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Efficacy of auditory integration therapy (AIT) on plasma syntaxin1A (STX1A) levels and amelioration of behavioral, social, and sensory symptoms in children with autism spectrum disorder (ASD)

Laila Yousif Al-Ayadhi [1, 2], Nadra Elyass Elamin [2, *], Dost Muhammad Halepoto [2], Abdulrahman Mohammed Alhowikan [1]

[1]*Department of Physiology, Faculty of Medicine, King Saud University, Riyadh, Saudi Arabia*
[2]*Autism Research and Treatment Center, Faculty of Medicine, King Saud University, Riyadh, Saudi Arabia*

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ABSTRACT

Autism spectrum disorder (ASD) is a pervasive neurodevelopmental disorder. Previous research reported the beneficial effects of Auditory Integration Training (AIT) on a considerable range of behavior and learning problems. Limited studies examined the association between AIT and biological biomarkers in autistic subjects. Therefore, this study aims to examine the effect of auditory integrative training on the plasma syntaxin1A protein (STX1A) level and also to assess its impact on behavioral, social, and sensory symptoms in autistic children, using a sandwich enzyme-linked immunoassay (ELISA). Total scores of the Childhood Autism Rating Scale (CARS), Social Responsiveness Scale (SRS), and Short Sensory Profile (SSP) were calculated before one month and three months after AIT for all participants. Results show that the plasma level of STX1A was significantly increased immediately, one month, and three months after AIT ($P<0.05$). Moreover, Pearson correlation *(r)* values between STX1A levels before and after AIT shows strong and positive significant correlations between STX1A levels before AIT and immediately after AIT ($r=0.594$, $p=0.01$) and one month after AIT ($r=0.819$, $p=0.01$). Additionally, our results revealed that behavioral, social, and sensory symptoms were significantly improved in terms of disease severity three months after AIT ($p<0.05$). The study supports the usefulness of AIT as a therapeutic intervention to improve some measures of ASD such as symptoms. It may also induce the up-regulation of STX1A in plasma in ASD subjects. However, Additional research, on a larger size population, is necessary to evaluate the AIT effect on behavioral and social changes in ASD children, and the up-regulation of STX1A.

1. Introduction

Autism spectrum disorder (ASD) is a pervasive neurodevelopmental disorder characterized by cognitive impairment, social communication deficits, restricted interests, and repetitive stereotyped behaviors, as well as abnormal sensory-motor behaviors (APA, 2013). The exact underlying causes are unknown; genetic and environmental factors are involved in its pathophysiology (Chaste and Leboyer, 2022). Hypersensitivity to sensory stimuli is commonly recognized in ASD. However, little is known about the relationship between sensory processing dysfunction and the biomarkers in autistic patients. Few studies examined sensory profiles in autistic children (El-Ansary et al., 2016). They reported dysfunction in tactile sensation, smell, taste, visual, and auditory stimulation. Abnormal sensitivity was associated with a considerable range of behavior and learning problems. It is also associated with high levels of social dysfunction and stereotypic and repetitive behaviors. Impairment in sensory processing has been reported in 42% to 88% of children with autism (Baranek, 2002; Balasco et al., 2020). Therefore, targeting the sensory processing abnormalities for therapeutic intervention may be beneficial in the improvement of some ASD conditions.

Auditory integration training (AIT) is widely used as a therapeutic intervention to overcome the common auditory sensitivity changes in autistic

* Corresponding Author.
Email Address: nadraelyass@hotmail.com (N. E. Elamin)
https://doi.org/10.21833/ijaas.2023.04.002
Corresponding author's ORCID profile:
https://orcid.org/0000-0001-8267-3804

patients. Children with ASD exhibited a reduction in behavioral problems and increased hearing acuity post-AIT intervention (Bérard, 1993; Baranek, 2002).

Previous studies reported beneficial effects of AIT in reducing some autistic features such as language deficit, social interaction, physical movement, mood, and sleep (Sokhadze et al., 2016). In a meta-analysis study, AIT reduced the ABC and ATEC score and increased the IQ score among Chinese children with ASD (Li et al., 2018). Previous studies by our group reported improvement in social awareness, social cognition, and social communication in children with ASD three months and six months after the AIT intervention (Al-Ayadhi et al., 2013; Al-Ayadhi et al., 2018; Al-Ayadhi et al., 2019). On the other hand, some research revealed contradictory findings on the efficacy of AIT in reducing auditory hypersensitivity in ASD children. Sinha et al. (2006) reported that there was no beneficial effect of AIT on children with ASD in some RCT studies (Sinha et al., 2006), while other studies reported improvements in autistic behaviors and reduced sound hypersensitivity three months after AIT based on the total mean of Aberrant Behavior Checklist scores (ABC) (Sinha et al., 2011). However, little attention has been given to examining the association between sensory processing dysfunction and biomarkers in autistic patients. Therefore, there is a great need to find reliable biomarkers and therapeutic interventions to improve tools for early diagnosis and treatment (El-Ansary et al., 2016).

On the other hand, synaptic proteins play a crucial role in neuronal health, synaptic plasticity, and learning and memory. Accumulating evidence of research implicated the crucial role of synaptic proteins in the pathogenesis of ASD. The loss of synapse integrity and function comprises the first step in the onset of neurodegenerative and neurodevelopmental disorders (Joo and Benavides, 2021). Synaptic protein loss enhances cognition, memory, and behavioral and social functioning impairment in ASD. It is also associated with the severity of the disease. Moreover, the genetic variation in synaptic proteins has also been described in ASD subjects (Pham et al., 2010).

Syntaxin1A (SXT1A) is a membrane protein belonging to the syntaxin family. It is abundantly expressed in presynaptic terminals; it coordinates synaptic vesicle fusion. SXT1A plays a vital role in chemical neurotransmission, synaptic vesicle exocytosis, and protein-protein interaction (Vardar et al., 2016; Melland et al., 2021). It supports insulin secretion in human β-cells. It also plays an important role in the regulation of synaptic plasticity and neurotransmitter transporters (Fujiwara et al., 2016; Fujiwara et al., 2017; Liu et al., 2021). Recent studies revealed that dysregulation of the soluble N-ethylmaleimide-sensitive factor attachment protein receptor complex (SNARE) and the SXT1A proteins or their targets has been implicated in several diseases such as ASD, Alzheimer, schizophrenia, and attention deficit hyperactivity disorder (ADHD), by causing impairment of intracellular membrane transport pathways in neurons and neurotransmitter release (Fujiwara et al., 2016; Kofuji et al., 2017). Additionally, STX1A gene expression has been reported to be altered in ASD patients (Nakamura et al., 2008; Nakamura et al., 2011; Kofuji et al., 2017).

STX1A among other synaptic proteins is generally involved in the functioning of the synaptic vesicles. Loss of STX1A causes the impairment of synaptic vesicle exocytosis and leads to impairment of neurotransmitter release and vesicle fusion (Chen et al., 2014; Sauvola and Littleton, 2021). Furthermore, recent genetic studies reported that dysregulation of STX1A expression is associated with social behavior impairments in patients with human neurodegenerative disorders, such as ASD and ADHD. These behaviors are believed to be part of the stereotypic behavioral profile (Nakamura et al., 2008; Fujiwara et al., 2016; Fujiwara et al., 2017).

Given its critical role in inducing behavioral changes, including reduced social interaction, and stereotypy, we hypothesized that core symptoms of ASD may improve after AIT intervention. Therefore, in this study, we aimed to examine the impact of AIT on the cognitive, social, and sensory profiles assessed by measuring the Childhood Autism Rating Scale (CARS), Social Rating Scale (SRS), and Short Sensory Profile (SSP) before and after AIT in ASD children. This study also investigated the contributing role of AIT on the plasma STX1A levels as a potential biomarker for ASD.

2. Materials and methods

2.1. Subjects

A total of 26 autistic male children, aged between 4 and 11 years (7.2±2.1 years), were enrolled in the present study. They recruited from the Autism Research and Treatment Center (ART Center) at King Khalid University Hospital, King Saud University. All participants were screened and diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (APA, 2013). Patients with any neurological diseases (such as cerebral palsy and tuberous sclerosis), metabolic disorders (e.g., phenylketonuria), seizures, allergic manifestations, autoimmune diseases, or a concomitant infection were excluded from this study.

2.2. Clinical evaluation of autistic patients

Before AIT intervention, scores of the Childhood Autism Rating Scale (CARS), the Social Responsiveness Scale (SRS), and the Short Sensory Profile (SSP), were calculated for each ASD patient, as previously described (Schopler et al., 1986; Dunn, 1999; Constantino et al., 2003). Again, the scores of the three scales were calculated one month and three months after AIT, for each subject.

2.3. Auditory integration training (AIT)

AIT was conducted according to the published protocol (Bérard, 1993) and a protocol previously used by our group (Al-Ayadhi et al., 2013). Before starting AIT, the children were examined to ensure that there was no excessive ear fluid and/or wax present. AIT sessions were performed over two weeks, for a duration of 30 minutes, twice a day with three-hour intervals between the two sessions. The patients had one or two days break after 5 days of listening. During the sessions of listening, the children listened to processed music. AIT sound amplifier attenuated high and low random frequencies from compact discs. Then the modified music is sent to the listener via headphones. The level of intensity (volume) during the listening sessions with AIT should not exceed 80 dBA (low scale). It was adjusted to a much lower intensity, which depended on the child's comfort level. The music was played at a moderate level, not at an uncomfortable level. However, an 80 dBA level for a total of one hour per day is still a nonhazardous noise level, according to the guidelines of the Occupational Safety and Health Act (OSHA). The OSHA Noise Standard allows noise exposure to an average of 85 dBA for eight continuous hours. Before the AIT session, audiograms were performed, at the midpoint, and at the end of the session. The first and two audiograms were used to set the AIT machines' filters. A filter is then used for dampening (≥40 dBA) the frequencies that the listener hears (peaks) (Sinha et al., 2006).

2.4. Blood samples collection

After overnight fasting, a 3-ml blood sample was collected from each patient in a test tube containing EDTA. Blood samples were immediately centrifuged at 3000 rpm for the collection of plasma samples, which were then stored in a freezer at–80 C until further analysis.

2.5. Biochemical assay of plasma human syntaxin1A

The concentration of STX1A was analyzed in the plasma from the ASD children, using a commercial sandwich enzyme immunoassay (ELISA) kit (EiAab Co., Ltd., Wuhan, China). Plasma STX1A levels were assessed before AIT, and they were repeated three times after AIT (immediately after, after one month, and after three months). To increase accuracy, all samples in the present study were in a double-blind manner in two independent experiments analyzed as duplicates to ensure reproducibility and determine inter-assay variations in the results (P<0.05).

2.6. Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS 22 for Windows; SPSS, Chicago, IL, USA). Results are presented as mean±standard deviation (SD). Paired t-test was used for the comparison of parametric data, while the Wilcoxon signed-rank test was used for the comparison of nonparametric data before and after AIT (Kolmogorov-Smirnov parametric test). The Pearson correlation coefficient "r" was used to determine the correlation between STX1A levels before and after AIT. For all tests, a value of $p<0.05$ was considered significant.

3. Results

Table 1 shows the changes in plasma levels of STX1A l before, immediately after, one month, and three months after AIT. Plasma levels of STX1A significantly increased immediately after AIT (2.06±1.44 ng/mL, $p<0.05$), one month after AIT (2.27±1.79 ng/mL, $p<0.01$), and three months after AIT (2.30±0.96 ng/mL, $p<0.01$) compared to its level before AIT (1.51±0.99 ng/mL).

Pearson correlation *(r)* values between STX1A levels before and after AIT are recorded in Table 2. It shows strong and positive significant correlations between STX1A levels before AIT and immediately after AIT (r=0.594, p=0.01) and one month after AIT (r=0.819, p=0.01).

Results of the behavioral rating scales (CARS, SRS, and SSP) revealed significant changes and hence improvement in terms of disease severity after AIT intervention. Before AIT, the score of CARS, an indicator of autism severity, was significantly decreased one month (30.42±5.28, $p<0.01$) and three months after AIT (32.54±7.40, $p<0.01$) compared to before AIT (40.29±7.96) (Table 3).

Table 1: Mean value of plasma syntaxin1A levels before and after AIT in children with ASD

Syntaxin1A	Minimum	Maximum	Mean±SD	*P*-value
Before AIT	0.1	3.25	1.51±0.99	
Immediately after AIT	0.36	5.75	2.06±1.44	0.027
One month after AIT	0.63	6.98	2.27±1.79	0.002
Three months after AIT	1.02	4.80	2.30±0.96	0.006

Table 2: Pearson's correlation (*r*) between STX1A before and after AIT

Syntaxin1A	Before AIT	Immediately after AIT	One month after AIT	Three months after AIT
Before AIT	1	0.594**	0.819**	0.046
Immediately after AIT	0.594**	1	0.317	- 0.109
One month after AIT	0.819**	0.317	1	0.265
Immediately after AIT	0.046	- 0.109	0.265	1

**: Correlation is significant at 0.01 level

Table 3: Mean value of CARS before and after AIT in children with ASD

CARS	Minimum	Maximum	Mean±SD	*P*-value
Before AIT	22	52	40.29±7.96	
One month after AIT	21	38	30.42±5.28	0.000
Three months after AIT	22	51	32.54±7.40	0.005

As presented in Table 4, SRS total score after one month didn't show any significant difference, while it significantly decreased three months after AIT (154.54±18.98, p<0.05). Regarding the total SSP score, there is a considerable decrease one month after AIT, but it didn't reach a significant value (p>0.05). Three months after AIT, a significant decrease in the mean SSP score was observed (152±22.85, *p*<0.05) (Table 5).

Table 4: Mean value of SRS before and after AIT in children with ASD

SRS	Minimum	Maximum	Mean±SD	*P*-value
Before AIT	34	203	170.84±39.06	
One month after AIT	86	218	171.62±34.96	0.7
Three months after AIT	113	189	154.54±18.98	0.04

Table 5: Mean value of SSP levels before and after AIT in children with ASD

SSP	Minimum	Maximum	Mean±SD	*P*-value
Before AIT	148	190	168.8±17.35	
One month after AIT	129	190	160.39±19.06	0.29
Three months after AIT	112	190	152±22.85	0.02

4. Discussion

To the best of our knowledge, the present study is the first to investigate the effectiveness of AIT on the plasma levels of STX1A and the amelioration of the behavioral, social, and sensory symptoms in ASD children.

In the present study, the mean value of CARS scores decreased significantly one month and three months after AIT (P=0.000, p=0.005 respectively). Furthermore, a significant decrease in SRS scores was observed 3 months after AIT (P=0.04). Additionally, the mean value of the SSP scores decreased significantly three months after AIT (P=0.037). The substantial decline in autistic behavior, as demonstrated by significant changes in the scores of the three scales of autism severity, may indicate that AIT may be of significant therapeutic importance in some children with ASD. Our findings are consistent with previous studies that indicate a significant improvement in cognitive ability, social communication, and sensory profile after AIT (Pfeiffer et al., 2011; Al-Ayadhi et al., 2013; Al-Ayadhi et al., 2018; Al-Ayadhi et al., 2019), demonstrated by significant changes in the three measured scales. This finding suggests the therapeutic effect of AIT on ASD symptoms. Recently, Li et al. (2018) explored the relationship between AIT and its effect on children with ASD using meta-analysis. They indicated that ASD children had a significantly decreased ABC score and ATEC score and a significantly increased IQ score after following AIT sessions compared to the control group. They also reported a negative association between CARS scores and AIT in subjects receiving AIT compared to controls (Li et al., 2018).

However, there is a controversy in the literature in regard to the effectiveness of AIT in reducing auditory hypersensitivity and behavioral impairment. Some previous studies didn't report any significant difference between ASD and control groups after AIT (Mudford et al., 2000), while others reported a significant improvement in Aberrant Behavior Checklist (ASC) scores in ASD subjects three months after AIT (Sinha et al., 2011). This discrepancy may be attributed to the difference in study designs, duration of the AIT intervention, small sample sizes, and variation in statistical methods.

This study is the first to study plasma STX1A levels; all studies were done at a genetic level. Our findings indicated a significant increase in the plasma level of STX1A coupled with improvement in some ASD behaviors demonstrated by significant changes in CARS, SRS, and SSP scores after AIT sessions.

Little is known about the role of AIT in blood biomarker changes in autistic patients; it was not possible to trace data in this regard. However, previous studies carried out by our group reported a significant impact of AIT on the improvement of some biomarkers and the severity of ASD, suggesting that AIT may play a key role in ameliorating some ASD biomarkers levels (Al-Ayadhi et al., 2018; Al-Ayadhi et al., 2019). Combinations of different approaches may help to facilitate the identification of potential therapeutic targets and the design of new treatment methods. Changes in these proteins play a crucial role in ASD pathophysiology; previous biomarkers studies proved their accuracy and reliability in the presentation of the disease outcome (Yao et al., 2021).

Our results showed that STX1A protein levels in the plasma of the ASD subjects were significantly increased after AIT intervention. As the previous studies confirmed that altered STX1A gene expression correlates with a higher rate of cognitive decline and unusual social behavior (Nakamura et al., 2008; Nakamura et al., 2011; Kofuji et al., 2017), so the improvement of autistic behaviors observed in the current study might be related to the brain plasticity after STX1A recovery. These findings may highlight the potential role of AIT in the upregulation

of plasma STX1A in ASD children and treatment decisions.

This may also be associated with the severity of repetitive behaviors in ASD. Kafuji et al. (2017) reported in their study on STX1A knockout mice that STX1A haploidy causes the decreased STX1A mRNA expression that is related to abnormal behavioral profiles in ASD. This reduction may impair SNARE complex formation and vesicle exocytosis, leading to unusual autism features (Kofuji et al., 2017). Additionally, they implicated the role of abnormal STX1A mRNA expression in the dysregulation of the serotonergic and hyperserotonemia which is responsible for autism behaviors observed in null mice (Kofuji et al., 2017).

Taken together, we speculate that increased plasma STX1A has a contributing role in the amelioration of the behavioral, social, and sensory symptoms in ASD children through its involvement in different pathways. The significant improvement of symptoms can be referred to the multiple roles of STX1A as a regulator of synaptic function and plasticity, vesicle fusion, neurotransmitters release, and SNARE complex integrity maintenance.

5. Conclusion

Our results suggest that AIT might initiate the cascade of events leading to the up-regulation of plasma STX1A and amelioration of the severity of behavioral impairments and associated symptoms in ASD children. Moreover, the increased STX1A level may influence behavioral impairment by maintaining its normal functions such as synaptic plasticity, vesicle fusion, and neurotransmitter release. However, this study suggests a relationship between AIT and/or STX1A and synaptic plasticity. Therefore, STX1a should be given more attention as a possible diagnostic biomarker. Moreover, a combination of AIT intervention with the search for biomarkers may provide significant guidance for future therapeutic strategies. However, future studies with larger sample sizes are needed to provide additional insights into how AIT may contribute to cognitive improvements and the elevation of STX1A levels in ASD.

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Compliance with ethical standards

Ethical consideration

The present study was approved by the Ethical Committee of the College of Medicine at King Saud University, King Khalid Hospital. All procedures performed were in accordance with the ethical standards of the institutional research committee, and with the most recent Helsinki Declaration. Informed written consent was obtained from the parents or the legal guardians of all subjects.

Conflict of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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