Wiley et al., J Pharm Drug Deliv Res 2015, 4:3
http://dx.doi.org/10.4172/2325-9604.1000136

Journal of Pharmaceutics & Drug Delivery Research

Review Article

A SCITECHNOL JOURNAL

H1R Antagonists for Brain Inflammation and Anxiety: Targeted Treatment for Autism Spectrum Disorders

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Abstract

Autism Spectrum Disorders, which covers Autism, Asperger's, and Disintegrative and Pervasive Developmental disorders, have risen in the awareness of researchers due to the dramatic increase in diagnosed cases over the last decade. Currently, one child in eighty is diagnosed while Autism Spectrum Disorder with the absolute cause remaining unknown. Since the number of cases of ASD is increasing, many physicians and clinicians are looking for a solution for some of the symptoms. For many patients that are diagnosed with ASD, exhibit symptoms include behavioral disabilities, insomnia, locomotor activity disability, anxiety, and communication issues. However, the current standard of care has been aimed at behavioral and medical treatments for these symptoms. Treatments can include medications ranging from antidepressants and serotonin-reuptake inhibitors to antipsychotics. However, many of these treatments can incite various side effects in children and adolescents. We show that current research correlates brain inflammation with many of these symptoms. Therefore, we present a theory that indicates that a patient may lessen or eliminate a variety of the aforementioned symptoms by directly reducing neuroinflammation through the use of the well-known antihistamine hydroxyzine. Furthermore, we present a general mechanism of action for use and delivery of hydroxyzine, which may be a much better choice over other multiple medications.

Keywords

Developmental disorders; Autism; Serotonin-reuptake inhibitors

Introduction

Autism Spectrum Disorders (ASD) includes a wide range of conditions from Autism and Asperger's to Disintegrative and Pervasive Development Disorder [1]. The variety of these conditions afflict as many as 1 in every 80 children [2]. In general, ASD is characterized by primary symptoms of impaired social interaction and communication, as well as stereotyped and repetitive behaviors or interests [3]. These are typically accompanied by more secondary symptoms where children with ASD tend to experience a number of disabilities including paramount sensory issues and behavioral difficulties such as anxiety, depression, insomnia, and general emotional problems [4-6].

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Received: July 22, 2015 **Accepted:** November 04, 2015 **Published:** November 11, 2015

Although there are a large number of studies characterizing the primary and secondary symptoms, effects, and complications of children with ASD, the general cause continues to remain unknown. One recent study points to the over-activation and over-growth of the neurological synapses in the brain as possible root cause [7]. Overall, an in-depth review of the ASD literature generates a number of possible avenues that point toward the understanding of ASD and its origins [8,9]. While the specific cause eludes physicians and researchers, evidence continues to indicate genetics, inflammation, environmental stressors, and immunology as the major contenders for the overarching cause of ASD [8,9]. This myriad of potential triggers has inevitably led to many physicians treating only selective symptoms with pharmaceutical drugs designed for adults.

A novel treatment plan to lessen or eliminate some of these symptoms with little to no side effects could help autistic children lead symptom-reduced lives and may help hone in on the distinct origin [10,11]. To accomplish this, we set out to examine how certain symptoms are currently handled and where crossover reactions to pharmaceutical aids may occur. From our survey of the known literature, we present a premise that generalized inflammation in the brain could be producing a number of the aforementioned symptoms observed in autistic children [12-14].

The symptoms of ASD, patient to patient, have been shown to be sporadic in the number of disruptions of daily activities [6]. These symptoms and their timing are indicative of environmental anxiety and sensory hyperstimulation, which in many areas can be considered one in the same [15]. Unfortunately, the current standard of care treatments for children with ASD are typically aimed at controlling these behavioral issues through the effects of sedative drugs. This is because ASD has such myriad of potential causes that medicine has not found a drug that can directly affect behavioral control both neurologically and perceptively.

Typically, physicians work to address the most difficult behavioral symptoms using anti-depressants and antianxiety medications. Most antidepressant drugs work by raising serotonin levels in the brain (SSRIs). This is in an attempt to help the patient gain impulse control, which can lead to the manifestation of other symptoms [16]. Furthermore, the effects of differently acting tricyclic antidepressants on children and adolescents have been investigated for their ability to block noradrenaline and increase serotonin. While this increases the availability of these neurotransmitters in the central nervous system [17], these tricyclics can cause tremors, drowsiness, and fatigue as adverse effects while having little to no reduction of ASD symptoms.

A newer approach to ASD has been to focus on the relationship of anxiety and other ASD symptoms through the use of antianxiety medications such as benzodiazepines, which work to enhance the effect of the neurotransmitter gamma-aminobutyric acid (GABA) at the GABA receptor to actually *lower* serotonin levels and therefore reduce anxiety [18]. This can result in an antianxiety state that relaxes muscle response and can produce a pronounced calming effect [19]. However, it seems illogical and overarching to state that this contributes to all of the symptoms treated by various pharmaceutical drugs.

In this article, we present the mechanism of action for this process and demonstrate that H1R antagonist antihistamines, in particular, hydroxyzine may have the ability to curb primary and secondary ASD symptoms in young children by lessening background inflammation in the brain, which should lower anxiety, enhance communication and improve behavioral issues. Our goals are to discuss why hydroxyzine may provide an alleviation of these ASD symptoms that are produced via brain inflammation, as well as specify general mechanisms of action to elucidate how and why this medication could benefit children and adolescents in controlling some or all of these symptoms. While this is not a proposed cure for ASD, we illustrate that many of the aspects of ASD lead to the conclusion that brain inflammation may be playing a much larger role and that antihistamines may be a possible avenue for better control of these symptoms and aspects in a more benign way.

Background

In 2011, Mc Pheeters et al. published a systematic review of the various treatments for children with ASD [2]. This study covers many different treatment methods that are derived from specific symptoms displayed by individual patients. These treatments can include psychostimulants (methylphenidate), serotonin-reuptake inhibitors, and/or antipsychotics. However, many of these medications can be harmful, both physically and mentally, to children and adolescents. A few of them even increase suicidal potential in adolescents [20,21]. Regardless of the wide range of treatment options, there has still been no evidence of any distinct overall modality of treatment for ASD. This may be due to the treatments only masking various secondary symptoms and not addressing the underlying problem or providing any reliable abatement of co-morbid symptoms. What may be more important is to look at the common denominator of the most common symptoms. By investigating the fundamental source of the primary symptoms (behavioral disorders and communication issues) and secondary symptoms (locomotor challenges and anxiety) in ASD patients, we look to demonstrate that a general medication might be able to treat multiple symptoms in children more safely and effectively without complications typically observed form the current standard of care.

Recently, the secondary, non-specific symptoms of anxiety and hyperactivity have appeared in the literature as a frequent component to autistic behavior. Many disorders revolving around ASD may be related to the inability of the brain to properly handle anxiety signals. This has shifted the focus to antianxiety drugs such as benzodiazepines, which have shown promising results in mice [22]. However, anxiety can also be produced through the deregulation in cytokine signaling that regulates various brain functions including neurotransmitter metabolism, neuroendocrine function, synaptic plasticity, as well as the neural circuitry of mood, which may be a likely overarching state in brain inflammation [23,24].

There are a number of studies linking frank brain inflammation to the onset of anxiety, locomotor activity, and communication disorders [11-14,24-26], as well as the possibility of other immune disorders [27,28]. While trials for antianxiety drugs are in the clinical stages, we look toward another, more reliable drug that has been shown to combat body-wide inflammation and many of the aforementioned symptoms. This medication is the antihistamine hydroxyzine.

Overall, hydroxyzine may have the ability to curb inflammation in the brain and provide relief for some, if not all, of these issues. Currently, the well-known drug hydroxyzine is used as both an anti-inflammatory and anti-anxiety medication [29-31]. Hydroxyzine is an antihistamine and H1R inhibitor that has been used since 1956 and is still widely employed today to help patients with anxiety and various obsessive-compulsive disorders as an immunomodulator, where it has been studied and used for over half a century [32]. Hydroxyzine has little to no adverse reactions, with the exception of a calming or sedative effect that has been shown to be dose dependent, which has been used by dentists, as vistaril, looking to calm autistic children for various office procedures [33]. This demonstrates that hydroxyzine (vistaril) is safe for use on children; where the calming effect has been effective in help dentists perform complicated procedures on children with behavioral issues. However, this calming effect is not productive for everyday activities. This will be addressed below.

Hydroxyzine and the Reduction of Inflammation

From the standpoint of symptomology, it seems that the common denominator of many primary and secondary ASD symptoms is brain inflammation [10-14], which may be reduced through the use of an older well-studied, first-line treatment for anxiety, insomnia, and immunological cutaneous symptoms, the antihistamine hydroxyzine. This treatment provides a possible avenue for children and adolescents through immunomodulation to gain some relief from various ASD symptoms [34,35]. This is critical considering a recent study that shows a distinct correlation between autism and autoimmunity [36]. Many antihistamines are already being investigated for other brain conditions, including Alzheimer's disease, multiple sclerosis, and the like due to the proven manifestation of brain inflammation [26,37,38].

As illustrated in Figure 1, hydroxyzine works through the mechanism of action as a potent H1 receptor (H1R) antagonist and serotonin reuptake inhibitor through a reduction of inflammation [39-41]. The reduction of H1R inhibits the production of pro-inflammatory cytokines [26] and brain mast cell activation [38-42], which induces a T-cell response that helps lower neuro inflammation. This mechanism can provide relief from the more debilitating ASD symptoms like insomnia, uncontrolled behavior, communication issues, and locomotor activity [26]. This has been shown to help multiple sclerosis patients with similar symptoms by improving the neurological status of patients with Hydroxyzine [26]. This is a critical component because studies have demonstrated that the increase in serotonin (hyperserotonema) leads to a reduction in the activation of serotonin terminals [43].

Furthermore, the lowering of H1R raises A2A, which, in turn, raises GABA [44,45]. The increase in GABA helps in the decrease serotonin levels [46]. This means that hydroxyzine is also acting as serotonin reuptake inhibitor (Figure 1). The decrease in serotonin provides an anti-anxiety effect for the patient. Another feedback loop occurs in that the effects of lowering of serotonin levels can further reduce inflammation [47,48] and decrease brain inflammation and hyper-dendritic spinning [49]. A decrease in neuroinflammation should induce a calming effect to quell behavioral issues and other ASD symptoms in children. While this can help them sleep, it can also increase GABA, which may reduce seizure events in the other 10% of those children with other genetic disorders like Fragile X [50].

We expect that behavioral issues such as loss of control and aggressive hyperactivity, which are typically associated with high anxiety and low serotonin levels, should be diminished as the hydroxyzine takes effect. The use of hydroxyzine should help ASD

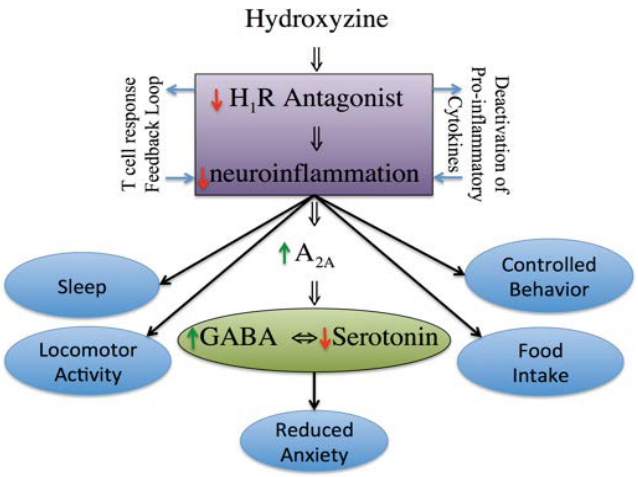

Figure 1: The proposed mechanism of action for the use of hydroxyzine in the reduction of the autism spectrum disorder symptoms through a reduction of inflammation, which produces a change in number of hormone receptor responses that leads to a serotonin reuptake inhibition and an increase in GABA. These actions can aid in the lowering of anxiety and produce a reduction in the level and severity of ASD symptoms. Furthermore, the lowering of anxiety can reduce overactive brain activity, which will help in decreasing behavioral disorders and other symptoms.

patients via a reduction in brain inflammation, which can have a direct effect on the symptoms of behavior disruptions and lower locomotor activity. Furthermore, since hydroxyzine is a serotonin reuptake inhibitor, it can provide relief from insomnia and anxiety through a reduction in serotonin and an increase in GABA levels.

While the calming effect from hydroxyzine can induce drowsiness dose-dependently, studies have shown that there is no "hangover" [51], and it fosters subsequent increased attention and memory [34]. Although, the sedative nature of the drug can be reliably reduced or even eliminated through the use of a transdermal application in a topical formulation [51]. This is predominantly because the transdermal applications escape the effects of metabolization caused by the first pass in the liver [52]. This can greatly reduce the issue of sedation while providing the patient with a non-invasive less bolus-like method of treatment that can be self-administered and is typically less expensive [52].

Since the calming effect is a major issue for patients only when the drug is taken orally, transdermal application of hydroxyzine reduces or eliminates sleepiness by avoiding first pass production of soporific metabolites [52,53]. However, since insomnia is a common symptom of ASD patients, the calming effect of a higher dose at night may be useful in helping some children reduce anxiety and hyperactivity to return to a normal sleep pattern.

While we in no way contend that hydroxyzine is a complete solution for all of the symptoms in ASD patients, we work to provide a method to safely and effectively help patients with ASD, especially given the broad and general nature of those symptoms across the board. We do expect this avenue of treatment to be useful to many patients. In particular, those that are dealing with increased anxiety, insomnia, and behavioral problems associated with brain inflammation.

Recently, an observational anecdotal report on a single 6-year-old female (50 lbs.) diagnosed with ASD has demonstrated outstanding results with the use of transdermal application of hydroxyzine [54]. She demonstrated multiple issues including little to no communication as well as disrupted sleep patterns (only sleeping 1-2 hours at a time). After a year of little to no progress in behavioral therapy, the girl started a regimen of hydroxyzine. Within 6 weeks of starting the regimen, both the physician and therapist noted multiple changes in the girl's behavior, including an alleviation of multiple symptoms: increase of speech, return of normal sleep patterns and appetite, and reduction in behavioral outbursts. The medication of hydroxyzine consisted of 10 mg applied transdermally three times a day (1 mg/0.1 ml). Symptoms were tracked using the standard metric of the physician and therapist. While this is not a placebo-based clinical trial or an A-B-A-B conditional trial, it does express optimism anecdotally for the possibility of a successful medication. Therefore, we believe that a standard clinical trial of age, gender, and symptom-matched patients using a similar transdermal-dosing regimen of hydroxyzine would produce fruitful results. The main advantage of a transdermal-dosing regimen is that it also allows for a customized approach wherein patients can receive variations of dosing throughout the day, which can also be an investigation parameter in a clinical trial.

Conclusion

We show that an antihistamine medication (specifically hydroxyzine) that targets inflammation may have the ability to reduce or eliminate the key primary and secondary ASD symptoms in young children and adolescents through a reduction in anxiety and changes in communication ability, locomotor skills, and mood disorders. Furthermore, we explain that the use of transdermal hydroxyzine may immunomodulate inflammation while eliminating the sedative effect. While this is not a genomic determination of the individual cause for ASD, this may lead to the ability to control symptoms and allow children and those afflicted by ASD to have a better quality of life. In conclusion, we suspect that antihistamines, like hydroxyzine, could provide relief for many children affected with ASD by reducing brain inflammation and leading to less anxiety and a reduction in ASD symptoms, which may have dramatic effects on behavioral and social disorders. This includes the effect of hydroxyzine on reduction of H1R resulting in the raising of GABA through the A2A channel, which has been shown to lower serotonin levels. Therefore, as shown above, we present clear mechanisms of action by which antihistamines (specifically hydroxyzine) may be able to ease the symptoms of ASD. Furthermore, since an unpublished, non-clinical trial on a single child has already presented promising results, we believe that further and more in-depth clinical trials should be done to assess the extent of these types of drugs on ASD symptoms and indicators.

Acknowledgements

We would like to thank W. Mc Guinness for useful and insightful discussions. We also thank P. Russell, C. Lorente and T. Ryan for their assistance on the preparation of this manuscript. There are no financial conflicts, and Wiley Compounding Systems supported this work.

Financial Support: This research was supported by Wiley Compounding Systems

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