypes (Born et al., 2021). At ages beyond 1.5 weeks old, deletion rats exhibited increases in delta power relative to wild type animals, and deletion rat pups showed a lower temperature threshold for hyperthermia-induced seizures (Born et al., 2021). These findings in mice and rats suggest that either partial or complete deletion of *Ube3a* can increase EEG delta power and epileptiform spiking activity or seizures (Born et al., 2021; Copping and Silverman, 2021), with the caveat that it is not clear whether audiogenic or hyperthermia-induced seizures in rodents, used to mimic febrile seizures found in AS (Born et al., 2021), affect circuitry and associated neural hyperexcitability in a manner that is homologous to that found in individuals with AS.

Additional observations in rodent models of AS further associate alterations in maternal *Ube3a* with this disorder. *Ube3a* maternally-deficient mice have been shown to exhibit sleep-related abnormalities, such as reduction of slow wave as well as REM sleep (Colas et al., 2005). Another study of *Ube3a* maternally-deficient mice found that sleep disturbances in these animals are due to deficient sleep-pressure accumulation, instead of altered circadian clock function (Ehlen et al., 2015), which may have implications for behavioral or pharmacologic treatment strategies in AS, including their timing within the day. Lastly, heterozygous mice lacking the beta3 subunit of the $GABA_A$ receptor, in contrast to *Ube3a*, have also been proposed as a model of AS, with male mice of maternally modified origin exhibiting more abnormalities and increased theta band activity (Liljelund et al., 2005). Collectively, these data in individuals with AS, as well as rodent model findings, suggest that EEG abnormalities include but are not limited to elevated delta band power, and are modulated by *UBE3A* phenotype.

4. Excitatory/inhibitory ratio

Elevated network excitability is thought to be a causative factor in AS and other neurodevelopmental disorders, consistent with the increased rates of epilepsy in these disorders (Antoine, 2022). Findings from mouse models of AS suggest that maternal loss of *Ube3a* affects widespread regions of the brain, resulting in elevated neuronal excitability, loss of synaptic spines, and behavioral abnormalities (Rotaru et al., 2020). One study found that mice with a null mutation of *Ube3a* exhibited reduced inhibitory drive onto cortical layer 2/3 pyramidal cells that may be due to dysregulation of multiple interneuron populations, thereby increasing the E/I ratio at both cellular and circuit levels and possibly contributing to seizures (Wallace et al., 2012). In a later publication, this group went on to show that GABAergic *Ube3a* loss is the main cause of circuit hyperexcitability in AS model mice, resulting in increases in cortical EEG delta power and enhancing seizure susceptibility, albeit without decreasing GABAergic inhibition onto layer 2/3 pyramidal cells (Judson et al., 2016). This group then showed that *Ube3a*-deficient mice exhibit weaker orientation tuning in visual cortex, which could relate to their elevated neural excitability in layer 2/3 regular-spiking neurons (Wallace et al., 2017). In another mouse model of AS with loss of functional UBE3A protein, neural hyperexcitability was observed in medial prefrontal cortex (a key node in emotional regulation), and restoring UBE3A in adult animals rescued these physiologic abnormalities (Rotaru et al., 2018). Computational modeling has also suggested that inhibition within the thalamic reticular nucleus may restrict thalamocortical signaling in such a way that prevents widespread synchronization that occurs in epileptic seizures, such as those observed in AS (Sohal et al., 2000). Thus, research conducted in rodent models of AS has helped elucidate the genetic and cellular mechanisms, including modulation of GABAergic and glutamatergic signaling, that result in elevated neural excitability and a higher E/I ratio.

5. Literature on existing pharmacologic and non-pharmacologic interventions

Pharmacologic or other approaches to management of epilepsy in AS can be difficult to optimize in a subset of individuals (Pelc et al., 2008a).

Physicians often have treated epilepsy in AS with GABAergic drugs such as phenobarbital and clonazepam (Mertz et al., 2016; Samanta, 2021), but due to unfavorable side effects with these, more recent approaches have included levetiracetam, clobazam, topiramate, lamotrigine, ethosuximide, or vagal nerve stimulation and carbohydrate-restricted diets (Samanta, 2021; Shaaya et al., 2016). Valproic acid has also been widely used to treat epilepsy in AS and may also partially act by increasing GABAergic signaling (Samanta, 2021). This drug, however, may also prevent seizures by having synaptic norepinephrine lowering properties through histone deacetylase (HDAC) inhibition, which increases cellular expression of the norepinephrine transporter and thereby pumps this neurotransmitter out of the extracellular space (More et al., 2011). Valproic acid may, however, have a less favorable side effect profile than newer agents (Shaaya et al., 2016). Controlling seizures in individuals with AS can require use of two or more pharmacologic agents, such as valproic acid, levetiracetam, lamotrigine, or benzodiazepines (Wang et al., 2020). It has been suggested that carbamazepine, oxcarbazepine, and vigabatrin should be avoided in AS, as these agents can induce nonconvulsive status epilepticus (Wang et al., 2020). In a survey of 461 family members of individuals with AS, the most commonly prescribed drugs used to treat epilepsy in their family member were valproic acid and clonazepam, although lamotrigine and levetiracetam had similar efficacy and tolerability to those drugs (Thibert et al., 2009). A pilot study of five subjects with AS found that chronic treatment with lamotrigine showed full to partial efficacy in each of these individuals (Dion et al., 2007). One possibility is that lamotrigine achieves its anticonvulsant properties in AS by enhancing GABAergic signaling (Dan et al., 2007). The benzodiazepine diazepam has shown robust therapeutic effects and was well-tolerated in a study of ambulatory nonconvulsive status epilepticus in children with AS, and it was suggested that this treatment may help avoid escalation to inpatient care (Worden et al., 2018). In sum, a wide range of drugs with anticonvulsant properties have been used to control seizures in AS, not limited to those with GABAergic enhancing mechanisms.

In addition to behavioral irregularities or problems with seizures, up to 80% of children with neurodevelopmental disorders such as AS have sleep disturbances (Blackmer and Feinstein, 2016), where an important general consideration is that sleep deprivation can promote seizures in susceptible individuals (Derry and Duncan, 2013). In a survey of fifty school-aged children with AS, 72% had taken medication to improve their disturbed sleep (Pereira et al., 2020). Disrupted sleep in AS is most commonly treated with melatonin or iron supplementation, and less commonly with melatonin receptor agonists, clonidine, gabapentin, hypnotics, trazodone, or atypical antipsychotics (Blackmer and Feinstein, 2016). Melatonin, clonidine, and trazodone do not appear to show differences in efficacy of improving sleep (Pereira et al., 2020). In a study of eight individuals with AS, who ranged in age from 3 to 16 and had a history of sleep disturbances, the atypical antidepressant mirtazapine increased total sleep time, decreased nocturnal awakenings, and decreased time to fall asleep (Hanzlik et al., 2020). Two of these subjects treated with mirtazapine reported positive behavioral effects as well (Hanzlik et al., 2020). These findings on sleep disturbances in AS suggest that a wide range of drugs that have sleep-inducing properties may be helpful in the disorder.

Neuropsychiatric symptomatology in AS includes anxiety, hyperactivity, and dysregulated behaviors such as aggression and self-injury, in addition to problems with seizures and disrupted sleep (Thibert et al., 2013). Pharmacologic management of problematic behaviors in AS is often carried out with antidepressant drugs such as SSRIs or antipsychotic drugs (Pelc et al., 2008b). An open label study in three individuals with AS, of the $5HT_{1A}$ receptor partial agonist buspirone, found that this drug was well-tolerated and produced improvement in anxiety symptoms (Balaj et al., 2019). A randomized study of 87 teenage to adult individuals with AS found that the $GABA_A$ agonist, gaboxadol, was generally well-tolerated and exploratory analysis revealed a significant improvement in the Clinical Global Impression-Improvement (CGI-I) scale (Bird et al., 2021).

Shedding light on the underlying pathophysiology of the disorder, AS model mice can exhibit altered glucocorticoid signaling, an elevated serum corticosterone level, decreased expression of parvalbumin in interneurons, as well as increased anxiety-like behavior (Godavarthi et al., 2014). These physiologic and behavioral irregularities can be counteracted by the SSRI fluoxetine (Godavarthi et al., 2014). Hippocampal neurogenesis is also impaired in *Ube3a* maternally-deficient mice, and this can be ameliorated by chronic treatment with fluoxetine (Godavarthi et al., 2015). Since alterations in hippocampal neurogenesis may play a role in major depressive disorder, these data suggest that fluoxetine may improve mood-related abnormalities in individuals with AS (Godavarthi et al., 2015). In *Drosophila melanogaster*, the gene *Dube3a* is the orthologue of mammalian *Ube3a*, where *Dube3a* can upregulate or downregulate monoaminergic neurotransmitter synthesis via the cofactor tetrahydrobiopterin (Ferdousy et al., 2011). These pathways in the fly may suggest that maternal deletion or deficiency of *UBE3A* in humans with AS could downregulate the levels of dopamine and serotonin in the brain, thereby affecting behavioral symptoms in the disorder, while also suggesting that SSRIs can be therapeutic (Ferdousy et al., 2011).

Acute treatment of AS model mice with cannabidiol, a principal molecular constituent of the cannabis plant, counteracted elevated delta and theta local field potential power that was present in these animals (Gu et al., 2019b). This finding suggests that cannabidiol may have therapeutic properties in individuals suffering from AS (Gu et al., 2019b). AS model mice lacking maternal *Ube3a* show increased mesolimbic dopamine release while also exhibiting decreased nigrostriatal dopamine release (Riday et al., 2012). These complex findings on dopamine may be relevant to using L-DOPA therapy, which may boost dopaminergic signaling in widespread regions of the brain, as a treatment strategy for AS (Riday et al., 2012). However, a randomized clinical trial of L-DOPA did not support a therapeutic effect of this drug in individuals with AS (Tan et al., 2018).

One possibility is that a particular drug may have overlapping therapeutic properties in the three domains of epilepsy, sleep disturbances, and neuropsychiatric manifestations, as may vagal nerve stimulation, dietary interventions, and gene and molecular precision therapies. While vagal nerve stimulation has been used to treat various genetic etiologies of epilepsy, including AS, its efficacy in this disorder is not well characterized at this time (Hajtovic et al., 2022). Non-pharmacologic approaches to controlling seizures in AS, such as vagal nerve stimulation and dietary modifications, suggest favorable tolerability and efficacy but need to be studied more extensively (Thibert et al., 2009). In a case series of three pediatric individuals with AS who had a vagal nerve stimulator implanted, stimulation reduced seizure frequency more than medication alone (Tomei et al., 2018). Low glycemic index treatment (LGIT) is a low carbohydrate dietary intervention that has been used in generalized epilepsy, and has begun to be experimentally addressed for seizure control in AS (Grocott et al., 2017; Thibert et al., 2012). These data, from children with AS mainly under age 10, suggest that LGIT treatment is well-tolerated and effective at reducing seizures when combined with antiepileptic drugs and even as monotherapy (Grocott et al., 2017; Thibert et al., 2012).

Particularly in the last several years, there is growing interest in using another technique, gene therapy, as a precision approach to AS, with several ongoing clinical trials and further innovation in rodent models of the disorder (Copping et al., 2021; Keary and McDougle, 2023; Markati et al., 2021; Ozlu et al., 2021; Tsagkaris, 2020). A rationale for these various genetic approaches in AS is that they directly target the underlying cause of this single gene disorder (Markati et al., 2021; Ozlu et al., 2021). A number of therapeutic approaches are being developed, including: 1) restoring the absent or nonfunctional UBE3A protein in the brain through gene replacement or transfer; and 2) inducing expression of the normal paternal copy of the *UBE3A* gene by targeting a long non-coding RNA, the *UBE3A-ATS* (Adhikari et al., 2021;

Table 1
Current and proposed treatments for Angelman syndrome. This table summarizes mainly pharmacologic approaches that are currently being used to treat individuals with Angelman syndrome (AS), as well as several novel treatments that are proposed in this publication. Abbreviations: histone deacetylase (HDAC), selective serotonin reuptake inhibitor (SSRI), melatonin type 1 receptor (MT_1), melatonin type 2 receptor (MT_2), histamine type 1 receptor (H_1), serotonin type 1A receptor ($5HT_{1A}$), serotonin type 2A receptor ($5HT_{2A}$), serotonin type 2B receptor ($5HT_{2B}$), serotonin type 3 receptor ($5HT_3$), alpha 2 adrenergic receptor (α_2), dopamine type 2 receptor (D_2), dopamine type 3 receptor (D_3), dopamine type 4 receptor (D_4), beta 1 (β_1), beta 2 (β_2), alpha 1 (α_1).

Treatment	Class	Mechanism of action	Target	Example reference	Note
ethosuximide	anticonvulsant	blocker of T-type calcium channels	epileptic seizures	(Samanta, 2021)	
lamotrigine	anticonvulsant	blocker of voltage-gated sodium channels, and possibly augments GABAergic signaling	epileptic seizures	(Samanta, 2021)	
levetiracetam	anticonvulsant	not well-characterized	epileptic seizures	(Samanta, 2022)	
phenytoin	anticonvulsant	blocker of voltage-gated sodium channels	epileptic seizures	(Thibert et al., 2009)	
topiramate	anticonvulsant	modulator of voltage-gated sodium and calcium channels, and the $GABA_A$ receptor	epileptic seizures	(Samanta, 2021)	
valproic acid	anticonvulsant	HDAC inhibitor	epileptic seizures	(Samanta, 2021)	may have a less favorable side effect profile than newer agents (Shaaya et al., 2016)
***carbamazepine	anticonvulsant	blocker of voltage-gated sodium channels	epileptic seizures		***should be avoided in AS, as can induce nonconvulsive status epilepticus (Wang et al., 2020)
***oxcarbazepine	anticonvulsant	blocker of voltage-gated sodium channels	epileptic seizures		***should be avoided in AS, as can induce nonconvulsive status epilepticus (Wang et al., 2020)
***vigabatrin	anticonvulsant	interferes with breakdown of GABA	epileptic seizures		***should be avoided in AS, as can induce nonconvulsive status epilepticus (Wang et al., 2020)
phenobarbital	barbiturate	allosteric modulator of the $GABA_A$ receptor	epileptic seizures	(Samanta, 2021)	
clobazam	benzodiazepine	allosteric modulator of the $GABA_A$ receptor	epileptic seizures	(Samanta, 2022)	
clonazepam	benzodiazepine	allosteric modulator of the $GABA_A$ receptor	epileptic seizures	(Wang et al., 2020)	
carbohydrate-restricted diets	non-pharmacologic treatment	not well-characterized	epileptic seizures	(Samanta, 2021)	
vagal nerve stimulation	non-pharmacologic treatment	boosting synaptic acetylcholine and norepinephrine	epileptic seizures	(Tomei et al., 2018)	
gabapentin	anticonvulsant	modulator of voltage-gated calcium channels	disrupted sleep	(Blackmer and Feinstein, 2016)	
trazodone	antidepressant	agonist or antagonist of various serotonergic and noradrenergic receptors	disrupted sleep	(Pereira et al., 2020)	
ramelteon	melatonin receptor agonist	agonist of MT_1 and MT_2 receptors	disrupted sleep	(Blackmer and Feinstein, 2016)	
iron supplementation	micronutrient	modulator of sleep-wake cycle by acting as a cofactor in dopamine-opiate system	disrupted sleep	(Blackmer and Feinstein, 2016)	
melatonin	neurotransmitter	activator of MT_1 and MT_2 receptors	disrupted sleep	(Buonfiglio et al., 2020)	
clonidine	alpha2 agonist	reducing synaptic norepinephrine	disrupted sleep and sometimes comorbid behavioral disturbances	(Blackmer and Feinstein, 2016)	
mirtazapine	atypical antidepressant	blocker of H_1, $5HT_{2A}$, $5HT_3$, and α_2 adrenergic receptors	disrupted sleep (and possibly behavioral disturbances)	(Hanzlik et al., 2020)	
citalopram	SSRI	boosting synaptic serotonin	behavioral disturbances	(Pelc et al., 2008b)	
escitalopram	SSRI	boosting synaptic serotonin	behavioral disturbances	(Pelc et al., 2008b)	
fluoxetine	SSRI	boosting synaptic serotonin	behavioral disturbances	(Pelc et al., 2008b)	
paroxetine	SSRI	boosting synaptic serotonin	behavioral disturbances	(Pelc et al., 2008b)	
sertraline	SSRI	boosting synaptic serotonin	behavioral disturbances	(Pelc et al., 2008b)	
aripiprazole	atypical antipsychotic	blocker of $5HT_{2A}$ receptor (and partial agonist of $5HT_{1A}$, inverse agonist of $5HT_{2B}$); partial agonist of D_2 and D_3 receptors	comorbid behavioral disturbances and disrupted sleep	(Blackmer and Feinstein, 2016)	not well-established in AS, but has been used in autism spectrum disorders
risperidone	atypical antipsychotic	blocker of $5HT_{2A}$, D_2, and D_4 (and partial agonist of D_3) receptors	comorbid behavioral disturbances and disrupted sleep	(Blackmer and Feinstein, 2016)	not well-established in AS, but has been used in autism spectrum disorders
donepezil	cholinesterase inhibitor	boosting synaptic acetylcholine			novel treatment for AS proposed here

(*continued on next page*)

Table 1 (*continued*)

Treatment	Class	Mechanism of action	Target	Example reference	Note
galantamine	cholinesterase inhibitor	boosting synaptic acetylcholine			novel treatment for AS proposed here
rivastigmine	cholinesterase inhibitor	boosting synaptic acetylcholine			novel treatment for AS proposed here
guanfacine	alpha2 agonist	reducing synaptic norepinephrine			novel treatment for AS proposed here
carvedilol	beta blocker	blocker of β_1 and β_2 noradrenergic receptors			novel treatment for AS proposed here
nebivolol	beta blocker	blocker of β_1 and β_2 noradrenergic receptors			novel treatment for AS proposed here
propranolol	beta blocker	blocker of β_1 and β_2 noradrenergic receptors			novel treatment for AS proposed here
prazosin	alpha1 antagonist	blocker of α_1 noradrenergic receptors			novel treatment for AS proposed here
terazosin	alpha1 antagonist	blocker of α_1 noradrenergic receptors			novel treatment for AS proposed here

Bailus et al., 2016; Judson et al., 2021; Lee et al., 2023; Markati et al., 2021; Nenninger et al., 2022; O'Geen et al., 2023; Pyles et al., 2018; Schmid et al., 2021; Wolter et al., 2020). Since AS is a neurodevelopmental disorder, an important consideration in gene therapy is whether to ameliorate abnormal gene expression during development, or rather whether targeting *UBE3A* during adulthood instead or in addition is effective (Adhikari et al., 2021; Bailus et al., 2016; Lee et al., 2023; O'Geen et al., 2023; Pyles et al., 2018). Some of these targeted approaches during adulthood have indeed shown some degree of effectiveness in rodent models (Adhikari et al., 2021; Lee et al., 2023; Meng et al., 2015; O'Geen et al., 2023).

6. Proposed drug treatments

Efforts are already underway, by a wide range of clinicians and researchers, to develop a comprehensive approach to treating AS (Duis et al., 2022). As noted above, pharmacologic approaches have typically used different classes of medications to treat epilepsy (anticonvulsants, GABAergic drugs), sleep disturbances (melatonin, mirtazapine), or neuropsychiatric manifestations (antidepressants, anxiolytics, antipsychotics) (Ascoli et al., 2022). Here we propose two novel pharmacologic strategies for treating neuropsychiatric, epileptic, and sleep irregularities in AS: boosting synaptic acetylcholine with acetylcholinesterase inhibitors (AChEIs: donepezil, galantamine, rivastigmine) and reducing noradrenergic transmission with various agents (alpha2 agonists: clonidine, guanfacine; beta blockers: propranolol, carvedilol, nebivolol; alpha1 antagonists: prazosin, terazosin). While these agents are not without significant side effects in some cases, a rationale for suggesting that they be tested more thoroughly in clinical and animal model studies of AS is that they may dampen the neural hyperexcitability that appears to underlie AS, irrespective of deletion phenotype. A number of studies suggest that serotonin can decrease neural excitability by enhancing GABAergic transmission or suppressing glutamatergic signaling (Cervantes-Ramírez et al., 2019; Shen and Andrade, 1998), which is consistent with the therapeutic efficacy of SSRIs in some cases of AS. In contrast, norepinephrine can *increase* neural excitability by suppressing GABAergic transmission or enhancing glutamatergic signaling (Brown et al., 2005; Talke and Bickler, 1996; Xiong et al., 2016), suggesting that the above noradrenergic transmission reducing drugs may also have efficacy in AS. While the effects of AChEIs on glutamate or GABA do not appear to have been widely studied with microdialysis in rodent models, one such study did find that acute treatment with the novel AChEI ENA713 significantly decreased extracellular glutamate in the hippocampus of freely moving rats (Trabace et al., 2001).

Theoretical and empirical findings, both from humans and animals, support the hypothesis that acetylcholine and norepinephrine have opposing effects in the brain (Fitzgerald et al., 2021a; Janowsky et al., 1972; Mineur et al., 2018), suggesting that AChEIs could also be efficacious in the disorder. (It should be noted that while AChEIs are widely used to treat symptoms of Alzheimer's disease and have antidepressant-like properties in rodents (Fitzgerald et al., 2021b; Papp et al., 2016), high levels of synaptic acetylcholine are associated with depression in human subjects and depression-like behavior in rodents (Fitzgerald et al., 2021a; Janowsky et al., 1972; Mineur et al., 2018). This latter finding may suggest that only low to moderate doses of these drugs may be therapeutic in AS.) It is suggested here that SSRIs and AChEIs could amplify the effects of various noradrenergic transmission reducing agents in AS. Since serotonin, norepinephrine, and acetylcholine play an important role in sleep, including direct involvement in brainstem circuits that affect sleep (Chu and Bloom, 1974; Gottesmann, 2002; Hobson et al., 1975; Mcginty and Harper, 1976), pharmacologic agents that act on these systems could in principle ameliorate sleep abnormalities in AS. (As noted above, the noradrenergic alpha2 agonist clonidine has already been used to treat sleep disturbances in AS (Blackmer and Feinstein, 2016; Pereira et al., 2020).) Likewise, since epilepsy is present in many individuals with AS, drugs that dampen neural excitability, as these agents may, could also be therapeutic for seizure occurrence or severity (Borowicz and Banach, 2014; Strac et al., 2016; Wong et al., 2019). Also, since vagal nerve stimulation may boost cholinergic signaling in the brain (as well as noradrenergic signaling, however) (Collins et al., 2021), it may achieve its putatively therapeutic effects in AS by dampening neural excitability through acetylcholine. Finally, a number of neurodevelopmental disorders besides AS, such as Rett syndrome, CDKL5 deficiency disorder, Dup15q syndrome, and SYNGAP1-related intellectual disability, also involve seizures or epilepsy (DiStefano et al., 2020; Leonard et al., 2022; Spagnoli et al., 2021; Weldon et al., 2018). If these disorders are also characterized by neural hyperexcitability, this raises the possibility that the cholinergic and noradrenergic treatments proposed here for AS would also be therapeutic in these disorders.

7. Conclusions

Here we have briefly reviewed data on epileptic seizures, EEG, and E/I ratio in AS, including some findings from rodent models of the disorder. We have suggested that generalized increases in neural excitability may underlie irregularities observed in the EEG, as well as neuropsychiatric symptomatology, sleep disturbances, and the greatly elevated rates of epilepsy found in AS. Different pharmacologic approaches, summarized in Table 1, have typically been used to counteract these distinct aspects of the disorder. Thus, it is not clear whether in the future, treatment will be guided by these various symptoms or perhaps

the underlying genetic abnormality in a given individual with AS, particularly in the case of gene therapy. We suggest that a more unified pharmacologic approach may not only make use of serotonergic boosting drugs such as SSRIs, but also repurposing of AChEIs and noradrenergic transmission reducing drugs, where these various classes of drugs may have the ability to ameliorate epileptic seizures, neuropsychiatric abnormalities, and sleep disturbances, simultaneously. Rodent behavioral neuroscientists as well as clinical researchers of AS should now investigate these translationally impactful topics in greater detail.

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Declaration of Competing Interest

The author declares that he has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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