Journal of Experimental and Basic Medical Sciences 2021;2(1):27-33

Review

Fructose Consumption Effect on Bipolar and Attention Deficit Hyperactivity Disorder

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ABSTRACT

Behavioral disorders, including bipolar disorder (BD) and attention deficit hyperactivity disorder (ADHD), have long been associated with sugar intake and inflammation. The factors that contribute to this link have been unclear. Here we represent a possible mechanism in which fructose, a component of sugar and high fructose corn syrup (HFCS), intake is related to the elevation of serum uric acid (a fructose metabolite), which can then become a risk factor for ADHD and BD. Studies have shown that uric acid can increase the stimulation of stress response from the hippocampus, the region of the brain that initiates stress response in humans. Hippocampus initiates the stress response by stimulating the pituitary-adrenal (HPA) axis, which eventually secretes cortisol, the hormone responsible to upregulate many other inflammatory markers, including cytokines in the body. In conclusion, we propose that uric acid and cytokines can serve as a connecting link between fructose intake and the occurrence of BD and ADHD. Moreover, we suggest that the mechanism of action of uric acid is by increasing the hippocampal stress response, inflammation in the brain, and also the foraging response. Foraging response stimulated by uric acid increase explains the behavioral patterns of BD and ADHD.

Keywords: Attention deficit hyperactivity disorder, bipolar disorder, fructose, inflammation, sugar.

Bipolar disorder (BD) affects nearly 46 million people worldwide, and 85% of the children with the condition also have co-occurring Attention Deficit Hyperactivity Disorder (ADHD).[1,2] Both conditions share similar adverse human behaviors, including irritability, impulsivity, emotional dysregulation, a racing brain, hyperactivity, and aggression.[2] The exact cause of both BD and ADHD is unknown, however, it is suggested that there may be multiple factors that contribute to the formation of one or both of the conditions.[2]

One of the factors that are associated with adverse human behaviors since early experimental research is sugar intake, especially in excess amounts, and during childhood.[3] Preliminary data suggested that sugar intake may be related to these conditions through allergic reactions or through reactive hypoglycemia, which describes the "impulsive" human behaviors in the absence of sugar.[4-6] However, these studies lacked consistent results, and a better explanation of the mechanism for why sugar intake could relate to BD and ADHD was still missing.[7,8]

Recent research on individual sugar molecules, namely glucose, sucrose, and fructose, gave different correlation rates with ADHD and BD. While the intake of glucose and sucrose did not significantly correlate with the occurrence of ADHD and BD, fructose intake was found to be a risk factor for the development of these psychiatric disorders.[7-9] The metabolite of fructose, uric acid, could be a possible reason why fructose is associated with ADHD and BD.[9]

Uric acid is the nitrogenous end-product of purine metabolism. Although imbalanced uric acid levels are primarily linked with medical conditions such as gout, the role of uric acid in mental health is

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Cite this article as: Başkaya E, Memişoğlu M, Erbaş O. Fructose Consumption Effect on Bipolar and Attention Deficit Hyperactivity Disorder. JEB Med Sci 2021;2(1):27-33.

doi: 10.5606/jebms.2021.75635

Received : January 05, 2021
Accepted : February 24, 2021
Published online : May 31, 2021

also an emerging area of research.[10] Several studies have linked uric acid levels to emotion-related psychopathologies, such as mood disorders, anxiety, and aggression.[11-15]

Uric acid may affect mental health by altering the emotional response to stress. In fact, it has been shown that the autonomic response (blood pressure) to acute stress decrease or increases as a function of baseline uric acid levels.[16,17] Moreover, Qu et al.[17] demonstrated that uric acid-lowering therapy by allopurinol significantly reduces blood pressure. On the other hand, low uric acid concentrations are associated with anxiety and depression.[18,19]

Uric acid levels are also positively correlated with the levels of pro-inflammatory cytokines, which are proteins, peptides, or glycoproteins that are secreted by the immune cells.[20] Cytokines act as signaling molecules that mediate and regulate the immune system and inflammation.

Cytokines such as plasma interleukin-6 (IL-6), interleukin-1β (IL-1β), tumor necrosis factor- α (TNF-α) and C-reactive protein (CRP) are positively correlated with uric acid levels.[20] Martinon et al.[21] demonstrated that uric acid stimulates the release of CRP upon entering the cells in the media layer of the arteries, vascular smooth muscle cells. Moreover, *in vitro* studies demonstrated that uric acid also stimulates the production of IL-6, IL-1β, and TNF-α from human mononuclear cells.[22] These results collectively support a positive relationship between serum uric acid levels, cytokine levels, and systemic inflammation.

FRUCTOSE AND URIC ACID PRODUCTION

Fructose, or fruit sugar, is one of the three dietary monosaccharides. It is naturally found in fruits, honey, agave, and most root vegetables. It is also added to processed foods in the form of high-fructose corn syrup. High-fructose corn syrup is commonly sourced from sugar cane, sugar beets, and corn.

Fructose metabolism is very different compared to other monosaccharides, and it is the only one that gives rise to uric acid during its metabolism.[9,23] Fructose is primarily metabolized in the liver and the key enzyme for metabolizing fructose is fructokinase. Fructokinase enzyme uses adenosine triphosphates (ATP) to phosphorylate fructose to fructose-1-phosphate. Because there is a lack of feedback mechanism to down-regulate fructokinase if too much ATP is used, fructose metabolism often results in ATP depletion inside the cells. Accumulation of ATP breakdown products (such as adenosine monophosphate or AMP) activates ATP deaminase, which catalyzes the degradation of AMP to inosine monophosphate and eventually to uric acid.[23]

The amount of uric acid production upon the ingestion of fructose has several variables, which include the amount of fructose, whether it was ingested as a solid or liquid, the amount of prior exposure, and the intracellular ATP stores.[9] It is also important to note that uric acid production may be stimulated independently from the fructose intake if a person is chronically eating fructose-rich food and beverages.[9] The fasting serum levels of uric acid of such subjects tend to be high regardless of fructose intake.[9]

URIC ACID, CYTOKINE SECRETION AND HIPPOCAMPAL RESPONSE TO STRESS

One characteristic of uric acid is that it can pass freely through the blood-brain barrier, and it has been observed that one of the locations in which it has a profound effect is the hippocampus.[24] The hippocampus is the critical brain region for learning and memory.[22] Additionally, the hippocampus acts as the start site of stress response in humans by regulating the pituitary-adrenal (HPA) axis.[25] The increased stress response that is signaled from the hippocampus to the HPA axis causes more secretion of cortisol, which is a biological marker for stress and inflammation.[25] As a major player in the stress response and inflammation, the hippocampus is important in the pathophysiology of altered cognitive disorders that can be traced back to oxidative stress in the brain.[25-27]

Studies showed that hippocampal response to stressful events increases as a function of uric acid levels.[10,28] There has been evidence that uric acid is a direct and potent enhancer for inflammatory activity. Johnson et al.[22] demonstrated that C-reactive protein can be upregulated by uric acid in human vascular cells and endothelial cells. Moreover, Ou et al.[17] demonstrated that the pro-inflammatory pathway, the Toll-like receptor 4 (TLR4)/nuclear factor (NF)-κB signaling pathway is activated in response to serum uric acid levels.[22] The potential of uric acid to raise the level of inflammation by inducing cytokine secretion from cells and by causing a higher level of stress response from the hippocampus may serve as an explanation for why uric acid levels, and thus fructose intake, could be linked to ADHD and BD.

URIC ACID, CYTOKINES AND ADHD

Attention deficit hyperactivity disorder (ADHD) is an increasing neurodevelopmental disorder that impairs the quality of life for both children and adults.[29] It is described as an ongoing pattern of the inability to pay attention and/or hyperactivity-impulsivity that interferes with learning, social life, and occupational life.[29] Though the exact pathophysiology of ADHD is not fully understood, it is characterized by structural and functional dysfunctions in a wide range of cortical and subcortical regions.[29,30] A study composed of 1,713 patients with ADHD and 1,529 controls demonstrated a volume reduction in the nucleus accumbens, amygdala, caudate, hippocampus, and putamen in patients with the disorder.[30]

It has been shown that patients with ADHD have increased serum inflammatory markers and that there are is strong comorbidity of ADHD with inflammatory and autoimmune disorders.[27,29,30] It has been shown that ADHD patients were more likely to have co-occurring asthma, allergic rhinitis, atopic dermatitis, and allergic conjunctivitis in comparison to the non-ADHD subjects from the population.[29]

There has been evidence from genetic studies that polymorphisms in genes related to inflammatory pathways also play a role in ADHD.[29,31] Smith et al.[32] performed a study evaluating a set of 164 single-nucleotide polymorphisms (SNPs) from 31 candidate genes in a total of 398 subjects. They found that 2 SNPs in a cytokine-related gene, the ciliary neurotrophic factor receptor (CNTFR), were associated with ADHD inattentive symptom severity.[33] Cumulative data suggests a strong relationship between increased inflammation and the occurrence of ADHD.[29-31,33]

A high serum uric acid has been observed in patients with hyperactivity, low attention span, and impulsivity.[32,33] These characteristics overlap with the manifestations of ADHD. The proposed explanation for the correlation of high uric acid levels and ADHD symptoms may be due to hippocampal inflammation and the increased circulatory cytokine levels that result in systemic inflammation. Barrera et al.[34] demonstrated that a higher serum uric acid is present in children and adults with hyperactivity, low attention span, impulsivity, and problems with anger control, consistent with ADHD. In agreement, a positive correlation exists between higher UA plasma levels and impulsiveness/excitement-seeking traits, as well as the inability to focus on tasks in humans.[31-35]

Numerous studies have also reported cytokines to be correlated with ADHD symptoms.[36-39] While increased hyperactive-impulsive symptoms and motor activity are correlated with increased IL-16, elevation in IL-6 is associated with an increased risk of attention problems.[36,38] A more comprehensive study analyzed cytokine levels inside the cerebrospinal fluid of children with ADHD. In this study, researchers found that 90% of the children with ADHD had detectable IL-2, 70% had detectable TNF-β levels, 60% had detectable IFN-γ levels, and 62% had detectable IL-5.[39] In agreement, studies supported the possibility of cytokines be likely involved in the pathogenesis of ADHD.

URIC ACID, CYTOKINES, AND BIPOLAR DISORDER

Bipolar disorder is an increasing mental disorder that causes extreme shifts in energy, mood, concentration, and the ability to carry out day-to-day tasks.[40] There are 3 types of bipolar disorder, namely Bipolar I Disorder, Bipolar II Disorder, and Cyclothymic Disorder (also called Cyclothymia).[40] These types are differentiated by whether the patient is experiencing primarily manic episodes or depressive episodes.[40] While manic episodes correspond with periods of extremely "up", irritable, and energized behavior, depressive episodes correspond with very "down", indifferent, and hopeless behavior. Less severe manic episodes are known as hypomanic episodes.[40]

Bipolar disorder I is characterized by manic episodes that last at least a week, if not so severe that the patient needs urgent hospital care.[40] BD II is characterized by a mix of depressive and hypomanic episodes, without the occurrence of extreme manic episodes.[40] Lastly, Cyclothymic Disorder is characterized by periods of hypomanic symptoms and depressive symptoms lasting for at least 2 years.[40] Symptoms seen in Cyclothymic Disorder do not meet the diagnostic criteria to be called "episodes".[40]

Several studies have associated Bipolar disorder with both diabetes, and subjects with bipolar disorder demonstrate a higher intake of sugar compared to a control population.[41-43] Additionally, Alten et al.[43] showed that the administration of high fructose corn syrup (HFCS) to adolescent rats results in clinical characteristics of both bipolar disorder and ADHD in association with inflammation of the hippocampus.

Uric acid levels have long been found effective on BD episodes.[9,10,40] Specifically, serum uric acid levels tend to be high in patients experiencing manic episodes and serum uric acid levels tend to be low in depressive episodes.[44,45] Uric acid's role in stimulating manic episodes have been also demonstrated in treatment studies of bipolar disorder. Jahangard et al.[12] showed that therapeutic reductions in uric acid concentrations via allopurinol (xanthine oxidase inhibitor) significantly reduces the severity of manic episodes.

The effect of uric acid on psychosocial behaviors has also been shown in non-BD patients.[10] Several studies demonstrated that low uric acid levels are associated with socially anxious, introverted, and avoidant tendencies, while high uric acid levels are associated with impulsivity, excitement seeking, hyperactivity, and disinhibited temperaments, which share similarities with ADHD and the manic episodes of bipolar disorder.[10,14,18,34,35,44,45]

Similar to uric acid, cytokine levels have also been found to be influential in BD episodes. Kim et al.[46] demonstrated that pro-inflammatory cytokines IL-6 and TNF-α are significantly higher in manic patients in comparison to normal controls. IL-4, on the other hand, is found to be significantly lower in manic patients in comparison to normal controls.[46,47] Unlike the effects of pro-inflammatory IL-6 and TNF-α, IL-4 has anti-inflammatory properties. These findings demonstrate an imbalance between the elevated pro-inflammatory cytokines and the decreased anti-inflammatory cytokines during manic BD episodes.

Furthermore, measurements of cytokine levels in BD patients in the early and late stages of the disorder have also been informative to understand the role of inflammation in disease progression.[48] It has been found that while IL-4, TNF-α, and IL-10 are all significantly higher than healthy controls during the early stages of BD, only IL-4 and TNF-α continued to be significantly higher during the late stages of the illness.[48] Maintained levels of elevated proinflammatory cytokines despite the decrease in anti-inflammatory cytokines in later stages of BD suggests the possible role of enhanced inflammation in the progression of BD.

URIC ACID, AND THE FORAGING RESPONSE

While the relationship between serum uric levels, cytokines, and inflammation has been established, researchers have yet to come up with an evolutionary-based explanation for why there is such a correlation. Recently, researchers have identified the foraging response, an evolutionary-based survival pathway in response to extreme starvation.[9] Foraging response is stimulated by increased protein breakdown and therefore increased serum uric acid levels.[9]

During the initial phases of starvation, it is common to see a reduced metabolic rate, as well as an increased breakdown of glycogen and fat stores.[49] Breakdown of glycogen and fat provides the animal with energy, as well as water from fat oxidation. During this period the animal calms down and rests.[49,50] If the starvation continues, however, the fat stores will be no longer sufficient to provide energy.

If fat stores get depleted due to extreme starvation, the animal starts to breakdown muscle protein for energy. The breakdown product of protein, uric acid, stimulates both an increased stress response from the hippocampus, and also an increased pro-inflammatory cytokine production by the human vascular cells.[10,22,28] This marks the beginning of the foraging response.[9] Foraging response corresponds with an exploratory behavior required to search for food.[9] Johnson et al.[9] describes foraging response as a behavior pattern that includes "risk-taking, impulsivity, novelty seeking, locomotor activity, quick decision making, rapid processing with minimizing focus and attention to specifics, and occasionally aggression." It is important for animals to exhibit foraging response as a built-in mechanism to resist starvation and survive in an environment with food shortages. Robin et al.[51] explain that an animal during foraging response can abandon eggs in search of food.

The behavioral pattern of foraging response shares similarities with ADHD and BD. To be successful in finding food, the animal needs to search for food in lands that are not familiar, which may become dangerous due to predators and unknown hazards. The animal needs to be aggressive, willing to take risks, exhibiting impulsive behaviors, and making decisions quickly.[9] These characteristics share similarities with both ADHD and manic episodes of BD. The underlying reason can be the fact that foraging response, ADHD, and BD all are linked to uric acid and cytokine levels. As uric acid and cytokine levels rise in the body during extreme starvation, a foraging response is seen. While the foraging response can be stimulated by increased uric acid and cytokine levels

due to protein breakdown, it can also be stimulated by increased uric acid after fructose breakdown. This shows us that the symptoms of ADHD and BD, which share similarities with foraging response, can also be stimulated by too much fructose breakdown.

DISCUSSION

There is an increasing body of evidence that supports the link between fructose intake and psychiatric disorders. Here we represented how the metabolite of fructose, uric acid, can explain this link. Uric acid is not only produced after fructose breakdown, but it is also produced after protein breakdown, which happens during extreme starvation. Extreme starvation, which is marked by elevated uric acid levels, initiates the stress response from the hippocampus and stimulates cells to secrete inflammatory cytokines. This marks the beginning of the foraging response.

Foraging response shares similarities with ADHD and the manic episodes of BD, such as impulsivity, aggression, inability to focus, and attention to specifics. One possible explanation for the increase in the number of ADHD and BD patients can be the mechanism in which fructose leads to uric acid production. Increased fructose intake due to increased HFCS may be one of the reasons for the increased ADHD and BD patients. We suggest further studies to investigate how fructose can be related to behavioral disorders.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

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