Metabolomics Alterations in Acute Stress Disorder: Neurotransmitters, Energy, and Inflammation Related Small Biomolecules Associated in Acute Stress

Nicholas C. Gary[1,2], Burook Misganaw[1,3], Rasha Hammamieh[1], Aarti Guatam[1]

[1]Medical Readiness Systems Biology, CMPN, Walter Reed Army Institute of Research, Silver Spring, MD; [2]The Geneva Foundation, Tacoma, WA; [3]Culmen International, Alexandria, VA

Abstract

Background: Acute Stress Disorder (ASD) is a psychiatric condition characterized by the onset of severe anxiety, dissociation, and other debilitating symptoms following an exposure to a traumatic event. This is often linked to the activation of the body's stress response system, which involves the release of stress hormones such as cortisol. Acute stress can impact the levels of neurotransmitter metabolites such as serotonin, dopamine, and norepinephrine. These neurotransmitters play a crucial role in regulating mood, stress response, and emotional well-being, and their abundance in relevant tissue can reflect the physiological impact of acute stress on the body. The release of stress hormones can influence energy metabolism such as elevated demand for glucose and other energy substrates associated with energy production and utilization. In addition, the impact of acute stress on the body's inflammatory response can lead to alterations in metabolites related to inflammation and immune function. This includes changes in metabolites such as cytokines, which play a role in the body's immune and inflammatory processes with implications for long-term health outcomes.
Methods: To find articles discussing ASD and Metabolomics studies we used the PubMed database when conducting the initial search. Searching the PubMed database for metabolomics on "Acute Stress Disorder" OR "Acute Stress Response" yielded 1,352 abstracts. We excluded articles that did not include mention of metabolomics despite discussing ASD.
Results: We briefly highlight metabolites association with other stress-related disorder to juxtapose it with that of ASD. We especially wanted to focus and highlight studies concerning physiological responses in human and animal data to acute stress disorder metabolomics. Most metabolites that have been reported to be associated with ASD can be classified/grouped into three broad categories: (1) amino acid and ketone body metabolites (2) lipids, and (3) carbohydrates. Next, the (reported) relationship of metabolites into the three categories will be described in more details.
Conclusion: Understanding the role of metabolites in acute stress disorder can offer new avenues for the development of biomarkers, therapeutic interventions, and targeted treatments aimed at mitigating the impact of acute stress on the body's metabolic and physiological processes.
Disclaimer: Material has been reviewed by the Walter Reed Army Institute of Research. There is no objection to its presentation and/or publication. The opinions or assertions contained herein are the private views of the author, and are not to be construed as official, or as reflecting true views of the Department of the Army or the Department of Defense.

Background

Acute stress disorder (ASD) is a prevalent psychiatric condition that can develop from individuals exposed to trauma. According to DSM-V classification, ASD is an intense and debilitating reaction occurring immediately after suffering an overwhelming traumatic event lasting for three days and less than a month. The International Classification of Diseases (ICD-10) criterion suggests acute stress reactions (ASR) is a transient response occurring immediately in post-trauma that normally resolves within 2–3 days. ASD is known to share a large proportion of its symptomatology with other psychiatric disorders such as post-traumatic stress disorders (PTSD) and other trauma-related disorders. The main distinguishing factor between them is the timing and duration of the symptoms with respect to the traumatic event. Diagnosis of the disorder initially emphasized that a person experiencing ASD should satisfy four symptom cluster such as dissociation, intrusion, avoidance, and arousal and should satisfy the five dissociative symptoms.

ASD has a well-documented history of leading to long-term psychiatric sequalae of trauma exposure. Research shows that about 80% of people that met ASD symptom criteria following acute trauma will develop PTSD six months later. However, it should be noted that an ASD diagnosis is not necessarily intended to function as a predictor of subsequent PTSD since at least one third of people who develop PTSD do not meet DSM-5 ASD criteria. The probability for the onset of ASD depends on the type and severity of the trauma. For example, studies show that 33% of people who experienced a mass shooting develop ASD, while only 14% of people who experienced a traumatic brain injury developed ASD. Other factors are also at play regarding ASD diagnosis These factors include psychiatric diagnosis, prior trauma, genetics and being female increases risk for developing ASD.

Relationship of ASD with various molecular traits in the brain as well as in peripheral tissue have been studied. Research indicates the role diverse set of functional and molecular layers to the pathophysiology of ASD. Here, we summarize metabolites, biomolecules of smaller molecular weight, that have been reported to be associated with ASD. We discuss four categories of metabolites: amino acids, ketone bodies, lipids, and carbohydrates.

Citations

1. A. B. Adler and I. A. Gutierrez, "Acute Stress Reaction in Combat: Emerging Evidence and Peer-Based Interventions," Curr Psychiatry Rep, vol. 24, no. 4, pp. 277–284, Apr. 2022, doi: 10.1007/s11920-022-01335-
2. A. P. Association, Diagnostic and Statistical Manual of Mental Disorders (DSM-5®). American Psychiatric Pub, 2013.
3. Ontario Health (Quality), "Internet-Delivered Cognitive Behavioural Therapy for Post-traumatic Stress Disorder or Acute Stress Disorder: A Health Technology Assessment," Ont Health Technol Assess Ser, vol. 21, no. 9, pp. 1–120, 2021.
4. R. A. Bryant, M. J. Friedman, D. Spiegel, R. Ursano, and J. Strain, "A review of acute stress disorder in DSM-5," Depress. Anxiety, vol. 28, no. 9, pp. 802–817, Sep. 2011, doi: 10.1002/da.20737.

Methods

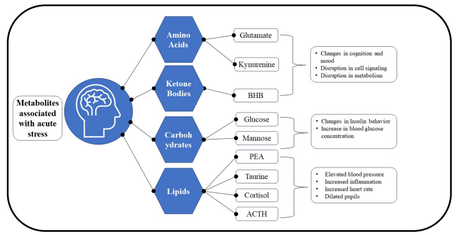

Figure 1. Pre-clinical and clinical studies of acute stress implicated multiple metabolites. Implication of 9 ASD associated metabolites.

Results

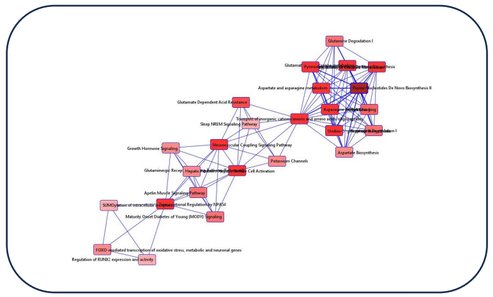

Figure 2. Pathway network analysis for ASD metabolites. Further examination of metabolite specific networks identified a network consisting of 35 biomolecules associated with diseases and biofunctions "amino acid metabolism, endocrine system development and post-translational modifications". Here we map biomolecule related pathways.

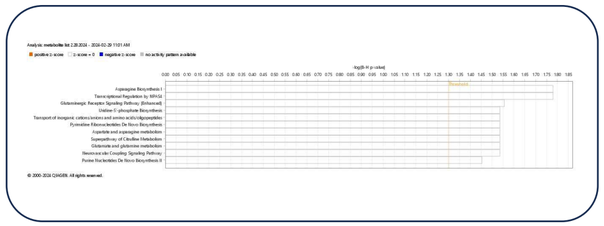

Figure 4. Overview of pathways significantly enriched in the set of ASD relevant metabolites.

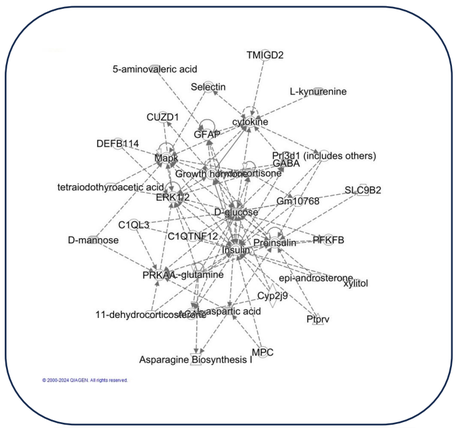

Figure 3. Network describing metabolic disease, hereditary and developmental disorder is obtained using IPA network analysis of ASD associated metabolites. ERK1/2 and Insulin appear at the center of the network; LEP levels affects glutamine, glutamate, insulin, palmitic acid, pro-insulin, LDL, CAMK2A, NFKB, ACTH and JNK which are also visible in this network. Dashed line represents indirect relationship.

- Although metabolomics study of acute stress related phenotypes began recently, given the central role of small molecules for stress response variabilities, there have been a few studies and promising findings.
- These include both preclinical studies with various animal models as well as clinical studies of military and civilian cohorts.
- By compiling results from literature search of clinical and pre-clinical studies, we want to highlight the most current research-based evidence.
- Most metabolites that have been reported to be associated with ASD can be grouped into four broad categories: (1) amino acids, (2) ketone bodies (3) Lipids, and (4) carbohydrates.

Conclusion

The potential benefit from metabolic studies is profound and wide-ranging; from developing biomarkers to identifying therapeutic targets. ASD is an important precursor for subsequent psychiatric illnesses in the longer term. Metabolomic events are downstream molecular consequences closer to the physiological changes and are likely to have a larger effect size and more readily interpretable results.

Scan for more information

For more information contact: Nicholas.c.gary3.ctr@health.mil