

Fructose and Cardiac Arrhythmogenesis

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Fructose is a main dietary sugar involved in the excess sugar intake-mediated progression of cardiovascular diseases and cardiac arrhythmias. Chronic intake of fructose has been the focus on the possible contributor to the metabolic diseases and cardiac inflammation. Recently, the small intestine was identified to be a major organ in fructose metabolism. The overconsumption of fructose induces dysbiosis of the gut microbiota, which, in turn, increases intestinal permeability and activates host inflammation. Endotoxins and metabolites of the gut microbiota, such as lipopolysaccharide, trimethylamine N-oxide, and short-chain fatty acids, also influence the host inflammation and cardiac biofunctions. Thus, high-fructose diets cause heart–gut axis disorders that promote cardiac arrhythmia. Understanding how gut microbiota dysbiosis-mediated inflammation influences the pathogenesis of cardiac arrhythmia may provide mechanisms for cardiac arrhythmogenesis.

Keywords: arrhythmia ; fructose ; heart–gut axis ; inflammation ; microbiota

1. Introduction

The excessive consumption of sweets is a risk factor for cardiovascular diseases (CVD), and the major chemical feature of sweets is fructose ^{[1][2]}. Moreover, high fructose intake can increase cardiovascular mortality ^[2]. Epidemiological studies have suggested a possible link between the intake of fructose, including high-fructose corn sugar, with CVDs ^{[3][4][5][6]}. The main source of fructose in the food comes from fructose-containing sweeteners, sucrose, and high fructose corn syrup, in sugar-sweetened beverages and food additives ^[7].

Intake of sugar-sweetened beverages has been consistently linked to an increased risk of obesity, type 2 diabetes, and CVDs in various populations ^[8]. Fructose mediates oxidative stress, inflammation, increased intestinal permeability, endothelial dysfunction, and gut microbiota dysbiosis, and it then further aggravates metabolic syndrome (MetS) by causing tissue and organ dysfunction ^[9]. Evidence has suggested that fructose induces systemic inflammation and activates inflammatory signaling in local tissues and organs, including the liver, kidneys, gut, and heart ^{[10][11][12]}. Additionally, excess fructose intake may be associated with risk factors for heart disease, such as non-alcoholic fatty liver disease (NAFLD), obesity, diabetes, kidney dysfunction, and dyslipidemia ^{[13][14][15][16][17][18]}. Controlled dietary intervention studies in humans have discovered that fructose intake increased the risk posed by cardiovascular risk factors, particularly increased circulating lipid level and reduced insulin sensitivity ^[2]. A low carbohydrate diet has been shown to improve blood lipids with an increase in high-density lipoprotein and decreases in triglycerides and small dense low density lipoprotein ^[19]. Moreover, low carbohydrate diet can reduce inflammation, blood pressure, and fasting blood glucose and enhance insulin sensitivity. These clinical and laboratory results indicate that fructose overconsumption plays a vital role in the pathogenesis of MetS and drives the chronic inflammation that promotes CVDs.

2. Therapeutic Strategies for Fructose-Mediated Inflammation

The targeting of inflammation can potentially reduce the risk of cardiac arrhythmia, and the blocking of gut microbiota-mediated inflammation by reducing fructose intake, inhibiting inflammation signaling, and administering probiotics and dietary short-chain fatty acids (SCFAs) may reduce the risk of CVDs. These approaches can ground novel therapies that target inflammation-associated cardiac arrhythmias and atrial fibrillation (AF).

2.1. Dietary Interventions

Low carbohydrate diet can help people with diabetes better manage their blood sugar levels and body weight ^[20]. In addition, low carbohydrate diet was shown to substantially and sustainably reduced blood pressure and body weight with marked improvement in lipid profiles of type 2 diabetes patients ^[21]. McKenzie et al., showed that adequate carbohydrate restriction to achieve nutritional ketosis in adults with type 2 diabetes for 10 weeks can be effective in improving glycemic control and weight loss with decreasing medication use ^[22]. A Mediterranean diet (Med-diet) can beneficially influence the

gut microbiota and related metabolome. Significant associations were found between the intake of vegetable-based diets and advantageous microbiome-correlated metabolomic profiles [23]. Conversely, higher urinary TMAO levels were found in individuals with a lower adherence to the Med-diet [23]. The Med-diet supplementation may also reduce the risk of AF, including reductions in systemic oxidative stress [24][25]. Higher fiber intake reduced inflammation and lowered the risks of major adverse cardiovascular events in end-stage kidney disease patients receiving dialysis [26]. These clinical results suggest that lowering sugar consumption, eating a balanced diet, and increasing vegetable intake help people maintain good health, reduce high-fructose-mediated cardiac inflammation, and lower CVD risk.

2.2. Probiotics for Controlling Cardiac Inflammation

As indicated in **Table 1**, an increasing amount of evidence has demonstrated that probiotics benefit the cardiovascular system. Clinical trials have revealed that when compared with a placebo, probiotic consumption reduced blood pressure, total cholesterol, and triglyceride levels in patients with type 2 diabetes [27]. Additionally, the administration of the probiotic *Lactobacillus (L.) rhamnosus* GR-1 attenuated postinfarction remodeling and heart failure (HF) in rats through its immunomodulatory activity in the gut [28]. Moreover, the co-supplementation of Vitamin D and a probiotic (containing *Bifidobacterium bifidum*, *L. acidophilus*, *L. reuteri*, and *L. fermentum*) for 12 weeks in patients with diabetes with coronary heart disease improved their mental health, serum high-sensitivity C-reactive protein levels, plasma NO levels, total antioxidant capacity, glycemic control, and HDL-cholesterol levels [29]. In a rat model, probiotics (containing *Bifidobacterium (B.) breve*, *L. casei*, *L. bulgaricus*, and *L. acidophilus*) exhibited a cardioprotective effect on infarct-like myocardial injury by suppressing oxidative stress damage and TNF- α [30]. In another study on rats, probiotic treatment (*L. plantarum* KY1032 and *L. curvatus* HY7601) lowered the levels of plasma glucose, insulin, triglyceride, and oxidative stress that had been induced by a high-fructose diet [31].

Table 1. Therapeutic effects of probiotics on cardiovascular diseases.

Probiotics	Protocol	Outcomes	References
<i>L. rhamnosus</i> GR-1	Coronary artery ligation rats fed rGR-1 (10^9 CFU/g, daily) in drinking water for 6 weeks.	Reduced cardiac hypertrophy and LV dysfunction.	[28]
<i>L. acidophilus</i> , <i>Bifidobacterium bifidum</i> , <i>L. reuteri</i> , <i>L. fermentum</i>	Patients with diabetic and coronary heart disease received vitamin D (50,000 IU) plus probiotics (8×10^9 CFU, every 2 weeks) for 12 weeks.	Reduced inflammation and increased antioxidant capacity, nitric oxide, glycemic control, and high-density lipoprotein.	[29]
<i>B. breve</i> , <i>L. casei</i> , <i>L. bulgaricus</i> <i>L. acidophilus</i>	Rats fed probiotics (2×10^6 CFU/mL, daily) for 2 weeks in response to isoproterenol-induced myocardial injury.	Reduced oxidative stress and inflammation and increased cardiac function.	[30]
<i>L. curvatus</i> HY7601, <i>L. plantarum</i> KY1032	Rats fed a high-fructose diet (70% w/w) for 3 weeks followed by a probiotic (10^9 – 10^{10} CFU, daily) for 3 weeks.	Reduced oxidative stress, insulin resistance, and levels of plasma glucose and triglycerides.	[31]
<i>L. rhamnosus</i> LS-8, <i>L. crustorum</i> MN047	Mice fed a high-fructose high fat diet (45% kcal fat, 10% w/v fructose) and a probiotic (10^9 CFU, daily) for 10 weeks.	Reduced insulin resistance and inflammation.	[32]
<i>L. kefir</i>	Mice fed fructose (20% w/v) and a probiotic (10^8 CFU, every 2 days) for 6 weeks.	Reduced adipose tissue expansion, plasma triglyceride and leptin levels, and inflammation.	[33]

L.rhamnosus GR-1, *Lactobacillus rhamnosus* GR-1; *B. breve*, *Bifidobacterium breve*; LV, left ventricular; CFU, colony-forming units; IU, international units.

2.3. Effects of SCFAs on Controlling Inflammation

SCFAs are the ligands for G protein-coupled receptors (GPCRs), which contain GPR43, GPR41, and GPR109A, that trigger anti-inflammatory signaling cascades [34]. SCFAs also modulate immune responses, partially by affecting gene expressions and the epigenome through the inhibition of histone deacetylases (HDAC) [35][36]. SCFAs are saturated aliphatic organic acids that comprise one to six carbon atoms, of which propionate, acetate, and butyrate are the most abundant and are produced by anaerobic fermentation of dietary fiber in the gut [37]. Firmicutes (gram-positive) and Bacteroidetes (gram-negative) are the most abundant phyla in the intestines, with members of Firmicutes mainly producing butyrate, whereas acetate and propionate are the primary metabolic end products of members of Bacteroidetes [38]. SCFA butyrate protects intestinal epithelial cells and stabilizes hypoxia-induced factors and, thus, attenuates local and

systemic inflammation [39]. Dietary-derived butyrate inhibits innate lymphoid cells and subsequently reduces lung inflammation, airway hyperreactivity, and eosinophilia in an allergic asthma murine model [40]. SCFAs can reduce impairments of the intestinal epithelial barrier due to their protection against high-fructose-diet-induced neuroinflammation [41]. Clinical studies have revealed that daily oral supplementation of 10^{10} of *Akkermansia muciniphila* bacteria (live or pasteurized) can improve insulin sensitivity and reduce insulinemia and plasma total cholesterol in overweight or obese insulin-resistant volunteers relative to a placebo. After 3 months of supplementation, *Akkermansia muciniphila* reduced the levels of the relevant blood markers for liver dysfunction and inflammation [42]. The butyrate–GPR109A axis inhibited LPS-induced NF- κ B activation in colonic cell lines and in the colon of mice [43]. SCFAs, as an HDAC inhibitor, can protect the intestinal barrier from disruption by inhibiting the LPS–NLRP3 inflammasome axis [44]. Acetate diminishes NLRP3 inflammasome activation through GPR43 and Ca^{2+} -dependent mechanisms, which underscores the mechanism of metabolite-attenuated NLRP3 inflammasome activity that mitigates CVD development [45]. As illustrated in **Figure 1**, SCFA treatment can inhibit NF- κ B/NLRP3 signaling, which may prevent inflammation-associated heart arrhythmia.

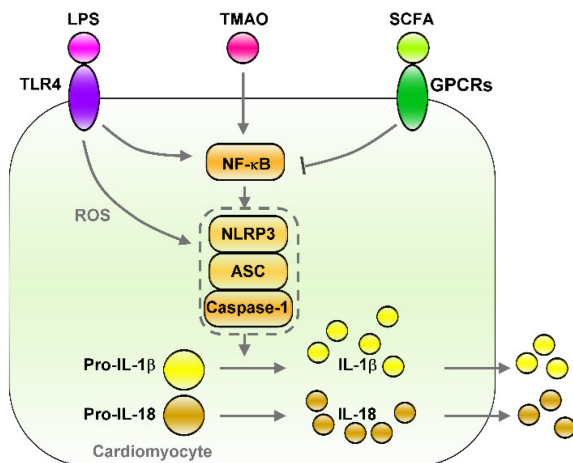


Figure 1. Effects of gut microbiota-derived endotoxin and

metabolites on the regulation of NF- κ B/NLRP3 inflammasome signaling. Gut microbiota-derived endotoxin or metabolite signaling (such as LPS/TLR4, TMAO, and SCFA/GPCRs) that altered down-stream NF- κ B/NLRP3 inflammasome signaling and their effects on cardiac physiology. LPS/TLR4 and TMAO activates NF- κ B/NLRP3 axis and induces secretion of IL-1 β /IL-18. However, SCFA/GPCRs signaling inhibit NF- κ B/NLRP3 signaling. LPS: lipopolysaccharide, TLR4: toll-like receptor 4, TMAO: trimethylamine-N-oxide, SCFA: short-chain fatty acid, GPCRs: G-protein coupled receptors, ROS: Reactive oxygen species, NLRP3: NLR family pyrin domain containing 3, ASC: apoptosis-associated speck-like protein containing a caspase recruitment domain, Pro-IL-1 β : Pro-form interleukin 1 beta, Pro-IL-18: pro form interleukin 18, IL-1 β : interleukin 1 beta, IL-18: interleukin 18.

2.4. HDACs' Inhibition of Cardiac Inflammation

SCFA exerts its beneficial effects by inhibiting inflammation through the activation of GPR41/43 signaling and reduction in HDAC levels [46]. HDACs play key roles in the progression of CVDs and contribute to AF generation [47]. Inhibition HDACs was recommended as a novel therapeutic strategy for cardiac arrhythmia and AF [47][48]. HDAC11 was significantly overexpressed in both human and mouse diabetic HF hearts [49]. Knockout of HDAC11 improved dyslipidemia and reduced inflammation in the heart of mice fed with fructose when compared with controls [49]. The HDAC inhibitor (HDACi) recovers cardiac function by reducing the expression of inflammatory cytokines and by ameliorating inflammatory cell infiltration in the heart [50]. Our previous laboratory results indicated that HDACi (MPT0E014 or MS-275) treatments ameliorated TNF- α -induced mitochondrial dysfunction with increased mitochondrial superoxide production and decreased ATP synthesis in atrial cardiomyocytes [51]. MPT0E014-treated pulmonary vein cardiomyocytes had reduced calcium transient amplitudes, sodium-calcium exchanger currents, and the expression of ryanodine receptor [52]. Additionally, MPT0E014-treated rabbits had less AF and shorter AF duration in AF-rabbit model (with rapid atrial pacing and acetylcholine infusion) rabbit model than controls [52]. Moreover, MS-275 ameliorated hyperglycemia, insulin resistance, TNF- α expression, and stress signaling in skeletal muscle in high fat high fructose-fed mice [53]. Therefore, HDACi treatment is a potential strategy for suppressing cardiac arrhythmogenesis.

3. Conclusions and Future Perspectives

The heart–gut axis is a potential target for cardiovascular therapy. High-fructose diets can induce inflammation and metabolic disorders in the heart–gut axis due to cardiac arrhythmogenesis (**Figure 2**). Excessive fructose intake causes dysbiosis of the microbiota, which leads to increased gut barrier permeability, inflammation, progression of metabolic disease, and IR. Reducing sugar consumption and consuming dietary fiber, a Med-diet, probiotics, and SCFAs and

receiving HDACi treatment can decrease high-fructose-diet-induced chronic inflammation. The targeting of excessive fructose intake-associated inflammation in the heart–gut axis can prevent cardiac arrhythmia. However, in general, studies have not determined: (1) the specific microbiota strains that can inhibit excessive fructose intake–induced heart disease; (2) how to maintain a healthy diet that avoids TMAO accumulation in the human body and how to prevent TMAO-mediated CVDs; or (3) how the SCFAs and HDACi regulate signaling that may exert an anti-inflammatory activity in the heart. Future investigations should focus on how one can maintain a balanced diet to keep their gut microbiota homeostasis and avoid systematic inflammation. Microbial population and microbiota biofunction analysis can help researchers explore the effects of probiotics on the heart–gut axis; such effects can ground promising strategies for maintaining gut microbiome homeostasis in particular and cardiac health in general. Although TMAO is a risk factor for CVD progression, TMAO mechanisms mediated CVDs, and therapeutic strategies to inhibit TMAO signaling should be explored for CVD interventions. Moreover, animal studies and clinical trials are required to analyze whether interventions that target microbiota homeostasis, inhibit TMAO signaling, or activate SCFA regulated pathways can reduce the likelihood of adverse cardiac events and prevent cardiac arrhythmogenesis. Thus, targeting the heart–gut axis may reduce the occurrence or severity of cardiac pathogenesis mediated by excess fructose consumption.

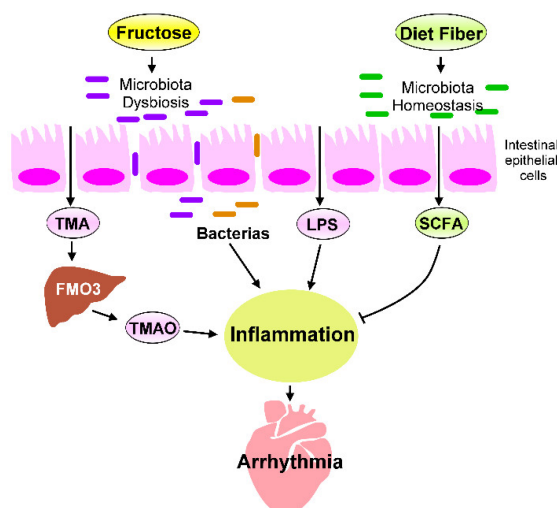


Figure 2. Fructose-mediated heart–gut axis disorder that promotes

inflammation and cardiac arrhythmogenesis. Dietary components, such as fructose or dietary fiber, serve as crucial environmental factors that influence the homeostasis of gut microbiota and alter gut microbiota-derived metabolites. Excessive fructose intake promotes microbiota dysbiosis, which increases the production of trimethylamine (TMA), which is then converted into trimethylamine-N-oxide (TMAO) by the flavin-containing monooxygenase 3 (FMO3) expressed in the liver. SCFAs are generated through the fermentation of dietary fibers by gut microbiota. SCFAs are crucial players in regulating the beneficial effect of dietary fibers. The microbiota endotoxin and metabolites, such as lipopolysaccharide (LPS), TMAO, and SCFAs, mechanistically regulate the chronic inflammation that affects cardiac rhythm. Targeting inflammation caused by imbalanced intestinal flora may prevent cardiac arrhythmogenesis.

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