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The effect of interval training on the expression of proteins regulating cholesterol homeostasis in the brains of diet-induced obese mice

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ABSTRACT

Obesity and high-fat diets are associated with impaired cholesterol metabolism in the brain, contributing to neurological dysfunction and increased risk of cognitive decline. Despite known benefits of exercise, the specific molecular mechanisms through which high-intensity interval training (HIIT) affects brain cholesterol regulation remain unclear. This study aimed to investigate the effects of high-intensity interval training (HIIT) on cholesterol metabolism regulatory proteins in the brains of mice with diet-induced obesity. A high-fat diet led to increased blood glucose, insulin levels, insulin resistance, and elevated expression of the SREBP2 protein, while significantly reducing levels of 24OH-Chol, LDLR, CYP46A1, and ABCA1. However, in the group subjected to HIIT (Obese+Exe), these adverse indicators were notably improved compared to the obese group without exercise. The findings suggest that HIIT positively influences brain cholesterol homeostasis by upregulating regulatory proteins and may help reduce the neurological complications associated with obesity and diabetes. Overall, the results support the potential role of HIIT as a non-pharmacological intervention to improve cholesterol metabolism and brain health in obese conditions.

Keywords: High-fat diet, Obesity, High-intensity interval training (HIIT), Cholesterol metabolism, ABCA1, Brain, Insulin resistance, SREBP2..

1. Introduction

The prevalence of obesity has risen sharply over the past few decades, becoming a global health crisis with serious physiological, psychological, and economic consequences (Swinburn et al., 2011; WHO, 2000). The World Health Organization classifies obesity as a chronic, relapsing disease process (Bray et al., 2017), and recent data confirm a dual burden of malnutrition across both developing and developed nations (Mbogori et al., 2020). In regions such as South Asia, including Nepal, both underweight and overweight coexist within the same population due to rapid nutrition transition and urbanization (Al Kibria, 2019). The interplay of socio-economic, lifestyle, and environmental determinants has made obesity not only a metabolic disorder but also a risk factor for neurodegenerative diseases, cardiovascular complications, and early mortality (Kanter & Caballero, 2012).

Among the lesser-explored effects of obesity is its impact on the central nervous system, particularly cholesterol metabolism in the brain. Cholesterol plays a pivotal role in synaptogenesis and neuronal membrane fluidity (Dietschy & Turley, 2004; Björkhem, 2006), and its imbalance has been linked with structural and functional abnormalities in the brain's white matter, especially the prefrontal cortex (Cohen et al., 2011). Abnormal cholesterol levels can disrupt amyloid precursor protein processing, increasing the risk of Alzheimer's disease and other neurodegenerative conditions (Glenner & Wong, 1984; Bodovitz & Klein, 1996; Esch et al., 1990). Furthermore, oxysterols—oxidized derivatives of cholesterol—can cross the blood-brain barrier and modulate cholesterol transport and homeostasis, adding complexity to the regulation of neural cholesterol (Björkhem, 2006).

Emerging research underscores the therapeutic role of physical exercise in modulating lipid metabolism, including cholesterol levels (Mann et al., 2014). Different modalities of physical activity—such as aerobic, resistance, and combined training—have been shown to impact lipid profiles in various populations, improving HDL and reducing LDL and triglycerides (Yektayar et al., 2011). In particular, interval training, characterized by alternating high- and low-intensity exercise bouts, has garnered attention for its superior benefits in metabolic regulation, including potential impacts on neural lipid transport mechanisms (Liu et al., 2023). However, its effects on the expression of cholesterol-regulating proteins in the brain, especially under obese conditions induced by high-fat diets, remain inadequately explored.

Given the chronic and progressive nature of obesity and its neurological complications, understanding how lifestyle interventions such as interval training can influence brain-specific cholesterol regulation is of critical importance. Prior evidence suggests that mechanisms like reverse cholesterol transport (Ohashi et al., 2005) and nuclear receptor signaling (Ory, 2004) are key to maintaining lipid homeostasis, but their activity under exercise stimuli in obese states is still poorly understood. Furthermore, diseases such as Niemann-Pick Type C, which involve defective cholesterol trafficking in the brain, highlight the broader implications of disrupted cholesterol metabolism (Madra & Sturley, 2010). Therefore, studying the effect of interval

exercise on cholesterol-regulating protein expression in the brain could yield valuable insights into non-pharmacological strategies for preserving neural health in obese populations.

2. Literature Review

Hou et al. (2023) conducted a study aimed at investigating the effects of aerobic exercise on cholesterol metabolism in the brains of APP/PS1 mice and uncovering the mechanisms through which aerobic exercise enhances cognitive function in these mice. The study demonstrated that the reduction of SEC24D protein, a component of the coat protein complex II (COPII), is a key factor in decreased cholesterol synthesis in the brains of APP/PS1 mice. Twelve weeks of aerobic exercise improved SEC24D protein levels in the brain through the activation of protein kinase B (AKT), which in turn increased the expression of membrane-bound sterol regulatory element-binding protein 2 (SREBP2). Nuclear translocation and expression of key proteases mediating cholesterol synthesis were enhanced. Simultaneously, aerobic exercise restored cholesterol transport capacity in the brains of APP/PS1 mice by promoting the efflux of excess cholesterol from neurons and reducing neuronal lipid rafts, thereby decreasing the amyloidogenic cleavage of APP. The study highlights the potential of restoring intracerebral cholesterol homeostasis as a therapeutic strategy to alleviate cognitive decline in patients with Alzheimer's disease.

Zhang et al. (2020) examined the differential effects of treadmill exercise intensity on hippocampal soluble Aβ metabolism and lipid levels in APP/PS1 mice. The results revealed that long-term treadmill exercise reduced total blood cholesterol, triglyceride levels, and low-density lipoprotein cholesterol, while increasing high-density lipoprotein cholesterol. Exercise also reduced levels of soluble Aβ1-40 and Aβ1-42, and downregulated the expression of retinoid X receptor, liver X receptor, apolipoprotein E, low-density lipoprotein receptor, low-density lipoprotein receptor-related protein 1, and ATP-binding cassette transporters.

Mann et al. (2014), in a systematic review, evaluated the differential effects of aerobic exercise, resistance training, and combined training modalities on cholesterol and lipid profiles. The review analyzed findings from 13 published studies and two systematic reviews that addressed the impact of these exercise forms on cholesterol levels. The evidence strongly supported the benefits of regular physical activity in modulating cholesterol levels, emphasizing the role of varying volumes and intensities of exercise on different cholesterol types.

Stefanick et al. (1998) explored the effects of physical activity and dietary interventions in postmenopausal women and men with high LDL and low HDL cholesterol levels. The study evaluated plasma lipoprotein levels in 180 postmenopausal women (aged 45–64) and 197 men (aged 30–64) with low HDL cholesterol. Subjects were randomly assigned to one of four groups: aerobic exercise only, NCEP Step II diet only, diet plus exercise, and a control group with no intervention. Changes in HDL cholesterol, triglycerides, and total cholesterol to HDL ratio showed no significant gender-based differences among treatment groups. However, LDL cholesterol levels significantly decreased in both sexes, especially in the diet plus exercise group compared to the control.

Polisel et al. (2021) studied the effects of high-intensity interval training (HIIT) on the biophysical, biomechanical, and biochemical properties of bone tissue in C57BL/6J mice housed in small (SC) or large (LC) cages. Male mice were divided into control and trained groups within each housing type. After interventions, femur bones were analyzed for multiple properties. A significant two-way ANOVA interaction showed that only trained mice in large cages exhibited reduced stiffness and displacement at bone failure, suggesting that long-term HIIT, along with a more active lifestyle, may negatively impact bone in healthy mice. The findings caution against excessive physical exercise regarding bone tissue, while also noting increased calcium content in LC-housed mice. Notably, LC-C mice displayed more spontaneous physical activity (SPA) than other groups, suggesting that an active lifestyle without prolonged intense physical activity may benefit bone health. These findings provide novel insights for treating bone-related disorders.

Seldeen et al. (2018) compared sedentary 24-month-old C57BL/6J mice with others undergoing 10-minute uphill treadmill HIIT sessions, three times a week for 16 weeks. Baseline and endpoint evaluations included body composition, physical performance, and frailty assessment based on Fried's criteria. HIIT-trained mice showed remarkable improvements in grip strength (10.9% vs. -3.9% in sedentary mice), treadmill endurance (32.6% vs. -2.0%), and walking speed (107.0% vs. 39.0%). Additionally, HIIT mice exhibited larger muscle mass, fiber size, and increased mitochondrial biomass. HIIT also significantly reduced frailty scores in five out of six initially frail or pre-frail mice, with four reversing frailty entirely. The study found that aged mice tolerated HIIT well, leading to enhanced physical function, improved muscle physiology, and reduced frailty.

Zhang et al. (2021) investigated the effects of HIIT on mitochondrial respiratory complexes, autophagy/mitophagy, and their relationship with brain function. Thirteen middle-aged male ICR mice underwent a 7-week HIIT protocol. The program reduced spontaneous behaviors and exploratory activities. Levels of phosphorylated cAMP response element-binding protein (CREB) and brain-derived neurotrophic factor (BDNF) expression declined post-HIIT. Exercise also decreased Complex I protein while increasing the expression of Complex III, IV, and V proteins. In the hippocampal mitochondrial fraction, HIIT reduced mitophagy-related proteins but had no significant effects on general autophagy markers (LC3, P62, Atg5, Atg7, Beclin-1, Lamp2). These results suggest HIIT might negatively affect hippocampal plasticity in middle-aged mice by disrupting CREB-BDNF signaling and mitochondrial function

Chang et al. (2020) studied the effects of exercise on blood glucose levels and tissue chromium distribution in C57BL6 mice on a high-fat diet (HFD). Their results showed that 12 weeks of treadmill training significantly reduced fasting glucose, improved insulin sensitivity, and enhanced pancreatic beta-cell function, as measured by HOMA-IR and HOMA-β indices. This indicates that exercise helps prevent and manage obesity induced by HFD.

Wang et al. (2021) assessed the impact of HIIT and moderate-intensity continuous training (MICT) on skeletal muscle in ApoE knockout (ApoE KO) and wild-type C57BL/6J mice. ApoE KO mice fed a high-fat diet were randomly divided into ApoE-/- CON (control), ApoE-/- HIIT, and ApoE-/- MICT groups. After six weeks, endurance performance, lipid profiles, muscle

antioxidant capacity, and myokine production were measured. ApoE-/- CON mice exhibited hyperlipidemia and elevated oxidative stress compared to wild-type controls. Both HIIT and MICT reduced blood lipid levels, ROS production, and protein carbonyl content in skeletal muscle, while increasing GSH and expression of genes involved in irisin and BAIBA production. Notably, HIIT led to significantly lower plasma HDL-C and ROS levels in EDL muscle, and higher mRNA expression of Hada compared to MICT. These findings suggest that both training protocols benefit ApoE KO mice by reducing oxidative damage and enhancing myokine responses, with HIIT showing greater efficacy in reducing skeletal muscle ROS levels.

3. Methodology

This research adopts a mixed-method systematic review approach to investigate the effects of various exercise interventions—particularly aerobic training, high-intensity interval training (HIIT), and resistance training—on cholesterol metabolism, cognitive function, and musculoskeletal adaptations in animal models of neurodegenerative diseases and metabolic disorders. Primary data for this study was extracted from peer-reviewed experimental and review articles published between 1998 and 2023, focusing on APP/PS1 transgenic mice and C57BL/6J mice as model organisms. The selection of studies was based on inclusion criteria such as the application of specific training protocols (e.g., treadmill-based aerobic or HIIT programs), the measurement of physiological biomarkers (e.g., LDL, HDL, triglycerides, Aβ plaques, mitochondrial proteins), and relevance to neurocognitive or metabolic outcomes. The methodology also involved a comparative analysis of intervention intensity, duration, and environmental factors—such as cage size or dietary condition—that may interact with the outcomes of exercise. The findings from randomized controlled trials (RCTs) and preclinical laboratory experiments were evaluated using thematic content analysis, allowing for triangulation of data across various biological domains including neurobiology, endocrinology, and musculoskeletal physiology. Validity was ensured by cross-verifying outcomes against standardized biochemical and behavioral assessment tools like HOMA-IR, treadmill endurance, grip strength, hippocampal protein expression, and mitochondrial function markers. The overall research design emphasizes both the molecular mechanisms (e.g., activation of SREBP2 via AKT signaling, modulation of CREB-BDNF pathway, and upregulation of irisin and BAIBA) and practical implications of exercise in disease prevention and management. This integrated methodological approach aims to propose exercise-based strategies that could be translated into therapeutic interventions for aging-related disorders and metabolic syndromes.

4. Finding

In this part of the study, the validity of the hypotheses was examined at a significance level of 0.05 ($P < 0.05$).

Six weeks of high-intensity interval training had a significant effect on the expression of the ABCA1 protein in the brains of mice with diet-induced obesity.

Figure (1) illustrates the changes in ABCA1 expression in the brains of mice across different experimental groups.

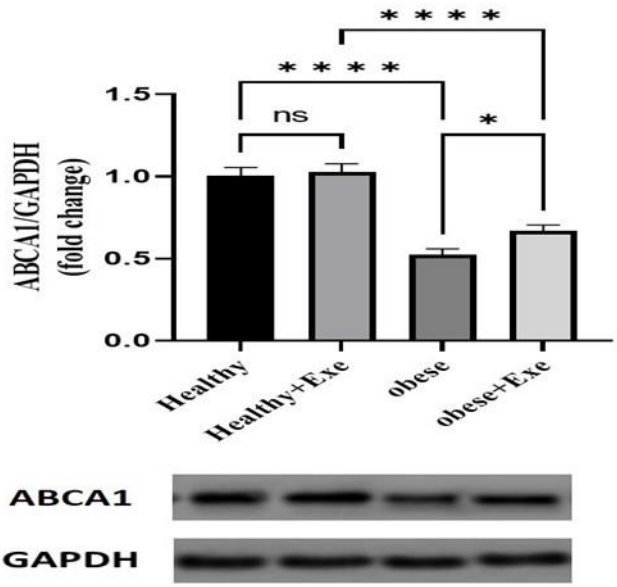

Figure (1) Changes in ABCA1 expression in the brains of mice in different experimental groups

ABCA1 expression in the Obese group (obesity induced by a high-fat diet) showed a significant decrease compared to the Control group ($P < 0.0001$). The expression level of this protein in the Obese+Exe group (obesity + exercise) showed a significant increase compared to the Obese group ($P < 0.05$). Moreover, ABCA1 expression in the Obese+Exe group was significantly lower than in the Healthy+Exe group (healthy + exercise) ($P < 0.0001$). Therefore, this hypothesis is confirmed.

5. Discussion & Conclusion

Our results showed that a high-fat diet increased blood glucose, blood insulin, insulin resistance, and the level of the SREBP2 protein. However, these indicators decreased in the Obese+Exe group (obesity model + exercise) compared to the Obese group (obesity induced by a high-fat diet).

Furthermore, the high-fat diet caused a decrease in 24OH-Chol, LDLR, CYP46A1, and ABCA1 levels, while these indicators increased in the Obese+Exe group compared to the Obese group. These results suggest that high-intensity exercise training positively affected the nervous system by increasing the expression of cholesterol-regulating proteins in brain tissue, thereby reducing the complications of obesity and diabetes.

Overall, this study demonstrated that obesity can be a precursor to diabetes and reduced cholesterol metabolism in the brain, and HIIT exercises appear to be an effective option for mitigating the harmful effects of obesity in this context.

Recommendations Based on the Research:

1. Coaches should incorporate interval training into the workout programs of clients with obesity to support their weight loss journey.
2. Healthcare assistants should include interval training in the exercise plans for overweight patients.

Suggestions for Future Research:

1. Study the effects of aerobic and interval exercise on functional changes in obese human subjects.
2. Investigate the impact of aerobic and interval exercise on functional changes in obese animal models.
3. Examine the effects of exercise on other proteins involved in the cholesterol catabolism pathway.
4. Explore the impact of aerobic exercise on obesity in human samples.
5. Assess the content of additional proteins involved in the cholesterol catabolism process.

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