

# Short-Term and Long-Term Effects of Low and High Fat Diets on Lipid Profile and Acetylcholinesterase Activity in Different Brain Regions of Male Wistar Rats

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## Abstract

High intake of saturated fat and cholesterol has been related to an increase risk of cardiovascular disease. Given their important role in neuronal function, there has been an increasing focus on altered lipid levels in brain disorder. In this study, the brain lipid profiles and acetylcholinesterase activity in 30 Wistar rats administered with low (8% lard, 1.3% cholesterol) and high (16% lard, 2.5% cholesterol) fat diets for two and four weeks were determined. High density lipoprotein cholesterol (HDL-C), total cholesterol (TC), triacylglycerol (TAG) and low density lipoprotein cholesterol (LDL-C) levels were determined using commercial diagnostic kits, while the activity of acetylcholinesterase was determined by Ellman's method. High fat diet (HFD) causes a significant decrease in high density lipoprotein cholesterol (HDL-C) in the plasma at both weeks when compared with the control ( $p < 0.05$ ). Total cholesterol (TC), triacylglycerol (TAG) and low density lipoprotein cholesterol (LDL-C) were significantly increase in the plasma of the experimental rats at four weeks when compared with the control ( $p < 0.05$ ). Significant increase was observed in HDL-C, TC, TAG and HDL-C in olfactory lobe, cerebellum and medulla oblongata at four weeks when compared with the control ( $p < 0.05$ ), while a significant decrease was observed in the cerebra lipid profile when compared with the control ( $p < 0.05$ ). Low fat and high fat diets cause a significant increase in the activity of acetylcholinesterase in olfactory lobe, cerebrum, cerebellum and medulla oblongata at four weeks when compared with the control group ( $p < 0.05$ ). In conclusion, consumption of high dietary fat in this study alters brain lipid profile, and decrease brain acetylcholine level, therefore may contribute to progressive cognitive impairment.

## 1. INTRODUCTION

The brain is one of the most complex organs belonging to the central nervous system and is involved with perception, learning and memory, motion, and metabolic activities, which result from the communication between neurons in the brain, via a combination of electrical and chemical signals (Lovinger, 2008; Scheiffele, 2003). The brain is highly enriched in lipids, supporting structural, biochemical and cell signaling functions (O'Brien and Sampson, 1965). Bioactive lipids within the brain are shown to be pivotal for central nervous system homeostasis by modulating neurotransmission, synaptic plasticity, enzyme function, ion channel activities, gene expression and inflammation (Cermenati *et al.*, 2015; Bazinet and Laye, 2014; Horrocks and Farooqui, 2004). Due to its important role, brain dysfunction may cause serious illness that deteriorates the quality of life. Changes in cerebral lipid homeostasis

are widely reported to be associated with neurodegenerative disorders, and several studies also suggest significant changes in brain lipids with non-pathological ageing (Cunnane *et al.*, 2012; Muller *et al.*, 2015, Chan *et al.*, 2012).

Chronic ingestion of Western styled diets enriched in saturated fats are causally associated with a range of neurodegenerative disorders including vascular dementia and Alzheimer's disease (Kanoski and Davidson, 2011; Kalmijn *et al.*, 1997). The mechanisms underpinning this association are not completely understood but broadly include capillary dysfunction; neurovascular inflammation; altered redox state and heightened oxidative stress (Breteler, 2000; Sparks *et al.*, 2000; Hsu and Kanoski, 2014; Aung *et al.*, 2016). With chronic ingestion of pro-inflammatory fat enriched diets, it is a reasonable proposition to suggest that changes of the brain lipidome may be realized and causally associated with some of the indicated

mechanistic pathways. Cerebral sequelae that may reflect changes in the brain lipidome following long-term consumption of high-fat diets may be broad and include compromised insulin signaling (Benoit *et al.*, 2009; Oh *et al.*, 2013), neuronal apoptosis (Moraes, 2009), and poorer cognitive performance (Pipatpiboon *et al.*, 2013; Greenwood and Winocur, 2001).

Furthermore, Acetylcholine (ACh) is a neurotransmitter that functions in conveying nerve impulses across synaptic clefts within the CNS (Tripathi and Sritvastava 2008). Following the transmission of an impulse across the synapse by the release of Ach, AChE is released into the synaptic cleft (Horton *et al.*, 2006). This enzyme hydrolyzes ACh to choline and acetate and transmission of the nerve impulse is terminated (Liesener *et al.*, 2007).

Cholinergic systems in the CNS play an important role in the learning and memory (Lena and Changeux, 1998; Levey *et al.*, 1995). Acetylcholine (ACh) is required for cholinergic neurotransmission in the central and peripheral nervous systems (Goodman and Soliman, 1991). Acetylcholinesterase activity has been used as a marker for cholinergic activity. Acetylcholinesterase plays a very important role in the acetylcholine-cycle, including the release of acetylcholine (Kouniniotou and Tsakiris, 1989). The duration of action of acetylcholine at the synaptic clefts is critically dependent on acetylcholinesterase activity (Cooper *et al.*, 2003). Acetylcholine plays an integral role in normal muscle functions, motor activity, attention, fear, anxiety and learning (Ferry *et al.*, 1999; Fujimaki *et al.*, 2000). Memory process is controlled through cholinergic interactions with their neurotransmitters (Ohno *et al.*, 1997).

In the present work, we evaluated the short-term and long-term effects of low and high fat diets on the lipid profile and acetylcholinesterase activity in different brain regions of male Wistar rats.

## 2. MATERIALS AND METHODS

### 2.1. Experimental Animals

Thirty male Wistar rats were used for this study with body weight ranging between 220- 250g. The rats were housed in clean plastic cages well ventilated, with 12 hours light/ dark cycle and acclimatized for two weeks. They were fed with standard rat pellet and water ad libitum.

### 2.2. Reagents and Chemicals

Ammonium ferrothiocyanate, chloroform, chloroform-methanol (2:1), K<sub>2</sub>PO<sub>4</sub> (potassium diphosphate), TritinX-100, Diethyl ether, acetylthiocholine, distilled water, ethanol (97%), HDL-C, cholesterol and triglyceride kits were procured from Sigma-Aldrich Chemicals, USA. All other chemicals and reagents were of the purest grade and were of an analytical grade.

### 2.3. Diet Formulation

The diet was formulated according to the modified method of Griffiths (1964), which is presented in Table 1 below;

The ingredients of the experimental diets were measured on a weighing balance, which were thoroughly mixed together and stored in a well-labelled plastic container appropriately.

**Table 1.** Composition of the experimental low and high fat diets

Contents	Control diet (g/100g)	Low fat diet (LFD) (g/100g)	High fat diet (HFD) (g/100g)
Wheat flour	70.7	61.9	52.6
Milk powder	23.6	23.1	23.2
Dried yeast powder	3.5	3.5	3.5
Sodium Chloride	1.2	1.2	1.2
Multivitamins	1.0	1.0	1.0
Cholesterol powder	0	1.3	2.5
Pork lard	0	8	16

### 2.4. Experimental Design

After acclimatization, the rats were randomly divided into three groups containing five rats each. Group one serves as the control group fed with control diet, while group two and three consist of rats fed with low and high fat diets respectively for two and four weeks.

#### 2.4.1. Animal Sacrifice and Sample Collection

Animals were sacrificed at the end of two and four weeks of dietary fat administration, respectively, blood was collected from the animals by cardiac puncture under light anaesthesia after an overnight fast, the blood collected was transferred immediately into a heparinized tube to prevent blood clotting.

Olfactory lobe, cerebrum, cerebellum and medulla oblongata were excised using scissors

and forceps from the intact brain, a representative from each group was placed in 10% formalin for histology, while others were placed in Eppendorf tubes and were stored at -4°C until they were homogenized.

**2.4.2. Separation of plasma from red blood cell**

The blood samples were then centrifuged at 4,000rpm for 10 minutes to separate the plasma from red blood cell. The supernatant was the plasma and it was kept in a clean eppendorf tubes and stored at -4°C for further analysis.

**2.4.3. Homogenization and Extraction of Lipid**

Ten percent homogenate of the tissues was prepared by homogenising 0.2g of tissues in 1.8ml of chloroform: methanol mixture (2:1v/v). The homogenate was centrifuged at 4000rpm for 10 minutes; the resulting supernatant was then washed with 200µl of KCl and re-centrifuged for 5 minutes to obtain the lipid extract (Folch *et al.*, 1957).

**2.4.4. Lipid Assay**

The concentrations of plasma and brain HDL-C, TC, TAG and LDL-C were determined using commercial diagnostic kits from Sigma-Aldrich Chemicals, USA.

**2.4.5. Determination of Acetylcholinesterase (AChE) Activity**

The method of AChE activity estimation is popularly known as Ellman’s method named after George Ellman who developed this method in 1961 (Ellman *et al.*, 1961). The esterase activity is measured by providing an artificial substrate, acetylthiocholine (ATC). Thiocholine released because of the cleavage of ATC by AChE is allowed to react with the -SH reagent 5,5’- dithiobis-(2-nitrobenzoic acid) (DTNB), which is reduced to thionitrobenzoic acid, a yellow coloured anion with an absorption maxima at 412nm. The extinction coefficient of the thionitrobenzoic acid is  $1.36 \times 10^4$ /molar/centimeter. The concentration of thionitrobenzoic acid detected using a UV spectrophotometer is then taken as a direct estimate of the AChE activity.

**2.4.6. Histology of Brain regions**

Histological examination was based on earlier protocol (Humason, 1979). Brain regions were fixed in 10% formalin solution for 24 h. All samples were then dehydrated in graded ethanol series, cleared in toluene and embedded in

paraffin wax; 5-6 µm sections were routinely stained with Harris hematoxylin and eosins stains (Sigma-Aldrich) and were assessed under light microscope (Nikon Eclipse E400).

**2.4.7. Statistical Analysis of results**

Results are expressed as mean ± standard error of the mean, and the differences among the experimental groups were analyzed using one way analysis of variance followed by Dunnett multiple comparisons with  $p < 0.05$  considered significant.

**3. RESULTS**

The experimental low and high fat diets was successfully formulated in accordance with the modified method of Griffiths (1964), as previously shown in Table 1. The low fat diet is made up of 1.3% cholesterol powder and 8% of pork lard, while the high fat diet is made up of 2.5% cholesterol powder and 16% of pork lard.

**3.1. Plasma Lipid Profile**

**Table 2.** Plasma lipid profile of rats administered with low and high fat diets for two weeks

Gro up	HDL-C (mg/dL)	TC (mg/dL)	TAG (mg/dL)	LDL-C (mg/d L)
Cont rol	53.48±0.79	54.25±0.70	45.74±0.38	29.27±0.41
LFD	4.37±0.11*	10.25±0.04*	30.47±0.23*	4.76±0.04*
HFD	0.39±0.04*	90.99±2.05*	26.60±0.31*	25.40±0.49*

Values represent mean ± standard error of the mean (n=5).

\*Significantly different from the control group at  $p < 0.05$

**3.1.1. Lipid profile of brain regions at two weeks**

**Table 3.** Olfactory lobe lipid profile of rats administered with low and high fat diets for two weeks

Grou p	HDL-C (mg/d L)	TC (mg/dL)	TAG (mg/dL)	LDL-C (mg/dL )
Contr ol	96.56 ± 1.26	203.91±2.76	57.12±0.45	82.37±1.19
LFD	25.32 ± 0.64*	52.01±1.06*	23.00±0.25*	33.64±0.77*
HFD	0.97±0.02*	10.63±0.01*	30.55±0.01*	6.19±0.02*

Values represent mean ± standard error of the mean (n=5).

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\*Significantly different from the control group at  $p < 0.05$

**Table 4.** Cerebrum lipid profile of rats administered with low and high fat diets for two weeks

Gro up	HDL-C (mg/dL)	TC (mg/dL)	TAG (mg/dL)	LDL-C (mg/dL)
Cont rol	53.48±0.79	255.11±3.73	82.25±0.29	173.89±2.63
LFD	4.37±0.108*	20.50±0.22*	64.31±0.51*	50.66±1.08*
HFD	0.39±0.004*	15.08±0.16*	50.27±0.27*	8.51±0.102*

Values represent mean ± standard error of the mean (n=5).

\*Significantly different from the control group at  $p < 0.05$

**Table 5.** Cerebellum lipid profile of rats administered with low and high fat diets for two weeks

Gro up	HDL-C (mg/dL)	TC (mg/dL)	TAG (mg/dL)	LDL-C (mg/dL)
Cont rol	19.72±0.275	135.85±2.89	83.67±0.15	104.14±2.35
LFD	9.47±0.23*	72.04±1.09*	73.47±0.43	49.30±0.66*
HFD	11.02±0.22*	56.26±1.18*	73.47±0.43	8.51±0.65*

Values represent mean ± standard error of the mean (n=5).

\*Significantly different from the control group at  $p < 0.05$

**Table 6.** Medulla oblongata lipid profile of rats administered with low and high fat diets for two weeks

Gro up	HDL-C (mg/dL)	TC (mg/dL)	TAG (mg/dL)	LDL-C (mg/dL)
Cont rol	21.54±0.29	54.25±0.70	45.74±0.38	29.27±0.418
LFD	0.696±0.1*	10.25±0.04*	30.47±0.23*	4.76±0.04*
HFD	54.25±1.39*	90.99±2.05*	26.53±0.31*	25.40±0.49

Values represent mean ± standard error of the mean (n=5).

\*Significantly different from the control group at  $p < 0.05$

**3.2. Plasma lipid profile at four weeks**

**Table 7.** Plasma lipid profile of rats administered with low and high fat diets for four weeks

Gro up	HDL-C (mg/dL)	TC (mg/dL)	TAG (mg/dL)	LDL-C (mg/dL)
Cont rol	51.16±0.35	251.66±2.51	35.69±0.28	120.57±1.42
LFD	39.17±0.55*	319.03±1.67*	57.23±0.29*	162.33±0.90*
HFD	31.59±0.69*	397.14±0.49*	68.45±0.39*	235.5±0.91*

Values represent mean ± standard error of the mean (n=5).

\*Significantly different from the control group at  $p < 0.05$

**3.3. Lipid profile of brain regions at four weeks**

**Table 8.** Olfactory lobe lipid profile of rats administered with low and high fat diets for four weeks

Gro up	HDL-C (mg/dL)	TC (mg/dL)	TAG (mg/dL)	LDL-C (mg/dL)
Cont rol	33.64±0.08	115.55±0.50	31.13±0.13	85.19±0.28
LFD	64.97±0.42*	190.52±0.71*	65.35±0.68*	95.90±0.82*
HFD	140.26±0.56*	290.68±0.68*	55.30±0.41*	125.41±0.71*

Values represent mean ± standard error of the mean (n=5).

\*Significantly different from the control group at  $p < 0.05$

**Table 9.** Cerebrum lipid profile of rats administered with low and high fat diets for four weeks

Gro up	HDL-C (mg/dL)	TC (mg/dL)	TAG (mg/dL)	LDL-C (mg/dL)
Cont rol	51.16±0.35	347.64±2.82	59.67±0.20	268.18±2.43
LFD	39.17±0.55*	340.30±1.59	64.08±0.63*	271.97±1.14
HFD	31.59±0.68**	192.07±3.50*	38.01±0.42*	139.99±2.67*

Values represent mean ± standard error of the mean (n=5).

\*Significantly different from the control group at  $p < 0.05$

**Table 10.** Cerebellum lipid profile of rats administered with low and high fat diets for four weeks

Gro up	HDL-C (mg/dL)	TC (mg/dL)	TAG (mg/dL)	LDL-C (mg/dL)
Cont rol	35.67±0.48	278.92±3.49	28.34±0.29	228.08±2.93

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LFD	74.43±0.80*	333.72±2.89*	64.58±0.68*	229.81±2.19
HFD	59.67±0.71*	332.06±3.86*	42.15±0.45*	252.01±3.06*

Values represent mean ± standard error of the mean (n=5).

\*Significantly different from the control group at  $p < 0.05$

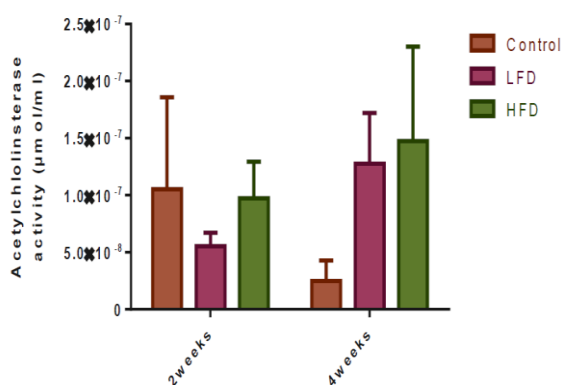
**Table 11.** Medulla oblongata lipid profile of rats administered with low and high fat diets for four weeks

Group	HDL-C (mg/dL)	TC (mg/dL)	TAG (mg/dL)	LDL-C (mg/dL)
Control	91.57±1.17	251.66±2.50	35.69±0.27	120.57±1.41
LFD	130.32±1.05*	319.02±1.67*	57.23±0.29*	162.34±0.99*
HFD	130.63±0.55*	397.14±0.49*	68.45±0.39*	235.50±0.91*

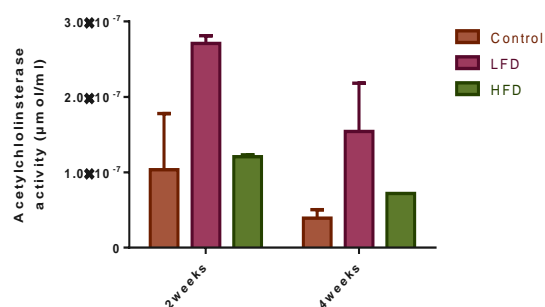
Values represent mean ± standard error of the mean (n=5).

\*Significantly different from the control group at  $p < 0.05$

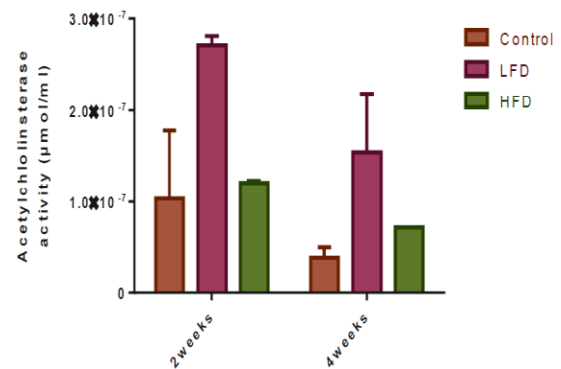
### 3.4. Acetylcholinesterase Activity in brain regions at two and four weeks



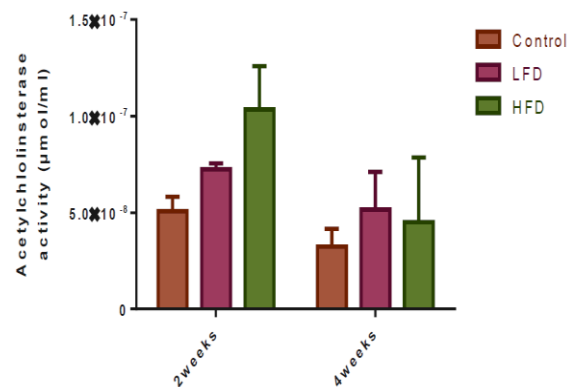
**Figure 2.** Olfactory lobe Acetylcholinesterase activity of rats administered with low and high fat diets



**Figure 3.** Cerebrum Acetylcholinesterase activity of rats administered with low and high fat diets

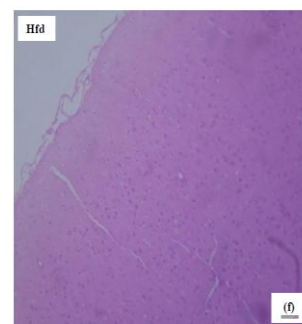
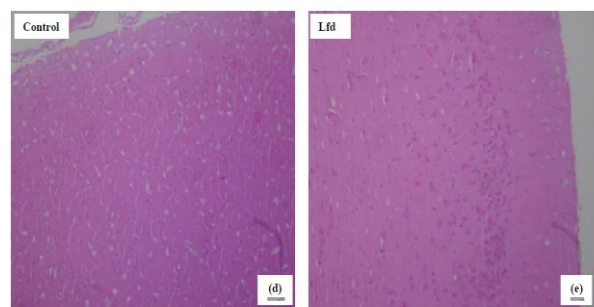


**Figure 4.** Cerebellum Acetylcholinesterase activity of rats administered with low and high fat diets



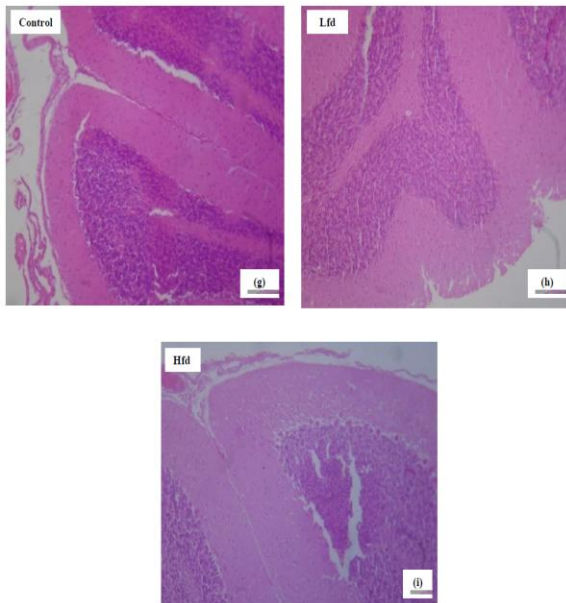
**Figure 5.** Medulla oblongata Acetylcholinesterase activity of rats administered with low and high fat diets

### 3.5. Histological Analysis



**Figure 8(d).** Photomicrograph of cerebrum showing neuronal cells on a background of neuropil at two weeks. No abnormalities are seen. (e) Photomicrograph of cerebrum showing neuronal cells on a background of neuropil at two weeks. No abnormalities are seen. (f): Photomicrograph of

cerebrum showing neuronal cells on a background of neuropil at two weeks. No abnormalities are seen. (X40).



**Figure 8** (g). Photomicrograph section of cerebellum shows cortex composed of molecular, ganglionic and granular layers, as well as a deeper medulla at two weeks. No abnormalities are seen. (h): Photomicrograph section of cerebellum showing cortex composed of molecular, ganglionic and granular layers, as well as a deeper medulla at two weeks. No abnormalities are seen. (i): Photomicrograph section cerebellum showing cortex composed of molecular, ganglionic and granular layers, as well as a deeper medulla at two weeks. No abnormalities are seen. (X40).

#### 4. DISCUSSION

High fat diet induced hyperlipidemia in rats including hypercholesterolemia and hypertriglyceridemia, which are major risk factors for the development of cardiovascular diseases (Makni *et al.*, 2008). In this present study, administration of high fat diet for four weeks causes a significant increase in plasma total cholesterol and triacylglycerol concentration. The rise in plasma total cholesterol observed in this study could be attributed to increase in HMG-CoA reductase activity in the liver of animals fed with high fat diet and the reduced rate of the clearance of LDL from circulation due to defective LDL receptors, which is associated with increase of plasma total cholesterol concentration (Zulet *et al.*, 1999). The significant rise in plasma triacylglycerols level may be attributed to the decrease of activity of lipase which is an insulin-dependent enzyme involved in triglyceride clearance from plasma by mediating

triglyceride lipolysis into glycerol and fatty acids (Yost *et al.*, 1995). Another possibility is that such significant increase in triglycerides might be a consequence of overproduction of VLDL by the liver. These results are consistent with those achieved by Diaz *et al.*, (2000) who reported that, rats fed with the high fat diet showed marked increase in plasma total cholesterol and triacylglycerols.

In addition, a significant increase in plasma low density lipoprotein cholesterol (LDL-C) was observed after four weeks when compared with normal control group. These results are similar to those reported by Abdel-Maksoud *et al.*, (2002) who reported that, mice and rats fed with high fat diet showed severe hypercholesterolemia, elevated plasma serum LDL-C and VLDL-C compared to those fed a normal diet. Yushchenko, (1959) recorded that, rabbits fed on hyperlipidemic diet showed significant increase of the plasma lipid levels; total lipids, total cholesterol,

triacylglycerols, and phospholipids. It should be noted that animals fed with normal diet had higher levels of triacylglycerol than the groups fed with low fat diet and high fat diet at two weeks. This may be due to the higher content of carbohydrate in the former diet as a consequence of its lower fat content, as shown in Table 1.

Elevated levels of plasma total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and triglyceride (TG) as well as reduced levels of plasma high density lipoprotein cholesterol (HDL-C) are often associated with an increased risk of coronary heart disease (Smith *et al.*, 2004).

The present study also shows that administration of high fat diet at four weeks significantly reduced the level of total cholesterol, high density lipoprotein cholesterol, triacylglycerol and low density lipoprotein cholesterol in the cerebrum. Cholesterol which is a major constituent of cell membranes modulates the physical properties of the brain which in turn affect the function of membrane proteins such as receptors and neuron transmission. More than a decade ago, Roses and colleagues demonstrated the existence of a genetic link between the risk of Alzheimer's diseases and the E4 allele of apolipoprotein E, a protein involved in cholesterol homeostasis (Myers and Goate, 2001). In addition, lowering of cholesterol concentration may inhibit neuron transmission

because neurons require cholesterol as building material for the assembly of presynaptic components such as synaptic vesicles (Porter, 2000).

The present study also shows that administration of high fat diet at four weeks significantly increase the level of high density lipoprotein cholesterol, total cholesterol and low density lipoprotein cholesterol in the olfactory lobe and medulla oblongata. These significant changes in the level of the lipid panel in the brain regions may be due to the disruption of the blood-brain barrier, which protects the brain from circulating blood. This barrier effectively prevents uptake of lipoprotein-bound cholesterol from the circulation, and *de novo* synthesis is considered to be responsible for practically all cholesterol in this organ. Such disruptions can result from consuming high-fat diet (HFD) and inflammation produced by alteration in brain vasculature resulted from chronic consumption of the high fat diets. The disruption of the permeability of blood-brain barrier, can make it vulnerable to systemic molecules that could trigger degenerative processes (Kanoski *et al.*, 2010; Hsu and Kanoski, 2014). It has been documented that rabbits fed with a diet containing 2% cholesterol for 8 weeks, have demonstrated that such type of diet disrupts BBB permeability, alters vascularity, and induce vessels inflammation and A $\beta$  peptide accumulation in parenchyma; and this accumulation is similar to that observed in brains of AD patients (Sparks *et al.*, 2008).

Acetylcholinesterase is an acetylcholine hydrolyzing enzyme that is responsible for the termination of cholinergic response. Acetylcholine as a neurotransmitter has a crucial role in the central nervous system and is implicated in behavioral as well as learning and memory and neurodegenerative diseases (Berger-Sweeney *et al.*, 2003; Schliebs and Arendt, 2006). Acetylcholinesterase activation leads to a fast acetylcholine degradation and a subsequent down stimulation of ACh receptors causing undesirable effects on cognitive functions (Soreq and Seidman 2001). Our results (Fig.4-7) show that the administration of low and high fat diets for four weeks caused an increase in the activities of acetylcholinesterase in the brain regions. This present finding is contradictory with previous reports on brain AChE activity in animal model of hypercholesterolemia (Paul and Borah, 2017). The differences in the results may be due to the

time of exposure of the fat diets to the animals and composition of the diet.

Considering these findings, it can be speculated that increased AChE activity caused by long-term administration of low and high fat diets may lead to a reduction of cholinergic neurotransmission efficiency due to a decrease in ACh levels in the synaptic cleft, thus contributing to progressive cognitive impairment.

## 5. CONCLUSION

This study reveals that long-term feeding of high fat diet leads to changes in the lipid profile of the different brain regions in Wistar rats as a result of disruption of the blood-brain barrier, which protects the brain from circulating blood. The disruption of the permeability of blood-brain barrier can make it vulnerable to systemic molecules which could trigger degenerative processes. Furthermore, the increase in the activity of acetylcholinesterase of the different brain regions as a result of administration of low and high fat diets for four weeks decrease the neurotransmitter, acetylcholine, and thus may contribute to progressive cognitive impairment.

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**Citation:** *Short-Term and Long-Term Effects of Low and High Fat Diets on Lipid Profile and Acetylcholinesterase Activity in Different Brain Regions of Male Wistar Rats.* Ebuehi, Osaretin A.T, Adewolu, Abiodun . *ARC Journal of Neuroscience.* 2020; 5(1):1-9. doi:dx.doi.org/10.20 431/2456-057X 0501001.

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