Iraqi Journal of Veterinary Sciences, Vol. 37, Supplement IV, 2023 (251-257)
Proceedings of the 4th Scientific Conference, College of Veterinary Medicine, University of Karbala

Iraqi Journal of Veterinary Sciences

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Effect of hypercholestermic diet on the β- amyloid deposition and microglial cells with some biomarkers alterations in male rats

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Article information

Article history:
Received 14 April, 2023
Accepted 25 November, 2023
Available online 04 January, 2024

Keywords:
Brain
Cholesterol-raising diet
Lipid profile
Immunohistochemistry

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Abstract

Unusually high lipid levels define a hypercholesterolemic diet (HCD) and are strongly linked to brain damage and cerebrovascular illnesses. HCD is a chronic brain disorder characterized by cognitive impairment, inflammation, β-amyloid (Aβ) deposition, and vascular injury. Recent studies have shown that high cholesterol levels are linked to AD pathology. This investigation aims to check out the physiological modifications of the brain that happen from receiving a high-cholesterol diet. We have previously shown that high brain cholesterol levels promote Aβ accumulation and oxidative stress**.** The experiment employed sixteen male rats. Which was split into two groups: the oversight group (8 rats) and the cholesterol group (8 rats), the latter of which received a 1% supplement of cholesterol in their food 28 days later, rats' blood was drawn for biochemical analysis and brain tissues were removed and processed for light microscopy inspection using H&E and CD68, an immunohistochemistry marker for microglia cells. Brain samples were homogenized to measurement of the Aβ. Significant increase in serum lipid profile, Aβ, Acetylcholinesterase (AChE), and Malnodialdehyde (MDA) levels, while Significant decrease of serum HDL-C and serum Glutathione (GSH) levels in cholesterol group compared to the control group. Rats' brains had visible morphological alterations, having pyknotic nuclei of degenerating neurons, lack of neurons, and pathological alteration in morphology of microglial cells in the cholesterol group compared to the control group. We concluded that an HCD has negative biochemical alterations linked to brain anatomical changes.

DOI: 10.33899/ijvs.2023.139742.2973,

Introduction

Cholesterol is a waxy, fat-like substance with pivotal pathophysiological relevance (1). A hydrophobic substance known as cholesterol is carried through the circulation by lipoproteins, proteins; John Gofman used an ultracentrifuge to isolate the lipoproteins in plasma (1). Multiple physiological conditions, such as fat, cardiovascular disease, and Alzheimer's disease, are brought on by high cholesterol levels (2). Additionally, hypercholesterolemia, or elevated plasma cholesterol levels, are linked to male infertility because they cause the male reproductive system's malfunction (2). A high-fat diet can worsen reactive stress and inflammation in the brain and negatively impact cognitive function (3). An environment that is susceptible to harm from a high-fat diet is the aging brain (3). The brain is particularly vulnerable to oxidative stress, which can be produced by an elevated cholesterol diet (4). A high cholesterol level and oxidative stress are substantial risk factors for various illnesses, including dementia and many central nervous system problems (4). Hypercholesterolemia increases levels of β-amyloid (Aβ), a

peptide that accumulates in Alzheimer's disease brains (5). For the brain to continue to have a regular shape and function, cholesterol is a crucial substance. However, a long-term high-cholesterol diet can result in several degenerative changes to the brain, including the buildup of β-amyloid (Aβ), hyperphosphorylation of Tau, reactive gliosis, neuroinflammation, cell mortality, and synaptic degeneration (6). These abnormal alterations interact with one another in intricate ways, impairing memory and contributing to the development of Alzheimer's disease (AD) (6). Oxysterols, oxidized versions of cholesterol, are more readily transported to the brain by high-fat diets, which may help explain the correlation between blood and brain cholesterol levels. It is thought that these cholesterol compounds may also help cerebral cholesterol carry out its intended tasks in the brain. In light of this, new research suggests that oxysterols are essential signaling molecules for brain processes (7). To avoid abnormal biochemical processes that result from an excessive buildup of cholesterol in tissues, cholesterol homeostasis is carefully kept. Although dyslipidemia impairs endocrine function and impairs reproduction in male rodents, no obvious regulatory variables or processes have been established (2). However, it is unclear what early hypercholesterolemia-related events cause brain degeneration (6).

The current study aims to investigate the effect of the hypercholesterolemic diet on some oxidative stress parameters, beta-amyloid deposition, and microglial cell activity by immunohistochemistry on the brain in male rats.

Materials and methods

Ethical approve

Under the reference number UOK. The VET.PH.2022.046 study was conducted at the Kerbala University, College of Veterinary Medicine's anatomical facility in Iraq.

Experimental protocol

16 white male rats' weight 200±20g were used in this research and came from the College of Pharmacy at the University of Kerbala in Iraq. They ranged in age from 11-14 weeks, and the animals were housed in clean, specialized plastic enclosures. They receive the proper air and surroundings. We utilized a 12-hour light cycle and a relative humidity of 55%. They were retained for two weeks to adjust to the usual testing conditions. The experiment began on the 15th of December and ended on the 12th of January. The temperature was maintained at 23-26ºC using a room thermostat; the room air was changed continuously using a ventilation vacuum, and the animal fed on the pellet of freshly prepared ration.

Experimental design

16 white male rats were arbitrarily split into two groups and given the following treatments. 8 rats of this group were given a regular meal orally as the comparison group. 8 rats received cholesterol. Rats in this group were given a meal rich in cholesterol for 28 days, comprising 1% cholesterol (w/w) (8).

The taking of blood samples

Fasting after 28 days of the trial, blood samples were taken, and before the blood was born, the animals were controlled and made comfortable by inhaling chloroform. Sterile medical syringes of 5 ml were accustomed to extract 5 ml of cardiac blood using the heart puncture method, and the blood was then put into the serum was centrifuged in a unique gel tube that did not contain an anticoagulant at a speed of 4000 revolutions per minute for 5 minutes. Once the serum had been separated, it was stored in Eppendorf tubes and kept in the fridge at -30°C while the assays worked.

Collecting of organs for the histological section

Rats were killed by chloroform anesthesia following the completion of the experiment, and the animals were dissected to extract sample brains. The organs were enumerated and then preserved in 10% formalin in sterile plastic containers until the histological section was carried out.

Gathering of the brain tissues

Weighed brain samples were crushed using Squishers in 200 l of 0.1 N perchloric acid for 4 minutes (to ensure the tissue was evenly distributed). The supernatants were meticulously removed after centrifuging the homogenates for 30 minutes in a cold environment (4ºC). The supernatants can be collected immediately for analysis or frozen at -80°C. Take 500 ml of anhydrous glacial acetic acid, 25 ml of acetic anhydride, and about 8.5 ml of perchloric acid (24h). Complete the combination with 1000 cc of anhydrous glacial acetic acid-the beta-amyloid measurement.

An immunohistochemistry

Stain (CD68) was used to detect microglial cells.

Statistical analysis

In the statistical program Graph Pad Prism 8.0, the t-test was used, and $P \leq 0.05$ was chosen as the standard of significance. The data points were shown as mean±SD.

Results

Blood serum parameters

Figure 1 in the present study showed a significant increase in the TC, TG, LDL-C, and VLDL-C in the cholesterol group 79.75±3.19, 78.00±7.90, 14.41±2.91, and 31.46±5.12 compare to the control group 46.63±3.46, 43.75±5.20, 8.25±1.36, and 10.97±7.17 respectively. In contrast, figure 1 showed a significant decrease in the HDL-C 10.13±2.94 in the cholesterol group when compared to the control group 40.88±9.71 and a significant increase in the MDA in the cholesterol group 0.28±0.18 compare with control group 0.07±0.026. Figure 1 revealed a considerable reduction in the GSH in the cholesterol group 336.91±64.82 compared with the control group 437.8±21.20, while a significant increase in the AChE 15.74±2.15 in cholesterol group when compared to the control group 9.331±0.38. A significant increase in the β-Amyloid in the cholesterol group 129.20±7.03 compared with the control group 43.11±9.76.

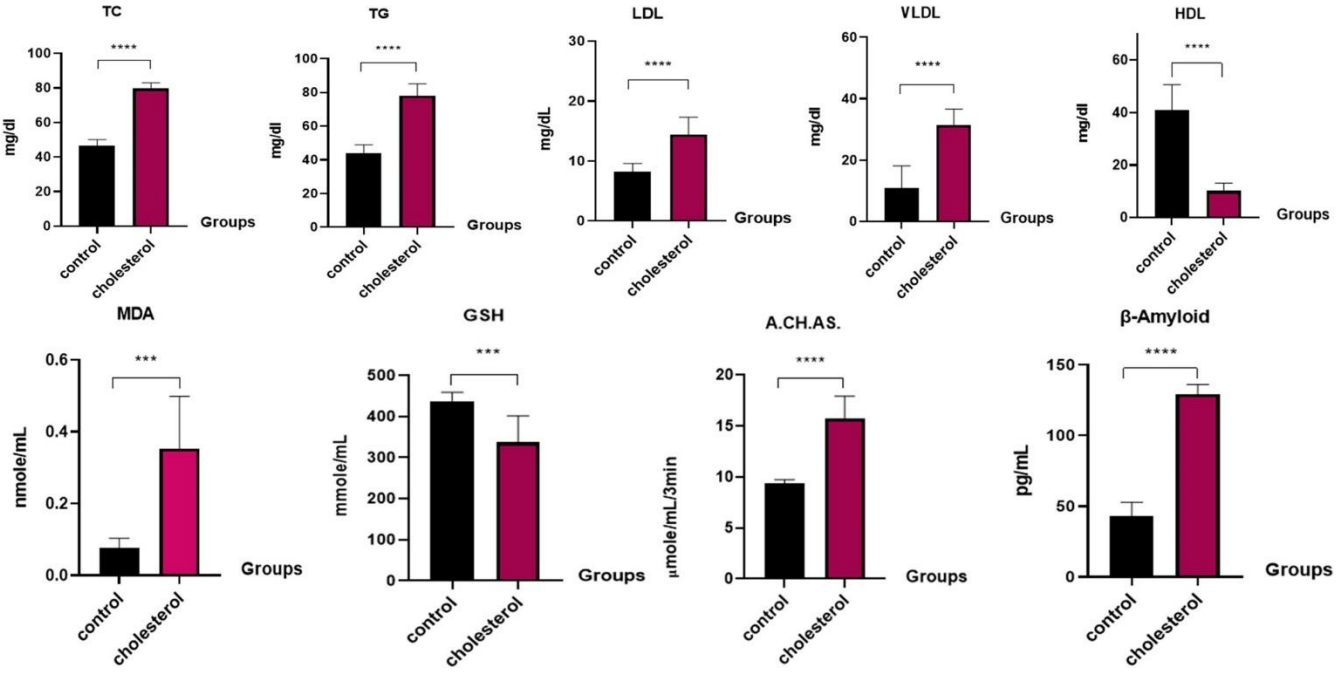

Figure 1: Effect of hypercholesteremic diet on the serum parameters concentration in the male rats.

Histopathological and immunohistochemistry examination

The control rats displayed normal morphology of microglial cells, while the histological analysis of hypercholesterolemia rats revealed a pathological alteration in the morphology of the microglial cells, resulting in a decrease in phagocytic activity and changes in bodily features with slight shortening in length. Additionally, astrocyte degenerative changes and marked pyknotic changes in oligodendrocytes were observed. Immunohistochemistry staining further confirmed the normal and altered morphology of microglia as shown in figure 2.

Discussion

Cholesterol is a widely recognized important lipid membrane modulator structure and fluidity, and as such, it is crucial for maintaining transmembrane transmission within and between cellular divisions. Cholesterol amounts in membranes are necessary for living. Despite making up only 2.2% of the body weight, the central nervous system (CNS) includes up to 25% of the body's overall cholesterol (9-12).

In the current research, a diet high in cholesterol improved TC, TG, LDL-C, and VLDL-C compared to the control group. At the same time, HDL-C showed a significant decrease in the cholesterol group in compares with the control group. This result is in agreement with (3,4,13-17). Although it is unclear how cholesterol can impact brain processes, its oxysterols and oxygenated products can cross lipophilic membranes even though cholesterol itself cannot (9,18). According to the study's findings, blood GSH levels significantly decreased and increased in the MDA in the cholesterol group compared to the control group. These results are in agreement with (19-23). It also showed a significant increase in the β-amyloid(Aβ) and AChE, which agrees with (18,24).

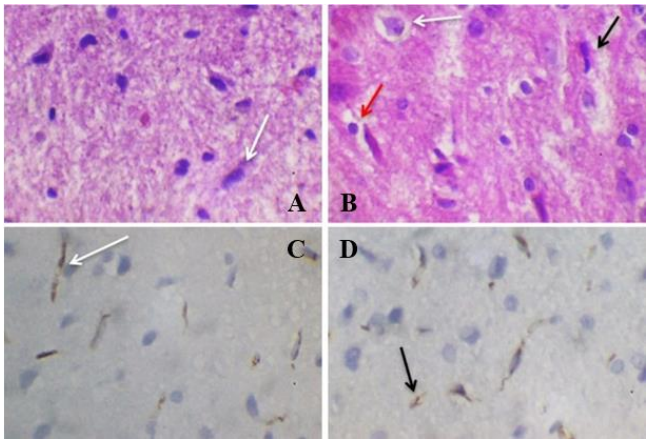

Figure 2: (A) Control rat showing normal morphology of microglial cells (cerebral macrophages) (white arrow) (B) histological picture showing pathological alteration in morphology of the microglial cell, towards lowering its phagocytic activity resulting in changes in its bodily features represented by slight shortening in their length (black arrow), astrocyte degenerative changes (white arrow) and marked pyknotic changes in oligodendrocytes (red arrow). (C) Immunohistochemistry staining for sections of a control rat showing normal morphology of microglial cells (cerebral macrophages) (white arrow) (D) histological picture showing pathological alteration in microglial cell morphology towards lowering its phagocytic activity resulting in changes in bodily features represented by slight shortening in their length (black arrow).

MDA levels significantly increased in hypercholesterolemic rats, and the antioxidant enzyme system was suppressed in the rats' liver, renal, heart, and brain tissues (20-23). In the etiology of many illnesses, oxidative stress is a key player. The relationship between hypercholesterolemia and oxidative stress in producing endothelial dysfunction in brain arterioles was observed despite the lack of atherosclerotic lesions. These were demonstrated and verified in this research by higher MDA concentration (9,25).

The antioxidant protection against Aβ induced mitochondrial ROS is reduced in neuronal cells with high cholesterol levels due to impaired mitochondrial GSH transfer (19,26). Before the formation of amyloid plaques and cognitive deficits, mitochondrial dysfunction is recognized as a frequent early occurrence in Alzheimer's disease (AD). Intracellular A can alter mitochondrial function and promote the generation of ROS, which is further exacerbated by cholesterol-mediated depletion of mitochondrial glutathione (GSH) (19,27). The pathogenesis of AD, including neuroinflammation, is accelerated and made worse by brain cholesterol enrichment by enhancing the mitochondrial oxidative damage caused by Aβ (24). Different experimental studies have demonstrated that elevated cholesterol encourages the synthesis and deposition of Aβ and that this abnormality has repeatedly been linked to Alzheimer's disease (AD) (25). We have also shown that the impairment of autophagy by intracellular cholesterol accumulation impacts Aβ elimination (26). Recently, we've discovered that cholesterol

Radicals and compounds called ROS are produced when molecular oxygen undergoes an imperfect reduction. They are created in tiny amounts due to four consecutive one-electron reductions of oxygen that result in the creation of water. They are essential for communication and are required to keep cells' homeostasis (27). Aβ adequate stimulus for causing the formation of Aβ is free radicals (28-31). That could have significant effects because it indicates that mitochondrial malfunction plays a crucial role in the etiology of Aβ despite mitochondrial malfunction and stress from oxidation; because mitochondrial malfunction associated with increased mitochondrial ROS generation is known to be strongly tied to the aging process, this might start a loop of increasing amyloid genic APP (32).

Elevated acetylcholinesterase (AChE) activity in the hypercholesteremic rats demonstrated cholinergic dysfunction; this increased AChE activity accelerated the hydrolysis of ACh and resulted in its scarcity at the synaptic connections (19). AChE activity alterations and variations in its variant in the blood, cerebrospinal fluid (CSF), and brain (22,33). There is a rise in acetylcholinesterase (AChE) activity within and around amyloid aggregates (30). AChE levels could rise due to a high rate of neuronal degeneration, which increases the amount of unbound AChE in the body and increases the cytotoxicity of amyloid components (34). There is a strong correlation between the prevalence of amyloid structures and changed glycosylation of some AChE forms in AD (22,35).

The hypercholesterolemic rats showed varying degrees of degenerative changes and Lack of neurons, oligodendrocytes with degenerating pyknotic nuclei, vacuolation of the neuropil linked to the growth of neuroglial cells, and abnormalities in the proliferation, phagocytosis, and clearing of microglia were all present (9). Hyperlipidemia The cerebrovascular system acquired atherosclerotic plaques, which resulted in reduced blood flow to the brain, reactive stress, and inflammation (9).

An essential molecule for maintaining brain balance, cholesterol is primarily produced by oligodendrocytes and astrocytes in the brain (9,11). Although the production of cholesterol by oligodendrocytes for the myelination process is well known, it has been demonstrated that astrocytes also create cholesterol for neural cells (36,37). Cholesterol is needed for active axonal development, synapse formation, and remodeling but cannot be supplied by the neuron's distant cell body (34). Microglia are crucial for maintaining brain balance and could be a therapeutic focus for neuronal injury (38-42). Microglia's phagocytic clearing is essential

for regulating neuronal balance and initiating tissue healing (39-43). The BBB was disrupted by the oxidized lipids, particularly oxysterol, which also caused endothelial failure (9). The BBB's injury and the preexisting cerebral hypoxia caused the brain to go through neurodegenerative processes (9). Due to up-regulated lipid metabolism and phagocytosis genes, microglia could not switch to an active state for A clearance, possibly contributing to the growth in amyloid pathology in AD patients (39,42,44). Damaged microglia with high cholesterol buildup may result from downregulated cholesterol production pathways (35). Growing evidence suggests that the cellular phenotypes and roles of microglia change as diseases and the development of the brain advance and Hyperlipidemia the cerebrovascular system acquired atherosclerotic plaques, which resulted in reduced blood flow to the brain, reactive stress, and inflammation (45,46).

Conclusion

Viewing our outcomes, we discovered that hypercholesterolemic diets are a prevalent danger factor for brain damage. We concluded that hypercholesterolemia has negative biochemical alterations linked to brain anatomical changes.

Acknowledgment

The University of Kerbala's College of Veterinary Medicine has been recognized for facilitating this investigation.

Conflict of interest

There is absolutely no apparent conflict, according to the author.

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تأثير اتباع نظام غذائي مفرط الكولسترول على ترسب بيتا اميلويد والخلايا الدبقية مع بعض التغيرات في المؤشرات الحيوية في ذكور الجرذان

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الخلاصة

يتميز النظام الغذائي بفرط كوليسترول الدم بارتفاع مستويات الدهون بشكل غير طبيعي ويرتبط بشكل إيجابي بأمراض الأوعية الدموية الدماغية وتلف الدماغ. النظام الغذائي بفرط كوليسترول هو اضطراب مزمن في الدماغ يتميز بضعف الإدراك والالتهاب وترسب البيتا أميلويد وتلف الأوعية الدموية. أظهرت الدراسات الحديثة أن ارتفاع مستويات الكوليسترول في الدم يرتبط بأمراض الزهايمر. الهدف من هذا البحث هو دراسة التغيرات الهيكلية التي تحدث في الدماغ بعد اتباع نظام غذائي عالي الكوليسترول. لقد أظهرنا سابقا أن ارتفاع مستويات الكوليسترول في الدماغ يعزز تراكم البيتا أميلويد والإجهاد التأكسدي، وقد تم استخدام ستة عشر من ذكورا الجرذان في الدراسة، والمواد والطرق، والتي تم تقسيمها إلى مجموعتين؛

المجموعة الضابطة (٨ الجرذان) مجموعة الكوليسترول (٨ الجرذان) الذين تم إطعامهم النظام الغذائي المكمّل بالكوليسترول بجرعة ١٪. بعد ٢٨ يوما، تم جمع عينات الدم من الجرذان للتقدير الكيميائي الحيوي والعينات المأخوذة من دماغ الجرذان ومعالجتها؛ الفحص المجهري الضوئي باستخدام الهيماتوكليسلين والايوسين فضلا عن خلايا التمايز ٦٨ هو صبغة كيمياء مناعية لخلايا الدبقية الصغيرة، حيث تم تجانس عينات الدماغ لقياس البيتا أميلويد. زيادة كبيرة في مستوى الدهون في الدم، البيتا أميلويد، أسيتيل كولينستراز، ومستويات مالونديالديهيد، مع انخفاض كبير في مستويات المصل (بروتين دهني عالي الكثافة) ومصل الكلوتاثيون في مجموعة الكوليسترول مقارنة بمجموعة التحكم. كانت التغيرات الهيكلية المصاحبة في دماغ الجرذان واضحة مثل النوى التقرحية للخلايا العصبية المتدهورة، ونقص الخلايا العصبية والتغيرات المرضية في مورفولوجيا الخلايا الدبقية الصغيرة في مجموعة الكوليسترول مقارنة بمجموعة التحكم. نستخلص إلى أن النظام الغذائي لفرط كوليسترول الدم له تغيرات كيميائية حيوية ضارة مرتبطة بالتغيير الهيكلي في الدماغ.