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The Protective Effects of Melatonin against Brain Disorders Induced by the Western Diet in Male Rats

Ahmed Raheem Rayshan[1], Ammar A. Abdulwahid[2]*, and Alyaa Abdulhussein Alsaedi[3]

[1]*Scientific affairs department, University of Al-Qadisiyah, Al-Diwaniyah, Al-Qadisiyyah, Iraq*
[2]*Lecturer, Department of Physiology and Pharmacology, College of Veterinary Medicine, University of Baghdad, Baghdad, Iraq*
[3]*Lecturer, Department of Microbiology, College of Veterinary Medicine, University of Al-Qadisiyah, Iraq*

*Corresponding author's Email: ammar.a@covm.uobaghdad.edu.iq

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ABSTRACT

Globally, the effects of consuming a diet rich in fat have gained great concerted attention. The current study was conducted to evaluate the protective effects of melatonin on neurological disorders induced by the western diet in rats. A total of 30 adult male white local Iraqi rats were randomly assigned to three equal groups, including control (CC), high-fat diet (HFD), and melatonin group (HFD+M, a high-fat diet along with intraperitoneal injections of 10 mg/kg body weight melatonin) for 8 weeks. The rats were analyzed in terms of brain tissue concentration of dopamine, tumor necrosis factor (TNF), and nervous system impairment using Barns maze task and elevated plus maze. The findings revealed a significant decline in the dopamine concentration of the HFD group after 8 weeks of treatment, compared to CC and HFD+M groups. Moreover, there was a significant increase in brain TNF-α concentration in the group fed HFD, compared with CC and HFD+M. Finally, the melatonin treatment significantly reduced spatial memory impairments and anxiety induced by HFD in rats. After 8 weeks, the histological examination revealed that brain section rats on an HFD indicated significant congestion in the blood vessels with marked cerebral edema, where there was a dilation of Virchow-Robin space, severe congestion, and infiltration of inflammatory cells in the meninges. The HFD+M groups showed normal meninges without any inflammatory exudate except for a few congestions in the blood vessels and no or mild vacuolations in the cerebral tissue, gliosis, and astrocytosis. In contrast, male rats fed an HFD showed vacuolation and aerophagia in brain tissue and a marked aggregation of the proliferation of astrocytes and a proliferation of microglial cells in the cerebral. In conclusion, HFD impairs brain neurotransmitters, induces pro-inflammatory changes, and affects learning ability and memory by changing the structure of neural tissue. Melatonin can ameliorate HFD-caused effects.

Keywords: Brain, High-fat diet, Inflammatory cells, Learning ability, Melatonin, Nervous system

INTRODUCTION

The earliest definition of a high-fat diet (HFD) as a nutritional strategy to enhance obesity was published in 1959 (Mašek and Fabry, 1959). The HFD can be well observed in the Western, high-energy, high-fat, cafeteria, and high-fat sugar diets. The precise nutrition structure of the control and fat diets, including the quantity and types of carbohydrates of fats, may vary and is not extensively detailed (Mozaffarian et al., 2011; Mota et al., 2023). It is unknown whether strains, ages, and species of animals may affect the outcomes of consuming HFD experiments or whether adjusting critical parameters, such as weight, behaviors, and memory, may be affected by the type and duration of diet exposure (Abbott et al., 2019). Obesogenic feed often contains 60% of total calories as fat, compared to 30-40% fat in a typical Western diet (Lai et al., 2014).

During lipopolysaccharide-induced end toxemia, the spleen releases newly-produced tumor necrosis factor-alpha (TNF) into the liver. The primary source of TNF is end toxemia, which is released from the liver and circulates throughout the body (Tracey, 2007). Tumor necrosis factor-alpha is a critical cytokine with different harmful effects, including the production of more inflammatory cytokines with the infiltration of macrophages (Tracey, 2007). The HFD can enhance the oxidative stress, inflammation, and activation of Nuclear Factor kappa Beta-cell (NF-kB) in the rat cerebral cortex, raising the possibility that HFD increases dementia risk (Zhang et al., 2022). Motivation, reward, punishment, energy expenditure, and working memory are all functions of dopamine, which has been recognized as an important neurotransmitter in brain function (Cools, 2008). Increased dietary fat intake has been linked to a decrease in dopamine signaling, which may increase the calorie intake to compensate for this decreased dopamine. Dopamine is a neurotransmitter that influences food intake, particularly pleasing dietary ingredients. However, increased dietary fat intake has been linked to a decrease in dopamine signaling, which may increase the calorie intake to compensate for this decreased dopamine (Vucetic and Reyes, 2010; Hryhorczuk et al., 2016; Joshi et al., 2021). Studies have confirmed that the brain is sensitive to dietary essential fatty acids, and such a diet can make remarkable changes in membrane composition, consequently altering neurons' metabolic

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properties. In other words, changes in dietary fat composition could have a significant effect on membrane composition and neuronal functions of the brain (Dyer and Greenwood, 1988; Adermark et al., 2021; Dyall et al., 2022).

The central nervous system consists of several distinct brain areas that control memory and learning processes; however, the hippocampus has a prominent function. The dorsal hippocampus appears to be primarily linked to cognition, while emotion, affect, and stress bind in the ventral hippocampus; this region is unique in that its anatomical activities are divided along the dorsoventral axis (Fanselow and Dong, 2010). Both the dorsal and ventral gyrus of the hippocampus are collectively referred to as the dentate gyrus and are sites of postnatal hippocampal neurogenesis. This process facilitates the maturation of new neurons, which eventually become integrated into the hippocampal circuitry and contribute to its function. The dorsal hippocampus, in particular, plays a crucial role in spatial memory processing (Bannerman et al., 2014; Bortolotto et al., 2014).

There may be a benefit to the Barnes Maze over the Morris Water Maze for subjected rodents which have swimming difficulty because of obesity or other metabolic problems brought on by an HFD (Pitts, 2018). The elevated plus maze test assesses anxiety in lab animals. As a general research instrument, a maze test is typically conducted on rodents for neurobiological anxiety studies and acts as a screening test for potential anxiolytic or anxiogenic substances (Kraeuter et al., 2019). The western diet (rich in fat and sugar) has also been linked to learning, memory (spatial), cognition, and hedonics (Francis and Stevenson, 2013). Spatial memory loss and cell death in the hippocampus can be caused by fat-rich meals (Asadbegi et al., 2017). Moreover, the unbalanced production of reactive oxygen species and the body's antioxidants play a significant role in the neurotoxicity caused by an HFD. When exposed to oxidative stress, cell death occurs due to hydroxyl radical formation, lipid peroxidation, and apoptosis (Ganji et al., 2017; Rozha et al., 2022). Studies have shown that a diet mainly containing saturated fatty acids with trans-fatty acids increases the melatonin hormone secreted from the pineal gland during the dark period and has a vital role in immunity. Daily melatonin administration affects some physiological parameters, including glycemic index, leptin, and dopamine (Al-Azawi et al., 2003). In addition, melatonin decreases lipid levels by increasing the conversion of endogenous cholesterol to bile acids and suppresses cholesterol synthesis and accumulation (Kara and Kara, 2022). Melatonin stimulates the synthesis of antioxidant enzymes, including superoxide dismutase, glutathione peroxidase, and glutathione reductase (Sabeeh and Khudair, 2017).

Melatonin N-acetyl 5methoxytryptamin, isolated for the first time from pineal glands of bovine (Lerner et al., 1958; Venegas et al., 2012), is an endo-neurohormone derived from tryptophan (García-Bernal et al., 2021). The lack of melatonin can lead to various health problems, including neurodegenerative illnesses, circadian rhythm and mood disorders deprivation, diabetes type two, and pain (Comai and Gobbi, 2014). Some health problems, such as obesity, diabetes, hypertension, and respiratory diseases, can be linked to sleep deprivation (Kuvat et al., 2020) since sleep deprivation negatively affects biological and physiological processes (McEwen, 2006; Yin et al., 2017). Melatonin secretion occurs just as sleep propensity since there is a decrease in core body temperature, alertness, and performance (Pandi-Perumal et al., 2008; Borbély et al., 2016). Hippocampal neurons directly respond to melatonin's effects on memory formation (Chang et al., 2021). Melatonin has been shown to have anti-nociceptive, antidepressant, anxiolytic, anti-neophobic, and locomotor activity-regulating effects (Uz et al., 2005; Mantovani et al., 2006; Fenton-Navarro et al., 2021). Melatonin can mediate the effects of mitochondria on physiological processes (Reiter et al., 2014). Melatonin improves the flow of electrons in the inner mitochondrial membrane, which in turn protects the morphology of the cell membrane. It also boosts the activity of antioxidant enzymes, scavenges free radicals, and enhances functional aspects of the cell (García et al., 2020). Improved membrane fluidity, decreased edema, and reduced infiltration of polymorphonuclear cells into damaged tissue are among the factors that result in a decrease in the expression of pro-inflammatory cytokines. Melatonin achieves this by preventing nuclear factor-kB translocation to the nucleus and binding to DNA, both of which are crucial factors in the inflammatory response (Mayo et al., 2005). Methamphetamine results in an expression reduction of dopamine transporter in the rat hippocampus, which was stopped and reversed by melatonin (Panmak et al., 2021). With this in mind, the current study aimed to examine the detrimental effects of a high-fat diet on animal behaviors and brain processes and to investigate the potential of melatonin to mitigate any negative effects.

MATERIALS AND METHODS

Ethical approval

Animal care and treatment in this study were carried out at the Faculty of Veterinary Medicine, University of Baghdad, Iraq, strictly following the code of ethics for animal experiments (P.G. 201 date 25-1-2023).

Study design

A total of 30 adult male white local rats with an average weight of 160-200 g were housed in special plastic cages (15×70×60 cm) in a room at the animal house of the Veterinary Medicine College, Baghdad University, Iraq. The rats were sustained under controlled conditions for 12 hours of light and 12 hours of darkness at the temperature of 22-25°C

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and 40% ± 5% relative humidity. The rats were acclimatized for 10 days prior to the trial. For adaptation, food and water were provided *ad libitum.* The study lasted 8 weeks. The experimental rats were divided randomly into three equal groups (10 rats in each group). The first group was the control group (CC), in which the rats were fed a basal diet throughout the experiment and received an intraperitoneal (IP) injection of normal saline (Table 1). The second group was fed an HFD for 8 weeks with an IP injection of normal saline during the experiment (Table 1). The third group received the HFD plus melatonin (HFD+M), so the rats were fed a saturated HFD for 8 weeks with an IP injection of 10 mg/kg/daily body weight melatonin (Taher and Arrak, 2016; Maher et al., 2020).

Preparation of the high-fat diet

The diet rich in fat used in the current study was made weekly and stored in sealed bags, kept out of light, and stored at 4°C and humidity less than 50% until used in pelleted form or as round. The HFD formulation and composition are shown in Table 1.

Table 1. Diet ingredients in the present study

Ingredient	High-fat diet (g/kg diet)	Normal diet (g/kg diet)
Corn starch	150	650
Casein	200	200
Tallow fat	400	0
Oil	0	50
Sucrose	40	40
Cellules	50	50
Vitamin mix	10	10
Methionine	3	3
Salt	2	2

Source: Mashmoul et al. (2017).

Tissue collection and homogenization

At the end of the 8-week experiment, all rats from all groups were anesthetized with intramuscular injection of Ketamine (60 mg/kg) and Xylazine, and subsequently decapitated to remove their entire brain. The brain was dissected and divided into the left and right. To conduct the ELISA test, the right part of the brain was put in 1 ml of cold phosphate buffer saline solution containing 0.5 grams of the right part of the brain. Afterwards, the mixture was homogenized using an electrical homogenizer on ice, tissue homogenates were then centrifuged at 5000 rpm for 5 minutes, and an aliquot of the supernatant was isolated to determine TNF-α and dopamine 40 µl from an aliquot for each parameter. The left part of the brain was kept in plastic containers with formalin (10%) for routine histological examination.

Parameters

Dopamine and TNFα concentration in a male rat brain (ng/L) were measured using ELISA kit (Bioassay Laboratory Technology, Chain). Nervous system impairment was assessed using Barns maze and Elevated plus maze. The Barnes Maze comprises a dry, raised circular platform with many potential escape holes around its perimeter. A secret escape box is concealed behind a single hole. The Barnes labyrinth was effective for testing spatial memory. The typical Barnes maze protocol includes three phases, including habituation, earning (training), and memory. To quantify rat anxiety, Elevated plus maze was used. It is a plus-shaped solid white apparatus with two arms of 84cm long and 10 cm wide. Opposite arms had sides that were 2cm high (open arms), and the sides of the other opposite arms were 17 cm tall (closed arms), elevated above the floor in high 80 cm from the floor.

Histopathological study

Immediately after animal sacrifice, brains from each group were preserved in 10% formalin, and the formalin level was 10:1 of the specimen's volume. The tissues were rinsed in tap water to remove the formalin solution from the samples for three or four hours. The samples underwent various processes to make the tissue suitable for histopathological examination. These steps include dehydration, clearing, embedding, blocking, cutting, and staining (Bancroft et al., 2013).

Statistical analysis

The collected data were analyzed statistically using the Two-way and One-way ANOVA in GraphPad Prism 9.1.0. Data were subjected to a Tukey's post hoc test in case the ANOVA was statistically significant. Results were represented as mean ± standard error, with p value less than 0.05 as statistically significant.

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RESULTS

The level of dopamine

After 8 weeks of treatment, the obtained data confirmed a statistically significant decrease ($p < 0.05$) in the dopamine concentration of the HFD group, compared with CC and HFD+M groups (Table 2). However, there was a significant increase in dopamine concentration in CC and HFD+M groups, compared to the HFD ($p < 0.05$). Melatonin could elevate dopamine influenced by an HFD and increase the concentration of dopamine, when compared with the HFD group.

Brain tissue level of tumor necrosis factor-alpha concentration cytokine (ng/L)

The findings indicated a significant increase in brain TNF-α concentration group fed HFD, compared with CC and HFD+M groups ($p < 0.05$). Moreover, there was a significant increase in TNF-α brain level in the HFD+M group, compared to the control group ($p < 0.05$). However, the increment was slight and the value of tumor necrosis factor-alpha concentration (TNF2-α) for the HFD+M group was close to that of the control group. There was a significant decline in TNF-α concentration in the HFD+M (223.9±1.041), compared to the HFD group ($p < 0.05$, Table 3). As can be seen in Table 4, there was a non-significant difference between the HFD+M group and the control group at the end of the study ($p > 0.05$). However, there was a significant difference between the HFD and control groups at the end of study ($p < 0.05$).

Assessment of spatial memory using Barnes maze task

The results indicated that the HFD had a significant negative impact on spatial memory performance ($p < 0.05$). This was demonstrated by an increased time taken by the HFD group to reach the escape box at 8 weeks (5.533 ± 0.020), compared to both other groups at 8 weeks and the same HFD group at the beginning of the treatment. However, the HFD+M group demonstrated a significantly shorter time to reach the escape box (3.872±0.020), compared to the HFD group at 8 weeks. This suggests that rats fed an HFD may have a deficit in spatial memory.

Determination of anxiety by elevated plus maze

The results of this Elevated Plus maze showed the HFD was more anxious than rats in the HFD+M and CC groups. The HFD rats spent a significantly longer time ($p < 0.05$) in the close arm (4.525±. 287), compared to the control (2.863 ± 0.157) and HFD+M (3.013 ± 0.147) groups in the same arm. However, the HFD+M group spent significantly less time in close arm than the HFD group ($p < 0.05$). The HFD rats spent significantly less time ($p < 0.05$) in the open arm (1.475 ± 0.287), compared to that of the control group (3.138 ± 0.157) and HFD+M groups (2.988 ± 0.147). This means that HFD rats were highly anxious, as they spent a longer time in the close arm, compared with the other groups (Table 5).

Table 2. Effect of high-fat diet and melatonin on dopamine concentration (ng/L) in brain tissue of adult male rats

Time \ Groups	Control	High-fat diet group	Melatonin plus a high-fat diet
8 Weeks	11.80 ± 0.23^{a}	2.36 ± 0.11^{c}	6.09 ± 0.19^{b}

Data represented as mean ± standard error mean, n = 10 for each group. ^{ab}Different superscript letters in the same row indicate significant differences ($p < 0.05$)

Table 3. Effect of high-fat diet and melatonin on tumor necrosis factor-alpha concentration (ng/L) in brain tissue of adult male rats

Time \ Groups	Control	High-fat diet group	Melatonin plus a high-fat diet
8 Weeks	213.7 ± 1.249^{c}	646.1 ± 1.098^{a}	223.9 ± 1.041^{b}

Data represented as mean ± standard error mean, n = 10 for each group; ^{abc}Different superscript letters indicate the significant differences in rows between groups ($p < 0.05$)

Table 4. The effect of melatonin and high-fat diet on spatial memory barns maze test

Time \ Groups	Control	High-fat diet group	Melatonin plus a high-fat diet
Beginning of study	3.765 ± 0.028^{Aa}	3.755 ± 0.016^{Aa}	3.783 ± 0.009^{Aa}
8 Weeks	3.877 ± 0.007^{Aa}	5.533 ± 0.020^{Bb}	3.872 ± 0.020^{Aa}

Data represented as mean ± standard error, n = 10 each group; ^{ab}Small superscript letters in the same column indicate significant differences between 8 weeks and beginning time ($p < 0.05$); ^{AB}Capital superscript letters in the same row indicate significant differences ($p < 0.05$).

Table 5. The effect of melatonin and high-fat diet on anxiolytic test by Elevated Plus maze

Time \ Groups	Control	High-fat diet group	Melatonin plus a high-fat diet
Open	3.138 ± 0.157^{Aa}	1.475 ± 0.287^{Ab}	2.988 ± 0.147^{Aa}
Close	2.863 ± 0.157^{Aa}	4.525 ± 0.287^{Bb}	3.013 ± 0.147^{Aa}

^{AB}Capital superscript letters denote the significant differences in the same column ($p < 0.05$); ^{ab}Lower superscript letters indicate significant differences in the same row ($p < 0.05$); Data represented as mean ± standard error, n = 10 pre-group.

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The recent histopathological examination indicated the detrimental effect of a high-fat diet on the brain tissues of rats, and also highlighted the antioxidant and anti-inflammatory properties of melatonin, which played a role in mitigating these effects. In the hippocampus of the CC group, brain sections showed all three layers the molecular layer (ML), the middle layer (pyramidal cell layer, PL), and the inner layer (polymorphic cell layer, PCL). A normal dentate gyrus consists of three layers, including the outer molecular layer, middle granular layer, and inner polymorphic layer. The blood vessels in the molecular and polymorphic layer of the dentate gyrus were normal (Figure 1). Moreover, normal thin meninge, normal brain tissue with normal blood vessels, normal glia cells, astrocytes with oligodendrocytes, and the neuronal cell showed normal triangular perikaryon with prominent central nuclei with apical dendrites (Figures 2 and 3).

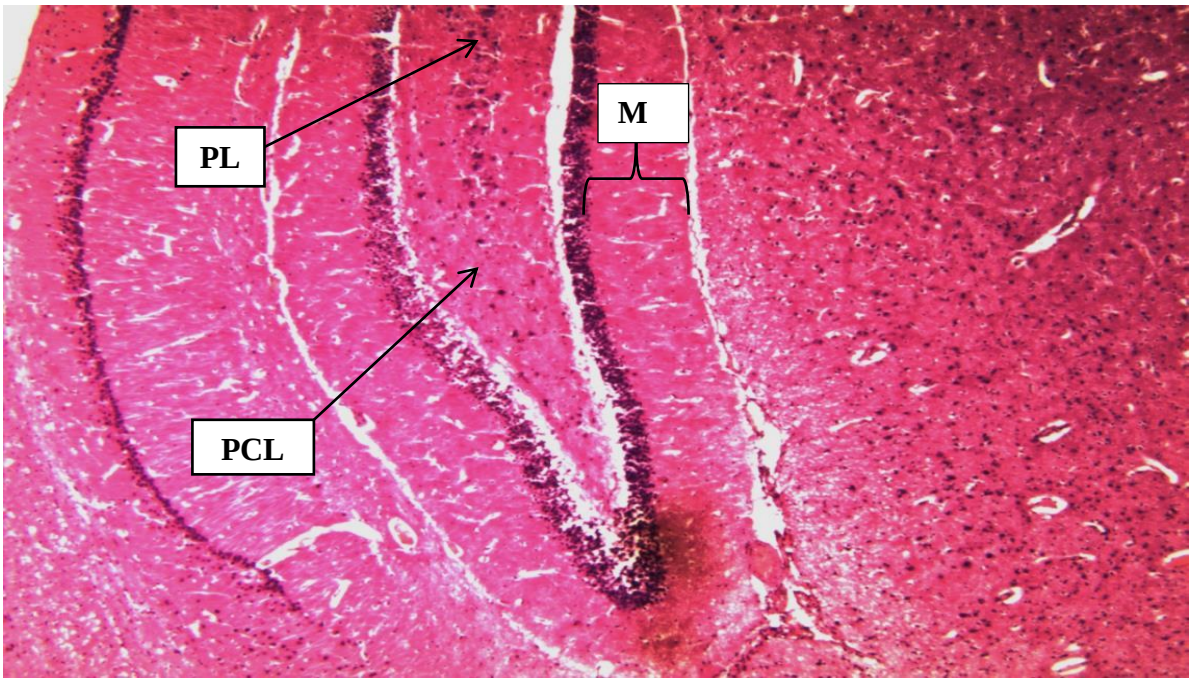

Figure 1. The brain tissue of a rat in control group. All layers of the hippocampus contain the outer layer molecular layer (ML), Middle layer pyramidal cell layer (PL), and inner layer polymorphic cell layer (PCL) are shown. There is normal dentate gyrus which contains three layers outer molecular layer, middle granular layer, and inner polymorphic layer. Normal blood vessels in the molecular and polymorphic layer of dentate gyrus. 20X (H&E).

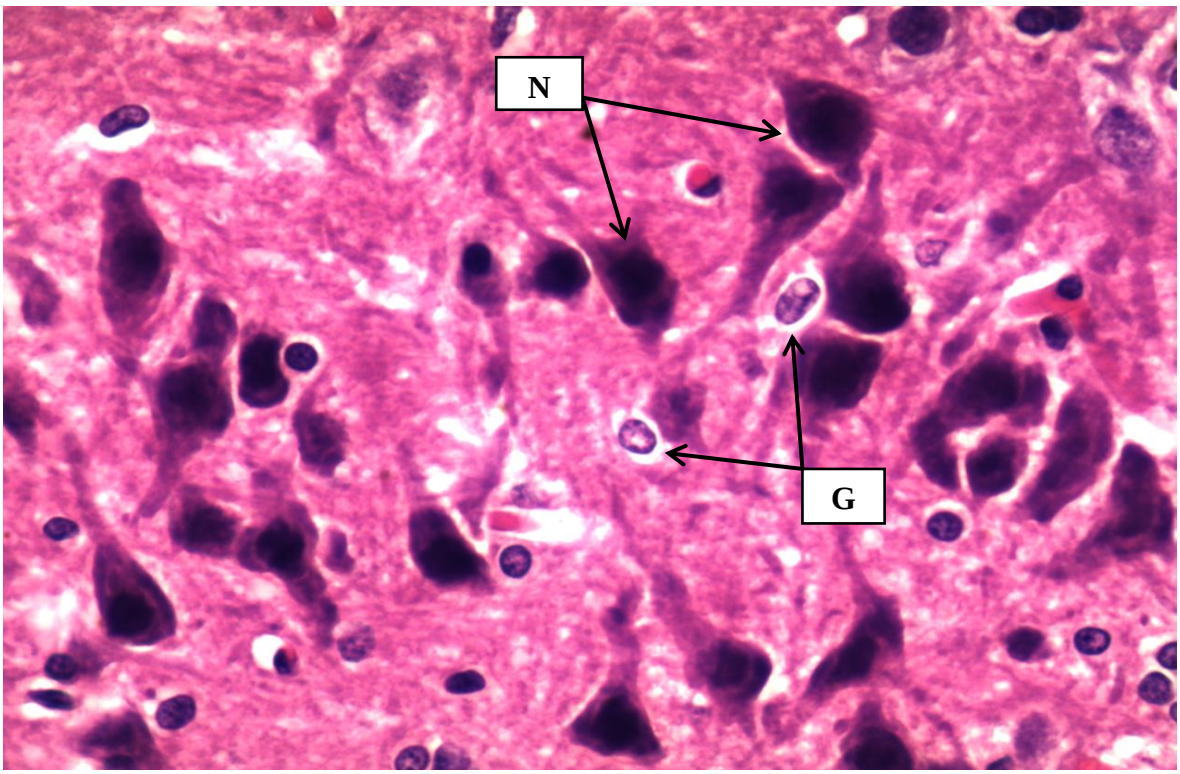

Figure 2. The brain tissue of a rat in control group. The neuronal cell (N) showed normal triangular perikaryon with prominent central nuclei with apical dendrites, and normal glial cell (G) is also seen. 200X (H&E).

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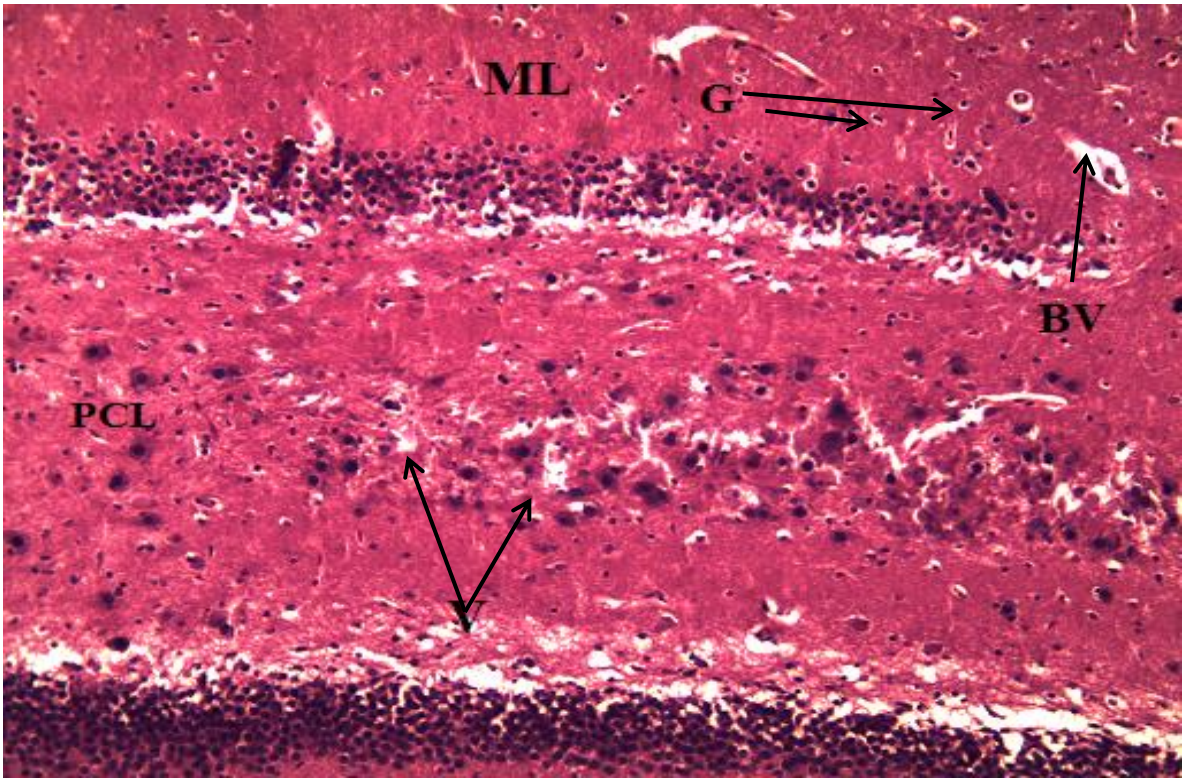

Figure 3. The brain tissue of a rat in the high-fat diet group. There is disorganization and degenerated pyramidal cells; these cells showed vacuolation (V) in the cytoplasm and pyknotic (condensed) nucleus. Dilation of blood capillaries (BV) and increased numbers of microglia (gliosis, G) in the molecular layer (ML) and polymorphic cell layer (PCL). 50X (H&E).

However, rat brain sections in the HFD group indicated disorganization and degenerated pyramidal cells. These cells showed vacuolation in the cytoplasm and pyknotic (condensed) nucleus, dilation of blood capillaries, and increased numbers of microglia (gliosis in ML and PCL), as in Figure 4. Figure 5 shows a thin pyramidal cell layer in the Cornu Ammonis with degeneration of neurons and V in the last area of cornu Ammonis and dentate gyrus at the brain of the HFD group. In addition, fine capillaries had congestion with cerebral edema in the inner polymorphic layer. In the same group, the histopathological change revealed vacuolation in the granular layer of the dentate gyrus with many glia cells (glia cells in ML and PCL of dentate gyrus), as in Figure 6. Higher magnification of the granular layer of the D indicated the marked vacuolation of the granular cells, which appear swelling, and vacuoles in their cytoplasm and pyknotic nuclei look (Figure 7).

Regarding the brain of HFD rats, the histopathological examination revealed congestion in the blood vessels with marked cerebral edema in which Virchow-Robin space dilated. Many neurological cells appeared shrunken and deeply stained, and infiltration of a high number of glia cells and Astrocytes Astrocytosis (Figure 8). In higher magnification, the neurological cell (neuron) indicated marked central chromatolysis in which the body of the neuron (perikayo) was spherical with nuclei disappearance. Moreover, gliosis and Astrocytosis were detected in the brain tissue (Figure 9). Representative photomicrographs were obtained using 40 × (200x with a factor of a camera, magnification objective). The brain rats in the HFD group indicated gliosis and Astrocytosis with the presence of Oligodendrocytes, marked central chromatolysis in the body of neurons (spherical and disappeared nuclei). Also, fine capillaries were congested in the brain tissue (Figure 10). The microscopic brain examination of rats in the HFD group can be seen in Figure 11. As indicated, there were marked degenerative areas and necrosis of neurons. The neuron showed pale color and disappearance of nuclei with marked aerophagia in the brain tissue. Cerebral edema and congestion of blood vessels were also seen. Moreover, at the same area but at a higher magnification, severe central Chromatolysis of perikaryo of neurons with gliosis and astrocytosis could be noticed (Figure 12). As can be seen in Figure 13, the brain tissue sections also exhibited severe congestion and infiltration of inflammatory cells in the meninges, vacuolation, and aerophagia and marked gliosis and astrocytosis.

According to Figure 14, most neuronal cells (neuron) appeared normal triangle perikaryo with central and prominent nuclei; however, a few of these cells had central chromatolysis with blood vessels. The histopathological section of the hippocampus in rats given melatonin was nearly similar to that of the control. The first area of Cornu Ammonis appears clear and thick, with a high number of pyramidal cells in the middle. There was a normal outer ML; however, the PCL showed few congestions in the fine capillaries. There were normal and high numbers with the normal shape of neurological cells in the last area of Cornu Ammonis, the thick dentate gyrus layer in which there were a high number and proliferation of granular cells with few vacuolations (Figure 15). Moreover, most neurons appeared normal

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with central nuclei in their perikaryo, but a few neurons underwent chromatolysis in the last area of Cornu Ammonis. There was little vacuolation in the dentate gyrus at the granular layer, mild perivascular edema in the molecular layer, and few glia cells in ML and PCL of the dentate gyrus (Figure 16).

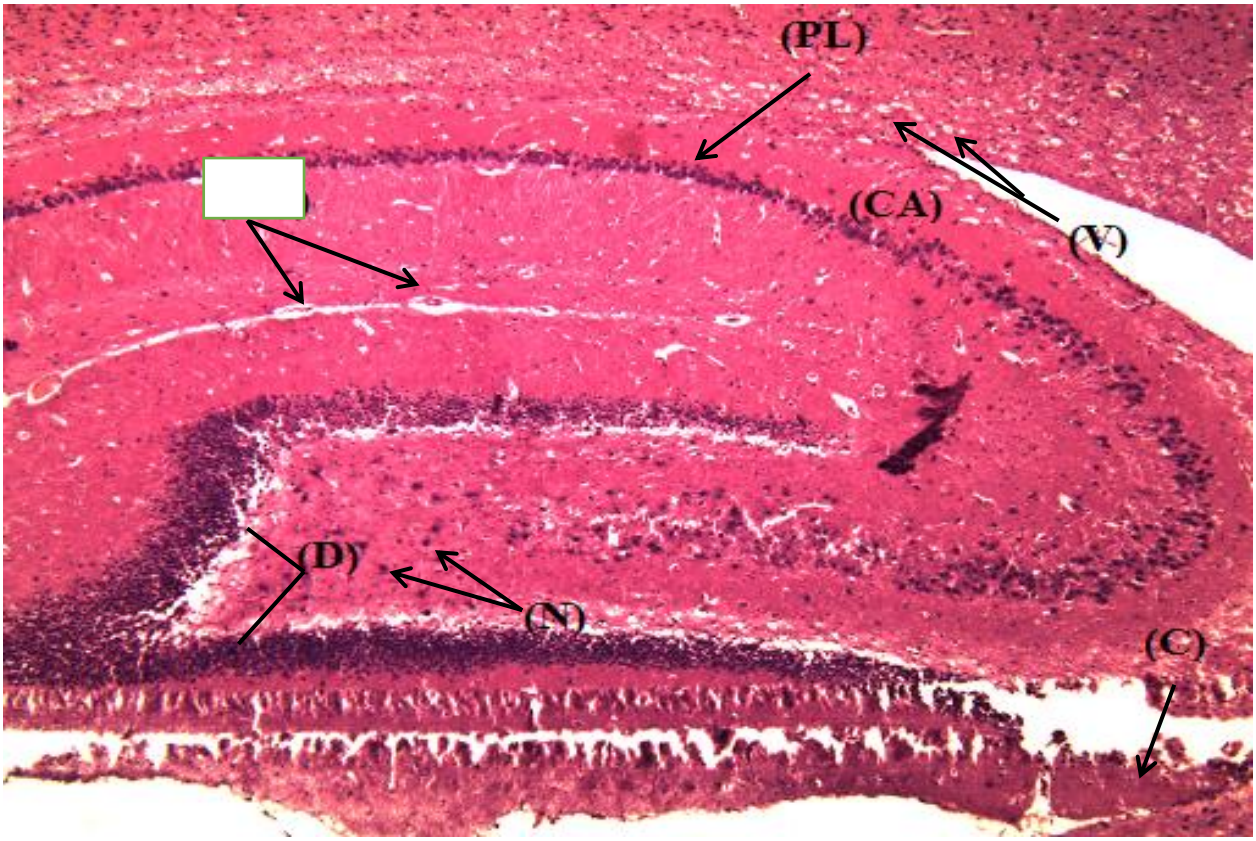

Figure 4. The brain tissue of a rat in the high-fat diet group. The thin pyramidal cell layer in the Crnu Ammonis (CA) with degeneration of neurons (N) and vacuolation (V) in the last area of Cornu Ammonis and dentate gyrus (D) are shown. There is congestion of fine capillaries (C) with cerebral edema (OD) in the inner polymorphic layer. 50X (H&E).

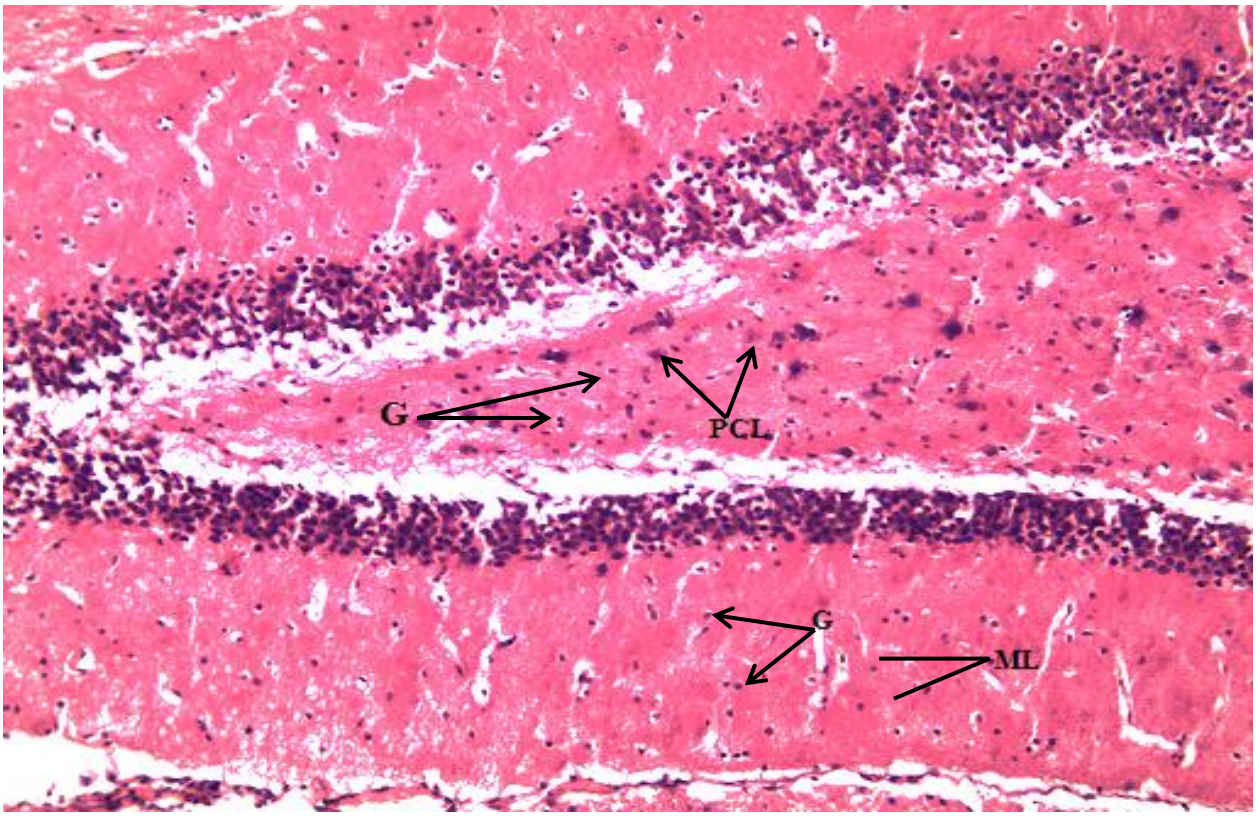

Figure 5. The brain tissue of a rat in the high-fat diet groups. There is vacuolation in the granular layer of the dentate gyrus with the presence of a high number of glia cells (gliosis, G) in the molecular (ML) and polymorphic layer (PCL) of the dentate gyrus (D). 50X (H&E).

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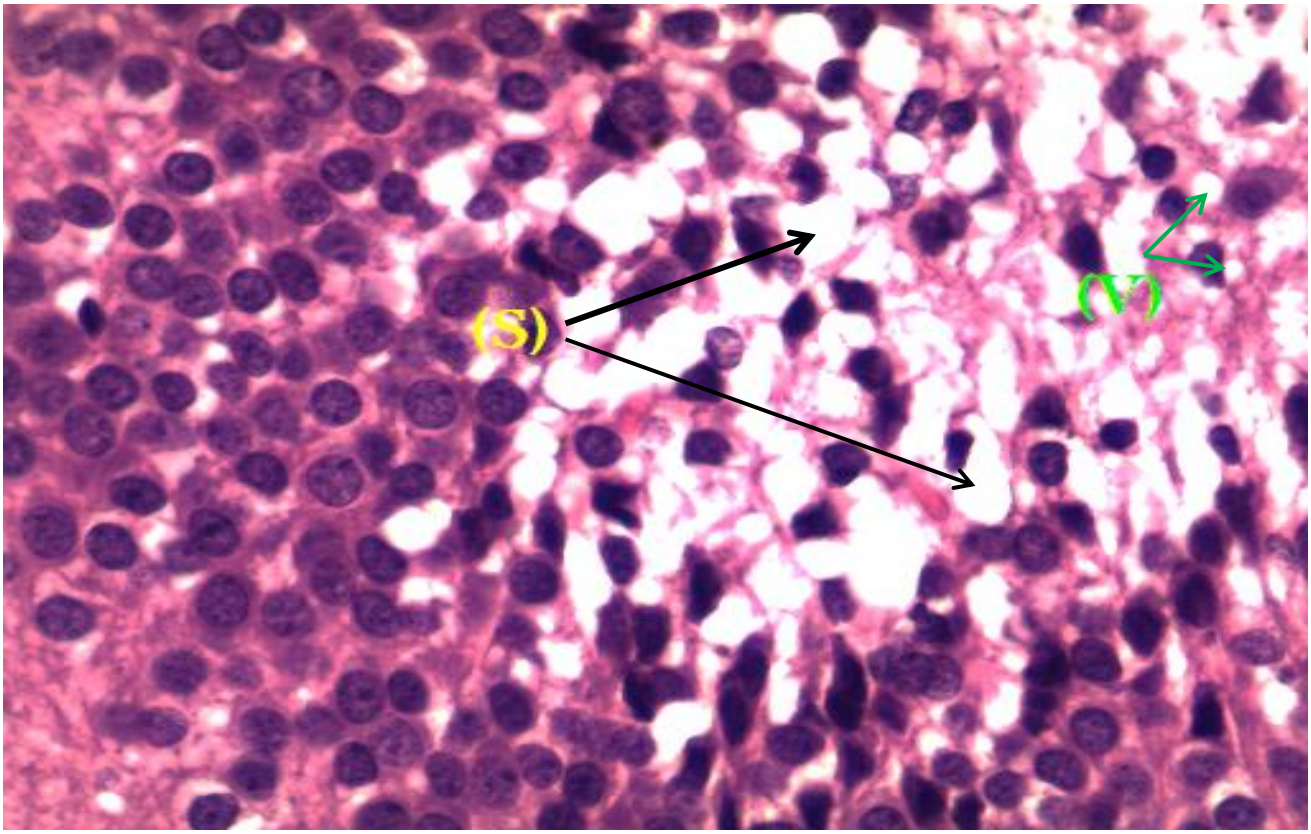

Figure 6. The brain tissue of a rat in high-fat group. The granular layer of the dentate gyrus shows the marked vacuolation of granular cells (V), which appear to be swelling (S) and vacuoles (V) in their cytoplasm and pyknotic nuclei. 200X (H&E).

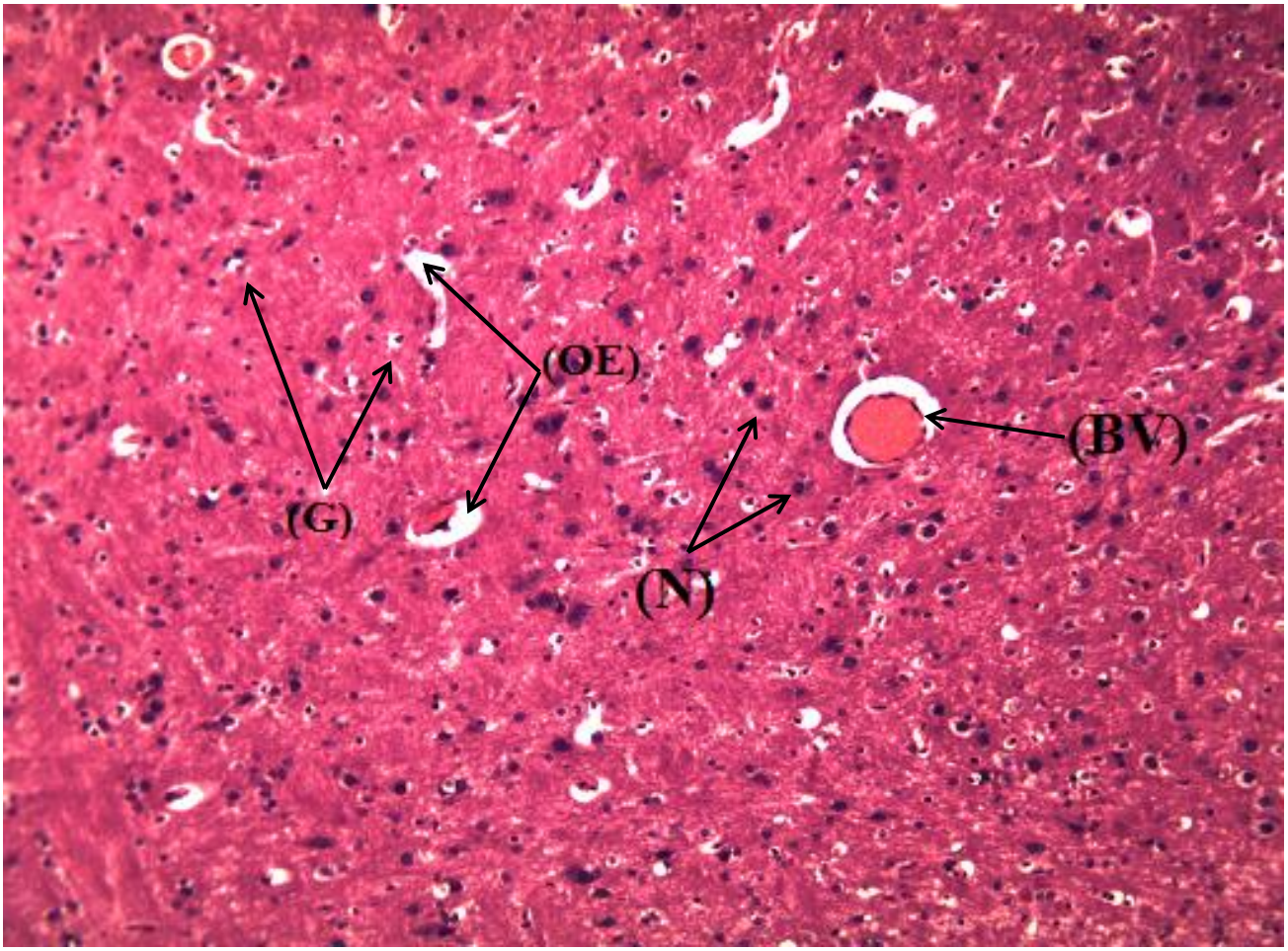

Figure 7. The brain tissue of a rat in high-fat diet group. The marked congestion in the blood vessels (BV) with marked cerebral edema (OE) in which there is dilation of Virchow-Robin space. Many neurological cells appeared shrunken and deeply stained (N). Infiltration of many glial cells (gliosis, G) and Astrocytes (Astrocytosis, A). 50X (H&E).

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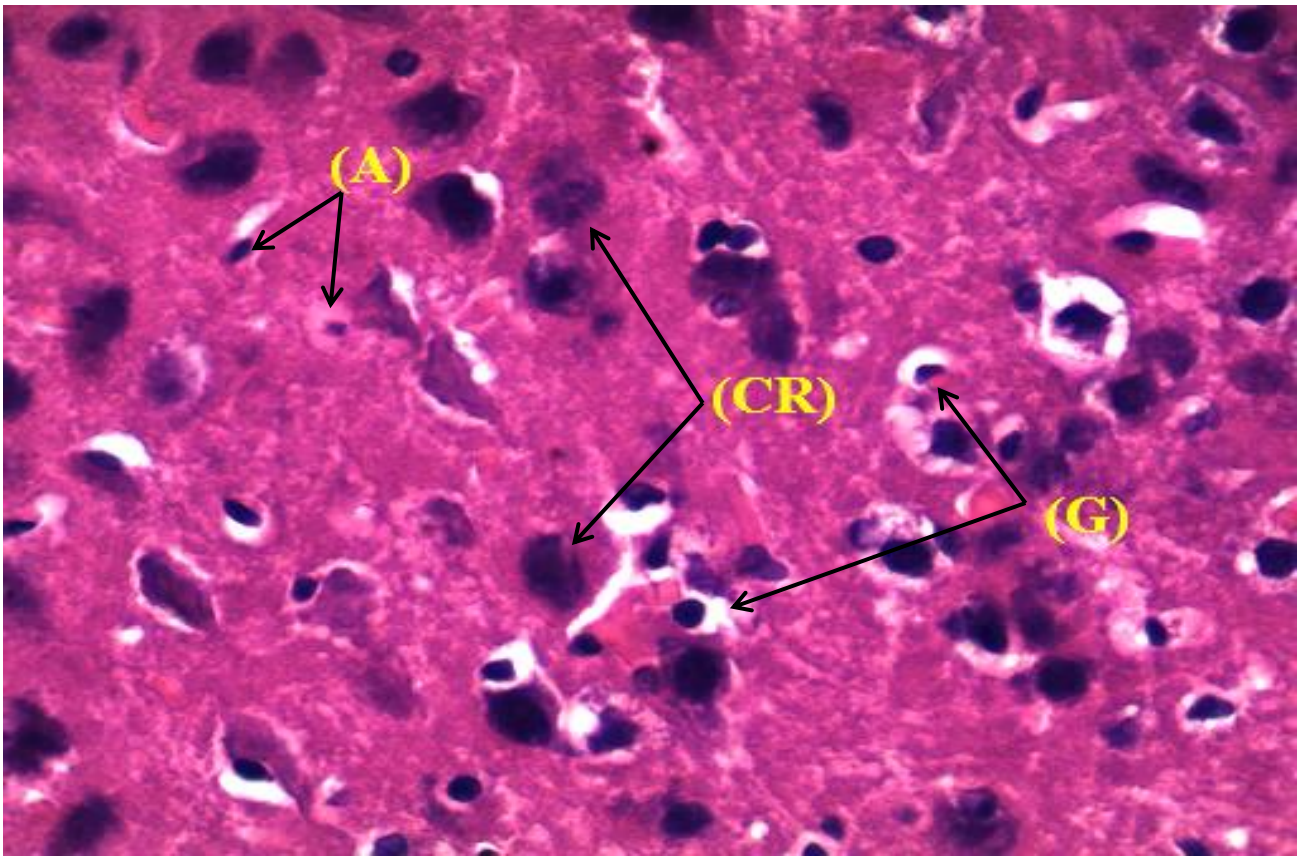

Figure 8. The brain tissue of a rat in the high-fat diet group. The neurological cell (neuron) shows marked central chromatolysis (CR) in which the neuron's body (perikaryon) shows spherical nuclei disappearance. There is gliosis (G) and Astrocytosis (A) in the brain tissue. 200X (H&E).

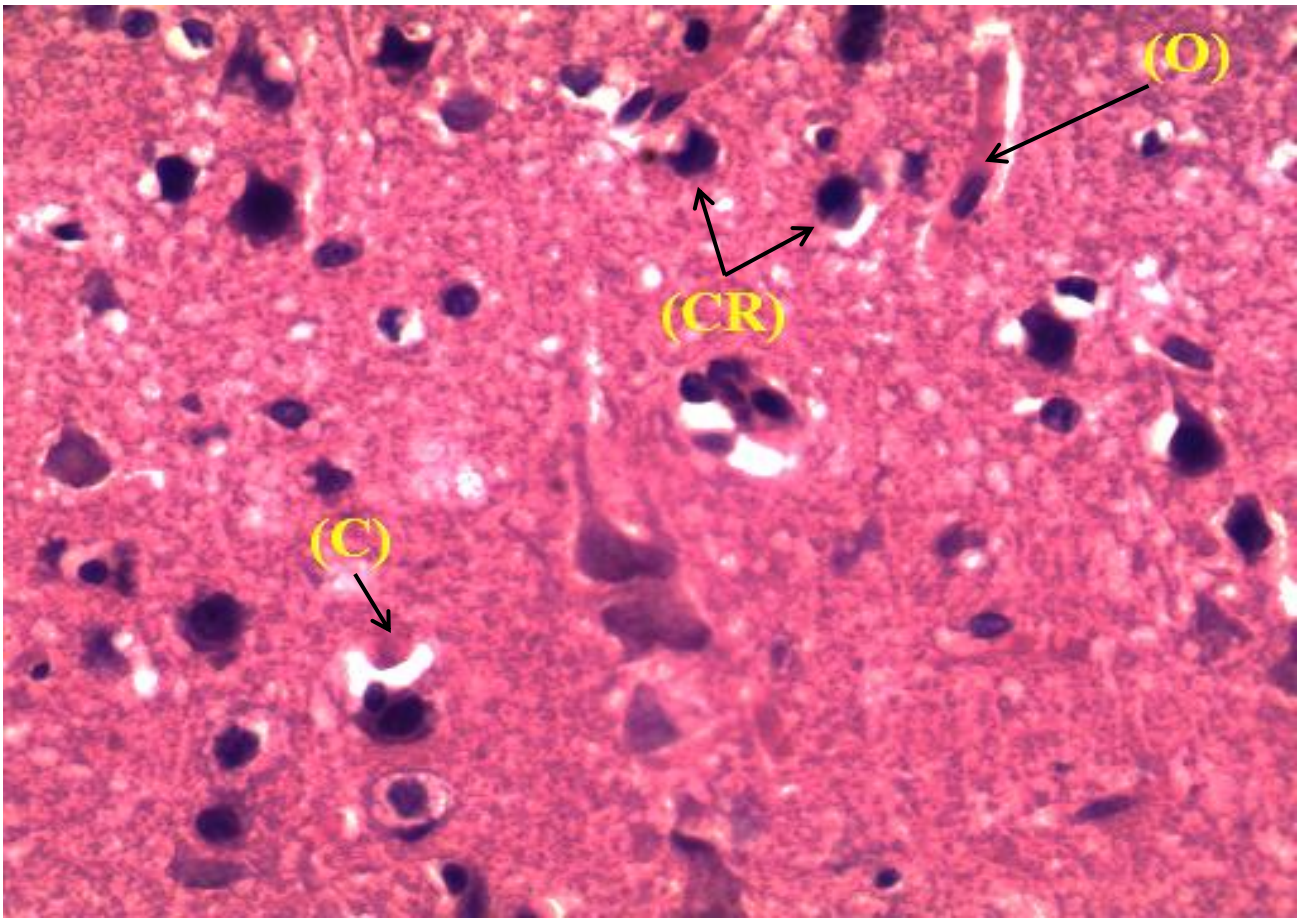

Figure 9. The brain tissue of a rat in high-fat diet group. There is gliosis and Astrocytosis with the presence of Oligodendrocytes (O). Marked central chromatolysis in the body of neurons (CR, spherical in shape and disappeared nucli). There is congestion (C) of fine capillaries in the brain tissue. 200X (H&E).

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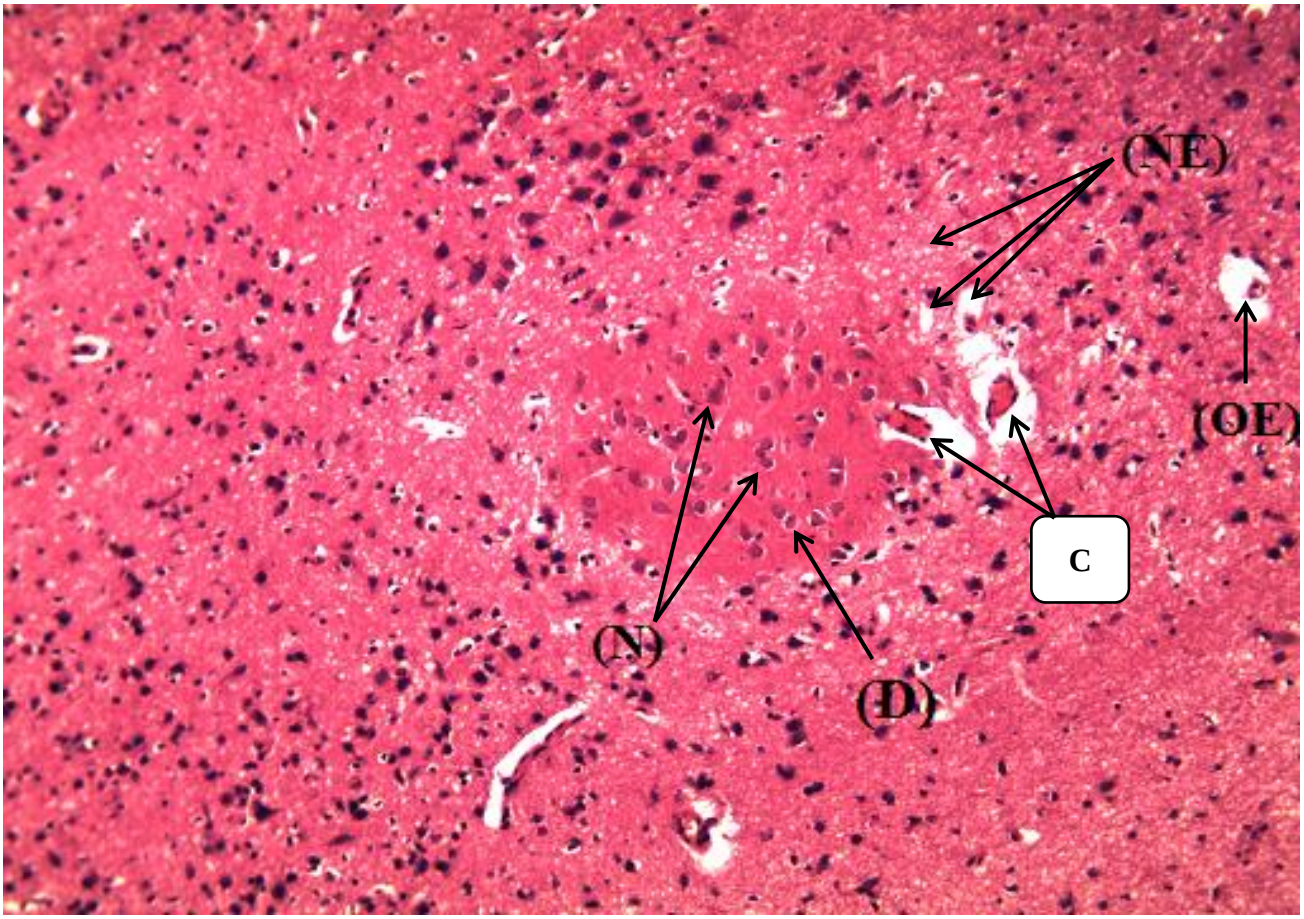

Figure 10. The brain tissue of a rat in high-fat diet group. Marked degenerative area thin the brain tissue (D) in which there is necrosis of neurons (N), the neuron showed pale in color and disappearance of nuclei with marked neurophagia in the brain tissue. Cerebral edema (OE) and congestion of blood vessels (C) are also seen. 50X (H&E).

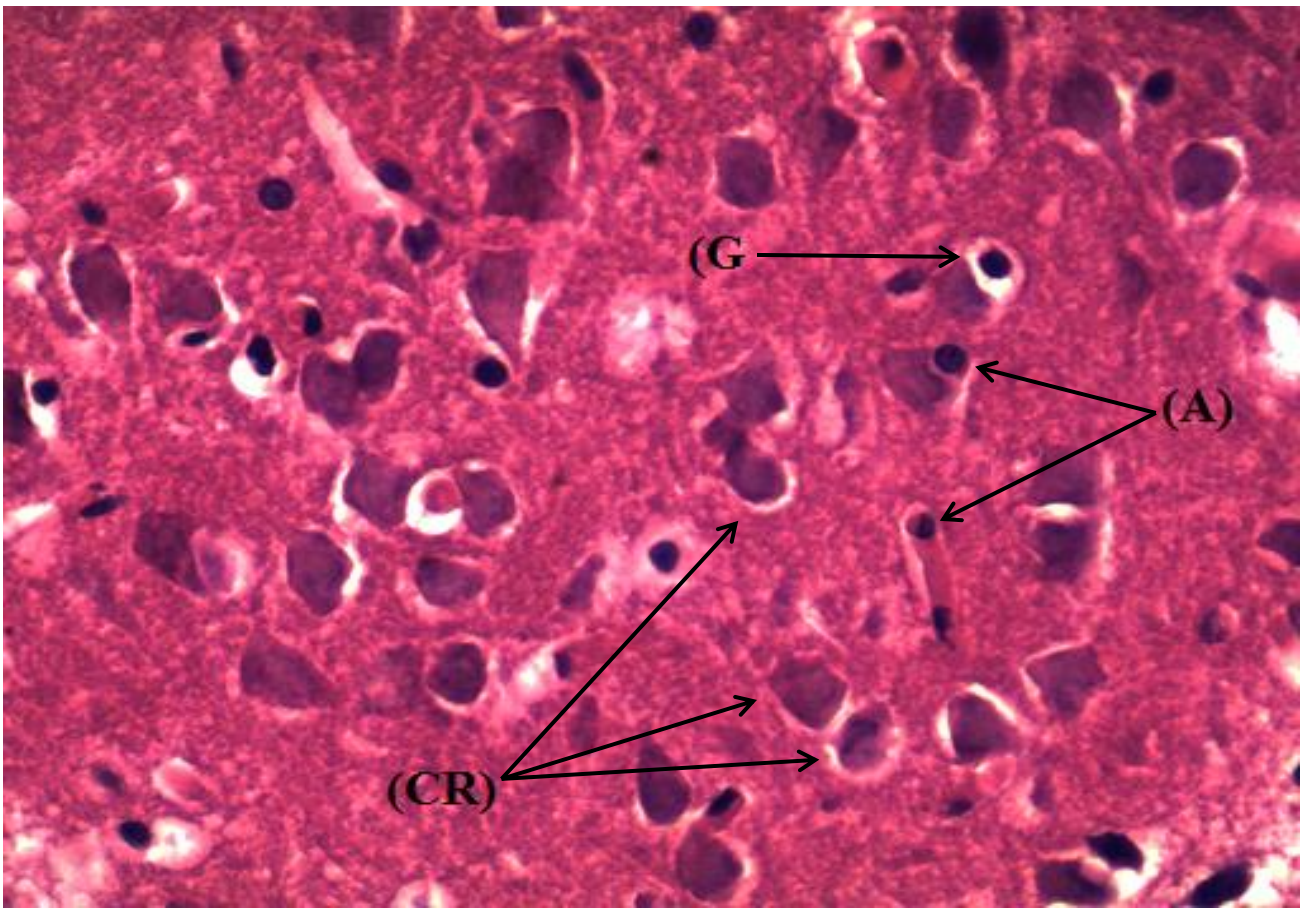

Figure 11. The brain tissue of a rat in the high-fat diet group. Severe central chromatolysis (CR)of perikaryon of neurons with gliosis(G) and Astrocytosis(A). 200X (H&E).

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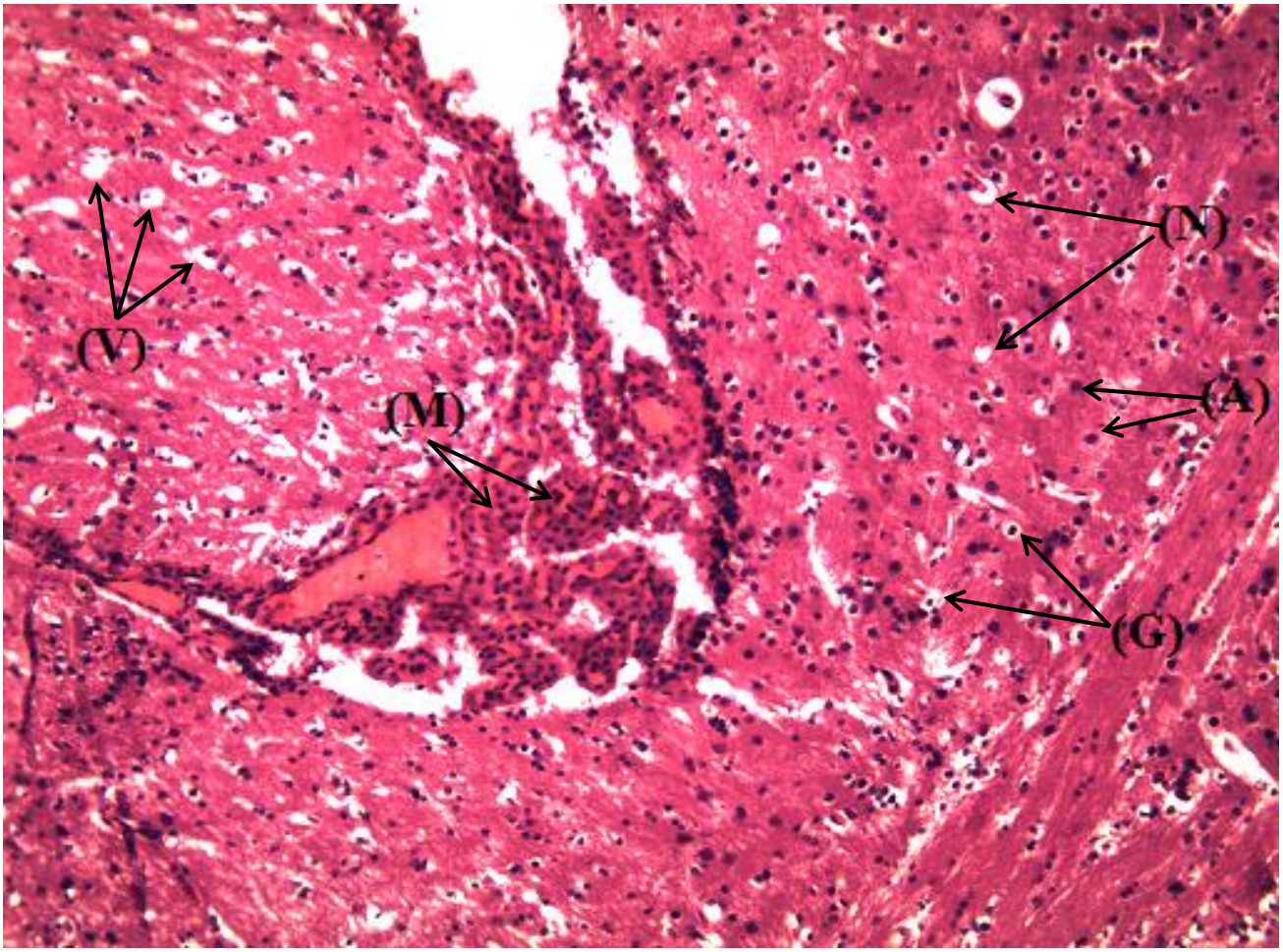

Figure 12. The brain tissue of a rat in high-fat diet group. Severe congestion and infiltration of inflammatory cells (M) in meninges (meningitis). Vacuolation (V) and neurophagia (N) in the brain tissue and marked gliosis (G) and astrocytosis (A) are noted in this section. 50X (H&E).

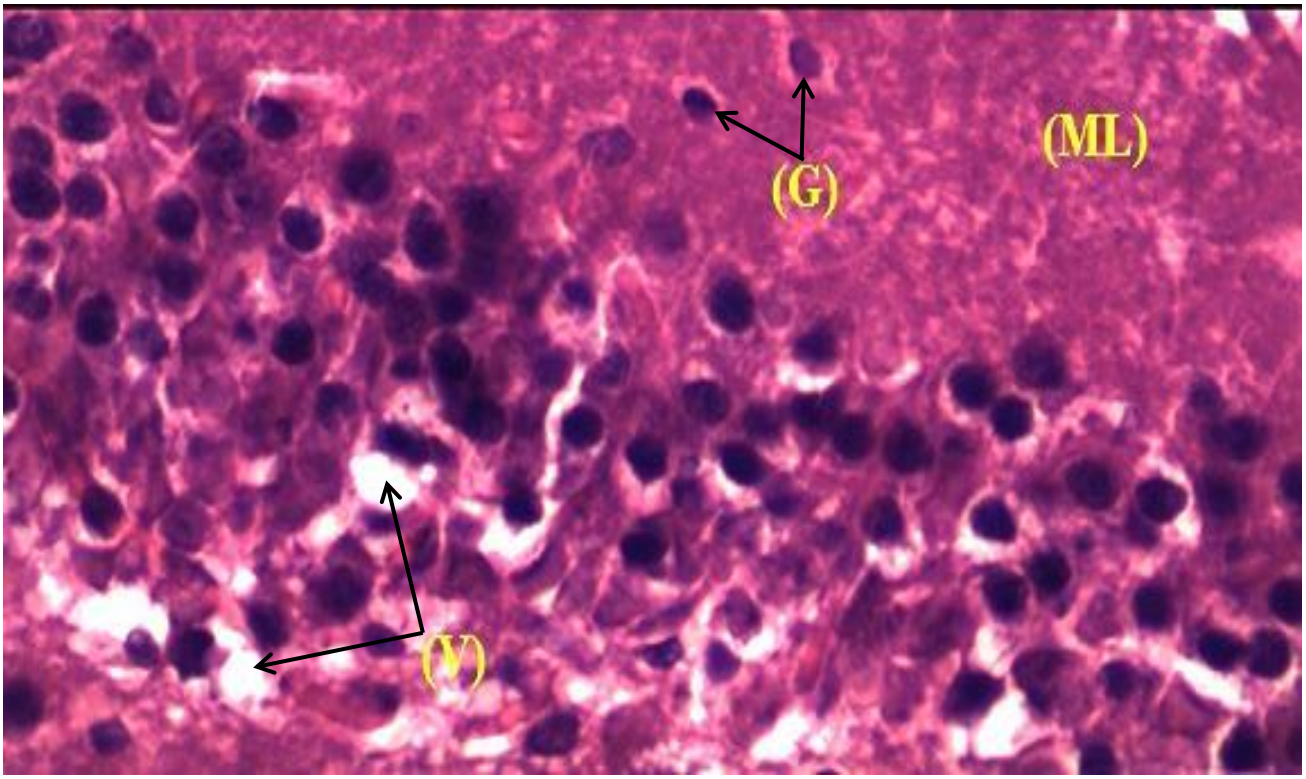

Figure 13. The brain tissue of a rat in the high-fat diet plus melatonin group. Few vacuolations in the granular cells (V) of the dentate gyrus, and most of these cells showed prominent nuclei. Few glia cells (G) in the molecular layer (ML) of the dentate gyrus. 200X (H&E).

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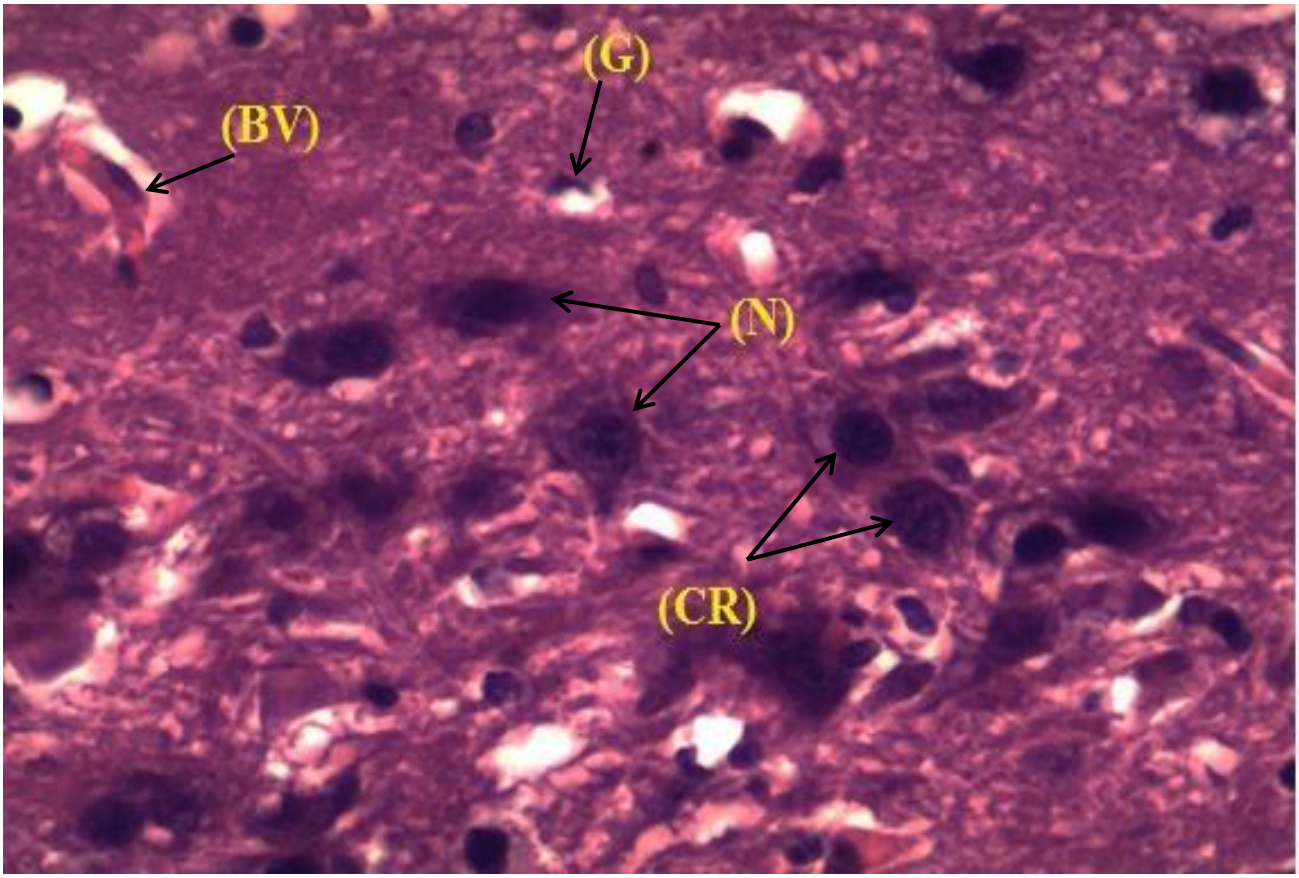

Figure 14. The brain tissue of a rat in the high-fat diet plus melatonin group. Most neuronal cells (neuron)(N) showed normal triangle perikaryon with central and prominent nuclei, but few of these cells suffer from central chromatolysis (CR). Normal blood capillaries (BV) and few glia cells (G). 200X (H&E).

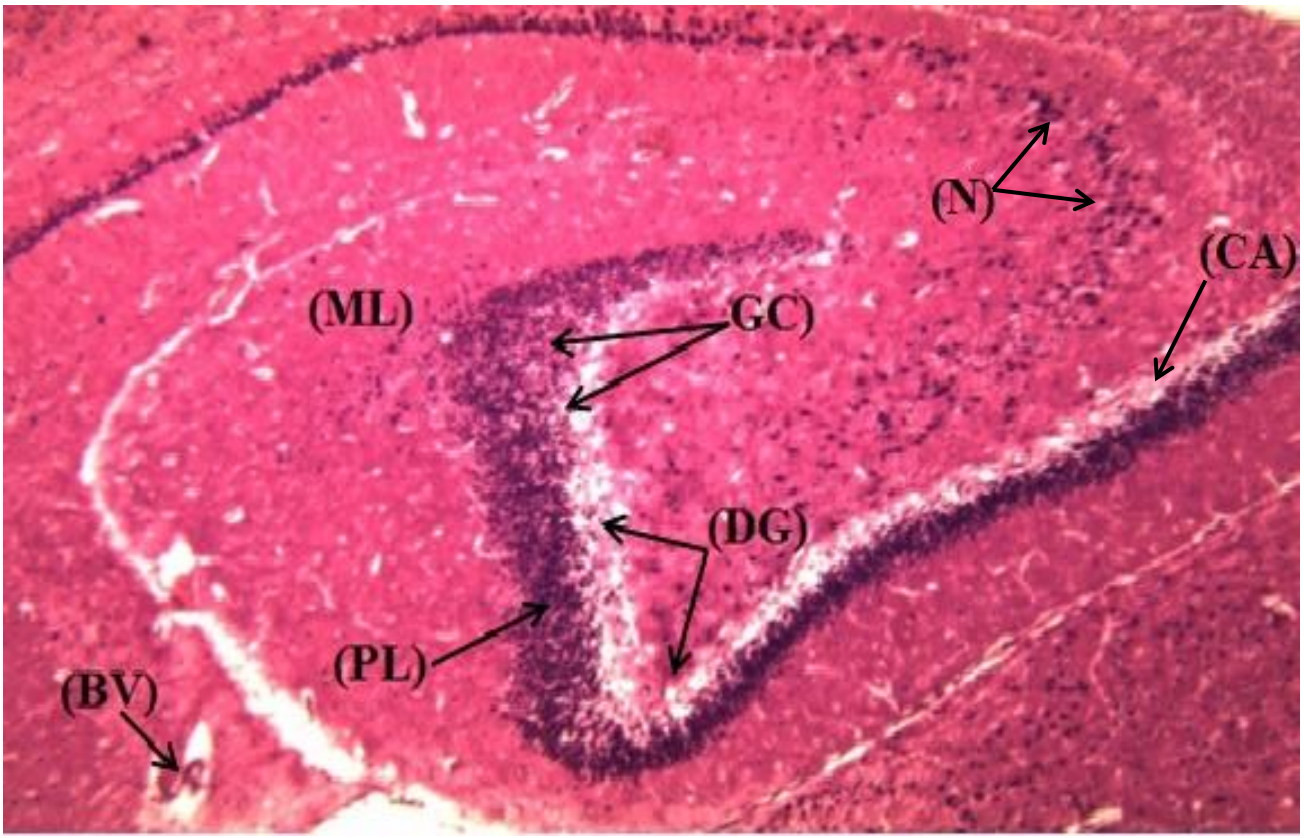

Figure 15. The brain tissue of a rat in high-fat diet plus melatonin group. The hippocampus showed nearly similar to the control. The first area of Cornu Ammonis (CA) is clear and thick, with a high number of pyramidal cells (PL) in the middle; there is a normal outer molecular layer (ML). But the inner polymorphic layer showed few congestions in the fine capillaries (BV). There are normal and high numbers with the normal shape of neurological cells (N) in the last area of cornu Ammonis. Thick dentate gyrus layer (DG) in which there is a high number and proliferation of granular cells with little vacuolation in it (GC). 20X (H&E).

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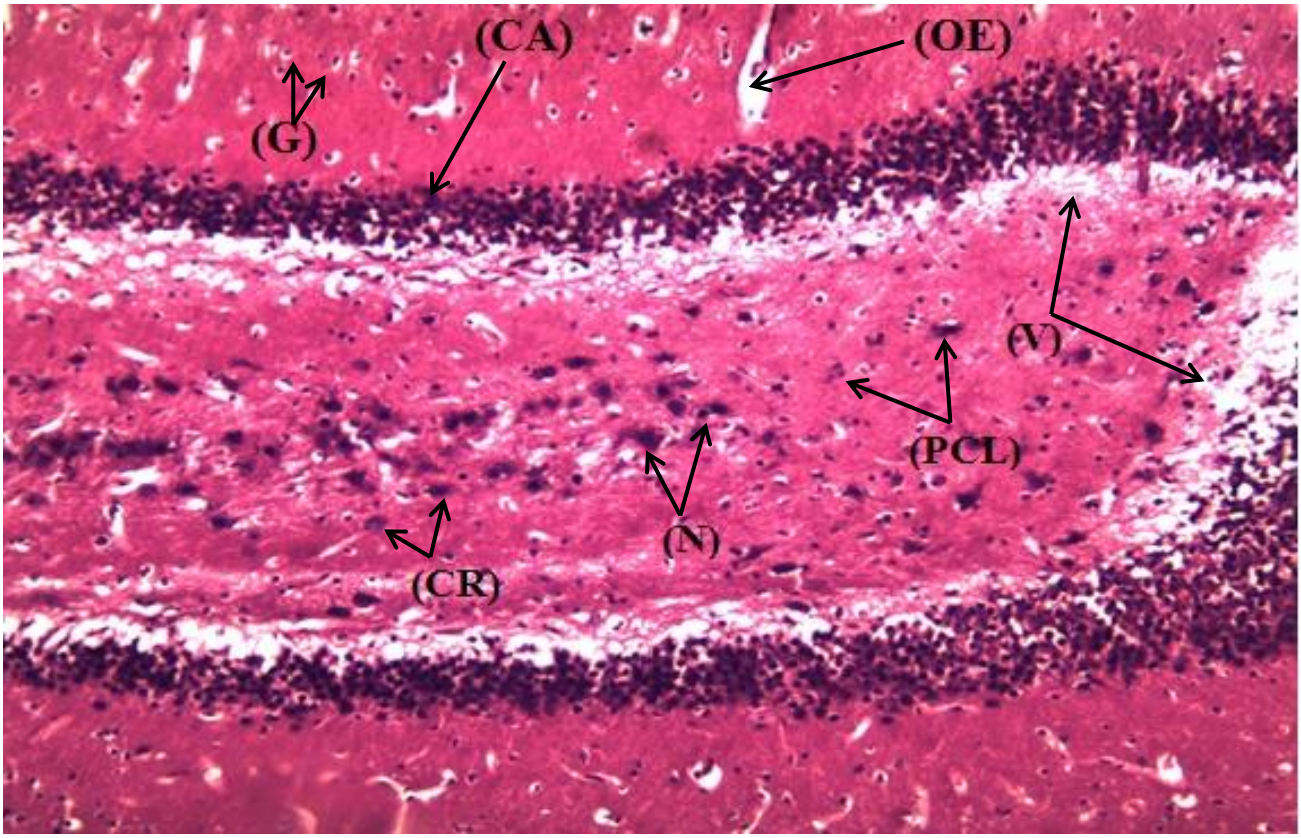

Figure 16. The brain tissue of a rat in the high-fat diet plus melatonin group. Most neurons showed normal with central nuclei in their perikaryon, but few neurons undergo chromatolysis (CR) in the last area of Cornu Ammonis (CA). Few vacuolation (V) at the granular layers of the dentate gyrus, mild perivascular edema (OE) in the molecular layer, and few glia cells (G) in the molecular layer and polymorphic layer (PCL) of the dentate gyrus. 50X (H&E).

DISCUSSION

The obtained findings were inconsistent with a recent study which revealed a dopamine decrease in male and female mice fed HFD, compared to the control group after a day and a week (Wallace et al., 2022). Not only significant effects on dopamine were reported, but fat rats were also shown to have lower levels of dopamine receptor D2 (DRD2) when fed a high-fat or high-sugar diet (Fritz et al., 2018). Moreover, another study indicated that 2 weeks of HFD consumption in adult Sprague Dawley rats induced disrupted dopamine networks, compared to the control group (Barnes et al., 2022). This result agrees with that of Han et al. (2021), showing that HFD-exposed mice had significantly higher midbrain DA and DRD2 protein levels compared to the control group. During the 8 weeks of HFD, obese rats showed 42% lower striatal DRD2 density and 30% lower total dopamine transporter (DAT) expression (Sharma and Fulton, 2013). These results agreed with a previous study that indicated lower striatal dopamine 2-receptor density, lower total dopamine transportal expression, and lower *in vitro* and *in vivo* dopamine transport function after an 8-week HDF exposure due to the positive correlation between circulating leptin and stress-induced dopamine release (Narayanaswami et al., 2013). The literature reviewed here suggests that leptin acts as a regulator of neuronal function and may provide an etiological mechanism for differences in dopamine neurotransmission in response to salient stimuli. When leptin is present, messages are sent to the brain's reward centers, where the dopamine system lowers the value of foods as a reward (Burghardt et al., 2012; Yeung and Tadi, 2020).

A high-fat, low-carbohydrate diet disrupts dopamine function linked to changes in brain neuroactivity due to dopamine dysregulation. Other behavioral-related neurochemical pathways may be impacted (Han et al., 2021). After 5 months of feed exposure, neurochemical studies showed that HFD-exposed mice had significantly greater DA and DRD2 protein levels in the midbrain, compared to the control group. They suggest that the effects of HFD on the C57BL/6J mice strain become apparent by the third month of dietary exposure (Han et al., 2021). Dopamine neurotransmission impairment has been linked to metabolic abnormalities produced by saturated fat (Serafine et al., 2016; Fordahl and Jones, 2017; Narayanaswami et al., 2013; Barnes et al., 2022).

However, it was indicated that dopamine levels were reduced in the melatonin groups, compared to the control group in a previous study (Lin et al., 2008). Previous studies have revealed that melatonin inhibits dopamine expression and serves as an antioxidant to prevent nigrostriatal neurodegeneration and alpha-syncline aggregation (Zisapel, 2001). Melatonin upregulation of the D2 receptor reduces the neuronal loss and downregulation of the dopamine transporter

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(Lin et al., 2008; Deng et al., 2015). Another investigation revealed that the group which received Acrylamide presented decreasing in neurotransmitters, such as dopamine. In contrast, dopamine was higher in the group that received Acrylamide and melatonin but still lower than in the control group as the melatonin protected the DNA damage and anti-inflammatory effect (Edres et al., 2021). Another study showed the IP therapy of 10 mg/kg body weight melatonin could lessen oxidative damage by boosting the activity of antioxidant enzymes, reducing lipid peroxidation and inflammation, and enhancing histopathological changes in the brain tissue of rats with pinealectomy (Bicer et al., 2022). Finally, melatonin may suppress neural nitric oxide synthase activity, leading to a decrease in NO and peroxynitrite formation (which play a critical role in the losses of dopaminergic neurons. This may inhibit the activity of tyrosine hydroxylase, a rate-limiting enzyme in dopamine synthesis (Teixeira et al., 2003; Ahmed et al., 2010; Pandi-Perumal et al., 2013).

A powerful pro-inflammatory cytokine called TNF is essential for starting and maintaining the inflammatory response. Elevated levels of TNF-α have been documented in several neurodegenerative disorders and insults with the potential to affect the Central Nervous System; for neurodegenerative diseases linked to neuroinflammation, controlling TNF-signaling may be advantageous (Frankola et al., 2011). The current experiment showed that the brain level of TNF-α cytokine was significantly higher in the HFD group, compared to other groups. These findings support the peripheral pro-inflammatory effects of inflammation of the used obesogenic diet. The current results of TNF-α, in parallel with many previous studies, revealed that the plasma biomarkers, TNF-α, and brain hippocampal significantly increased in HFD group rats, compared with the normal control rats (Xu et al., 2019; Ebrahim et al., 2021; Hsu et al., 2021). Further, the results of the study were similar to those of a previous study that examined HFD and inflammation. In rats who were given HFD for many weeks compared with those who were given a normal diet for the same period, TNF-alpha levels in the brain and different serum parameters were elevated (Spagnuolo et al., 2015).

The possible immunological mechanism that led to the elevation of TNFα has been explained in different studies. The Saturated fatty acids and lipopolysaccharides operate as agonists for the toll-like receptor 4 (TLR4), which it can bind to and activate. This causes nuclear factor kappa B (factor NF-B), leading to pro-inflammatory synthesis of cytokine, such as TNF-α (Rogero and Calder, 2018). Neuronal stress in response to HFD is associated with increased NF-kB signaling (Vykhovanets et al., 2011). Consuming an HFD raises oxidative stress and decreases mitochondrial activity in the brain (Tan and Norhaizan, 2019; Langley et al., 2020). Astrocytes and microglia produce substantial amounts of TNF in pathological settings; this de novo synthesis is a crucial part of the so-called neuroinflammatory response linked to several neurological disorders (Montgomery and Bowers, 2012). Although astrocytes and neurons can generate TNF-α, the microglia are believed to be the primary source of this cytokine during neuroinflammation (Chung and Benveniste, 1990; Welser-Alves and Milner, 2013). The cytokine interferon-gamma (IFN-α) is a strong inducer of TNF production in microglia (Mangano et al., 2012; Olmos and Lladó, 2014).

In the current study, melatonin administration restored the normal level of TNF-α in HFD+M. This agrees with previous investigations in which 10 mg/kg of melatonin was administrated for 20 days. The results indicated that administration of melatonin led to significant lowering levels of IL-1β, NF-κB, and TNF-α as the melatonin exerts anti-inflammatory influence by reducing TNF-α, interleukin-1β and iNOS, markers in diabetes mellitus (DM) induced animals (de Melo et al., 2020). However, in a recent study, it was reported that the administration rats with melatonin at the dosage of 500 µg/kg/day in diabetes mellitus DM rats for 6 weeks resulted in significant of the liver and adipose tissues TNF and NF-κB lower than in the control animals (Yapislar et al., 2022). Moreover, it has been demonstrated that melatonin inhibits the synthesis of pro-inflammatory cytokines, such as TNF-α. Rats had significantly lower levels of the transcription factor NF-$_{k}$B, which is crucial for innate immunity and mediates the production of the pro-inflammatory cytokines TNF-α (Somade et al., 2019; Brazão et al., 2022). On the other hand, another study showed the effect of melatonin on ischemic brain injury in the apoptotic response and inflammation in aged rats. It was found that the animals given melatonin starting 24 hours before surgery and continuing for the first 7 days after an ischemic stroke led to oxidative stress, blood-brain barrier dysfunction, post-ischemic inflammation, and microvascular injury. Moreover, there was a significant decline in tumor TNF-α and interleukin-1 beta (IL-1 beta) levels (Rancan et al., 2018). Prior research has shown that melatonin can prevent the transcriptional activation of IL1 and TNF-α by blocking NF-κB binding to DNA (Chuang et al., 1996; Li et al., 2005; Farid et al., 2022). In addition, melatonin therapy attenuates the inflammatory signals triggered by insulin resistance/hyperinsulinemia, reducing adipose/hepatic inflammation (Obayemi et al., 2021).

The recorded findings agreed with a previous study that revealed that a diet rich in fat drastically lowered spatial working memory performance in the Y-maze test (Ajayi et al., 2021). Moreover, feeding rats with a diet rich in fat for two months impaired their learning ability, and rats took longer and traveled a longer distance compared with the control in the Morris Water Maze task (Sepehri et al., 2019). There is still much mystery about how a high-fat, low-carbohydrate diet can impair mental acuity. Multiple studies have shown HFD to increase oxidative stress and free radical generation, leading to lipid peroxidation and changes in the blood-brain barrier's structural components (Reiter et al., 2014; Alzoubi et al., 2017; Alzoubi et al., 2018). Moreover, Abdulwahid (2019) stated that HFD impaired hippocampal neural function by impairment of inhibitory neurotransmitters. Furthermore, the activation of astrocytes might be a remarkable indication of inflammation in the hippocampus (Abdulwahid, 2019). Neuronal damage markers, such as serotonin, dopamine, and

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glutamate were significantly altered in the brains of HFD rats, which may explain the resulting apoptosis of hippocampus cells and cognitive impairment (Labban et al., 2020; Parkington et al., 2020). it was suggested that melatonin improved spatial learning and memory by reducing isoflurane-induced endoplasmic reticulum stress and neuroapoptosis in the hippocampus and serum levels of neuroinflammatory markers (Fang et al., 2022). A decrease in the inflammatory response in pro-inflammatory cytokines, such as interleukin-1 (IL-1), and tumor necrosis factor Alfa (TNF-α), and an increase in anti-inflammatory cytokines like IL-4 have been observed in an animal study where exogenous melatonin was administered before acute conditions (Carrasco et al., 2013). In addition, melatonin reduces the formation of high amounts of prostanoids and leukotrienes, and other mediators of the inflammatory process, such as chemokines and adhesion molecules, by inhibiting the expression of cyclooxygenase and inducible nitric oxide synthase (iNOS, Liu et al., 2017). To measure the anxiety-like behavior in experimental animals, Elevated plus maze (EPM) was used. The current EPM findings agreed with previous studies, which reported that an HFD impairs assessed anxiety-like as well as working memory behaviors by decreased open arm time in the EPM, and increased movement and rest episodes and decreased rearing in the open field test (Hu et al., 2017; Holl et al., 2018; Deal et al., 2020). Previous studies on the cognitive deficits and anxiety-like behavior in rodents fed an HFD indicated that indoleamine 2,3-dioxygenase (IDO) activity and pro-inflammatory cytokines were involved in the proposed mechanism (André et al., 2014; Parkington et al., 2019). On the contrary, Kaczmarczyk et al. (2013) reported that HFD rapidly impacts dopamine metabolism in the brain, appearing to trigger anxiety-like behaviors and learning/memory impairments. In the reduction of the ratio of reduced glutathione GSH: oxidized glutathione GSSG, by elevation of cytosolic reactive oxygen species, anxiety-like behaviors in mice can be observed (Llorente-Folch et al., 2013). Finally, in rat research, it has been demonstrated that amphetamine withdrawal causes depression and anxiety-like behavior associated with DA dysregulation. In the hippocampus and amygdala, the dopamine D1 and D2 receptors are associated with anxiety-related behaviors (Svingos et al., 2001; Lee et al., 2018).

In a sporadic rat model of Alzheimer's, melatonin administration during the disease's active stage of progression decreased amyloid deposition in the hippocampus (β1-42 and β1-40) and frontal cortex (β1-42), decreased degenerative changes in the hippocampus, prevented mitochondrial dysfunction, and postponed anxiety and cognitive decline (Rudnitskaya et al., 2015). Prolonged melatonin use prevents neurodegeneration in rat's hippocampus by reducing hyperphosphorylation and Aβ mediated memory impairments following intracerebroventricular Aβ1-42-injection (Ali and Kim, 2015). After intracerebroventricular injections of soluble A1-42, it has also been found that melatonin enhances spatial memory, decreases astrogliosis in the rat hippocampus, and decreases synaptic dysfunction (Zhang et al., 2016). In a sporadic rat model of Alzheimer's disease, it has been discovered that long-term oral melatonin administration and maintains the neuronal and glial structure increases hippocampus synaptic development (Stefanova et al., 2015). Previous studies have revealed that feeding heavily on fat and carbohydrates can increase blood-brain barrier permeability and impair cognition (Davidson et al., 2013). These results confirm that rats administered HFD have lower hippocampus plasticity. Additionally, hippocampus volume shrinks, and the hippocampus volume will inevitably decline due to neuronal death (Cherbuin et al., 2015).

An electron microscopy analysis revealed that rats fed an HFD had degenerative neurons, swallowed mitochondria, expanded endoplasmic reticulum cisterns, and increased lysosomes and vacuoles (Alkan et al., 2021). Similar to previous studies, inflammation caused by fatness leads to various disorders and affects the nervous system. In the CNS, mild cognitive impairment can be attributed to obesity-induced altered hippocampal structure and function (D O'Brien et al., 2017).

Rats on the HFD displayed decreased mRNA expression of the blood-brain barrier capillary system's tight junction proteins, Claudin-5 and Claudin-12. The claudins, among the tight junction proteins, are thought to be the main proteins that create the tight junction features of the endothelial cells and are significant in permeability restriction (Wolburg and Lippoldt, 2002). The HFD was also connected to increased sodium fluorescein (NaFl) permeability from the vasculature to the hippocampus region, which is consistent with the lower production of these proteins (Kanoski et al., 2010). Accordingly, such a diet can alter the brain's internal environment by disrupting the function of the blood-CSF and blood-brain barriers. In conjunction with the hippocampus' apparent vulnerability to increased NaFl permeability, behavioral findings imply that this brain area is more susceptible to the neurotoxic effects of saturated fats and refined carbohydrates on blood brain barrier permeability and cognitive function (Hargrave, 2014; Clasen et al., 2020). By making contact with the endothelial basal lamina, astrocytes control leptin's capacity to penetrate the blood-brain barriers (Hsuchou et al., 2009). According to the previous study, reactive gliosis alters the production and function of these connexins proteins in astrocytes, particularly via opening the connexins hemichannel (Giaume et al., 2021). Certain circumstances, such as reduced pH, oxidative stress, as well as inflammation brought on by injuries, may cause the hemichannel to open (Turovsky et al., 2020). In addition, gliotic astrocytes may directly contribute to tissue injury through local proinflammatory signals. Similar to microglial activation, astrogliosis is triggered by an HFD in mice. This gliosis can be produced by several factors, including the release of nitric oxide (NO, Gzielo et al., 2017). Fat and cholesterol-rich diets are a known risk factor for cognitive decline due to their effects on hippocampus-dependent

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memory, blood-brain barrier dysfunction, and hippocampal neurogenesis (López-Taboada et al., 2020). It is worth mentioning that the changes occurring in the brain tissue are due to oxidative stress, changes in the mitochondria, and inflammation evident in the microscopic examination through the increase of cells that show inflammation. The majority of the cited research revealed that the effects of insulin on the tissues lead to alterations, which was supported by biochemical investigation through the brain tissue by TNF examination. A previous study revealed Lipid peroxidation reduced after the melatonin infusion, most notably in the brain. An increase in antioxidants, such as GSH-Px activity was also observed after melatonin treatment. This means that melatonin increases the levels of the antioxidative enzyme GSH-Px and removes free radicals (Baydaş et al., 2001). Melatonin inhibited lipid peroxidation in the mitochondria and the cytoplasm in a different experiment that looked at its capacity to prevent oxidative damage in brain tissue and decrease antioxidative enzyme activity in brain tissue (Shen et al., 2002). Another recent study by Bicer et al. (2022) about the neuroprotective of melatonin gains brain damage so melatonin increased the activities of antioxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT) and improved brain total antioxidant status (TAS) and suppressed lipid peroxidation, inflammatory pathways, and apoptosis. Treatment with melatonin considerably improved the histological features in the hippocampus, cortex, and cerebellar region, which included vacuolation, inflammatory cells, and pyknotic cells (Sarena et al., 2022). Moreover, melatonin applied before radiotherapy protects against early-period radiotherapy-induced brain damage (Aras et al., 2021). Thus, results indicate that melatonin therapy could reduce reactive gliosis. Due to its great efficacy, low toxicity, and ability to cross the blood-brain barrier, it had a neuroprotective impact that reduced cell death and reactive astrogliosis (Alonso-Alconada et al., 2012). The result agreed with a recent study that melatonin protects memory, oxidative stress, and inflammation when dopamine decreases (Amin et al., 2021). Some suggest that melatonin could inhibit the intrinsic pathway of apoptosis to prevent neurodegenerative diseases (de Lima et al., 2005; Tuzcu and Baydas, 2006; Ferreira et al., 2010). This confirms the role of melatonin in pathophysiological mechanisms, such as edema in the central nervous system and peripheral organs (Xu et al., 2017). In a similar study on histopathological examination, melatonin significantly reduced the rates of necrosis, neuronal degeneration, and edema (Erol et al., 2004). The ability of melatonin to stop neuroinflammation caused by a diet rich in fat and heavy sugar in an HFD-T2DM rat model by restoring pancreatic function, reducing adipose tissue mass, and easing dyslipidemia. This will decrease systemic inflammation, eventually stopping neuroinflammation by reducing oxidative stress in the brain and stopping the expression of iNOS (Maher et al., 2020). These results conclude that melatonin's antioxidant activities improve the brain tissues, the neuroprotective ability of melatonin, and the daily administration of 10 mg/kg /body weight of melatonin. These results agreed with a previous study (Favrais et al., 2021), which indicated that the IP injection of melatonin (5 mg/kg/daily) had promising neuroprotective effects due to its antioxidant, anti-inflammatory, and anti-apoptotic properties.

CONCLUSION

Feeding animals with high-fat diets impaired brain neurotransmitters and induced pro-inflammatory changes, as well as affected learning ability and memory by changing the structure of neural tissue. Injection of melatonin at a dose of 10 mg/kg/daily can repair the harmful effect of HFD and restores the normal histological structure of the brain, and biochemistry function, such as dopamine. Future studies are suggested to investigate the effect of different doses of melatonin and its injection time for assessing memory and cognition using Open field test, forced swim test, and Radial arm maze.

DECLARATIONS

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Authors' contributions

Dr. Ammar A. Abdulwahid conceptualized the idea and developed an experiment to conduct the laboratory work. Ahmed Raheem Rayshan, Ammar Ahmed Abdulwahid and Alyaa Abdulhussein Alsaedi analyzed data and contributed to the drafting, editing, and production of the final draft. All authors checked and approved the final version of the manuscript.

Competing interests

The authors declare that they have no conflict of interest.

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Ethical consideration

Ethical issues (including plagiarism, consent to publish, misconduct, data fabrication and/or falsification, double publication and/or submission, and redundancy) have been checked by all the authors.

Availability of data and materials

The data presented in this study are available on request from the corresponding author.

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