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Fish oil administration effectively prevented hippocampus alterations and improved spatial memory performance in an animal model of hyperglycemia-neuroinflammation

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Abstract

It is widely established that neuroinflammation can impair cognition and brain histology in diabetes. Substantial evidence showed that fish oil decreases Alzheimer's disease (AD) development but has conflicting effects on diabetes progression. Thus, the study examines how fish oil administration affects hyperglycemia, spatial memory, and hippocampus histology in hyperglycemia-neuroinflammation rats. Male Wistar rats (n=30) were divided into five groups: control rats (NS group), rats given 3 g of fish oil (NS+FO3 group), rats injected with streptozotocin-lipopolysaccharide (STZ-LPS) (STZ-LPS group), rats injected with STZ-LPS and given 1 g/kg of fish oil (STZ-LPS+FO1 group), and rats injected with STZ-LPS and given 3 g/kg of fish oil (STZ-LPS+FO3 group). After six weeks of fish oil treatment, the spatial memory performance of the animals was evaluated using a Y-maze test. Subsequently, a blood sample was collected to quantify the blood glucose concentration, while brain tissue was acquired for histological examination. The finding revealed that fish oil supplementation reduced hyperglycemia. It also showed improved spatial memory performance, as evidenced by the increased number of novel arm entries and time spent. Further, it is proposed that the finding of the Y-maze test had a strong association with the effectiveness of fish oil in preventing cornu ammonis 3 (CA3) alterations. This study found that fish oil supplementation successfully defends neuronal damage in the hippocampus, resulting in improved cognitive performance in an animal model of hyperglycemia-neuroinflammation. Hence, regular administration of fish oil supplements to patients with diabetes is suggested to avoid cognitive impairment.

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Introduction

Several studies have demonstrated that diabetes can have detrimental effects on the central nervous system, which may cause cognitive impairment (1-4). This cognitive impairment can manifest as a secondary result in both type 1 and type 2 diabetic mellitus (DM) (5). Indeed, many studies have suggested a link between hyperglycemia, neuroinflammation, and the risk of developing neurodegenerative disorders such as Alzheimer's disease (AD) (6-8). In AD brains, neuroinflammation is believed to be the result of one or more of the other AD pathologies or associated risks, and it promotes the development of the disorder (9). Furthermore, it is established that hyperglycemia, or elevated blood sugar levels, could trigger neuroinflammation, which affects the blood-brain barrier (BBB), resulting in memory loss (10). Indeed, previous studies have demonstrated that high glucose concentration

can affect the activity of microglial cells, leading to a series of reactions known as NF-κB cascades (11,12). It also promotes abnormal expression of apoptosis-associated genes, ultimately resulting in neuronal death in the hippocampus and cognitive dysfunction (13). Given the importance of regulating blood sugar, regularly administering antidiabetic medicine is highly recommended despite the likelihood of experiencing certain adverse effects (14). Moreover, it is commonly recognized that maintaining a healthy lifestyle and consuming a well-balanced diet will substantially decrease the incidence of diabetic complications alongside taking prescribed medication (15). Research has indicated that omega-3 fatty acids, particularly EPA and DHA, derived from marine oils, demonstrate the strongest anti-inflammatory and immunomodulatory effects (16,17). Indeed, studies have shown compelling evidence that fish oil, rich in omega-3 fatty acids, is highly effective in reducing brain inflammation and cognitive dysfunction (18,19). Additionally, it has been proven to enhance brain structure (20). Likewise, numerous studies have provided evidence that omega-3 fatty acids may have a beneficial effect on the regulation of blood glucose. Omega-3 fatty acids have been shown in vitro and in vivo studies to inhibit apoptosis in pancreatic acinar cells, thereby maintaining normal glucose and insulin levels (21-23). However, other studies found that omega-3 fatty acids may make little or no difference to glucose metabolism, including HOMA of insulin resistance (HOMA-IR) levels, glycated hemoglobin (HbA1c), fasting insulin or glucose (24,25).

Thus, the study aims to investigate the effects of fish oil, rich in omega-3 fatty acids, on hippocampal histology and spatial memory function in a hyperglycemia-neuroinflammation animal model.

Materials and Methods

Ethical approval

The animal studies followed international guidelines for the care and use of laboratory animals. They were approved by the Institutional for Animal Care and Use Committee (IACUC), Universiti Putra Malaysia, Selangor, Malaysia (Approval NO: UPM/IACUC/AUP-R017/2022).

Materials

Menhaden fish oil (Cat no: F8020) and lipopolysaccharide (LPS) (Cat no: L2630) were purchased from Sigma-Aldrich company (USA). Streptozotocin (STZ) (Cat no: SC-200719) was purchased from Santa Cruz Biotechnology Company (USA). Other chemicals used throughout this study were analytical grade.

Animals

This study involved 30 healthy adult Wistar rats aged 8 weeks weighing 250-280 g. The animals were housed in three groups per cage and provided unlimited food and water access. The animals were housed under standard laboratory conditions, which included a 12-hour light/dark cycle and a temperature ranging from 22 to 24 °C.

Experimental groups

The animals were randomly divided into five groups (N=6). Group 1 (NS group): The rats received an i.p. injection of 0.5 mL of 10 mM citrate buffer normal saline for 3 days, followed by 0.5 mL of normal saline for 7 days with supplemented p.o. with 0.5 mL normal saline for 6 weeks. Group 2 (NS+FO3 group): The rats received an i.p. injection of 0.5 mL of 10 mM citrate buffer normal saline for 3 days, followed by 0.5 mL of normal saline for 7 days continually with supplemented p.o. with 3 g/kg of fish oil for 6 weeks. Group 3 (STZ-LPS group): The rats received an i.p. injection of STZ (45 mg/kg BW dissolved in 0.5 mL of 10 mM citrate buffer) daily for 3 days, followed by LPS (250 µg/kg dissolved in 0.5 normal saline) for 7 days continually with supplemented p.o. with 0.5 mL normal saline for 6 weeks. Group 4 (STZ-LPS+FO1 group): The rats received an i.p. injection of STZ (45 mg/kg BW dissolved in 0.5 mL of 10 mM citrate buffer) daily for 3 days, followed by LPS (250 µg/kg dissolved in 0.5 normal saline) for 7 days continually with supplemented p.o. with 3 g/kg of fish oil for 6 weeks. Group 5 (STZ-LPS+FO3 group): The rats received an i.p. injection of STZ (45 mg/kg BW dissolved in 0.5 mL of 10 mM citrate buffer) daily for 3 days, followed by LPS (250 µg/kg dissolved in 0.5 normal saline) for 7 days continually with supplemented p.o. with 3 g/kg of fish oil for 6 weeks.

Experimental design

Induction of hyperglycemia-neuroinflammation rat model. In this study, a rat model of hyperglycemia was induced with i.p injection of STZ at 45 mg/kg/day (i.p) in 0.5 mL of 10 mM citrate buffer (pH 5.5) for three continuous days. Following a week of STZ injection, blood glucose levels were assessed using a blood glucometer (Gluco Dr, South Korea) by extracting blood from the tail vein. Only animals with blood glucose levels equal to or over 250 mg/dL were selected for the subsequent stage, which involved injecting LPS to create a rat model of neuroinflammation. The animal was administered a diluted solution of LPS (250 µg/kg) and normal saline via intraperitoneal injection for seven days (26). Y-maze spatial short-term memory test. All animals were tested in a dark acrylic Y-maze apparatus with three equal-sized arms (start arm, familiar arm, and novel arm) with distinct card cues. Each arm measurements are 60 cm long, 15 cm wide, and 23 cm high, and the three arms are connected at an angle of 120° (Figure 1). The Y-maze test was performed described by Hafandi *et al.* and Sofian *et al.* (27,28). In brief, the Y-maze test was divided into two sessions. The novel arm is blocked with dark plastic acrylic during the first session. The animal was placed in the start arm for a 10-minute trial of free

exploration without being recorded. Subsequently, the animal was removed from the Y-maze and rested for an hour. In the second session, the plastic acrylic was removed from the novel arm, and the animal was placed again in the start arm for a five-minute exploration of all three arms. Then, record the entry number and total amount of time spent in each arm during the second session for each animal. The higher quantity of entries and duration spent in the novel arm suggests an enhancement in the animal's cognitive function.

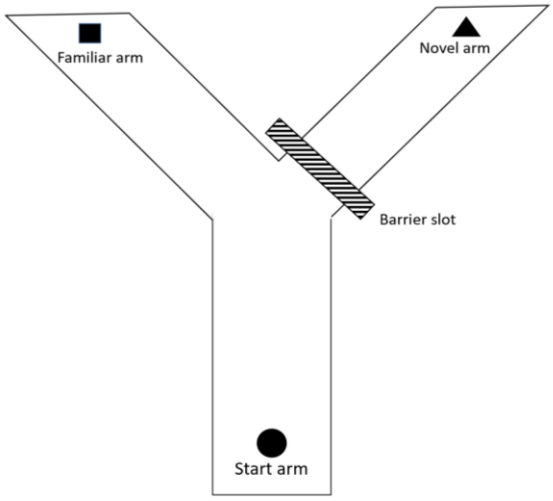

Figure 1 Image representations of the Y-maze apparatus.

Necropacy and tissue sampling. After completion of the Y maze test, the rats fasted overnight. The following morning, the rats were weighed and anesthetized with a single intraperitoneal injection of a combination drug containing ketamine hydrochloride (100 mg/kg) and xylazine (10 mg/kg). Blood samples were then collected from the tail to test blood glucose levels. Next, the rats were immediately decapitated, their skull vaults removed, and their entire brains promptly and carefully removed from outside their skulls. The brains from each group were preserved by immersing them in a 10% neutral buffered formalin solution for 2 hours. This process served to harden the brain and prevent the deterioration of brain tissue. Afterward, the specimens that had been fixed were separated along the sagittal plane, resulting in a left hemisphere and a right hemisphere.

Hematoxylin and Eosin (H&E) study. The left hemisphere of the cerebrum underwent histopathological processing and was stained using H&E staining. The staining methods consist of several steps, including deparaffinization, hydration, washing, staining, dehydration, clearing, and mounting. These steps are performed according to the method described by Slaoui and Fiette (29), with minor alterations. The brain slides were further analyzed using a light microscope (Brand: Olympus, Japan) with an objective lens magnification of 40x for the hippocampus.

Statistical analysis

Data was presented as mean ± SD and analyzed using a one-way ANOVA test, followed by the Duncan test post hoc using the statistical software GraphPad 20. The statistical significance for the null hypothesis being true by chance was set at $P<0.05$, and the confidence interval was 95%.

Results

Fish oil supplementation effect on blood glucose level in rats

The GlucoDr™ digital glucose meter was used to display the data in mg/dL. Table 1 presents the average values and standard deviations (SD) of each group's fasting blood glucose measurements. One week following the administration of STZ, the findings indicated that the STZ-LPS groups (groups 3, 4, and 5) exhibited hyperglycemia, characterized by blood sugar levels exceeding 250 mg/dL, as reported in a study (19). By the end of the experiment, only the STZ-LPS group remained diabetic. Conversely, the STZ-LPS rats given fish oil supplementation (group STZ-LPS+FO1 and STZ-LPS+FO3) showed markedly reduced blood glucose levels compared to the STZ-LPS group without treatment.

Table 1: Effect of fish oil supplementation on blood glucose (mg/dL) in an animal model of hyperglycemia-neuroinflammation

Groups	Baseline	End of experiment
One	80.00 ± 19.78[a]	91.25 ± 17.07[a]
Two	88.75 ± 22.23[a]	103.00 ± 36.87[a]
Three	355.50 ± 105.57[b]	274.00 ± 88.15[b]
Four	314.25 ± 124.69[b]	122.25 ± 37.79[a]
Five	327.25 ± 116.95[b]	108.25 ± 42.09[a]

Values are shown as mean±SD for 6 rats in each group. Values with different alphabetical superscripts [a,b, and c] in a column differed significantly at $P < 0.05$ as determined by one-way ANOVA.

Fish oil supplementation effect on spatial memory ability in rats.

Figure 2 presents the results of the Y-maze test, which evaluated animal spatial memory performance after 6 weeks of fish oil intake in all experimental groups. The NS and NS+FO3 groups had lower entries and duration in the start arm and familiar arm compared to the STZ-LPS group. Meanwhile, the STZ-LPS group exhibited the highest number of entries and the most extended duration in both the start arm and familiar arm compared to all other experimental groups. However, the administration of fish oil in the STZ-LPS+FO1 and STZ-LPS+FO3 treatment groups had identical Y-maze results in the start arm and familiar arm, which displayed fewer arm entries and time spent. Furthermore, the novel arm result showed that the STZ-LPS

group showed a significant reduction ($P < 0.05$) in the number of entries and time spent compared to the other groups. The study found that 1g/kg and 3g/kg fish oil supplements enhanced the number of entries and the duration of time spent in the novel arm in STZ-LPS-induced rats, compared to the STZ-LPS non-treatment group.

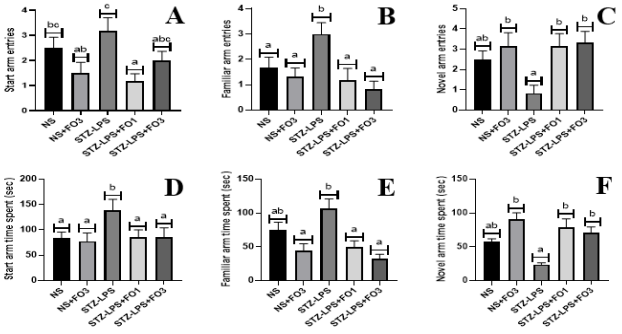

Figure 2: Effect of fish oil supplementation on rat's cognitive ability in STZ-LPS-induced rats. Values are shown as mean ± SD for 6 rats in each group. Values with different alphabetical superscripts a,b, and c differed significantly at $P < 0.05$ as determined by one-way ANOVA.

Fish oil supplementation effect on hippocampus region in rats

In the cornu ammonis 3 (CA3) region (Figure 3), the STZ-LPS group had a noticeable presence of loosely arranged pyramidal neuron cell bodies. Many degenerated neurons exhibited a dark and shrunken appearance, and pericellular haloes in the PCL were detected. Meanwhile, the PCL of STZ-LPS+FO1 (Figure 3D) and STZ-LPS+FO3 (Figure 3E) exhibited fewer degenerated pyramidal cells characterized by dark cytoplasm and contracted nuclei. Additionally, specific cells displayed pericellular haloes, whilst other neuron cells appeared unaffected.

Discussion

In this current study, one week after STZ injection, the animals have higher blood glucose levels over 300 mg/dL. It was also discovered that six weeks of fish oil treatment reduced the blood glucose level, which was not significantly different from the NS group. This finding aligns with a prior investigation which demonstrated that fish oil has the potential to inhibit hyperglycemia in animal models (22,29,30) due to anti-inflammatory properties such as omega-3 polyunsaturated fatty acid (31,32). Omega-3 fatty acids have many mechanisms that influence inflammation, often via modifying the composition of fatty acids in cell membranes. These modifications can impact the membrane's flexibility, the transmission of signals within cells, the activation or deactivation of genes, and the production of lipid mediators (33).

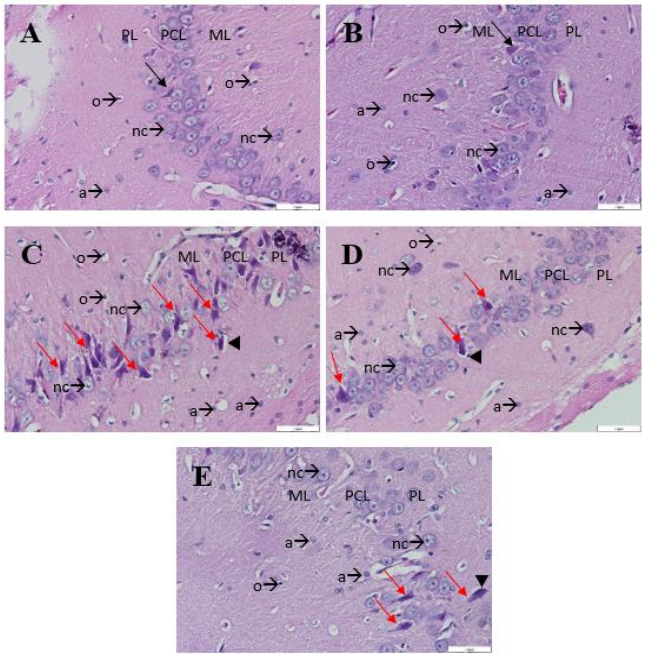

Figure 3: Photomicrograph of CA3 from different experimental groups with H&E staining. The NS (A) and NS+FO3 (B) showed normal histological structures. The PCL contained pyramidal neuron cell bodies that appeared large (black arrow) with vesicular nuclei that were loosely packed, prominent nucleoli, and limited cytoplasm. The STZ-LPS (C) showed scattered degenerated neuron cells (red arrow), some with pericellular haloes (arrowhead), and others appeared normal. The PCL of STZ-LPS+FO1 (D) and STZ-LPS+FO3 (E) appeared loosely arranged of dark, shrunken pyramidal cells (red arrow) and pericellular haloes (arrowhead), while some neuron cells appeared normal. The images are presented as 20x magnification (scale bar: 50 μm). ML: molecular layer; PCL: pyramidal cell layer; PL: polymorphic layer; a: astrocyte; nc: neuron cell; o: oligodendrocyte.

Furthermore, the Y-maze test outcome confirmed the spatial memory dysfunction of the animals in the STZ-LPS group. It is believed that the hyperglycemia induced by STZ and the neuroinflammation induced by LPS may impact the animal's brain function. Indeed, a study conducted by Murtishaw (34) has found that the combination of STZ-LPS, as used in the current study, results in a rapid inflammatory response in the brain due to microglia activation (34). Microglia activation releases pro-inflammatory substances that induce neurotoxicity in the brain, impairing memory and learning (35).

On the other hand, the rats treated with STZ-LPS and given fish oil supplementation for six weeks (referred to as STZ-LPS+FO1 and STZ-LPS+FO3 groups) showed significant improvement in spatial memory performance. This was demonstrated by detecting more entries and

increased duration spent in the novel arms, in contrast to the STZ-LPS group. The findings were consistent with previous research that found administering fish oil could enhance cognitive function in rats with chronic inflammation induced by STZ (18), in aging mice (36), or rats with aluminium-induced AD (37). Omega-3 fatty acids, found in fish oil, have anti-inflammatory and neuroprotective characteristics that can enhance neuronal cell lifespan, reduce neurodegeneration, and prevent cognitive decline (38).

The hippocampus, responsible for memory and learning, is formed by infolding the dentate gyrus, four cornu ammonis (CA) regions, and subiculum (39). The CA had three distinct layers: the polymorphic layer (PL), consisting of glial cell nuclei and blood capillaries; the pyramidal cell layer (PCL), consisting of pyramidal cells that constituted the main cell layer; and the molecular layer (ML) consisting of branching apical dendrites of the pyramidal neurons, small glial cell nuclei and blood capillaries (40). This current study implies that dark pyknotic nuclei, considered dysfunctional or dead neurons (41), could not perform their primary function of transmitting electrical impulses to other neurons via synapses. As a result, the disruptions in the neural circuits ultimately affect memory and information processing, as seen in many neurodegenerative diseases such as AD (42). The histological changes in the STZ-LPS group appeared dispersed loosely and disorganized, with almost all neuron cells displaying dark pyknotic nuclei. The bodies of the nuclei also contracted, causing a pericellular halo. The term dark neuron is frequently used to refer to a degenerating or dead neuron. Dark neurons may suggest a severe pathological change despite the possibility of recovery over time (43,44).

On the other hand, the fish oil supplementation groups showed less dark pyknotic cells and a more organized PCL layer. Studies have determined that CA3 lesions can interfere with spatial learning and memory tasks (45). The CA3 region of the hippocampus plays a critical role in storing new spatial information in short-term memory, which lasts seconds to minutes (46). This can easily be observed in tasks that require rapid information processing, recognizing unfamiliar stimuli, temporarily storing knowledge, and retrieving spatial information based on a single cue, such as the Y-maze test (47). Hence, it is hypothesized that fish oil supplementation inhibited the CA3 region alteration, affecting cognitive performance test improvement.

Moreover, it was assumed that the histopathological changes observed in the brains of the rats injected with STZ-LPS in the present study were associated with oxidative stress and brain inflammation. Both LPS and STZ induction are well-known to cause chronic brain inflammation, which has the potential to harm brain neurons (48-50). In addition, it was noted that inflammation and oxidative stress are inseparable. Inflammation and oxidative stress have a reciprocal relationship, where inflammation can lead to oxidative stress, and oxidative stress can trigger signalling pathways that induce inflammation (51). On the other hand, numerous studies in human and animal models have demonstrated the beneficial effects of omega-3 fatty acids on preserving brain health and function (28,52-54), which is consistent with the findings of this study. Fish oil rich in omega-3 fatty acids provides brain neuroprotection (38,55) because of its antioxidant and anti-inflammatory properties (56-58). In fact, a clinical trial study conducted on type 2 DM patients showed that fish oil supplementations for eight weeks could increase antioxidant capacity, enhance the antioxidant defence system, and prevent diabetes complications (59). Other studies have discovered that fish oil can boost brain antioxidants, amplifying the harmful effects of ROS (60). Thus, it was concluded that the anti-inflammatory action of fish oil was related to the cognitive performance assessment results in this study.

Conclusion

The present study shows that fish oil can prevent cognitive and memory problems caused by neuroinflammation resulting from high blood sugar levels. The beneficial impact of fish oil on spatial memory performance was linked to a decrease in blood glucose levels and tissue alterations in the hippocampus. Thus, regular supplementation of fish oil may offer crucial health benefits in preventing cognitive dysfunction caused by neuroinflammation resulting from long-term high blood sugar levels.

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None.

Conflict of interest

None.

References

1. Moheet A, Mangia S, Seaquist ER. Impact of diabetes on cognitive function and brain structure. Ann N Y Acad Sci. 2015;1353(1):60-71. DOI: 10.1111/nyas.12807
2. Nguyen TT, Ta QTH, Nguyen TO, Nguyen TD, Van Giau V. Type 3 diabetes and its role implications in Alzheimer's disease. Int J Mol Sci. 2020;21(9):3165. DOI: 10.3390/ijms21093165
3. Behl T, Arora A, Sehgal A, Singh S, Sharma N, Bhatia S, Chand P, Gupta R, Verma M. Molecular and biochemical pathways encompassing diabetes mellitus and dementia. CNS Neurol Disord Drug Targets. 2021;21(7):542-556. DOI: 10.2174/1871527320666211110115257
4. Cameron FJ, Northam EA, Ryan CM. The effect of type 1 diabetes on the developing brain. Lancet Child Adolesc Health. 2019;3(6):427-436. DOI: 10.1016/S2352-4642(19)30055-0
5. Jash K, Gondaliya P, Kirave P, Kulkarni B, Sunkaria A, Kalia K. Cognitive dysfunction: a growing link between diabetes and Alzheimer's disease. Drug Dev Res. 2020;81(2):144-164. DOI: 10.1002/ddr.21579

6. De Felice FG, Ferreira ST. Inflammation, defective insulin signaling, and mitochondrial dysfunction as common molecular denominators connecting type 2 diabetes to Alzheimer disease. Diabetes. 2014;63(7):2262-2272. DOI: 10.2337/db13-1954
7. De Sousa RAL, Harmer AR, Freitas DA, Mendonça VA, Lacerda ACR, Leite HR. An update on potential links between type 2 diabetes mellitus and Alzheimer's disease. Mol Biol Rep. 2020;47(8):6347-6356. DOI: 10.1007/s11033-020-05693-z
8. Pugazhenthi S, Qin L, Reddy PH. Common neurodegenerative pathways in obesity, diabetes, and Alzheimer's disease. Biochim Biophys Acta Mol Basis Dis. 2017;1863(5):1037-1045. DOI: 10.1016/j.bbadis.2016.04.017
9. Kinney JW, Bemiller SM, Murtishaw AS, Leisgang AM, Salazar AM, Lamb BT. Inflammation as a central mechanism in Alzheimer's disease. Alzheimer's Dement Transl Res Clin Interv. 2018;4:575-590. DOI: 10.1016/j.trci.2018.06.014
10. Rom S, Zuluaga-Ramirez V, Gajghate S, Seliga A, Winfield M, Heldt NA, Miller RJ. Hyperglycemia-driven neuroinflammation compromises BBB leading to memory loss in both diabetes mellitus (DM) type 1 and type 2 mouse models. Mol Neurobiol. 2019;56(3):1883-1896. DOI: 10.1007/s12035-018-1195-5
11. Hsieh CF, Liu CK, Lee CT, Yu LE, Wang JY. Acute glucose fluctuation impacts microglial activity, leading to inflammatory activation or self-degradation. Sci Rep. 2019;9:13025. DOI: 10.1038/s41598-018-37215-0
12. Hung HC, Tsai SF, Sie SR, Kuo YM. High glucose enhances lipopolysaccharide-induced inflammation in cultured BV2 microglial cell lines. Immun Inflamm Dis. 2022;10(5):e610. DOI: 10.1002/iid3.610
13. Wang H, Deng JL, Chen L, Ding K, Wang Y. Acute glucose fluctuation induces inflammation and neuronal apoptosis in hippocampal tissues of diabetic rats. J Cell Biochem. 2021;122(9):1239-1247. DOI: 10.1002/jcb.29523
14. Corathers SD, Peavie S, Salehi M. Complications of diabetes therapy. Endocrinol Metab Clin North Am. 2013;42(4):947-970. DOI: 10.1016/j.ecl.2013.06.005
15. Asif M. The prevention and control of type-2 diabetes by changing lifestyle and dietary pattern. J Educ Health Promot. 2014;3(1):1. DOI: 10.4103/2277-9531.127541
16. Mori TA, Beilin LJ. Omega-3 fatty acids and inflammation. Curr Atheroscler Rep. 2004;6(6):461-467. DOI: 10.1007/s11883-004-0087-5
17. Simopoulos AP. Omega-3 fatty acids in inflammation and autoimmune diseases. J Am Coll Nutr. 2002;21(6):495-505. DOI: 10.1080/07315724.2002.10719248
18. Wang G, Zhang X, Lu X, Liu J, Zhang Z, Wei Z, Zhou Y. Fish oil supplementation attenuates cognitive impairment by inhibiting neuroinflammation in STZ-induced diabetic rats. Aging. 2020;12(15):15281-15289. DOI: 10.18632/aging.103426
19. Gholamhosseinian A, Abbasalipourkabir R, Ziamajidi N, Sayadi M, Sayadi K. The anti-inflammatory effect of omega-3 polyunsaturated fatty acids dramatically decreases by iron in the hippocampus of diabetic rats. Life Sci. 2020;245:117393. DOI: 10.1016/j.lfs.2020.117393
20. Witte AV, Kerti L, Hermannstädter HM, Fiebach JB, Schreiber SJ, Schuchardt JP, Flöel A. Long-chain omega-3 fatty acids improve brain function and structure in older adults. Cereb Cortex. 2014;24(11):3059-3068. DOI: 10.1093/cercor/bht163
21. Park KS, Lim JW, Kim H. Inhibitory mechanism of omega-3 fatty acids in pancreatic inflammation and apoptosis. Ann N Y Acad Sci. 2009;1171:421-427. DOI: 10.1111/j.1749-6632.2009.04887.x
22. Habib EK. Possible role of omega-3 on the pancreas of streptozotocin-induced diabetes in adult albino rats: histological and immunohistochemical study. Egypt J Histol. 2013;36(3):579-591. DOI: 10.1097/01.EHX.0000431956.27366.8f
23. Soltan SM. The effects of various sources of omega-3 fatty acids on diabetes in rats. Food Nutr Sci. 2012;3(10):1404-1412. DOI: 10.4236/fns.2012.310184
24. Brown TJ, Brainard J, Song F, Wang X, Abdelhamid A, Hooper L. Omega-3, omega-6, and total dietary polyunsaturated fat for prevention and treatment of type 2 diabetes mellitus: systematic review and meta-analysis of randomized controlled trials. BMJ. 2019;366:l4697. DOI: 10.1136/bmj.l4697
25. Gao C, Liu Y, Gan Y, Bao W, Peng X, Xing Q, Li X. Effects of fish oil supplementation on glucose control and lipid levels among patients with type 2 diabetes mellitus: a meta-analysis of randomized controlled trials. Lipids Health Dis. 2020;19(1):101. DOI: 10.1186/s12944-020-01214-w
26. Mahdi O, Baharuldin MH, Nor NM, Chiroma SM, Jagadeesan S, Moklas MM. Chemicals used for the induction of Alzheimer's disease-like cognitive dysfunctions in rodents. Biomed Res Ther. 2019;6(11):3460-3484. DOI: 10.15419/bmrat.v6i11.575
27. Sopian NA, Ajat M, Shafie NI, Noor MM, Ebrahimi M, Rajion MA, Mustafa MZ. Does short-term dietary omega-3 fatty acid supplementation influence brain hippocampus gene expression of zinc transporter-3?. Int J Mol Sci. 2015;16(7):15800-15810. DOI: 10.3390/ijms160715800
28. Hafandi A, Begg DP, Premaratna SD, Sinclair AJ, Jois M, Weisinger RS. Dietary repletion with ω-3 fatty acid or with COX inhibition reverses cognitive effects in F3 ω-3 fatty-acid-deficient mice. Comp Med. 2014;64(2):106-109. [available at]
29. Parveen K, Siddiqui WA, Arif JM, Kuddus M, Shahid SA, Kausar MA. Evaluation of vegetables and fish oils for the attenuation of diabetes complications. Cell Mol Biol. 2019;65(7):38-45. DOI: 10.14715/cmb/2019.65.7.8
30. Keapai W, Apichai S, Amornlerdpison D, Lailerd N. Evaluation of fish oil rich in MUFAs for antidiabetic and anti-inflammation potential in experimental type 2 diabetic rats. Korean J Physiol Pharmacol. 2016;20(6):581-593. DOI: 10.4196/kjpp.2016.20.6.581
31. Inoue T, Tanaka M, Masuda S, Ohue-Kitano R, Yamakage H, Muranaka K, *et al.* Omega-3 polyunsaturated fatty acids suppress inflammatory responses of lipopolysaccharide-stimulated mouse microglia by activating SIRT1 pathways. Biochim Biophys Acta Mol Cell Biol Lipids. 2017;1862(5):552-560. DOI: 10.1016/j.bbalip.2017.02.010
32. Behl T, Grover M, Shah K, Makkar R, Kaur L, Sharma S, Gupta J. Role of omega-3 fatty acids in the management of diabetes and associated complications. In: Watson RR, De Meester F, editors. Bioactive food as dietary interventions for diabetes. USA: Elsevier; 2019:185-192 p. DOI: 10.1016/B978-0-12-813822-9.00012-6
33. Calder PC. Omega-3 fatty acids and inflammatory processes. Nutrients. 2010;2(3):355-374. DOI: 10.3390/nu2030355
34. Murtishaw AS. The effect of acute LPS-induced immune activation and brain insulin signalling disruption in a diabetic model of Alzheimer's disease [Ph.D. dissertation]. USA: University of Nevada, Las Vegas; 2014. DOI: 10.34917/6456429
35. Hou Y, Xie G, Miao F, Ding L, Mou Y, Wang L, Xu H, Liu X, Chen J. Pterostilbene attenuates lipopolysaccharide-induced learning and memory impairment, possibly via inhibiting microglia activation and protecting neuronal injury in mice. Prog Neuropsychopharmacol Biol Psychiatry. 2014;54:92-102. DOI: 10.1016/j.pnpbp.2014.03.015
36. Fu CXu, Dai L, Yuan XY, Xu YJ. Effects of fish oil combined with selenium and zinc on learning and memory impairment in aging mice and amyloid precursor protein processing. Biol Trace Elem Res. 2021;199(5):1855-1863. DOI: 10.1007/s12011-020-02280-y
37. Al-Okbi SY, Mohammed SE, Al-Siedy EK, Ali NA. Fish oil and primrose oil suppress progression of Alzheimer's-like disease induced by aluminum in rats. J Oleo Sci. 2020;69(7):771-782. DOI: 10.5650/jos.ess20015
38. Kim HY. Neuroprotection by docosahexaenoic acid in brain injury. Mil Med. 2014;179(11):106-111. DOI: 10.7205/MILMED-D-14-00162
39. Anand K, Dhikav V. Hippocampus in health and disease: an overview. Ann Indian Acad Neurol. 2012;15(4):239-246. DOI: 10.4103/0972-2327.104323
40. Chauhan P, Jethwa K, Rathawa A, Chauhan G, Mehra S. The anatomy of the hippocampus. In: Dheen ST, editor. Cerebral ischemia. Australia:

Exon Publications; 2021. 17-30 p. DOI: 10.36255/exonpublications.cerebralischemia.2021.hippocampus
41. Zimatkin SM, Bon EI. Dark neurons of the brain. Neurosci Behav Physiol. 2018;48(8):908-12. DOI: 10.1007/s11055-018-0648-7
42. Xiong H, Tang F, Guo Y, Xu R, Lei P. Neural circuit changes in neurological disorders: evidence from in vivo two-photon imaging. Ageing Res Rev. 2023;87:101933. DOI: 10.1016/j.arr.2023.101933
43. Csordás A, Mázló M, Gallyas F. Recovery versus death of dark (compacted) neurons in non-impaired parenchymal environment: light and electron microscopic observations. Acta Neuropathol. 2003;106(1):37-49. DOI: 10.1007/s00401-003-0694-1
44. Ahmadpour S, Behrad A, Vega IF. Dark neurons: a protective mechanism or a mode of death. J Med Histol. 2019;3(2):125-31. DOI: 10.21608/jmh.2020.40221.1081
45. Cherubini E, Miles R. The CA3 region of the hippocampus: how is it? What is it for? How does it do it?. Front Cell Neurosci. 2015;9:9-11. DOI: 10.3389/fncel.2015.00019
46. Kesner RP. Behavioural functions of the CA3 subregion of the hippocampus. Learn Mem. 2007;14(11):771-81. DOI: 10.1101/lm.688207
47. Ghafarimoghadam M, Mashayekh R, Gholami M, Fereydani P, Shelley-Tremblay J, Kandezi N, Homayouni K, Karimi N, Yazdi S, Azizi R. A review of behavioural methods for the evaluation of cognitive performance in animal models: current techniques and links to human cognition. Physiol Behav. 2022;244:113652. DOI: 10.1016/j.physbeh.2021.113652
48. Catorce MN, Gevorkian G. LPS-induced murine neuroinflammation model: main features and suitability for preclinical assessment of nutraceuticals. Curr Neuropharmacol. 2016;14(2):155-64. DOI: 10.2174/1570159x14666151204122017
49. Qin L, Wu X, Block ML, Liu Y, Breese GR, Hong JS, Knapp DJ, Crews FT. Systemic LPS causes chronic neuroinflammation and progressive neurodegeneration. Glia. 2007;55(5):453-62. DOI: 10.1002/glia.20467
50. Yang H, Fan S, Song D, Wang Z, Ma S, Li S, Chen X, Zhang J, Tang X, Wang M. Long-term streptozotocin-induced diabetes in rats leads to severe damage of brain blood vessels and neurons via enhanced oxidative stress. Mol Med Rep. 2013;7(2):431-40. DOI: 10.3892/mmr.2012.1227
51. Djuricic I, Calder PC. Beneficial outcomes of omega-6 and omega-3 polyunsaturated fatty acids on human health: an update for 2021. Nutrients. 2021;13(7):2421. DOI: 10.3390/nu13072421
52. Zhang W, Li P, Hu X, Zhang F, Chen J, Gao Y. Omega-3 polyunsaturated fatty acids in the brain: metabolism and neuroprotection. Front Biosci. 2011;16:2653-70. DOI: 10.2741/3878
53. Bakre AT, Chen R, Khutan R, Wei L, Smith T, Qin G, Danat IM, Zhou W, Schofield PW, Ye W, Lv Y, Chen X, Kantaris X, Yang Q, Hu Z, Chen L, Hong Z, Prince M. Association between fish consumption and risk of dementia: a new study from China and a systematic literature review and meta-analysis. Public Health Nutr. 2018;21(10):1921-32. DOI: 10.1017/S136898001800037X
54. Wood AR, Chappell HF, Zulyniak MA. Dietary and supplemental long-chain omega-3 fatty acids as moderators of cognitive impairment and Alzheimer's disease. Eur J Nutr. 2022;61(2):589-604. DOI: 10.1007/s00394-021-02655-4
55. Afshordel S, Hagl S, Werner D, Röhner N, Kögel D, Bazan NG, Eckert GP. Omega-3 polyunsaturated fatty acids improve mitochondrial dysfunction in brain aging - impact of Bcl-2 and NPD-1 like metabolites. Prostaglandins Leukot Essent Fat Acids. 2015;92:23-31. DOI: 10.1016/j.plefa.2014.05.008
56. Ahmmed MK, Ahmmed F, Tian H, Carne A, Bekhit AD. Marine omega-3 (n-3) phospholipids: a comprehensive review of their properties, sources, bioavailability, and relation to brain health. Compr Rev Food Sci Food Saf. 2020;19(1):64-123. DOI: 10.1111/1541-4337.12510
57. Barde SR, Sakhare RS, Kanthale SB, Chandak PG, Jamkhande PG. Marine bioactive agents: a short review on new marine antidiabetic compounds. Asian Pac J Trop Dis. 2015;5(S1):S209-S213. DOI: https://doi.org/10.1016/S2222-1808(15)60891-X
58. Mateos R, Pérez-Correa JR, Domínguez H. Bioactive properties of marine phenolics. Mar Drugs. 2020;18(10):501. DOI: 10.3390/md18100501
59. Hajianfar H, Paknahad Z, Bahonar A. The effect of omega-3 supplements on antioxidant capacity in patients with type 2 diabetes. Int J Prev Med. 2013;4(2):S234-S238. [available at]
60. Sánchez-Romero L, Pacheco-Moisés FP, Mohammed EH, Mireles-Ramírez MA, Cruz-Serrano JA, Velázquez-Brizuela IE, Ortiz GG. Effect of fish oil on oxidative stress markers in patients with probable Alzheimer's disease. Arch Latinoam Nutr. 2020;70(2):123-133. DOI: 10.37527/2020.70.2.005

إعطاء زيت السمك يحمي بشكل فعال تغييرات الحصين ويحسن أداء الذاكرة المكانية في نموذج حيواني عنده ارتفاع في سكر الدم - التهاب العصب

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الخلاصة

ثبت على نطاق واسع أن الالتهاب العصبي يمكن أن يضعف الإدراك وأنسجة الدماغ في مرض السكري. أظهرت أدلة قوية أن زيت السمك يقلل من تطور مرض الزهايمر ولكن له آثار متضاربة على تطور مرض السكري. وبالتالي، تبحث الدراسة في كيفية تأثير إعطاء زيت السمك على ارتفاع السكر في الدم والذاكرة المكانية وأنسجة الحصين في ارتفاع السكر في الدم-فئران الالتهاب العصبي. تم تقسيم ذكور جرذان ويستار (عدد ٣٠) إلى خمس مجموعات: الجرذان الضابطة، والجرذان المعطاة ٣ جم من زيت السمك، والجرذان المحقونة بالستربتوزوتوسين-عديد السكاريد الدهني، والجرذان المحقونة بالستربتوزوتوسين-لبس وأعطيت ١ جم/كجم من زيت السمك، والجرذان المحقونة بالستربتوزوتوسين-لبس وأعطيت ٣ جم/كجم من زيت السمك. بعد ستة أسابيع من معالجة زيت السمك، تم تقييم أداء الذاكرة المكانية للحيوانات باستخدام اختبار المتاهة. بعد ذلك، تم جمع عينة دم لتحديد تركيز الجلوكوز في الدم، بينما تم الحصول على أنسجة المخ للفحص النسيجي. كشفت النتيجة أن مكملات زيت السمك قللت من ارتفاع السكر في الدم. كما أظهر أداء محسنا للذاكرة المكانية، كما يتضح من زيادة عدد إدخالات الذراع الجديدة والوقت المستغرق. وعلاوة على ذلك، يقترح أن النتيجة التي توصل إليها اختبار المتاهة كان لها ارتباط قوي مع فعالية زيت السمك في منع التغيرات في كورنو أمونيس ٣ (كا ٣). وجدت هذه الدراسة أن مكملات زيت السمك تحمي بنجاح الخلايا العصبية في الحصين من التلف، مما أدى إلى تحسين الأداء المعرفي في نموذج حيواني لارتفاع السكر في الدم-التهاب الأعصاب. ومن ثم، يقترح إعطاء مكملات زيت السمك بانتظام لمرضى السكري لتجنب ضعف الإدراك.