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Neuronal Endosomal Trafficking: One of the Common Molecular Pathways Disrupted in Autism Spectrum Disorders and Schizophrenia

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Abstract

Current research has examined the overlap of genetic risk factors and phenotypic behaviors in Autism Spectrum Disorders (ASDs) and Schizophrenia (SZ). We compiled a table of functional groups of genes altered in both ASDs and SZ and grouped them based on function. We described several functional groups altered in both neurodevelopmental disorders including the dopamine pathway, signaling molecules, GABA and glutamate signaling, and endosomal proteins. Previous work has explored the roles of dopamine, signaling cascades, GABA and glutamate in these disorders. The purpose of this review is to analyze the endosomal pathway members implicated in both disorders. These genes include an endosomal solute carrier, endosomal GTPases, endosomal coat proteins and endosomal coat-associated proteins. Deeper understanding of the endosomal pathway could lead to the progress of biomarker development for ASDs and SZ, enhanced therapeutics, and greater knowledge of how specific molecular pathways contribute to neurodevelopmental disorders.

Introduction

Autism Spectrum Disorders (ASDs), including Fragile X Syndrome (FRX) and Rett Syndrome (RTT), are neurodevelopmental diseases characterized with cognitive deficits, compulsive repetitive behaviors, social anxiety and impaired social interactions. These phenotypes are observed within the first two years of life and persist throughout the patient's lifetime. For ASDs, genetic studies in patient populations have identified multiple genes as potential risk factors. Although this suggests that ASDs are polygenetic in nature, the causes of ASDs remain unknown. Classified under the spectrum of ASDs, FRX and RTT have known genetic causes. Studies examining the impact of the genetic mutations observed in FRX and RTT are necessary because they describe possible pathways and mechanisms disrupted in the shared phenotypes of ASDs.

Schizophrenia (SZ) is a neurodevelopmental disorder with phenotypes usually observed in early adulthood. There are similar behavioral phenotypes observed in patients with SZ and ASDs. SZ is characterized by cognitive deficits, including disorganized thoughts, paranoia, auditory and visual hallucinations, and impaired social interactions. Prior to better differentiation between ASDs and SZ, children with ASDs or SZ were often misdiagnosed due to the similar phenotypes. Similar to ASDs, there are hundreds of genes that have been identified as risk factors for SZ, though the cause of SZ also remains unknown.

Genetic causes and risk factors for ASDs and SZ

Current research has described genetic risk factors for ASDs that are also risk factors for SZ [1-5]. Studying those diseases within the spectrum of ASDs with known genetic causes aids in studying the mechanisms of shared phenotypes in all ASDs. RTT and FRX have known genetic mutations that are concurrently found in SZ. Affecting primarily females, RTT results from genetic mutation in the methyl CpG binding protein 2 (MeCP2) [6]. The transcriptional regulator MeCP2has been identified as the genetic cause of 50-70% of RTT cases as well as a risk factor for SZ [6-17]. In addition, mutations in the Cyclin-Dependent Kinase-like 5 (CDKL5), which is a serine/threonine kinase that regulates the phosphorylation of MeCP2 protein, result in atypical forms of RTT and have been implicated in SZ as well [11,18-23]. Finally, accounting for 5% of ASDs, FRX is a result of trinucleotide repeats that repress expression of Fragile X Mental Retardation 1 (FMR1). Mutations in the FMR1 gene have likewise been observed in SZ [24].

Genes associated with risk of SZ are also implicated in ASDs. Several genes are consistently classified among the strongest genes associated with risk of SZ including, DTNBP1, NRG1 and DISC1. The Consortium on the Genetics of Schizophrenia (COGS) reported 94 proteins that are risk factors for SZ, including DISC1, NRG1, and endosomal proteins; specifically, four subunits of the octomeric Biogenesis for Lysosome-related Organelles Complex 1 (BLOC-1), (BLOS1, BLOS2, Muted, and DTNBP1) [25,26]. Of the subunits making up the endosomal BLOC-1, DTNBP1 encodes for dysbindin, which is among the strongest genes associated with risk of SZ [27]. Postmortem examinations of brain tissue from patients with SZ have a reduction of dysbindin in the hippocampus [28,29]. Recent

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Table 1: Genes affected in ASDs and SZ based on functional groups.

Dopamine			
Gene Symbol	**Gene Name**	**Autism**	**Schizophrenia**
DRD1	Dopamine Receptor D1	[44]	[45]
DRD2	Dopamine Receptor D2	[44]	46-58
DRD3	Dopamine Receptor D3	[59]	[52,60-66]
Signaling Molecules			
Gene Symbol	**Gene Name**	**Autism**	**Schizophrenia**
BDNF	Brain derived neurotrophic factor	[67-72]	[73-78]
PTEN	Phosphatase and tensin homolog	[79-81]	[82]
MAPK	Mitogen Activated Protein Kinase	[83,84]	[85]
GSK3B	Glycogen synthase kinase 3 beta	[86-88]	[88,89]
GABA			
Gene Symbol	**Gene Name**	**Autism**	**Schizophrenia**
GABRA3	GABA A receptor, alpha 3	[90]	[90]
GABRQ	GABA A receptor, theta	[90]	[90]
Glutamate			
Gene Symbol	**Gene Name**	**Autism**	**Schizophrenia**
GAD1	Glutamate decarboxylase 1	[91,92]	[93-95]
GRID1	Glutamate receptor, ionotropic, delta 1	[96,97]	[98-101]
GRIK2	glutamate receptor, ionotropic, kainate2	[102-105]	[106-108]
GRIN2A	glutamate receptor, ionotropic, N-methyl D-aspartate 2A	[109-111]	[110,112-115]
GRIN2B	glutamate receptor, inotropic, N-methyl D-apartate 2B	[109,110,116]	[110,117,118]
GRIP1	glutamate receptor interacting protein 1	[119,120]	[106,121]
GRM1	Glutamate receptor, metabotropic 1	[122]	[123-125]
GRM5	Glutamate receptor, metabotropic 5	[126-129]	[130-133]
Endosomal Vesicle Trafficking			
Gene Symbol	**Gene Name**	**Autism**	**Schizophrenia**
RAB39B	Rab39B	[134,135]	[134]
RAB11FIP5	Rab11 family interacting protein 5	[136,137]	[25,27,28,138,139]
RAB3A	Rab3a	[26]	[140]
DNTBP1	Dysbindin	[31]	[25]
AGAP1	ArfGTPase-activating protein 1	[141]	[142]
SLC9A6	Solute carrier family 9 (NHE family member)	[143,144]	[145]

research has established the importance of BLOC-1 in ASDs and SZ by linking a common mutation in a gene regulating the BLOC-1 complex in RTT and SZ [30]. Also, in patients with ASDs, mutations in a chromosomal region containing DTNBP1 have been reported [31]. Another gene that is a risk factor for SZ is NRG1, which codes for the neuregulin 1, a glycoprotein that regulates cell signaling and cell growth during development [32,33]. Additional research in both animal models and in patient populations indicate that NRG1 is also a risk factor in ASDs [34,35]. Finally, another genetic risk factor highly associated with SZ is disrupted in schizophrenia 1 (DISC1). DISC1 protein is involved in neurite outgrowth and the development of the cortex. It is required for neural progenitor proliferation during development and in the adult hippocampus. Genetic variations of DISC1 have been reported both in patient populations with SZ and those with ASDs [36-43].

To effectively study the risk factors in both ASDs and SZ, the genes can be classified based on the resulting protein function, yielding functional groups of genes. Functional groups disrupted in ASDs and SZ include dopamine, GABA, glutamate, signaling pathways, and trafficking genes. Altered genes in ASDs and SZ within these functional groups are summarized in Table 1. Considering the strong overlap in the genetic components and the redundancy in phenotypic behaviors between ASDs and SZ, one prediction asserts that they both share an alteration in an underlying molecular pathway or mechanism. Based on the functional groups, several theories regarding the underlying causes of ASDs and SZ have been developed.

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Dopamine hypothesis

Dopamine is one of the first neurotransmitters implicated in SZ. Research has explored the hypothesis of alterations in the dopamanergic signaling pathway in patients with SZ [48,52,53,55]. D2 receptors are elevated in patients with SZ [146]. Patients with SZ treated with dopamine-agonists demonstrate significant improvements in some positive symptoms. In contrast, patients treated with dopamine-like drugs display exacerbated psychotic symptoms, demonstrating the extreme sensitivity of patients with SZ to dopamine levels [146].

The dopamine hypothesis in ASDs has less evidence. Some brain regions associated with symptomatic behaviors of ASDs, such as the cerebellum, amygdala, prefrontal cortex, parietal lobes, and hippocampus, are affected by dopamine levels [147]. Some genes within the dopamine pathway are altered in ASDs, suggesting a potential role of dopamine in the disorders, however no improvement with dopamine agonists has been observed in patients with ASDs. Dopamine plays an active role in many of the primary deficits characteristic of ASDs, including neurogenesis, seizures, motor problems, and repetitive behaviors [147]. This close relationship warrants further investigation into how dopamine influences ASDs [147]. Kriete & Noelle carried out one such investigation, reporting that reducing the efficacy of the dopamine signal resulted in deficits of cognitive flexibility and cognitive control as seen in ASDs. This research also revealed that weakened dopamine gating mechanisms can manifest as the impaired cognitive flexibility characteristic of ASDs later on in development. While the dopamine hypothesis is supported, it cannot be the only pathway disrupted in both ASDs and SZ and therefore other hypotheses should be considered as well.

Signaling molecules hypothesis

There are several signaling molecules that have been implicated in ASDs and SZ, including MAPK, PTEN, BDNF and GSK3β.

MAPK: Alterations in the Mitogen Activated Protein Kinase (MAPK) pathway have been linked to both ASDs and SZ. The MAPK pathway is involved in activating transcription factors for cognitive functions compromised in ASDs and SZ, such as learning and memory. Hyperactivity of the ERK MAPK pathway has been identified in ASDs along with modifications to genomic areas containing the MAPK gene83. Specifically, micro deletions and micro duplications within the genomic area containing MAPK3, 16p11.2, have been distinguished as risk factors for ASDs [83]. Similarly, abnormal activity of the MAPK pathway has been linked to SZ. Funk et al. reported abnormal expression of MAPK, compromised by proteins and phospho-proteins, in the anterior cingulate and the dorsolateral prefrontal cortex in patients with SZ [85]. There is strong evidence supporting the role of changes in the MAPK pathway in both ASDs and SZ, however further research is required to assess the extent to which these changes correspond with both disorders in terms of pathway involvement.

PTEN: There have been studies investigating the role of Phosphatase and Tensin Homolog (PTEN) mutations in both ASDs and SZ. PTEN mutations such as D326N and H93R are thought to be related to ASDs due to their role in tumor suppression and synaptic plasticity [79,81]. Additional studies, such as those conducted by Lugo et al., have also observed the impact of PTEN deletion in relation to ASDs. PTEN deletion results in the synaptic abnormalities featured in ASDs, as well as behavioral alterations in social behavior, repetitive behavior, activity, and anxiety [80]. Mice with PTEN depletion showed an increase in both phosphorylated and total Fragile X Mental retardation protein. Human subjects with developmental delays, as seen in ASDs, had a 12.2% prevalence rate of PTEN mutation [80]. Mutations of PTEN have also been linked to cases of SZ. The PTEN-Induced putative Kinase 1 (PINK1) gene is associated with a variety of psychiatric disorders. For example, in Steinlechner et al.'s study, SZ was found in 61% of PINK1 mutant carriers [82]. Mutations or deletions in genes related to tumor suppression or psychiatric disorders are present in a portion of the population with ASDs or SZ, however any commonalities between these risk factors applicable to both diseases require future investigation.

BDNF: The relationship between SZ and Brain Derived Neurotrophic Factor (BDNF) is well documented, while the relationship between ASDs and BDNF is still in the early stages of investigation. In patients with RTT, the expression of BDNF is deregulated [69], suggesting that the modulation of BDNF levels could have a strong influence over disease progression [71]. BDNF plays a role in multiple processes that are found to be compromised in patients with SZ; such processes include neuronal differentiation, neurite outgrowth, neuron survival, the development and function of neurotransmitter systems, and those involving general cognitive functioning [73,74]. The biological mechanism responsible for cognitive impairment in patients with SZ may be due in part to a deficiency in pro-BDNF processing [74]. Further research is required to better understand how extensively BDNF impacts both SZ and ASDs.

GSK3β: Glycogen Synthase Kinase 3 beta (GSK3β) regulates hippocampus-dependent cognition [88], and has been thoroughly studied in regards to its relationship with ASDs and SZ. In FRX, the most common cause of intellectual disability in ASDs, hyperactivity of hippocampal GSK3β was found. In addition, GSK3β inhibitors were found to rescue deficits in long-term potentiation [86]. Additional studies have inferred that the impairment of inhibitory regulation of GSK3β may be a contributing factor to social deficits commonly seen in ASDs [87]. In relation to SZ, GSK3β is most notably observed in the role it plays in signaling pathways targeted by antipsychotic medications88. Further studies are necessary to discern the role GSK3β may play in the pathology of SZ, as well as more in-depth studies of how it interacts with antipsychotic medications.

Excitatory/Inhibitory imbalance hypothesis

Stemming from the functional groups is the hypothesis of excitatory/inhibitory (E/I) imbalance in ASDs and SZ [148-153]. Both the excitatory and inhibitory inputs altered in ASDs and SZ have been well documented. Current research is taking these studies further by examining the overall circuitry of brain regions with altered E/I signaling. E/I imbalance during development could explain improper neuronal connections observed in both ASDs and SZ.

ASDs and SZ exhibit alterations in GABAergic transmission [147]. In ASDs and SZ, GABA A receptors have been implicated as risk factors [90]. Potential risk factors of ASDs and SZ include

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glutamate decarboxylase 1, glutamatergic ionotropic receptor subunits, glutamate receptor interaction protein 1, and glutamatergic metabotropic receptor subunits (Table 1). Based on the genetic studies, both ASDs and SZ could potentially have alterations in excitatory/inhibitory balance during development. This is a current area of inquiry among many neurodevelopmental research groups.

Endosomal trafficking

This review will put forth another hypothesis of the underlying mechanisms potentially shared in ASDs and SZ-altered endosomal vesicle trafficking. This review will examine the known role of endosomal trafficking in relation to ASDs and SZ through analyzing the alterations of trafficking proteins in both neurodevelopmental disorders, and investigating how changes in endosomal functions have been described in ASDs and SZ.

Endosomal trafficking has been implicated as a common molecular pathway disrupted in both ASDs and SZ. Endosomal trafficking regulates budding and targeting of vesicles from donor membranes to acceptor membranes within the organelles involved in the endosomal pathway: the Golgi complex, lysosome, early endosome, late endosome, and recycling endosomes [154]. Endosomal trafficking is necessary for proper neuronal function. Neurons utilize endosomal trafficking to regulate the subcellular transport of neurotransmitters and receptors. Endosomal trafficking is also imperative for proper neuronal outgrowth, in particular dendritic spine outgrowth. And endosomal trafficking in neurons also regulates spine-dependent growth during Long-Term Potentiation (LTP). Taken together, endosomal trafficking is necessary for proper neuronal development and synaptic formation.

Membrane-enclosed organelles, such as endosomes, have distinct protein complexes associated with them that are necessary for vesicle formation and cargo recruitment on the donor membrane, and targeting and fusion with the acceptor membrane [154,155]. In order for endosomes to function properly, they utilize ion exchange pumps in order to maintain an acidic pH. Solute carriers that maintain the proper pH in endosomes have been implicated in both ASDs and SZ. Recent work by Kondapalli et al. reviews the role of Na^+/H^+ exchangers in ASDs and other neurological disorders [145]. In particular, SLC9A6 is an endosomal solute carrier necessary for maintaining the proper pH of endosomes. Mutations in SLC9A6 have been observed in ASDs and SZ [143,145], suggesting altered endosomal pH in both neurodevelopmental disorders.

Endosomal GTPases

Studies have implicated three different Rab and Rab-associated proteins as risk factors for ASDs and SZ. Members of the endosomal pathway include Rabs, which are GTP-binding proteins (GTPases) that recruit necessary proteins for proper vesicle formation and trafficking [154]. After budding from the donor membrane, vesicles shed their coats as the GTPase is switched from the GTP-bound form to the GDP-bound form by GTPase-Activating Proteins (GAP) [156-161].

In both ASDs and SZ, mutations in Rab39B have been reported [134,135]. Localized to the Golgi, Rab39B is involved in vesicle trafficking and synapse formation. Down regulation of Rab39B results in significant reduction in synapses, as well as alterations in the number and the morphology of the growth cones [134], which could lead to improper synaptic development. Increased expression of Rab39B results in decreased neuronal complexity and decreased synaptic numbers [135,162], which could lead to cognitive impairments as well. Another Rab disrupted in neurodevelopmental disorders is the RAB11 family interacting protein 5 (RAB11FIP5), which is involved in protein trafficking from recycling endosomes to the plasma membrane. To date, Rab11FIP5 has not been reported in SZ, but it has been reported in ASDs, where there is a translocation between chromosomes 2 and 9 which disrupts RAB11FIP5 protein function [137]. Mutations in RAB11FIP5 were observed in another patient population study and are described as risk factors for ASDs [136], Finally, Rab3a regulates the late steps in vesicle fusion with the acceptor membrane and is reduced in postmortem tissue from patients with SZ in the frontal cortex and hippocampus [140]. In the hypothalamus of a mouse model lacking functional MeCP2, Rab3 is altered, as well as Rab4b, Rab14, and Rab15, all of which have known endosomal functions [26,161,163-165]. Using genetic analyses of patient populations and animal model research, three endosomal Rab GTPases and GTPase interacting proteins have been implicated in ASDs and SZ. Considering the role that GTPases play in vesicle formation, a modification in GTPase function could lead to a failure of proper vesicle formation and trafficking. Depending on what cargo was being trafficked, this failure in trafficking could result in the phenotypic behaviors observed in ASDs and SZ.

Endosomal coat proteins

In addition to endosomal solute carriers and Rabs, coat proteins and coat-associated proteins specific to the endosomal pathway have been implicated in both ASDs and SZ. The coat and the coat-associated proteins recruited from the cytosol begin vesicle formation, which initiates the curvature of the donor membrane as it is forming a vesicle. One group of proteins associated with the vesicle coat are the Adaptor Proteins (APs), which are either heterotetrameric proteins, such as AP1-AP5, or monomeric proteins including β-arrestin and GGA1-GGA3 (Golgi-associated, gamma adaptin ear-containing, Arf binding protein 1-3) [166-171]. One of the important coat-associated complexes is BLOC-1, which consists of eight subunits (Pallidin, Cappuccino, Dysbindin, Snapin, Muted, BLOS1, BLOS2, and BLOS3) and is necessary in trafficking BLOC-1 dependent vesicles from the endosome to the lysosome or, in neurons, synaptic vesicles targeted to the axon terminal [139,168,172-177].

First, Copy Number Variations (CNVs) of the Arf GTPase-Activating Protein 1 (AGAP1) have been described in patients with ASDs and SZ [141,142]. As part of endosomal vesicle formation, AGAP1 interacts with adaptor proteins, clathrin, and the BLOC-1 complex to form vesicles on the endosome [177-180]. Second, work in our lab has demonstrated a decrease in functional subunits of the BLOC-1 complex in mouse models lacking the functional MeCP2 gene [30]. The region of the chromosome 6 where DNTBP1 is located is deleted in a patient with ASDs [31]. Further work examining the role of BLOC-1 in ASDs is necessary to determine if BLOC-1 is altered in other ASDs.

To date, several Rab and Rab associated proteins have been implicated in ASDs and SZ along with endosomal coat-associated

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proteins BLOC-1 and AGAP1, and the solute carrier SLC9A6. These studies support the hypothesis that endosomal vesicle trafficking is one of the underlying molecular mechanisms altered in both ASDs and SZ.

Endosomal function

Endosomal trafficking regulates proper receptor trafficking, proper trafficking of membrane proteins, and regulation of LTP, all of which are phenotypes that have been described as altered in ASDs and SZ. Examining LTP, the electrical correlate for learning and memory, is necessary because cognition is impaired in both ASDs and SZ. Animal model systems of ASDs and SZ have demonstrated alterations in LTP as a result of disruptions of endosomal function, specifically endosomal regulation of spine formation and AMPA receptor (AMPAR) trafficking [86,153,181-185].

Recycling endosomes located at the base of the dendritic spines control spine growth during LTP [186-189]. Recycling endosomes are recruited to the spine during LTP, and if this recruitment is blocked, spines remain immature and LTP is inhibited [188,189]. Mushroom and stubby spines propagate incoming signals whereas thin, filamentous spines isolate the signal from the rest of the dendrite. Thin, immature, filamentous spines have been observed in numerous neurological disorders such as ASDs, SZ, Down syndrome, Parkinson's disease, Alzheimer's disease, X-Linked Mental Retardation, FRX, and RTT [186,190-210]. Interestingly, Cytoplasmic FMR1-Interacting Protein (CYFIP1), which is a risk factor for both ASDs and SZ, is associated with spine maturation and dendritic development204. Specifically, CYFIP1protein regulates spine morphology and dendritic complexity, which is regulated by endosomal trafficking. Endosomal-regulated spine maturation necessary for LTP is altered in ASDs and SZ and the CYFIP1 protein, which has a role in spine maturation, is a risk factor for both ASDs and SZ, further supporting the hypothesis that dysfunctional endosomal trafficking regulates phenotypes observed in ASDs and SZ. The endosomal proteins necessary for spine maturation altered in ASDs and SZ remain unknown.

In addition to immature spines, altered AMPAR trafficking inhibits LTP. LTP requires endosomal dependent localization of AMPARs in the spine head. When recycling endosomes are blocked, AMPAR insertion is blocked, and LTP is inhibited [188,189]. Work by Carroll et al. has demonstrated that AMPARs are localized to AP-2 endocytic regions and AMPAR endocytosis is dependent on clathrin-mediated endosomal trafficking [211]. Prior to LTP, AMPARs are clustered at the base of the dendritic spines. After LTP induction, the AMPARs are localized to the spine head. Clustering and insertion of the AMPARs is required for LTP and regulated by endosomal trafficking [189,212]. Interestingly, ASDs and SZ have impaired AMPAR function [213-216]. Patients with ASDs have mutations in AMPARs and increased mRNA levels for several AMPAR genes [217]. CYFIP1, altered in ASDs and SZ, also regulates AMPAR lateral diffusion necessary for LTP, which is regulated by recycling endosomes located in the spine head. In SZ, not only is AMPAR trafficking impaired, but it is also impaired in mice lacking the dysbindin subunit of BLOC-1, suggesting that proper AMPAR function requires the endosomal BLOC-1 complex [218]. However, the role of AMPARs in SZ is debatable. In immune isolated endosomes extracted from elderly post-mortem tissue, Hammonds et al. reported an increase in the AMPAR subunits in the early endosome, but not the late endosome [219]. While this study concludes AMPAR trafficking is intact in the cortex of patients with SZ, this study does not take into account what is occurring during development or in other brain regions such as the hippocampus. The majority of these studies demonstrate altered AMPAR trafficking in both ASDs and SZ, which impacts LTP in animal models and potentially the cognitive abilities of patients.

Altered endosomal functions of spine morphology and AMPAR trafficking further support the hypothesis that endosomal trafficking is one of the common molecular pathways altered in both ASDs and SZ. Additional research is necessary to understand the role of endosomal trafficking in the spine morphologies, AMPAR trafficking, and LTP. If endosomal trafficking does impair dendritic spine maturation and AMPAR trafficking in ASDs and SZ, repairing proper endosomal trafficking function could restore proper spine morphology, AMPAR trafficking, and potentially rescue LTP.

Conclusion

In order to better understand the molecular pathways that underlie the neurodevelopmental disorders SZ and ASDs, we must approach genetic studies by examining functional groups of genes rather than a select few genes. In doing so, we will better describe the molecular pathways that underlie certain neurodevelopmental disorders. Potentially we may find that molecular pathways regulate certain phenotypes, and dysregulation of those pathways may be common to all neurological disorders characterized by that specific phenotype. Exploring functional groups of genes implicated in neurological disorders is necessary to better understand the phenotypes regulated by a specific molecular pathway.

Several functional groups have been described in ASDs and SZ including dopamine, signaling molecules, and the genes regulating the E/I balance. In this review, we focused on one of the functional groups of genes implicated in both ASDs and SZ: the endosomal trafficking pathway. Taking into account the solute carrier SLC9A6, GTPases, and endosomal coat and endosomal coat associated proteins that are candidate risk factors for ASDs and SZ, it is evident that endosomal trafficking is a key vesicle pathway altered in both disorders. Endosomal trafficking controls spine morphology and AMPAR trafficking, both of which are necessary for LTP. ASDs and SZ both demonstrate altered LTP due to alterations in spine morphology and AMPAR trafficking. More research is necessary to understand the role of endosomal trafficking in spine morphology, AMPAR trafficking, and LTP in ASDs and SZ. This research could lead to potential therapeutic targets that could increase cognitive ability in the patient population.

The research reviewed here examining endosomal trafficking genes, as well as regulators of endosomal function, supports the hypothesis that the endosomal trafficking pathway is disrupted in both ASDs and SZ. The functions of endosomal trafficking during development, and how it might be disrupted with altered genetic expression of endosomal genes implicated in ASDs and SZ remains to be discovered.

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