In silico cholinergic pathway analysis indicates possible role for exogenous choline in modulating sensory processing in autism spectrum disorder

Audrey Olson[1,2], MS; Fuquan Zhang[3], PhD; Hongbao Cao[1,4], PhD; Ancha Baranova[1], PhD; Margaret Slavin[2], PhD, RDN

[1]Department of Bioinformatics and Computational Biology, School of Systems Biology, College of Science, George Mason University, Manassas, VA;
[2]Department of Nutrition and Food Studies, College of Health and Human Services, George Mason University, Fairfax VA;
[3]Department of Psychiatry, The Affiliated Brain Hospital of Nanjing Medical University, Nanjing, China;
[4]Department of Psychiatry, First Hospital/First Clinical Medical College of Shanxi Medical University, Taiyuan, Shanxi Province, China

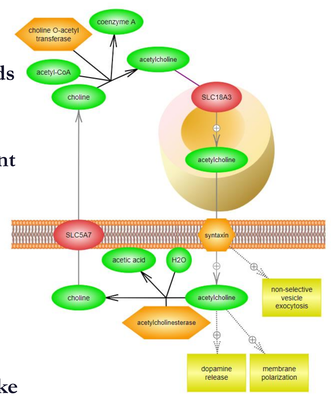
School of Systems Biology for TAGC 2020 online

OBJECTIVES

- To investigate a potential role of dietary choline intake as a means for bolstering sensory processing function, through use of scientific literature analysis using natural language processing (NLP) as a means for assessing potential gene ontological overlap between autism spectrum disorder (ASD) associated genes and cholinergic signaling pathways.

BACKGROUND

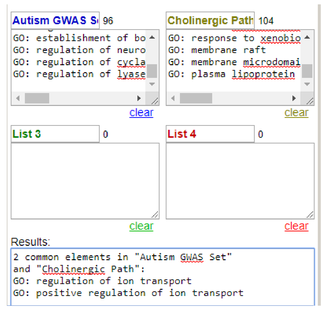
- Sensory processing dysfunction is common in ASD.
- Sensory processing relies upon sensory gating – ligand-activated, ion-channel-mediated pathways built upon cholinergic signals.
- Acetylcholine plays roles in sensory processing, including auditory signal pathways, as well as cognitive function, memory, and learning.
- Choline, the precursor to acetylcholine, is an essential nutrient that must be consumed from exogenous sources (foods) to meet the body's needs for acetylcholine production. (Figure 1, right ©Elsevier)
- Rodent models have demonstrated choline deficient diets are associated with lower levels of acetylcholine in the brain and impaired sensory gating function.
- Many American children, including a majority of American children with ASD, do not consume recommended levels of dietary choline.
- Combined, this evidence supports further investigation of the impact of dietary choline intake upon sensory processing in autism.



METHODS

- Gene set enrichment analysis was conducted to identify Gene Ontology database[1,2] pathways shared between MSig-DB curated cholinergic pathway gene sets (345 genes total) and a set of 53 autism genes identified by meta-analysis of genome-wide association studies[3,4].
- Ontologies associated with both the autism GWAS set and the MSig-DB functional pathway sets were identified using gene ontology association analysis within Pathway Studio (Elsevier)[5]. The lists of ontologies assigned to each of these gene sets were trimmed at approximately the lowest 100 p-values ($p < 0.01$), while using a shift in p-value order of magnitude as the final determinant in list cutoff.
- The gene ontology lists' respective areas of overlap were identified using Venny[6].
- Associated pathways and ontologies were integrated graphically, using Pathway Studio to both illustrate and model the potential influence of dietary choline deficiency sensory pathways affected in autism.

RESULTS



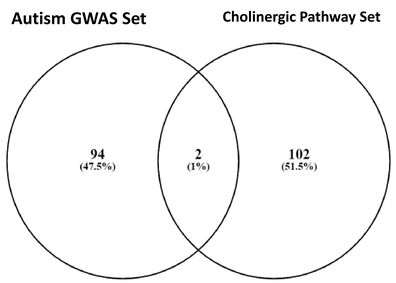


Figure 2. Gene ontological overlap between the autism GWAS set and cholinergic pathways set, conducted using Venny. The two areas of ontological overlap between these gene sets were identified as "regulation of ion transport" and "positive regulation of ion transport".

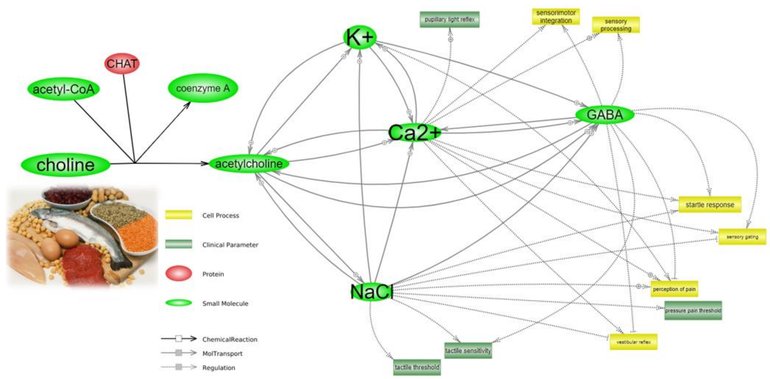


Figure 3. Subsequent analysis was conducted within Pathway Studio's platform, using natural language processing (NLP) to identify regulatory and functional relationships between acetylcholine, ions, and aspects of sensory processing, as currently supported within the scientific literature. Arrows generated by Pathway Studio within the diagram upon relationship query indicate demonstrated literature support as identified through NLP.

As can be seen from the left, all acetylcholine-driven relationships, and potentially those indirect relationships downstream, may be supported through adequate intake of dietary choline. The neurotransmitter gamma aminobutyric acid (GABA) is also deeply embedded functionally, both with ion transport and in a type of feedback loop regulation of acetylcholine supply, but also with respect to sensory processing domains.

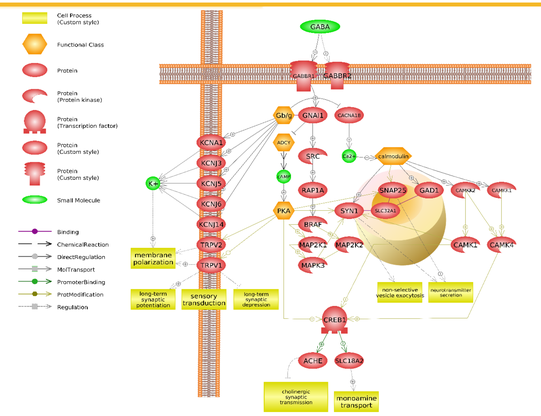


Figure 4. As seen in Figure 3, acetylcholine prompts release of GABA, which goes on to bind with membrane protein GABBR1 (top), eventually preventing ongoing degradation of acetylcholine in the interneuronal junction by acetylcholinesterase (ACHE). GABBR1 protein's gene is among those on the autism GWAS analysis set for this project, indicating a potential for GABBR1 variant vulnerability in GABA/GABBR1 pathways - especially when combined with low dietary choline – to result in dysregulated acetylcholine supply and sensory processing. © Elsevier

CONCLUSIONS

- Because acetylcholine has long been identified as a modulator of ion transport throughout the body, the findings highlight a potential use for adequate dietary choline intake as a means to bolster acetylcholine supply, and therefore, ion transport related functionality across sensory domains.
- Future study of sensory processing associated with autism should not only include identified genetic components, but also associated sensory processing pathway components, including acetylcholine, and its exogenous precursor, dietary choline.

ACKNOWLEDGEMENTS

This project was funded by a research grant from the American Egg Board / Egg Nutrition Center.

REFERENCES

1. Ashburner et al. Gene ontology: tool for the unification of biology. Nat Genet. May 2000; 25(1):25-9. http://geneontology.org/
2. The Gene Ontology Consortium. The Gene Ontology Resource: 20 years and still GOing strong. Nucleic Acids Res. Jan 2019; 47(D1):D330-D338. http://geneontology.org/
3. Liu, S., Rao, S., Xu, Y. et al. Identifying common genome-wide risk genes for major psychiatric traits. Hum Genet 139, 185–198 (2020). https://doi-org.mutex.gmu.edu/10.1007/s00439-019-02096-4
4. Molecular Signatures Database, MSig-DB, https://www.gsea-msigdb.org/gsea/msigdb
5. Elsevier's Pathway Studio https://www.elsevier.com/solutions/pathway-studio-biological-research
6. Oliveros, J.C. (2007-2015) Venny. An interactive tool for comparing lists with Venn's diagrams. https://bioinfogp.cnb.csic.es/tools/venny/index.html