HIGH SCHOOL EDITION
Journal of Student Research
Volume 12 Issue 3 (2023)

Climate Change and Metabolism: Impact on Fructose Metabolic Pathways and Health Outcomes

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ABSTRACT

The effects of climate change have been well-documented in the scientific literature for decades, spanning all aspects of global environmental and social health. While not as commonly researched, the smaller-scale effects on human metabolism have also been observed, with a rise of metabolic disorders such as diabetes and obesity rising in tandem with global temperatures. Biochemical metabolic pathways are also being affected, as dysregulated endogenous fructose metabolism has been highly implicated in such disease states (1). This review will explore the relationships between human health, endogenous fructose metabolism, and the overarching impact of climate change on these factors. As endogenous fructose metabolism has been shown to increase under evolutionarily stressful conditions, such as thermal pressures, the result of rising global temperatures on climate change is a key concern in a variety of fructose-mediated disease states. Further experimental research is necessary to elucidate the nature of these relationships and pinpoint biomolecular mechanisms, as understanding is key to better preparing the public for the ongoing physiological effects of the world's changing climate, which this review hopes to illuminate.

Background

Climate Change and Global Implications

It has become undeniable that climate change, as it is understood, will have far-reaching consequences on the globe. Scientists are well aware of how the climate is affecting regular seasonal weather patterns, with high-impact weather events such as heatwaves, droughts, extreme rainfall, and storms becoming more intense and variable each year. Such changes in large-scale weather patterns can bring new types of weather to different areas, increasing the risk of multiple bread-basket regions that saturate global agriculture being affected at the same time (2). The fluctuating food supply and alternating spiking and crashing food prices will disrupt supply chains and economic trade (2). This resultant variability in crop yields is expected to increase in the future, and the Global Food Security Program reports the estimated risk of severe disruptions in global production has increased three times over (2). This subsequently could create opportunities for food fraud through the substitution of cheaper ingredients as well as result in increased rates of malnutrition in areas of interrupted supply (3).

While some colder high-latitude regions may see an increase in crop yield due to reduced cold stress and increased growing seasons (4), an overall decrease in the quantity and quality of land due to changing soil composition, coupled with decreasing water supplies from evaporation could also drive an increase in the intensity of agriculture and food prices (2). Rising sea levels due to glacial retreat further reduce available habitable and arable land for agriculture (2). Hotter and drier conditions will likely increase the water requirements of plants and animals, increasing pressure on water resources, especially in regions already water-stressed. Higher temperatures, unpredictable precipitation, and extreme events such as floods and droughts are likely to decrease water quality for animal consumption, further decreasing agricultural supply and increasing demand (4). There is already precedent for such climate change

effects, such as the 2007/8 and 2010/11 European food price spikes caused by production shortfalls generated by weather extremes (2).

Furthermore, climate change is likely to impact agricultural pests and diseases (2), as changing weather patterns and warming temperatures may cause pest and disease distribution to shift and increase stress on key pollinators (4). Impacted feed supply and increased heat stress resulting in increased animal mortality will also restrict animal husbandry (4). The impacts of climate change are likely to increase in frequency and magnitude, driving increased food system volatility and resulting in short-term societal shocks, such as disruptions to supply chains, displacement of vulnerable populations, and violent conflicts over food (2). Climate change more generally can exacerbate social, economic, and political tensions, leading to an increased risk of conflicts that can result in death and long-term health consequences for affected populations (5). This may result in mass population displacement and forced migration due to natural disasters, conflicts over resources, and loss of habitable land along coastal regions from rising sea levels (6).

Human mortality overall will be on the rise due to increased illness and disease spread. Increasing temperatures can lead to heat exhaustion, heatstroke, and dehydration, especially in at-risk populations such as the elderly, infants, and those with pre-existing health conditions (7). Exacerbations in air pollution due to increased ground-level ozone and particulate matter can result in hyperreactive respiratory illnesses, such as asthma. Warmer temperatures and changes in rainfall will also expand the range and seasonality of vector-borne diseases such as malaria, West Nile Virus and Lyme disease (8). Similar increases may occur in waterborne diseases such as cholera and dysentery, due to compromised water quality from extreme weather events and changing precipitation (9). Rising temperatures can result in increased bacterial growth in food sources, leading to a rising risk of foodborne illnesses such as salmonella (10). Such increased temperatures can also drive the evolutionary adaptation of potentially pathogenic fungal species to adapt to human core body temperatures, introducing new virulent fungal diseases into human populations (11). As a result of such rising disease rates, human labor availability and productivity may also be negatively impacted due to heat stress and increased risk of disease transmission, impacting the day-to-day lives of many individuals (4).

Physiological Influence of Climate Change

However, climate change may also impact humanity much closer to home, affecting metabolic processes of thermoregulation directly. The average body temperature regulated by the human brain is 36.8°C, and it can tolerate up to 42°C without health consequences due to thermoplasticity in protein function (12). This is achieved through thermal acclimation, or the body's conditioning to function in the heat. In order to acclimate effectively to rising temperatures from climate change-induced global warming, one behavioural adaptation to global warming necessary may be switching to a sub-nocturnal sleep schedule, in order to avoid heat accumulation from metabolic heat production and environmental absorption during the day (12).

Humans also require an increased carbohydrate intake during prolonged periods of physical exertion in the heat, as exercise and heat both suppress hormonal signals that promote overall energy intake. For example, a combination of overeating and exercise without exposure to heat can reduce appetite due to ghrelin levels being lowered and other hormones involved in satiety being increased in the bloodstream (12). Elevated concentrations of CO2 in the atmosphere resulting from greenhouse gas emissions could reduce plant protein and mineral concentrations, even increasing toxicity in some species (4). *Downstream, impacted nutritional quality may negatively affect food metabolism long-term.* Moreover, it should come as no surprise that heat acclimation is not a perfect process; climate change is expected to increase the frequency and severity of heat waves, leading to increased heat-related morbidity and mortality (12).

Fructose and Climate Change

Certain carbohydrates are particularly concerning in the conversation around climate change, specifically the monosaccharide fructose. Fructose is naturally present in fruits and is commercially combined with glucose to make sucrose, or further modified to make the common additive of high-fructose corn syrup in processed foods and beverages (13). The majority of fructose found in the human body is metabolized by the liver, with the rest occurring at distal tissue sites (14). Fructose can be obtained exogenously through food supplies or produced endogenously through anabolic pathways. There has been sizable research finding that high levels of exogenous fructose intake promote oxidative stress, inflammation, higher serum uric acid levels, hypertriglyceridemia, higher systolic blood pressure, and insulin resistance (14). However, the endogenous production of fructose is less well understood, but theorized to have a greater health impact in response to the effects of climate change, as will be discussed below.

Discussion

Endogenous Fructose Metabolism and Disease

While fructose has been long studied as an exogenous carbohydrate source, its endogenous role in human metabolic processes and pathophysiological dysregulation is still under study. The last five years have provided mounting evidence of the relevance of endogenous fructose production and metabolism in the pathogenesis of metabolic syndrome and associated conditions such as chronic kidney disease, inflammatory bowel disease, and non-alcoholic fatty liver disease (13, 15). Much of this evidence has been derived from mice model studies**.** Subsequently, an active two-step polyol pathway converting glucose into fructose mediated through the up-regulation of aldose reductase has been found to be implicated in the pathogenesis of end-stage diabetic complications (16). The polyol pathway and its activation have been detected in various body tissues and organs during the progression of metabolic syndrome and related conditions; as shown in Figure 1, impacted diseases and disorders include type 2 diabetes, cardiovascular disease (CVD), nonalcoholic fatty liver disease (NAFLD), and more (15). Further research is necessary to understand the exact mechanism of fructose's involvement and clinical relevance in metabolic disease, however, it clearly has some degree of involvement. Studies blocking endogenous fructose metabolism with fructokinase knockout mice resulted in significant functional health improvements such as reduced fatty liver, which suggests that targeting endogenous fructose synthesis pathways may be clinically relevant in preventing and treating metabolic diseases (15). One particular research field connecting such public health concerns and more precise biochemical pathways on endogenous fructose is its mechanistic relationship with climate change as a metabolic stressor, which is discussed further below.

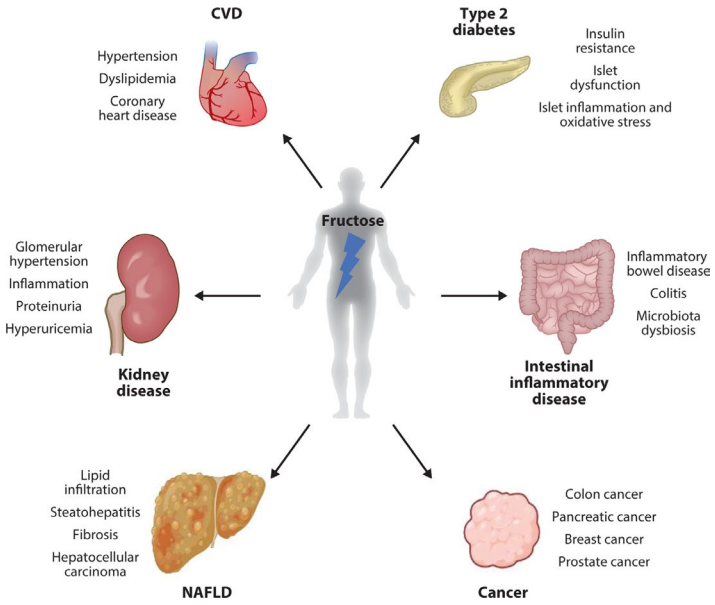

Figure 1. Disease states endogenous fructose pathways have been implicated in. Retrieved from: Jung S, Bae H, Song WS, Jang C. Dietary Fructose and Fructose-Induced Pathologies. Annu Rev Nutr. 2022 Aug 22;42:45-66. doi: 10.1146/annurev-nutr-062220-025831

Endogenous Fructose and Climate Change

On a molecular level, the endogenous pathway may be directly influenced by the biochemical strain of climate change. Researchers have postulated that under excess environmental stresses, such as high temperatures, ingested glucose may be increasingly endogenously converted into fructose through the polyol pathway (please refer to Figure 2). Fructose is then rapidly phosphorylated to fructose-1-phosphate by fructokinase in the liver, intestine, kidney, pancreatic islets, adipose tissue, and brain matter (1). Fructose-1-phosphate is further metabolized by aldolase B to produce glucose, lactate, glycogen, and triglycerides. This metabolic cycle pushes humans to store these macronutrients as fuel (fat, glycogen) along with water generated in the process for future use. Uric acid and the survival hormone vasopressin are also highly implicated in the action of fructose breakdown, which can result in sodium retention and increased blood pressure, theorized to help in dehydration or deprivation scenarios (1). By increasing anaerobic glycolysis through a shift away from mitochondrial oxidation, this further aids in survival scenarios when oxygen is largely unavailable. Therefore metabolic stress factors such as hypoxia, hyperosmolarity, ischemia, oxidative stress, and heat stress all stimulate fructose production pathways.

While this stress-activated process may prove vital under short-term survival scenarios, too much fructose may prove harmful in the scenario of climate change due to the particular concern of rising temperatures as a metabolic stressor. These processes can lead to mitochondrial dysfunction, as well as a shift from energy production to energy storage in homeostatic balance (1). The heat stress in climate-change-affected geographical regions may push endogenous fructose production further as a survival response until there is too much fructose in the body, so that the amount of fructose-1-phosphate in the glycolysis process completely overwhelms the production of ATP and GTP inside cells for respiration, and thereby through negative feedback on the cycle results in energy produced at a much slower rate and slowing the body's metabolism (1). Fructose is also theorized to result in central leptin resistance, which manifests as a persistent hunger. This persistent hunger coupled with the slower generalized metabolism then creates increased storage of glycogen and fats, which can lead to weight gain. These concerns are not merely hypothetical; studies have already shown the connections between rising global warming and obesity (17). Moreover, thermal stress from rising

global temperatures has also been implicated in chronic kidney disease epidemics in numerous countries, thought to be due to a fructose-mediated pathway in the kidneys (18). Therefore, the danger of climate change-related thermal stress exacerbating the evolutionary activation of the polyol pathway may pose a significant ongoing risk to human health.

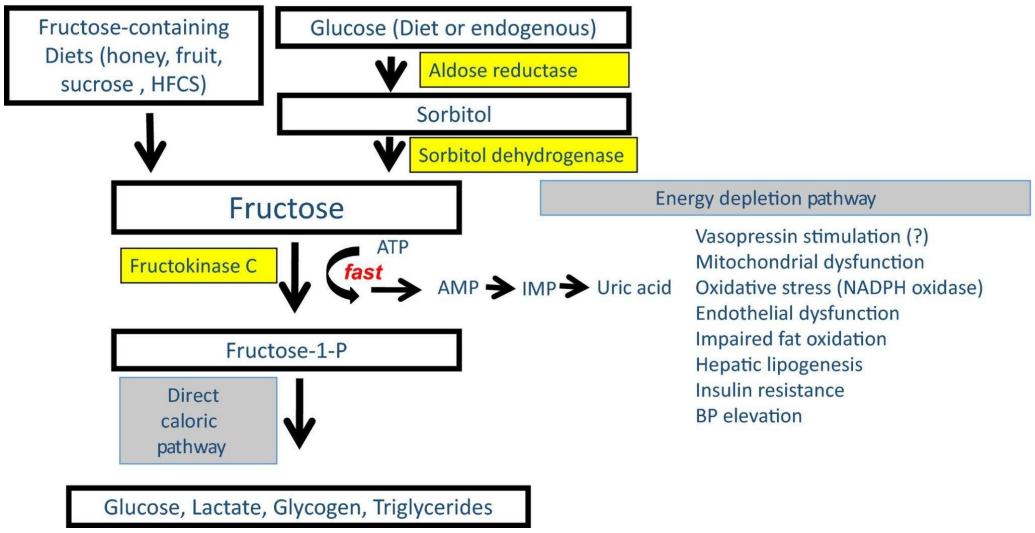

Figure 2. The biochemical endogenous fructose pathway and resultant metabolic disturbances from its overactivation. Retrieved from: Johnson RJ, Stenvinkel P, Andrews P, Sánchez-Lozada LG, Nakagawa T, Gaucher E, Andres-Hernando A, Rodriguez-Iturbe B, Jimenez CR, Garcia G, Kang DH, Tolan DR, Lanaspa MA. Fructose metabolism as a common evolutionary pathway of survival associated with climate change, food shortage and droughts. J Intern Med. 2020 Mar;287(3):252-262. doi: 10.1111/joim.12993.

Limitations

The causative mechanism underlying the endogenous fructose pathway's influence on health states is poorly understood and highly theoretical, with most studies that directly measure the effects of survival stressors on the path done in animal models. Little testing could even be authorized in humans due to ethical and public health concerns. Furthermore, when considering the influence of climate change on this pathway, it becomes very difficult to measure its effects quantitatively, as there are few consistent parameters or evidence-based guidelines developed for such research.

Next Steps

However, such limitations should not stop the development of further observational research on the effects of climate change on human health, coupled with more direct testing of thermal stress conditions mimicking potential climate change conditions in mice along with correlating endogenous fructose measures. Potential lab conditions could stimulate heat waves or extremely cold temperatures seen in weather fluctuations, and measure changes in metabolic function as key markers of the endogenous fructose pathway activating (19). Further biomolecular studies could examine changes in gene expression or enzymatic pathway protein levels in response to different environmental stressors. From a larger epidemiological perspective, studies observing populations more susceptible to climate change

stressors, such as urban regions with low economic status and high pollution would add further strength to the correlative findings (20). Overall, such climate change research on metabolic complications and pathophysiological pathways driving them is a highly underdeveloped area of research that requires further exploration.

Conclusion

Climate change cannot just be considered an "environmental" issue with an indirect impact on health; it is very clear from biomolecular research that it is influencing health outcomes directly as a physiological stressor on metabolism. Additional experimental investigation is required to clarify the nature of these associations and identify the specific biomolecular mechanisms involved. While this review does not argue for how to stop or reverse the effects of climate change or global warming, its intent is to better prepare for the public health needs arising from the phenomenon, and promote additional research into the etiology of resultant adverse health outcomes.

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