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Review Article

Chronic Nutritional Stress and Transgenerational Epigenetic Remodelling of Glial Pathways Linking Metabolic Risk and Brain Health

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Abstract

Chronic nutritional stress, characterized by sustained consumption of energy-dense yet micronutrient-deficient diets, has emerged as a pervasive environmental determinant of metabolic dysfunction and neurological vulnerability. Beyond classical metabolic and vascular mechanisms, accumulating evidence identifies epigenetic regulation as a central molecular pathway through which long-term dietary exposures exert persistent effects on brain structure and function. Epigenetic processes including DNA methylation, histone post-translational modifications, and non-coding RNA-mediated regulation enable stable yet reversible modulation of gene expression in response to nutritional signals. Within the central nervous system, glial cells, particularly astrocytes and microglia, act as metabolic sensors and immune regulators and exhibit pronounced sensitivity to nutritionally induced epigenetic remodeling. Dysregulation of glial epigenetic programs promotes sustained neuroinflammation, impaired metabolic support of neurons, and increased susceptibility to cognitive decline and neurodegenerative disease. Importantly, epigenetic alterations established during critical developmental windows may persist throughout the lifespan and, in certain contexts, be transmitted across generations, thereby linking ancestral nutritional environments to inherited metabolic and neurological risk. This review critically synthesizes current evidence on chronic nutritional stress-induced epigenetic regulation of glial pathways, integrates findings within the Developmental Origins of Health and Disease framework, examines emerging data on transgenerational inheritance, and discusses therapeutic and preventive strategies targeting nutriepigenetic mechanisms to preserve brain health.

Keywords: Chronic nutritional stress, Epigenetic regulation, Glial cells, Astrocytes, Microglia, Metabolic dysfunction, Brain health, Transgenerational inheritance, Neuroinflammation, Nutriepigenomics

Introduction

Nutrition represents one of the most influential environmental determinants of human health, shaping metabolic regulation, immune function, and brain development across the lifespan. While early nutritional research primarily focused on acute deficiencies and their overt neurological consequences, modern dietary environments are increasingly characterized by chronic nutritional stress defined as prolonged exposure to calorically excessive, highly processed, and micronutrient-poor diets. Such dietary patterns are strongly associated with obesity, insulin resistance, and metabolic syndrome and have been consistently linked to accelerated cognitive decline, mood disorders, and increased risk of neurodegenerative disease [14, Yates et al., 2012].

The neurological consequences of chronic nutritional stress cannot be fully explained by systemic metabolic dysfunction alone. Growing evidence indicates that long-term dietary exposures become biologically embedded through epigenetic mechanisms that alter gene expression profiles in a persistent manner [1]. Epigenetic regulation provides a molecular framework through which environmental factors interact with the genome to shape cellular function without altering DNA sequence. In the brain, epigenetic processes are essential for cellular differentiation, synaptic plasticity, and adaptive responses to environmental stressors.

Glial cells have emerged as central mediators of nutritionally induced epigenetic effects. Astrocytes and microglia regulate cerebral energy metabolism, maintain synaptic homeostasis, and orchestrate innate immune responses within the central nervous

system. Chronic nutritional stress disrupts these functions by inducing epigenetic remodeling of glial gene networks, promoting neuroinflammatory states and compromising neuronal resilience [17]. Moreover, evidence from developmental and transgenerational studies suggests that epigenetic programming induced by nutritional stress during sensitive periods may persist across the lifespan and, in some cases, across generations, thereby extending the impact of dietary environments beyond directly exposed individuals [2,18].

Epigenetic Mechanisms Underlying Nutritional Programming

Epigenetics encompasses a dynamic set of molecular mechanisms that regulate chromatin structure and gene expression in response to environmental cues. The principal epigenetic mechanisms DNA methylation, histone post-translational modifications, and non-coding RNA–mediated regulation are highly sensitive to nutritional inputs, positioning epigenetics as a key biological interface between diet and long-term health outcomes [1].

DNA Methylation

DNA methylation involves the covalent addition of a methyl group to cytosine residues, predominantly at CpG dinucleotides, and plays a fundamental role in transcriptional regulation and cellular identity. Nutrients involved in one-carbon metabolism, including folate, methionine, choline, and vitamin B12, directly influence methyl group availability and DNA methyltransferase activity [Waterland & Michels, 2007]. Chronic nutritional stress disrupts these pathways, leading to aberrant methylation patterns in genes governing metabolic homeostasis, inflammatory signaling, and neural plasticity.

Importantly, DNA methylation patterns established during early development exhibit long-term stability, rendering them particularly relevant to disease susceptibility later in life. Nutritional imbalance during prenatal and early postnatal periods has been shown to induce persistent epigenetic alterations that influence metabolic and neurological outcomes well into adulthood [13].

Histone Modifications

Histone proteins undergo a diverse array of post-translational modifications, including acetylation, methylation, phosphorylation, and ubiquitination, which collectively regulate chromatin accessibility and transcriptional activity. Nutrient-derived metabolites such as acetyl-CoA and S-adenosylmethionine serve as essential cofactors for histone-modifying enzymes, thereby coupling cellular metabolic state to epigenetic regulation [Mathers, 2017].

Under conditions of chronic nutritional stress, histone modification profiles shift toward transcriptional programs that favor inflammation and metabolic dysregulation. In the brain, such changes contribute to sustained activation of neuroimmune pathways and impaired synaptic plasticity, reinforcing the link between diet, epigenetic regulation, and cognitive decline [17].

Non-coding RNAs

Non-coding RNAs, including microRNAs and long non-coding RNAs, represent an additional regulatory layer through which nutrition influences gene expression. These molecules modulate mRNA stability, translation, and chromatin organization and are increasingly recognized as mediators of metabolic and neuroinflammatory signaling [16]. Dietary patterns have been shown to alter non-coding RNA expression profiles, thereby contributing to epigenetic regulation of glial and neuronal function.

Glial Cells as Central Mediators of Nutritional Epigenetic Effects

Astrocytes: Metabolic Integrators and Epigenetic Integrators

Astrocytes play a central role in cerebral energy metabolism, neurotransmitter recycling, and maintenance of the blood-brain barrier. They respond dynamically to metabolic cues by regulating glucose uptake, lactate production, and antioxidant defenses. Chronic nutritional stress induces a shift toward reactive astrocyte phenotypes characterized by enhanced inflammatory signaling and diminished metabolic support for neurons [19].

Epigenetic remodeling underlies many of these astrocytic changes. Altered DNA methylation and histone acetylation regulate genes involved in lipid metabolism, oxidative stress responses, and cytokine production [17]. Persistent astrocytic dysfunction compromises synaptic homeostasis and increases neuronal vulnerability, providing a mechanistic link between metabolic stress and cognitive impairment.

Microglia: Epigenetic Programming of Neuroimmune Responses

Microglia serve as the resident immune cells of the central nervous system and are essential for synaptic pruning, immune surveillance, and tissue repair. Their phenotypic states are governed by epigenetic mechanisms that integrate environmental signals, including nutrient availability and metabolic stress [15].

Chronic exposure to high-fat or high-sugar diets induces durable epigenetic reprogramming of microglial chromatin, favoring pro-inflammatory transcriptional profiles and impairing phagocytic capacity [20,6]. Epigenetically primed microglia exhibit exaggerated inflammatory responses to secondary insults, contributing to accelerated brain aging and increased susceptibility to neurodegenerative disease.

Developmental Origins of Health and Disease and Epigenetic Programming

The Developmental Origins of Health and Disease (DOHaD) framework posits that environmental exposures during critical developmental periods permanently shape physiological systems via epigenetic mechanisms (Barker, 2007, Gluckman et al., 2008). During prenatal and early postnatal development, epigenetic

landscapes are highly plastic, allowing nutritional signals to exert long-lasting effects on gene regulation in glial progenitors and neurons [21].

Nutritional stress during these sensitive windows has been associated with increased risk of obesity, insulin resistance, cognitive deficits, and mood disorders in later life. Epigenetic modifications established during development may persist as a form of biological memory, linking early nutritional environments to lifelong brain health trajectories.

Transgenerational Epigenetic Inheritance

Evidence from animal models demonstrates that epigenetic modifications induced by nutritional stress can be transmitted across generations via germline epigenetic marks or early embryonic programming (Skinner, 2014). Offspring of nutritionally stressed parents display altered metabolic phenotypes and neurobehavioral outcomes even in the absence of direct dietary exposure [3].

Human evidence remains more limited but is supported by historical cohort studies, including famine exposure models, which reveal persistent epigenetic differences and increased metabolic and cognitive risk in subsequent generations [10]. These findings underscore the potential societal implications of widespread chronic nutritional stress.

Gut-Brain Axis and Nutritional Epigenetics

The gut microbiome constitutes a critical mediator of diet–brain interactions. Microbial metabolites, particularly short-chain fatty acids, influence histone acetylation and DNA methylation in glial cells, thereby modulating neuroinflammatory and metabolic pathways [5]. Chronic nutritional stress disrupts microbial diversity and metabolite production, amplifying maladaptive epigenetic signaling within astrocytes and microglia and exacerbating neuroinflammation [4] (Figure 1).

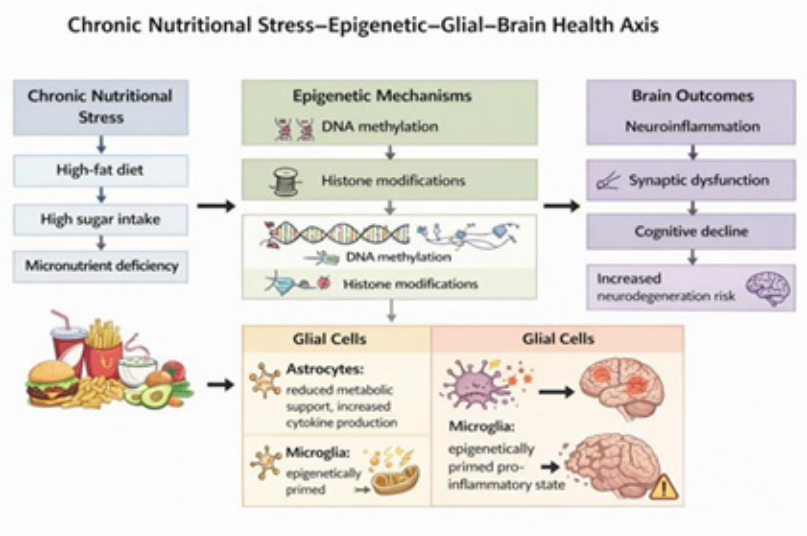

Figure 1: Chronic Nutritional Stress-Epigenetic-Glial-Brain Health Axis. Schematic representation of the mechanistic links between chronic nutritional stress and brain health. Sustained dietary imbalance induces epigenetic remodeling via DNA methylation, histone modifications, and non-coding RNA regulation, leading to dysregulated astrocytic metabolism and microglial inflammatory priming. These alterations promote persistent neuroinflammation, synaptic dysfunction, and increased vulnerability to cognitive decline.

Metabolic Risk, Cognitive Decline, and Epigenetic Links

Metabolic syndrome is strongly associated with increased risk of cognitive decline and dementia. Epigenetic dysregulation provides a mechanistic bridge linking systemic metabolic stress to impaired brain function. Chronic nutritional stress induces epigenetic changes in glial and neuronal genes involved in oxidative stress, inflammation, and synaptic plasticity, contributing to accelerated brain aging [14].

Conversely, diets rich in polyphenols, omega-3 fatty acids, and dietary fiber are associated with protective epigenetic profiles, reduced neuroinflammation, and improved cognitive outcomes [Vauzour et al., 2017].

Therapeutic and Preventive Implications

Understanding nutritionally induced epigenetic remodeling opens novel avenues for prevention and intervention. Nutritional strategies targeting sensitive developmental windows may prevent maladaptive epigenetic programming, while dietary modification in adulthood may partially reverse epigenetic dysregulation [Mathers, 2017]. Pharmacological modulation of epigenetic enzymes, including histone deacetylases and sirtuins, represents an emerging therapeutic approach to attenuate neuroinflammation and enhance cognitive resilience [11].

Conclusion

Chronic nutritional stress exerts profound and lasting effects on brain health through epigenetic remodeling of glial pathways.

Astrocytes and microglia act as central mediators linking systemic metabolic stress to neuroinflammation and neuronal dysfunction. Epigenetic programming initiated during early development may persist throughout life and, in some cases, across generations, extending the impact of nutritional environments beyond directly exposed individuals. Integrating nutritional science with epigenetic and glial biology provides a robust framework for developing preventive and therapeutic strategies aimed at mitigating the long-term neurological consequences of chronic nutritional stress.

Author Contributions

A.R. conceptualized the review, conducted literature analysis, and wrote the manuscript.

Conflict of Interest

The author declares no conflict of interest.

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Ethics Statement

Not applicable, as this study is a narrative review and does not involve human or animal subjects.

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