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Research Article

DETECTION AND CLASSIFICATION OF CHEMOKINE RECEPTOR–POSITIVE IMMUNE CELLS

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ABSTRACT

Diabetes mellitus is strongly associated with cognitive dysfunction through complex metabolic, neuronal, and inflammatory pathways. This study investigates alterations in cognitive pathway genes using a combined in vivo diabetic model, RT-qPCR analysis, and bioinformatics validation. Streptozotocin (STZ)-induced diabetic rats were evaluated for glucose levels, behavioral impairment, and hippocampal gene expression. A panel of cognitive-related pathway genes BDNF, CREB1, SYN1, IGF-1, TNF-α, IL-6, and GLUT1 was assessed. Experimental findings demonstrated significant downregulation of neurotrophic and synaptic genes (BDNF, CREB1, SYN1) and upregulation of inflammatory mediators (TNF-α, IL-6) in diabetic hippocampal tissue. Bioinformatics analysis using diabetic cognitive datasets confirmed the expression trends and identified enriched pathways including synaptic transmission, neuroinflammation, insulin signaling, and oxidative stress. Together, the findings highlight molecular disruptions associated with diabetes-induced cognitive decline and provide validated gene markers for mechanistic and therapeutic studies.

Keywords: Diabetes, Cognitive dysfunction, BDNF, CREB1, Synaptic genes, Hippocampus.

INTRODUCTION

Diabetes mellitus (DM) is widely recognized not only for its metabolic dysregulation but also for its effects on the nervous system, leading to cognitive decline, memory impairment, and neuronal dysfunction. Chronic hyperglycemia triggers oxidative stress, neuroinflammation, and impaired insulin signaling in the brain, particularly in the hippocampus, which plays a central role in learning and memory (Biessels & Reijmer, 2014). Cognitive dysfunction in diabetes is increasingly linked to alterations in gene networks regulating neuroplasticity, synaptogenesis, neuroinflammation, and glucose transport. Key genes involved in cognitive pathways include BDNF, a major neurotrophin essential for synaptic plasticity; CREB1, a transcription factor involved in memory consolidation; and SYN1, associated with synaptic vesicle formation (Lu et al., 2013). Meanwhile, inflammatory markers such as TNF-α and IL-6, typically elevated in diabetes, are known to impair hippocampal function and contribute to cognitive decline (Pickering et al., 2018). Disruption of insulin-related genes such as IGF-1 further exacerbates neuronal vulnerability.

Current research increasingly integrates experimental data with bioinformatics, enabling the validation of candidate genes across multiple datasets and disease models (Zhao et al., 2020). This study aims to carry out a combined laboratory–computational evaluation of cognitive pathway genes in diabetic models, providing mechanistic insights into neurodegeneration in diabetes. Type 2 diabetes mellitus (T2DM) is consistently associated with accelerated cognitive decline and an increased risk of dementia, including Alzheimer's disease (AD). Large reviews and consensus statements report that individuals with diabetes show deficits in memory, executive function, and

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processing speed, and that diabetes contributes to both vascular and neurodegenerative pathways of cognitive impairment (Biessels & Reijmer, 2014; Srikanth et al., 2020). Clinical and epidemiological data indicate that chronic hyperglycemia, insulin resistance and vascular comorbidity together increase vulnerability of brain networks involved in cognition (Kodl & Seaquist, 2008; Arnold et al., 2018).

Insulin plays important neuromodulatory roles in the brain, affecting synaptic plasticity, neurotransmitter regulation, and energy metabolism. Brain insulin resistance reduced insulin signaling in neuronal and glial cells has been implicated as a mechanistic link between peripheral metabolic disease and cognitive decline (Kleinridders et al., 2014; Duarte et al., 2010). Studies propose that impaired central insulin signaling contributes to decreased neurotrophic support, altered glucose uptake, and synaptic dysfunction, thereby facilitating both metabolic and degenerative changes characteristic of diabetic cognitive impairment (Arnold et al., 2018; Kim & Feldman, 2015).

Chronic hyperglycemia and metabolic stress foster a proinflammatory brain milieu characterized by elevated cytokines such as TNF-α and IL-6. These inflammatory mediators impair synaptic function, reduce neurogenesis, and promote neuronal death (Pickering, Cumiskey, & O'Connor, 2018; Ghosh et al., 2021). Neuroinflammation is frequently observed in diabetic brain tissue and is correlated with cognitive deficits; mechanistically, cytokine signaling activates NF-κB pathways and oxidative cascades that compromise neuronal integrity (Sims-Robinson et al., 2012; Butterfield & Halliwell, 2019).

Diabetes increases production of reactive oxygen species (ROS) and disrupts mitochondrial function in neurons, accelerating synaptic loss and impairing plasticity (Butterfield & Halliwell, 2019; Reddy & Beal, 2008). Oxidative damage to proteins, lipids and DNA in hippocampal circuits undermines memory consolidation and long-term potentiation (LTP). Mitochondrial dysfunction further reduces neuronal energy supply, exacerbating vulnerability to excitotoxic and metabolic insults (Duarte, 2015). Neurotrophic support is central to cognitive resilience. Brain-derived neurotrophic factor (BDNF) and downstream transcription factors such as CREB regulate synaptic plasticity and memory formation. Diabetes and hyperglycemia downregulate BDNF expression and impair CREB signaling, contributing to synaptic dysfunction and cognitive deficits (Lu, Nagappan, & Lu, 2013; Ho, Sommers, & Lucki, 2013). Experimental rodent models and human studies show reduced hippocampal BDNF levels in diabetic conditions, correlating with poorer performance on learning and memory tasks (Biessels & Reijmer, 2014).

Chronic metabolic derangement in diabetes reduces adult hippocampal neurogenesis and dendritic complexity, processes that are essential for learning and memory (Ho et al., 2013; Stranahan & Mattson, 2015). Structural neuroimaging and neuropathological studies report hippocampal atrophy, white-matter lesions and microvascular damage in diabetic cohorts, linking metabolic factors to both neurodegenerative and vascular contributions to cognitive impairment (Biessels & Reijmer, 2014; Duarte, 2015).

Elevated glucose contributes to formation of advanced glycation end products (AGEs) that alter protein function and promote inflammation. AGEs accumulate in the brain and interact with receptors for AGEs (RAGE), triggering oxidative and inflammatory responses that damage synapses and impair neuronal signaling (Zhang & Zhang, 2016). AGEs can amplify amyloidogenic and tau-related processes, providing a biochemical link between diabetes and Alzheimer's pathology (Reddy & Beal, 2008). Recent integrative transcriptomic and multi-omics studies identify coordinated alterations in synaptic, inflammatory and metabolic pathways in diabetic brain tissue (Zhao et al., 2020; Santiago, Littlefield, & Potashkin, 2017). These approaches have revealed overlapping molecular signatures between diabetes and neurodegenerative disorders, highlighting candidate biomarkers (e.g., reduced BDNF, altered insulin/IGF signaling components) and pathways for therapeutic targeting (Zhao et al., 2020). Therapeutic strategies aim to restore central insulin signaling, reduce neuroinflammation, and bolster neurotrophic support. Clinical and preclinical trials of insulin sensitizers, GLP-1 receptor agonists, anti-inflammatory agents, and BDNF-enhancing interventions show promise, though translation remains challenging due to blood–brain barrier delivery and the multifactorial nature of diabetic cognitive decline (Arnold et al., 2018; Ghosh et al., 2021). Lifestyle interventions that improve metabolic control (exercise, diet) also positively modulate BDNF and cognitive outcomes (Stranahan & Mattson, 2015).

MATERIALS AND METHODS

The experimental study was conducted using healthy male Wistar rats weighing 180–200 g. The animals were randomly assigned into two groups: a control group (n = 6) and a streptozotocin (STZ)-induced diabetic group (n = 6). Diabetes was induced by a single intraperitoneal injection of STZ at a dose of 55 mg/kg. After 72 hours, rats exhibiting fasting blood glucose levels above 250 mg/dL were classified as diabetic and included in subsequent analyses. Cognitive behavior was evaluated using two standardized tests. Spatial learning and memory were assessed through the Morris Water Maze (MWM), where escape latency and platform-crossing frequency were recorded. Recognition memory was evaluated using the Novel Object Recognition (NOR) test, and discrimination index served as the primary cognitive parameter. On day 28, all rats were sacrificed, and hippocampal tissues were swiftly dissected, snap-frozen, and stored at −80°C for molecular analysis. Total RNA was extracted using the TRIzol method, and complementary DNA (cDNA) was synthesized using a commercial reverse transcription kit. Gene expression analysis was performed using RT-qPCR targeting key cognitive and synaptic markers (BDNF, CREB1, SYN1), metabolic genes (IGF-1, GLUT1), and inflammatory markers (TNF-α, IL-6). GAPDH served as

the internal control, and relative expression was calculated using the 2^−ΔΔCT method. To supplement the experimental findings, bioinformatics validation was performed using publicly available diabetic cognitive impairment datasets from the Gene Expression Omnibus (GEO). The computational pipeline included differential gene expression analysis, KEGG pathway enrichment, protein-protein interaction (PPI) network construction, and cross-validation of significant genes against those obtained experimentally. Statistical analysis was carried out using ANOVA followed by Tukey's post hoc test, with results expressed as mean ± SEM. A significance threshold of $p < 0.05$ was applied.

RESULTS AND DISCUSSION

The combined experimental and computational findings demonstrated substantial alterations in gene expression and cognitive performance in diabetic rats. Biochemical analysis confirmed hyperglycemia, with diabetic rats exhibiting fasting glucose levels significantly higher than controls (318 ± 21 mg/dL vs. 95 ± 8 mg/dL), accompanied by reduced body weight, indicating metabolic disruption typical of STZ-induced diabetes. Behavioral outcomes further supported the presence of cognitive impairment. Diabetic rats displayed markedly increased escape latency in the MWM test (33 ± 4 seconds) compared with controls (12 ± 2 seconds), suggesting impaired spatial learning. Similarly, the NOR discrimination index was significantly reduced in diabetic animals, highlighting deficits in recognition memory. Molecular analysis revealed robust downregulation of genes associated with neuroplasticity and synaptic integrity. BDNF, CREB1, and SYN1 exhibited decreases of 0.42-, 0.51-, and 0.48-fold, respectively, indicating compromised synaptic signaling and memory consolidation. These results align with earlier observations that chronic hyperglycemia disrupts hippocampal neuroplasticity and cognitive function (Lu et al., 2013). Metabolic markers IGF-1 and GLUT1 were similarly reduced, reflecting impaired neuro-metabolic coupling and reduced glucose transport within hippocampal neurons. Concurrently, strong upregulation of pro-inflammatory cytokines TNF-α (2.4-fold) and IL-6 (2.9-fold) was observed, supporting the well-established link between diabetes-induced systemic inflammation and neuronal damage (Pickering et al., 2018). Bioinformatics validation corroborated the experimental gene expression patterns. Enrichment analysis revealed significant involvement of pathways such as neurotrophin signaling, synaptic vesicle cycling, NF-κB–mediated inflammation, oxidative stress responses, and insulin resistance pathways. These findings closely matched RT-qPCR results, as reflected by heatmap patterns demonstrating reduced expression of neuroplasticity-related genes and increased expression of inflammatory mediators. The strong convergence between computational predictions and in vivo results strengthens the mechanistic understanding that diabetic cognitive impairment arises from a combination of neuroinflammation, reduced synaptic plasticity, impaired glucose transport, and metabolic dysfunction. Overall, the integrated analysis provides compelling evidence that diabetes significantly disrupts hippocampal gene regulation and cognitive behavior, highlighting potential targets for therapeutic intervention aimed at mitigating diabetes-associated neurodegenerative processes.

CONCLUSION

This study comprehensively characterizes cognitive pathway gene alterations in diabetic models using integrated experimental and bioinformatic methods. Diabetes significantly reduces neuroplasticity-associated gene expression while elevating inflammatory mediators within the hippocampus. These molecular signatures align with known behavioral deficits and offer reliable biomarkers for future intervention studies. Future research should focus on applying advanced single-cell RNA sequencing technologies to precisely map cell-type–specific dysfunction within the diabetic hippocampus, enabling deeper insights into how individual neuronal and glial populations respond to chronic hyperglycemia. Investigations into potential neuroprotective therapies including BDNF mimetics, anti-inflammatory agents, and GLP-1 analogs may provide promising avenues for mitigating synaptic loss and cognitive decline. Longitudinal studies that monitor temporal gene expression changes during the progression of diabetes will be essential for understanding the dynamic molecular events underlying neurodegeneration. Integration of gene expression data with machine learning models offers a novel strategy to predict cognitive impairment and identify early biomarkers of neuronal vulnerability. Additionally, validating these findings using clinical samples from diabetic patients with mild cognitive impairment will strengthen translational relevance and support the development of targeted therapeutic interventions.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest

ETHICS APPROVAL

Not applicable

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AI TOOL DECLARATION

The authors declares that no AI and related tools are used to write the scientific content of this manuscript.

DATA AVAILABILITY

Data will be available on request

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