Impact Driven by Sugars on Mental Illness: Exhaustive Research on the Composition of Sugar Types and Influences on Mental Health

Shuocheng Zhu

Shanghai Concord Bilingual School, Shanghai, China

Zhushuochengapp@163.com

Abstract. Nowadays, dietary sugars are appearing in processed foods more often. An increase in damages that result in neurological health beyond their established metabolic effects. This review comprehensively analyzes the mechanisms by which two distinct sugars, fructose and D-galactose, lead to neurotoxicity and associated diseases. Fructose achieves this through its unique metabolism, inducing a cerebral energy crisis resulting from a lack of ATP, which promotes the formation of fructose-derived advanced glycation end-products (Fru-AGEs). To this end, it leads to mitochondrial dysfunction, neuroinflammation, and synaptic impairment. In parallel, D-galactose acts as an oxidative stressor that hyperactivates the JNK signaling pathway, which, in turn, triggers neuroinflammation, apoptotic cascades, and cognitive decline. The comparative analysis presented shows that although fructose and D-galactose cause neurotoxicity via divergent primary insults, they ultimately yield similar results. This research clarifies the link between dietary sugars and brain health, and analyzes mechanisms that aim to showcase the process by which these sugars result in similar damage.

Keywords: Dietary; Neurotoxicity; Fructose; D-galactose; Mitochondrial.

1. Introduction

The modern diet has undergone a significant transformation over the past half-century, characterized by a dramatic increase in the addition of refined sugars to processed foods. Among these, fructose consumption has increased dramatically since 1979. Many standard soft drinks and products that require a sweet taste often contain fructose as an ingredient (Taskinen et al., 2019). While the metabolic consequences of excessive sugar consumption, such as obesity and diabetes, are well-documented, their possible impact on the central nervous system and contribution to neuron-related diseases represent an area that is worth researching. In addition to fructose, another dietary sugar, D-galactose, has also been implicated in potential neurological impairment.

This review analyzes current evidence on the neurotoxic pathways induced by two distinct sugars: fructose and D-galactose. It will also showcase how they influence normal brain function through different pathways. It will explore the unique metabolic fate of fructose, which disrupts the brain's energy supply and promotes the formation of toxic advanced glycation end-products (Fru-AGEs) (Monar et al., 2025). In parallel, it will examine how D-galactose instigates a cascade of oxidative stress and neuroinflammation, primarily through the hyperactivation of the JNK signaling pathway (Ahmad et al., 2021; Ullah et al., 2020). Ultimately, this analysis aims to illustrate these divergent initial insults, energy crisis, and oxidative stress, thereby illustrating the link between dietary sugar intake and neuron-related diseases.

2. Fructose

Within the past few decades, the amount of fructose added to processed food for sweetness has increased critically, reaching a level about 50% higher than 5 decades ago (Barrett et al., 2022). ‘Especially since the food industry introduced high fructose corn syrup to various foods in the 1960s’ (Andersen et al., 2023).

2.1 Adenosine Triphosphate (ATP) and Mitochondria

Fructose has a unique metabolism process. Specifically, it is the phosphofructokinase 1 (PFK-1) feedback inhibition, which allows the fat storage of a person to rise significantly (Monar et al., 2025). ‘The small intestine initially helps metabolize ingested fructose, shielding the liver and brain from excessive exposure.’ (Monar et al., 2025) However, consuming fructose in excessive amounts leads to metabolic disorders related to functions such as insulin production and fat storage (Monar et al., 2025). The hormone and neurons in our body are activated or inhibited by various signals, including the level of lipids. Once the lipid level becomes too high, leptin levels are observed in the circulation. Leptin is a peptide hormone regulating food intake, body mass, etc. (Obradovic et al., 2021). ‘Additionally, leptin exerts an anorexigenic effect, which lowers the willingness to eat, and reduces food intake by increasing the POMC/CART neurons, which reduce appetite, and inhibiting the NPY/AgRP neurons, which promote hunger (Monar et al., 2025).’ Insulin also plays a crucial role in regulating food intake. As the insulin level increases, it will also exert anorexigenic effects as food is consumed. To that end, the food consumed is reduced, and a feeling of energy deficit will also occur, resulting in a decrease in adenosine triphosphate (ATP) production.

The energy supply for the brain's neuron-related functions is highly reliant on sources such as mitochondria and aerobic oxidative phosphorylation, indicating the importance of energy (ATP) for the brain to function correctly (Monar et al., 2025). The extracellular ATP is one of those that plays an essential role in regulating quite a lot of neuronal functions in our brain (Shigetomi et al., 2024). As a reduction in ATP occurs, the condensation of axoterminal cytosol, synaptic vesicles, and active zone components affects synapse function. Proteins involved in the pathogenesis of Parkinson’s disease (PD), Alzheimer’s disease (AD), and amyotrophic lateral sclerosis (ALS) condensed and underwent ATP-dependent liquid phase separation in vitro.’ (Guillaud et al., 2025)

2.2 AGEs and Mitochondrial Deficiency

Accordingly, fructose will result in the accumulation of more advanced glycation end-products (AGEs), specifically Fru-AGEs, in hippocampal neurons. ‘It triggers NF-κB signaling and induces mitochondrial dysfunction, reactive gliosis, and neuronal impairment—hallmarks of early neurodegenerative processes (Monar et al., 2025).’ As mentioned in the research (Sharma et al., 2021), with the increase of mitochondrial dysfunction and amyloid-beta (Aβ), which is produced through the proteolytic processing of a transmembrane protein, amyloid precursor protein (APP), by β- and γ-secretases (Chen et al., 2017), is contributing to an early event in AD pathogenesis.

The deficiency of mitochondrial function resulting from fructose will eventually lead to neurodegeneration through core pathological pathways. The metabolic insult triggers the opening of the mitochondrial permeability transition pore (mPTP), which collapses the membrane potential and leads to osmotic rupture. This breach allows cytochrome c to leak out, activating the apoptotic cascade and disrupting mitochondrial dynamics, which promotes pathological fission. For neurons that are critically dependent on oxidative phosphorylation, this comprehensive mitochondrial compromise constitutes a fundamental mechanism driving the ensuing neuroinflammation and cognitive decline (Norat et al., 2020).

3. D-Galactose

Galactose is another kind of sugar that can actively result in AGEs, which is worth evaluating other possible ways that it may lead to some neuron-related diseases (Haase et al., 2024). The D-isomer of galactose (D-galactose), the naturally occurring form, is associated with neuroinflammation, oligodendrocyte apoptosis, and ultimately, neurodegeneration and cognitive impairment in both aging models and models of neuroinflammatory diseases (Haase et al., 2024; Ahmad et al., 2021).

3.1 Oxidative Stress

As demonstrated in the D-galactose-induced aging model created by Ahmad et al. (2021), chronic exposure to D-galactose triggers a series of neuropathological events. It critically elevates oxidative stress and dampens endogenous antioxidant defenses (SIRT1/Nrf2/HO-1). Additionally, it oxidative burden subsequently activates pro-inflammatory pathways (p-JNK/NF-κB), leading to glial activation (Iba-1/GFAP) and the release of inflammatory cytokines (IL-1β, TNF-α).

3.2 JNK Pathway Activation

The neuropathological process induced by chronic D-galactose exposure is a complex process resulting from sustained oxidative stress, which subsequently orchestrates a network of interlinked signaling pathways. The hyperactivation of the c-Jun N-terminal kinase (JNK) stress pathway is a central component of this pathogenesis. As demonstrated in the paper (Ullah et al., 2020), D-galactose-induced oxidative stress robustly increases the levels of phosphorylated JNK (p-JNK), which transduces oxidative insults into downstream apoptotic and inflammatory events. This is corroborated by interventional evidence, showing that the specific inhibition of JNK signaling, either by the pharmacological inhibitor SP600125 or by the amino acid glycine, is enough to lead to a reduction in D-galactose-induced neuroapoptosis (via Bax/Bcl-2 and caspase-3), neuroinflammation (via GFAP, Iba-1, IL-1β, and TNF-α), synaptic dysfunction, and cognitive deficits (Ullah et al., 2020).

3.3 Synaptic Dysfunction

These processes will result in synaptic protein loss, neuronal apoptosis, and significant cognitive deficits, effectively recapitulating hallmarks of neurological disorders. The role of NF-κB in this context is nuanced and context-dependent. In contrast, it can exhibit antioxidant and anti-apoptotic properties under certain conditions by suppressing JNK activation and upregulating genes such as MnSOD. Some evidence suggests that in the D-galactose model, its role may be replaced by the predominant JNK-driven pathology. In fact, in other disease contexts, such as diabetic cardiomyopathy, NF-κB activation has been shown to promote ferroptosis and inflammation unequivocally (Wu et al., 2024), highlighting that its functional output is not intrinsic but rather determined by the cellular environment and the nature of the stressor. Therefore, within the D-galactose-induced aging model, the net neurotoxic effect is mainly mediated through the JNK-centric activation of apoptotic, inflammatory, and synaptic toxicities. This evaluation of JNK as a pivotal core pathway clarifies the mechanistic underpinnings of D-galactose neurotoxicity, positioning it as a promising and rational therapeutic target for intervening in the associated neurodegenerative processes.

4. Comparative Analysis

While fructose and D-galactose are distinct dietary sugars, analyzing how these two kinds of sugar may lead to similar results in neuron-related diseases via totally different pathways and mechanisms seems critical. This process aims to understand how different metabolic insults can ultimately lead to the same outcomes.

The two sugars have different effects on the brain. Fructose causes an energy problem, resulting in a lack of ATP in the cells. It's special metabolism bypasses a key control point (PFK-1), which leads to more fat being stored in the body (Monar et al., 2025). This problem leads to a lack of energy in the brain, preventing it from functioning normally. As a result, an essential part of fructose toxicity is that it produces Fru-AGEs, which accumulate in brain cells and lead to mitochondrial dysfunction that can be regarded as poisonous to the brain (Monar et al., 2025).

On the other hand, D-galactose does not start by causing an energy shortage. Instead, it causes a problem with cell signals that begins with oxidative stress. When the body processes it, a large amount of ROS (reactive oxygen species) is produced (Ahmad et al., 2021). This ROS acts as a powerful signal that over-activates stress pathways in the cell. The most important of these is the JNK pathway. When JNK becomes activated (p-JNK), it functions as a central control point, converting the oxidative stress signal into harmful downstream events, which is similar to inflammation and can severely result in cell death (Ullah et al., 2020).

4.1 Mitochondria Problems

Both sugars critically damage the mitochondria's functions. Fructose, through energy deficiency and Fru-AGEs, causes the mitochondrial permeability transition pore (mPTP) to open, releasing cytochrome c and resulting in cell death (Norat et al., 2020). D-galactose, which induces severe oxidative stress, directly damages mitochondria and triggers the activation of the JNK pathway. This leads to the mitochondrial membrane mPTP opening, causing the release of cytochrome c and the activation of the apoptotic cascade, ultimately resulting in neuronal cell death (Ahmad et al., 2021; Ullah et al., 2020).

4.2 Brain Inflammation

Both sugars cause strong brain inflammation. Fructose primarily achieves this through the accumulation of Fru-AGEs, which activate the NF-κB signaling pathway and induce inflammatory cytokines (Monar et al., 2025). D-galactose does this by using its JNK/NF-κB pathway, which also makes inflammation molecules and activates glial cells in the brain (microglia and astrocytes) (Ahmad et al., 2021; Ullah et al., 2020).

4.3 Synapse and Memory Damage

Both fructose and D-galactose ultimately lead to significant damage in synaptic integrity and cognitive function, with different mechanisms each. In fructose, the reduction in ATP availability disrupts synaptic vesicle cycling and the maintenance of the energy-dependent processes that are responsible for learning and memory storage. The accumulation of Fru-AGEs further increased dysfunction by promoting oxidative stress and inflammatory signaling within hippocampal neurons (Monar et al., 2025). Similarly, D-galactose-induced oxidative stress and JNK hyperactivation, disrupting synaptic plasticity and eroding structural and functional foundations of memory (Ullah et al., 2020).

In summary, fructose and D-galactose harm the brain from different angles. Fructose will result in a metabolism disrupt that causes problems related to energy and makes toxic proteins. D-galactose will result in oxidative stress that causes problems related to harmful signals. The fact that both these different attacks lead to mitochondria failure, inflammation, and synapse loss gives us a clear picture of how they can contribute to brain diseases.

5. Conclusion

The evidence synthesized in this review demonstrates that excessive dietary intake of specific sugars, namely fructose and D-galactose, will lead to significant and independent risk factor for the pathogenesis of neuron-related diseases through distinct yet severely damage the neurotoxic pathways.

Fructose, primarily resulting in a brain energy crisis, disrupts its unique metabolism. This energy deficit, compounded by forming Fru-AGEs, triggers mitochondrial dysfunction, NF-κB-mediated neuroinflammation, and ultimately, synaptic failure and neuronal impairment. It eventually creates an environment based on those, making it easy to damage neurons (Monar et al., 2025; Norat et al., 2020). What fructose does to damage is mainly due to ATP. It restricts its production so that the brain can function normally.

In parallel, D-galactose initiates a cascade of oxidative stress, overwhelming endogenous antioxidant defenses (SIRT1/Nrf2/HO-1). This primary upstream signal activates the JNK pathway (p-JNK). This pathway plays a critical role, leading to neuroinflammation, synaptic dysfunction, and neuronal apoptosis, ultimately resulting in cognitive impairment. (Ahmad et al., 2021; Ullah et al., 2020). What D-galactose do to damage is mainly about inflammation, which causes cells to die.

These two sugars converge on a common pathological endpoint: mitochondrial failure. Despite their different entry points, energy depletion for fructose and oxidative stress for galactose precipitate the opening of the mitochondrial permeability transition pore (mPTP), the release of cytochrome c, and the activation of apoptotic cascades. This common mechanism of mitochondrial collapse highlights the organelle's critical role in glucose-induced neurotoxicity and establishes it as a key therapeutic target.

From a public health perspective, these findings sound a clear alarm regarding the neurological consequences of the modern high-sugar diet. With the widespread addition of fructose to food products and the potential neurotoxicity of galactose, reducing dietary sugar should be regarded as crucial for metabolic health and an essential part of preventing neurological disorders.

Future research should focus on several key areas: first, illustrating the potential synergistic effects of combined sugar exposures; second, further exploring the efficacy of targeting shared pathways, such as mitochondrial dysfunction, or specific pathways, like JNK inhibition, as therapeutic strategies; and third, determining whether some strategy can be developed to act upon them.

As a result, this review illustrates fructose and galactose. Although chemically distinct, they are both potent in causing neuron-related diseases. They also exemplify the principle that divergent metabolic insults can converge on common mechanisms of brain dysfunction, with two different pathways affecting them.

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