Melatonin as Neuroprotective effect in some brain impairments

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Abstract

The aim of the current study is to investigate the role of melatonin in protecting the brain of male adult rats from the effect of oxidative stress induced by high-fat diet consumption and the accompanied neurodegenerative disorder.

In Conclusion: High fat diet caused metabolic disorders, inflammation in rat brains and influenced brain neurotransmission, reflecting that to abnormal rat behaviors. However, melatonin can reverse the normal activity of the brain.

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List of Abbreviations

Abbreviations	Full name
AAR	Adipose afferent reflex
AD	Alzheimer disease
ADHD	Attention deficit hyperactivity disorder
AFMK	N1-acetyl-N2-formyl-5-methoxykynuramine
AMK	N1-acetyl-5-methoxy-kynuramine
AT	Adipose tissue
BBB	Blood brain barrier
BDNF	Brain-derived neurotrophic factor
BM	Barnes Maze
BMI	Body Mass Index
BMI	Body mass index
CHD	Coronary heart disease
CLS	Cluster like structure
CNS	Central nervous system
Cox	Cyclooxygenase
COX-2	Cyclooxygenase-2
CSF	Cerebrospinal fluid
CV	Cardiovascular
DA	Dopamine
DAT	Dopamine transporter
DCX	Double cortin

DG	Dentate gyrus
dH	Hippocampus
DM	Diabetes mellitus
EFAs	Essential fatty acids
ELISA	Enzyme-linked immunosorbent assay
EPM	Elevated plus-maze
fEPSP	Field excitatory post synaptic potentials
FHFD	Female rats on HFD
GABA	γ-amino butyric acid
GFAP	Glial fibrillary acidic protein
GLUT4	Glucose transporter type 4
HbA1c	Glycosylated hemoglobin
HFD	High fat diet
HFD+M	High fat diet and melatonin
hNG	Hippocampal neurogenesis
Iba1	Ionized calcium binding adaptor molecule 1
IFN-γ	Interferon gamma
IL	Interleukins
iNOS	Nitric oxide synthase
IP3	Inositol-1,4,5-trisphosphate
IR	Insulin resistance
lean AT	Lean athletic body
LTP	Long-term potentiation
M1	Activated macrophages microbicidal

M2	Activated macrophages allergic
MDA	Malondialdehyde
MHFD	Male rats on HFD
MS	Metabolic syndrome
MWM	Morris water maze
Na, K-ATPase	Sodium–potassium pump
NAc	Nucleus accumbens
NAFLD	Non-alcoholic fatty liver disease
NF-κB	Nuclear factor kappa B-cell
NO	Nitric oxide
Nrf2	The nuclear factor erythroid 2
PS	Population spike
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
SCN	Supra chiasmatic nucleus
SFAs	Saturated fat acids
SNc	Substantial nigra parcompacta
SOD	Superoxide dismutase
T2D	Type 2 diabetes
T2DM	Type 2 Diabetes Mellitus
TCA	Tricarboxylic acid
TFAs	Trans fatty acids
TLR4	Toll like receptor 4
TNF-R	Tumor necrosis factor-Receptor

TNFR1	Tumor necrosis factor receptor 1
TNF-α	Tumor necrosis factor-Alfa
VAN	Vagal afferent nerve
VCM	Vicious cycle model
VIDA	Variable interval delayed alternation
VTA	Ventral tegmental area
WDs	Western diets
WHO	World Health Organization
β-cells	Beta cells

Chapter one

Introduction

1.1 Introduction

The term "high-fat diet" refers to a variety of diets with fatty acid compositions that are quite distinct from one another **(Storlien *et al.*, 1991, 1996)**. Consumption of a diet rich in fat can lead to the accumulation of fat mass and imbalance distribution of fat in the body, the overweight or obese even lean people, on the high- fat diet bodies don't tend to induce the rate of fat oxidation in the same way in the people with normal diets **(Westerterp *et al.* 2008)**.

One of the major health issues in developed nations is obesity. It is primarily defined as an abnormal rise in body weight and an unproportional accumulation of body fat mass brought on by long-term excess energy intake over energy expenditure **(Paternain *et al.*, 2011)**. Obesity can result to visceral fat accumulation, insulin resistance, dyslipidemia and glucose intolerance **(Rawshani *et al.*, 2020; Börgeson *et al.*, 2022)**.

Obesity is becoming more common everywhere and has already increased to worrying levels, especially in areas of North Africa and the Middle East **(Musaiger, 2011)**. Fatness or Obesity is serious health issue that increases the risk of

illnesses chronic like cardiovascular disease and diabetes mellitus **(Wang and Lobstein, 2006; Roh and Jung, 2012)**.

Obesity or fatness is characterized by an abnormal accumulation of extra fat followed by an imbalance between energy intake and expenditure **(Kopelman, 2000; Spiegelman and Flier, 2001)**. Furthermore, the Organization of World Health (WHO) categorized being high weight or obese as an excessive or abnormal buildup of fat that poses a risk of health **(WHO, 2000)**. The epidemic of obesity in the twenty-first century is one of the greatest threats to public health. According to the Organization of World Health in 2019 **(WHO, 2019)**. Fat accumulation can take place through either adipocyte hypertrophy or adipocyte hyperplasia **(Shao *et al.*, 2018)**.

The link between adipocyte hypertrophy and extreme weight gain is well established **(Gustafson *et al.*, 2013)**, marked by the rapid expansion of fat depots due to the expansion of preexisting fat cells and by the presence of abundant fibrosis and type one macrophage infiltration **(Gustafson *et al.*, 2013)**, because of these factors, the abnormal growth is linked to ongoing inflammation and white adipose tissue dysfunction. The amount of fat you consume on a daily basis is positively correlated with the

amount of fat that store in the body **(Rodrigues *et al.*, 2012)**. Adipokines like adiponectin, resistin, and leptin are secreted by visceral fat tissues, which are considered a dynamically endocrinal organ. Intake, metabolism, energy kolary balance, insulin sensitivity and generation, functionally of endothelial, and inflammation are all impacted by the later Adipokines **(Grundy, 2016)**.

High dietary fats, contributes to fatness, neurodegenerative diseases, memory loss, and decrease the level of brain derived neurotropic factor in the hippocampus **(Park *et al.*, 2010)**. Fatness lowers cognition and causes atrophy in the brain's learning and memory-related areas, moreover, cognition impairment was connected to synapse loss, decreased dendritic spine numbers and production of synaptic proteins, as well as structural changes in the immune cells called microglia in the brain **(Bocarsly *et al.*, 2015)**.

A large proportion of inflammatory and metabolic disorders, including obesity, are directly associated with Oxidative stress **(Furukawa *et al.*, 2017)**. The second hit resulted from oxidative stress and peroxidation of lipids subsequent along with pro-inflammatory cytokines and tumor necrosis factor production TNFα **(Neri *et al.*, 2016)**,

and hormones derivative from adipose tissue **(McCullough *et al.,* 2006)**.

Obesity prevalence is growing and becoming a global problem among the adult population, and the interest in of nutritional effects on the brain is expanding nowadays **(Popkin *et al.,* 2012)**. The pathophysiologic foundation of the metabolic syndromes is made up of central obesity, changes in adipokine secretion, and concurrent fat storing in several metabolic active tissues such as the liver, pancreas and muscle **(Carr *et al.* 2004; Whitehead *et al.,* 2006)**, Moreover, is frequently included alongside the aforementioned typical factors hepatic steatosis **(den Boer *et al.,* 2004)**.

Exposure to an high-fat diet over time may develop obesity by influencing factors at a number of control levels, this may involve the development and the creation and reception of adiposity-indicating signals in the brain, the reception of meal-related signals that influence food intake and metabolism, and/or the brain's neurotransmitter systems that control these processes **(Woods *et al.,* 2003)**.

Through its ability to safely interact with free radicals and before the cellular damage occurs worked to stop the chain reaction, antioxidants work to prevent or delay the cellular

damage **(Lobo *et al.*, 2010)**. As well as its ability to reduce inflammatory processes, oxidative stress, counteract lipid profile and insulin, improve the mitochondrial function in brain tissues and sensitivity **(Agil *et al.*, 2021)**.

The antioxidant process neutralized the free radicals but inadequately this because of the cumulative damage of oxidative stress in the body **(Valdecantos *et al.*, 2009)**. Free radicals have been shown to be adversely affected by cell survival via damage in the plasma membrane resulting from lipid and protein oxidation and un-repairable DNA changes **(Mishra *et al.*, 2004; Crochemore *et al.*, 2021)**, thiobarbituric acid and hydroperoxides are indicating substances for lipid peroxidation whereas carbonyl proteins indicating to oxidation of proteins **(Olusi *et al.*, 2002; Uzun *et al.*, 2007; Yavuzer *et al.*, 2016)**.

Melatonin: Melatonin is a potent antioxidant melatonin is produce (synthesized) and secreted by the pineal gland **(Rehman *et al.*, 2019)**, In addition to its antioxidant characteristics, this neuro hormone works as a strong free radical scavenger and activates the brain's primary antioxidant enzymes such superoxide dismutase (SOD) and catalase **(Rodriguez *et al.*, 2004)**, Melatonin has been studied due to its Neuroprotective actions in several neurodegenerative disease such as Alzheimer’s

diseases**(Rehman *et al.*, 2019)**. Furthermore, Melatonin exerted anxiolytic and anti-depressant effects and it assists to improve cognition ability **(Lamtai *et al.*, 2020)**. Recent studies reveal that the affordable, safe drug melatonin may enhance metabolic health. Its effect on issues associated with obesity is uncertain, though. In this study, we explored the possibility that supplementing male rats with melatonin will lessen the metabolic dysfunction of their adipose tissues brought on by their high-fat diet-induced obesity.

1.2 Aim of the study: -

We hypothesized that exposure to high fat diet alters the brain functions and structure during oxidative damage and that could be avoided by an antioxidant agent such as melatonin.

The aims of the present study are:

1- Investigating the harmful effect of high fat diet on animal behaviors and brain functions.

2- Possibility of melatonin to repair the damage that could result from high fat diet.

Chapter two
Literatures Review

2. Literatures Review

2.1. High-fat diet:

The earliest definition of a "high-fat diet" was as a nutritional strategy to promote obesity was published in 1959 **(Mašek and Fabry 1959)**. Some expressions used to describe diets a contain higher fat are Western diet, high energyhigh-fat diets, cafeteria diets and high fat sugar diets. The precise nutrition structure of the control diets and fat diets used, including the carbohydrates quantity and types of fats, may vary and is not extensively detailed. It's unknown if the use of different strains, ages and species of animals experimental results in different outcomes or if adjusting critical parameters that is measured it in experimental, such as the time and duration of diet exposure and the sort of behavior estimates, has a significant impact, obesogenic rat food often contains sixty percent of total calories as fat, compared to thirty to forty percent fat in a typical Western diet **(Mozaffarian *et al.*, 2018)** reviewed in **Abbott *et al.*, (2019)**. Additionally, most high fat diets used in rodent research exhibit an inverse relationship between the content of fat and sucrose, with the lowest fat diets carrying the highest levels of sucrose, the exact reverse of the pattern

observed in human diets **(Speakman, 2019)**. This could be a problem given the role that sugar consumption plays role in metabolic dysfunctions. It should be highlighted that lard is almost always the main source of fat in rodent models of high fat diet (HFD). Therefore, rather than being generalized to high-fat diets, these findings exclusively apply to meals heavy in animal sources of saturated fatty acids **(Rusu *et al.*, 2020)**. Compared to primates, rodents may have different mechanisms for controlling body weight, only increases in dietary fat were found to increase obesity in a study that used five distinct strains of laboratory rats and (29) different diets; increases the amount of (sucrose or protein) content had no effect **(Hu *et al.*, 2018)**. However, high-carbohydrate diets easily result in excessive calorie consumption and weight gain in human research **(Stubbs *et al.*, 2001)**.

A rodent's age and gender affect the body's adipose tissue distribution and weight growth while feeding HFD, which can have a substantial impact on how well the mouse does **(Nishikawa *et al.*, 2007)**. High fat diet induced more body weight gain in female rats and female rats increase storage of fat in female rats, however, lower hepatic steatosis in female FHFD than in male MHFD rats was observed **(Shi *et al.*,2020)**.

According to the World Health Organization (WHO), at least one third of people over the age of 20 are already overweight or obese, and throughout the previous three decades, obesity prevalence has increased **(Arroyo-Johnson and Mincey, 2016)**. Chronic metabolic disorders have been linked to high energy diets such as diabetes type two **(Freeman *et al.*, 2014)**. Worryingly, recent research indicates that dietary fat has an effect on how the brain and behavior work **(Davidson *et al.*, 2013)**. Overeating combined with decreased physical activity leads to obesity, additionally, a number of ecological and hereditary factors have a significant role in this illness **(Nijhawan *et al.*, 2019)**.

One of the most pressing health issues facing modern civilization is obesity **(Torres and Nowson, 2007)**. It is primarily defined as an excessive rise in body weight and an unbalanced accumulation of body fat mass brought on by long-term excess energy intake over energy expenditure. In addition to the well-known set of metabolic changes, obesity may also be linked to psychiatric conditions like anxiety and depression **(Paternain, 2011)**. Obesity is an epidemic and is an increasing international health concern **(WHO, 2012)**. Conditions like metabolic syndrome and diabetes are usually the complications of a high fat human intake which have

been interpreted in rodent models, in addition, epidemiology and animal studies have shown the interaction of obesity with conditions such as hypertension and cardiovascular dysfunction in adults **(Manna and Jain, 2015)**.

Global nutrition has undergone a change in the previous few decades from undernourishment to overconsumption, global obesity has become a pandemic as traditional diets have been replaced by inexpensive, readily accessible manufactured meals high in edible oils refined carbohydrates and fat source from animal although it is typically thought of as a problem growing middle classes in developing countries are facing the same obesity epidemic that has plagued the industrialized world **(Trail *et al.*, 2014)**. In addition, alterations in the endocrine response, folic acid deficiency and fetal insulin resistance were associated with obesity **(Cuthbert *et al*., 2017)**.

One of the key factors contributing to overweight and obesity is the increased consumption of HFD, which is of concern to public health organizations. These diets' detrimental effects appear to be related to their abundance of easily digestible and assimilated carbs and saturated fat, as well as the fact that they encourage irregular eating habits

such as repeated energy bushy snacking and /or large meals just prior bedtime **(Corwin and Hajnal, 2005)**. This is closely related to the idea of comfort food, which refers to the ingestion of pleasant calorie dense diets to reduce tension, anxiety and worry **(Leow *et al.*, 2018)**. Although excessive weight Body Mass Index (BMI) significantly raises the risks of developing a number of pathological conditions, such as metabolic syndrome, stroke, gallbladder disease, nonalcoholic steatohepatitis, coronary heart disease, diabetes, some types of cancers, osteoarthritis, cognitive decline, and Alzheimer's disease, it may not have a significant impact on life anticipation per se **(Finkelstein *et al.*, 2010)**, **(Nepal *et al.*, 2014)**.

Obesity causing dysregulation of adipose tissue (AT) functions resulting in increased secretion of adipocytokines and proinflammatory cytokines like resistin, inducing insulin resistance and endothelial dysfunctions **(Atawia *et al.*, 2017)**. Adipose tissue forms a cross communication network between various organs in the body that reflects the diversity of the physiological role of adipocytokines **(Apostolopoulos *et al.*, 2016)**.

2.2. Influence the high-fat diet on Body Health

In developed nations, rotundity (obesity) is a growing problem due to the buildup of excess fat, which results in a high body mass index. Obesogenic diet is the largest cause of death and it's linked to heart disease, diabetes type two and cancers **(Kopelman, 2000)**. However, obesity can be considered to be the result of an energy intake that exceeds and decline energy expenditure **(Xing and Chen, 2004)**.

Moreover, obesity is linked to a decline in mitochondrial function, Malonyl-CoA processing is favored by excess fat, which reduces the effectiveness of Glucose transporter type 4 (GLUT4), Tricarboxylic acid (TCA) and beta oxidation cycle byproducts boost reactive oxygen generation in the organism. Restoring mitochondrial function and insulin sensitivity can be crucial in the treatment or prevention of obesity, which can be achieved through regular physical activity **(Coelho *et al.*, 2011)**. Increased adiposity is a side effect of high -fat diets because they promote a healthy fat balance in the body **(Braeuner, 2022; Ludwig *et al.*, 2022)**. Both obese and slim people who follow these regimens don't seem to get the same increase in fat oxidation **(Westerterp *et al.*, 2008)**. In addition, it appears that the type

of dietary fat consumed has an effect on how much fat that gained, however, in contrast to (Omega-3 fat), which has negatively impacted insulin sensitivity due to changes in cell membranes, saturated fat has insulin sensitivity goes in the opposite direction (Omega 3 fatty acids), on the other hand, have been shown to protect healthy older adults from cognitive loss **(Uranga *et al.*, 2010)**. Furthermore, compared to diets rich in Omega-6 and meals rich in Omega-3 fatty acids, diets high in saturated lipids will lead to an increase in body fat **(Wang *et al.*, 2009)**. Excess fatty tissue in the body may relate not just with regard to energy supply and expenditure in humans, but even in extra types of diets, particularly HFD, which could cause a variety of metabolic changes like human hyperphagic, reduced leptin secretion and/or sensitivity, reduced lipolysis activity in fat tissue, impairment of mitochondrial metabolism, hypothalamic neuron apoptosis, obesity and insulin resistance **(Crispino *et al.*, 2020; Sigit *et al.*, 2021)**.

Studies showed that HFD effects are not limited to hepatic or cardiovascular impairments, however in a recent study, feeding HFD rats for (5) weeks or more leads to an increase the percentage of fat to body weight. HFD changed rat's behavior and intellect in early and late life

(Abdulwahid, 2019). According to **Fried *et al.* (2008)**, obesity significantly increases the chance of developing fatty liver, dyslipidemia, which can advance to nonalcoholic fatty liver disease, coronary heart disease (CHD) and cardiovascular (CV) and disorders such as heart failure **(Artham *et al.*, 2008)**.

Exposure to high fat for ten weeks causes a significant increase in the size and weight of body fat depots: total fat, epididymis, mesenteric and retroperitoneal **(Goyal Amit *et al.*, 2020)**. The NAFLD defines as non-alcoholic fatty liver disease is brought on by an abnormal buildup of fat in the liver that is unrelated to alcohol consumption, it is one of the most prevalent chronic diseases in the world with in a (25%) a prevalence rate, it causes liver damage that can proceed from simple steatosis to steatohepatitis, fibrosis, and cirrhosis **(Adams *et al.*, 2005)**. Excessive hepatic lipotoxicity, oxidative stress, and inflammation are the pathological traits of the earliest stage of NAFLD, hepatic steatosis, is caused by the buildup of lipid droplets in the hepatocytes' cytoplasm, lipid buildup damages the liver, making it more susceptible to oxidative stress, proinflammatory cytokines, lipid peroxidation, and mitochondrial dysfunction, as a result of

structural liver damage brought on by oxidative stress **(Bullón-Vela *et al.*, 2018; Kim *et al.*, 2021)**.

Due to the oxidative alteration of lipids and proteins in the heart, lipid peroxidation causes cellular membrane integrity to be lost, which can ultimately result in cardiac arrhythmias, cardiac failure, poor contractility, sudden death, or infarction **(Vincent *et al.*, 2001)**. Increased lipid substrate within the myocardium may serve as a larger target for free radical oxidation, and myocardial effort and mechanical overload are associated with consequently lipid peroxidation due to a raise in free radical generation, these factors are thought to be the potential mechanisms for increased lipid peroxidation in cardiac tissue **(Vincent *et al.*, 2001)**.

A high-fat diet resulted in a decrease in the diameter of the convoluted tubules, a reduction in the volume of the cells in Bowman's capsule, and a rise in the number of positive cells for the sodium-potassium pump (Na,K-ATPase), but it also decreased the Na,K-ATPase activity and the amount of cholesterol in the kidney cell membrane, favoring lipid peroxidation instead **(Garcia *et al.*, 2018)**. It has been demonstrated that obesity is connected with alterations in gastrointestinal motility, Changes in stomach motility can

have significant effects on appetite and fullness. The digestive tract regulates the rate of digestion and appetite to stimulate or suppress hunger **(Camilleri and Grudell, 2007)**.

Several tissues, including the colon, liver, fat cells, muscle fibers, and the hypothalamus have been demonstrated to be affected by HFD consumption's persistent low-grade inflammation and resulting in altered homeostasis **(Duan *et al.*, 2018)**. Overweight women in the Asia Pacific have an increased risk of developing esophagus, thyroid, colon and renal malignancies, there is also a clear link between obesity and both premenopausal and postmenopausal breast tumors **(Renehan *et al.*, 2008)**. The endothelium level exhibits elevated concentrations of the circulatory adhesion molecules (E-P) selectin, and intracellular can see the level of adhesion molecule-1, obesity, in particular visceral obesity, reduces endothelial-dependent vasodilatation **(Arcaro *et al.*, 1999; Preston *et al.*, 2019)**.

The obtained findings agreed with several studies in different ways as with **Hafizur and colleagues (2015)** who revealed blood glucose increase after 1 month of HFD animals and remained elevated at a rate of ~5 mg/dl throughout the six-month study period also the serum insulin, insulin resistance were increased progressively with

respect to the passage of time **(Hafizur *et al.*,2015)**, moreover, this study was agreed with Johnson and his team (2019) who studied glucose mediates insulin sensitivity via a hepatoportal mechanism in high-fat fed rats fed for 3 weeks and found the glucose and insulin resistance was significantly increased compared to the control group **(Johnson *et al.*,2019)**.

Furthermore, Liu and his colleagues (2015) investigated how a high-fat diet affected brain synaptic plasticity and discovered that hyperglycemia set in after 8 weeks of HFD feeding and persisted through week 12. This was demonstrated by 92.8% and 109.8% higher circulating glucose levels than the control group at these two-time points, respectively. These changes in circulating glucose and insulin levels brought on by the HFD were also reflected in a significant rise in the HOMA-IR index, a measure of **(Liu *et al.*, 2015)**.

Some studies suggested that HFD feeding developed insulin resistance concomitant with high blood glucose levels **(Zhang *et al.*,2008a)**, Body's resistance to insulin and falling insulin production of pancreatic β cells are two main factors in HFD induced type 2 diabetes **(Li *et al.*, 2020a)**. The exact

relationships between high-fat diet, insulin resistance, and type 2 diabetes are pathological accumulation roles of fatty acids or fatty acid derivatives such as polyunsaturated fat in muscle or liver that produced impairment of insulin sensitivity **(Ghiasi *et al.*, 2015; Bene *et al.*, 2018)**. The elevation of glucose and insulin in the HFD group attributed to the HFD is known to accelerate the onset and severity of diabetes in some spontaneously occurring diabetes models, it has been proposed that glucotoxicity conditions promote internalization of K_{ATP} channels leading to a decrease in the membrane hyperpolarized state, thereby inducing insulin secretion (**Han *et al.*, 2018; Yan *et al.*, 2018)**. The activity of the glucose transport system, the number of insulin receptors, and the intercellular metabolism of glucose may all be decreased by a high-fat diet, according to **(Grundleger and Thenen, 1982; Olefsky and Saekow, 1987).** Furthermore, **(Mainz *et al.*, 1973)** higher-fat and high-calorie foods have been linked to pancreatic enlargement and the stimulation of cholecystokinin secretion **(Matters *et al.*, 2014; Nadella *et al.*, 2018)**. In addition, a study by Saito and his team demonstrates that HFD induces fatness-associated hyperinsulinemia and insulin resistance by inhibition (suppression) of AMP-activated protein kinase through

increase gluconeogenesis with lipogenesis and decreased fatty acid oxidation **(Saito *et al.*, 2016)**. Nevertheless, the current study agreed with the recent mentioned study in regard of insulin and insulin resistance, the elevation in insulin secretion elevate risk of fat accumulation with insulin resistance **(Nylander *et al.*, 2016; Johnson, 2021; Salehidoost and Korbonits, 2022)**. Fasting glucose levels rise after high-fat overeating due to elevated hepatic glucose production **(Xu *et al.*, 2018)**, and increased insulin secretion occurs prior to the occurence of peripheral insulin resistance, dysfunction of mitochondrial, and fatness in response to overeating, an indication that both insulin and Glucose-dependent Insulin tropic Polypeptide may contribute to the onset of peripheral insulin resistance and obesity **(Jia *et al.*, 2020)**. An increase in insulin secretion may make up for hepatic insulin resistance that may be caused by elevated Glucose-dependent Insulin tropic Polypeptide secretion **(Thondam *et al.*, 2020)**.

Adipokines function a significant part in the emergence of type 2 diabetes and insulin resistance and have a variety of impacts on lipid and glucose metabolism, leptin is a glut hormone that could improve hepatic glucose production and peripheral insulin sensitivity, additionally, adiponectin raises

insulin sensitivity of peripheral and hepatic **(Fasshauer and Paschke, 2003)**. Therefore, in response to the consumption of fat plasma leptin's raise could help to increase hepatic glucose production, and the rise in both adiponectin and leptin can help to dissect why overt peripheral insulin resistance has not developed as would otherwise be expected **(Brøns *et al.*, 2009)**.

Another reason explains the increase in the secreted of insulin due to the significant increase in fasting gastric inhibitory polypeptide after food, is one of the incretion hormones that signal by the gut such as glucagon-like peptide-1 and gastric inhibitory polypeptides that increases secretion of insulin from pancreatic after diet consumption **(Meier *et al.*,2003)**. When developing insulin resistance, a decreased number of insulin receptors on cells are observed, as well as the number of glucose receptors, GLUT2, on pancreatic β cells, impaired intracellular signaling prevents glucose uptake into the cell **(Lee *et al.*, 2011)**. Demonstrated a high-fat diet impairs glucose metabolism in skeletal muscle by reducing transcription of GLUT 4 via suppression of plasma insulin without affecting gene expression of the receptor of insulin **(Kim *et al.*, 1995)**.

Glucose taken from the blood is actively oxidized in the skeletal muscles and brown adipose tissue, therefore, reduced glucose uptake in those tissues in the rats put on a diet rich in fat may contribute to the higher plasma glucose level observed in those rats **(Turcotte and Fisher, 2008)**.

In addition, **(Stark *et al.*,2000)** HFD may reduce the activity of the intracellular enzymes involved in fatty acid production and the capacity of cells to use glucose, both of which impair the response of glucose metabolism to insulin **(Huang *et al.*, 2004; Qi *et al.*,2020)**. Furthermore, increased plasma glucose levels in rats given a diet high in fat were caused by a decrease in glucose uptake in the skeletal muscles **(Matsuo *et al.*, 1999)** and adipose tissues **(Yang *et al.*, 2020)**.

Despite the reduced transfer of vesicles carrying GLUT-4 is believed to be linked to insulin resistance, HFD also affects other mechanisms, such as the expression of GLUT-4 mRNA in adipocytes, according to research on the level of Glut4 gene expression in rats fed the diet. Demonstrated that HFD also had a time-dependent effect on the expression of GLUT-4mRNA; GLUT-4 is regarded as a key component of insulin-stimulated glucose transport in

adipose tissues **(Hafizur *et al.*, 2015; Sutthasupha and Lungkaphin 2020)**.

It's interesting to note that meals with high fat have been demonstrated to cause changes on mitochondrial oxidative phosphorylation function, indicating that nourishment may affect mitochondrial function in both qualitative and quantitative ways **(Sparks *et al.*, 2005; Chanseaume *et al.*, 2006; Brehm *et al.*, 2006; Longo *et al.*, 2021)**, who found increase in glucose level after consuming high-fat diet (**Lasker *et al.*, 2019; Moustafa *et al.*, 2021)**.

There is evidence that dopamine (DA) **(Uefune *et al.*, 2022)** functions as a negative regulator of glucose-stimulated insulin secretion (GSIS), the direct effect of dopamine on the release of glucose from primary cultured rat hepatocytes were studied in Japan by **Shiroyama *et al.*, (1998)** , the authors concluded that mediating by beta adrenergic receptors dopamine has a direct effect on hepatocytes of increasing glucose release in the glycogenolytic and gluconeogenic pathways **(Blum *et al.*,2014)**.

In this context, our results showed that HFD increased blood glucose (after eight weeks of treatment), and melatonin prevent this increase. However, in rats fed diet of high fat

and daily injection with 10mg/kg BW melatonin the glycemic index was close to the normal range after eight weeks.

Melatonin has been shown to enhance pancreatic induce-cell regeneration **(Kanter, 2006)**, and stimulate hepatic glycogen synthesis **(Li *et al.*, 2018)**, thus reducing the elevation of glucose levels in rodents. Melatonin administration efficiently attenuates liver dysfunction and glucose metabolism disorders by promoting hepatic expression and phosphorylation **(Chen *et al.*, 2019)**. Melatonin has been shown to prevent liver glucolipid metabolism disorders **(Li *et al.*, 2018)**.

Melatonin predominantly affects the pancreatic islets of Langerhans; as a result, it can promote insulin and glucagon production and release **(Peschke *et al.*, 2013)**. Melatonin receptors MT1 and/or MT2 help melatonin's effects on decreasing glucose-stimulated insulin secretion (GSIS) in insulinoma beta cells and isolated pancreatic islets in rats **(Stumpf and Peschke, 2008; Gomes *et al.*, 2021)**. Melatonin contributes to the potentiation of the central and peripheral actions to insulin by activating the insulin signaling pathway or controlling the production of GLUT4,

through its G-protein coupled membrane receptors, it thereby stimulates the phosphorylation of the insulin receptor and its intracellular substrates. In addition, giving rats with pinealectomy melatonin avoided excessive glucose or cholesterol levels **(Prunet-Marcassus *et al.*, 2003)**.

Although there is still much to learn about melatonin's role in energy homeostasis **(Hansda and Haldar, 2021; Arendt and Aulinas, 2022)**, the present study's finding that melatonin reduced blood glucose levels to normal agreed with **Yapislar *et al.*, (2022a)**. Findings in which studied the effects of melatonin on diabetes-induced rats and found that blood glucose levels were significantly higher (**Yapislar *et al.*, 2022a)**. Despite studies demonstrating a melatonin influence on blood glucose levels in diabetic rats (**Abdulwahab *et al.*, 2021; Hajam *et al.*, 2022a**). Recent research suggests that melatonin therapy may promote lipolysis by promoting intramuscular adipocyte lipolysis by activating protein kinase A (PKA) signaling as well as activating the sympathetic nervous system **(Liu *et al.*, 2019; Suriagandhi and Nachiappan, 2022)**.

Furthermore, normalizes insulin levels from burning glucose by mitochondria and preventing insulin resistance

and fat accumulation **(Xu *et al.*, 2020; Martín Giménez *et al.*, 2021; Moustafa *et al.*, 2021)**. Corroborating these data, other studies **(Lima *et al.*,1998)** employing stated reduction in the expression of the glucose transporter4 (GLUT 4), as well as glucose intolerance and insulin resistance, which were reverted by melatonin treatment **(Nogueira *et al.*, 2011; Guo *et al.*, 2022)**.

It has been hypothesized that melatonin's involvement in the full range of physiological processes that constitute the daily activity-wakefulness/rest-sleep rhythm could have an effect on body mass index and help maintain energy balance **(Teodoro *et al.*, 2014; Amaral *et al.*, 2014)**, by increasing energy expenditure, BAT uncoupling protein 1 (UCP1) expression, and heat production, melatonin reduced weight gain, adipocyte hypertrophy, insulin resistance and inflammation brought on by the HFD. Notably, melatonin caused a change in energy metabolism that favors the use of fat, and it increased AMP-activated protein kinase phosphorylation and fibroblast growth factor 21 in skeletal muscle and circulatory and metabolic tissues. FGF-21 promotes brown adipocyte development, upregulates hepatic fatty acid oxidation, and has a regulatory function in lipolysis in WAT **(Xu *et al.*, 2022)**.

Obayemi *et al.*, (2022) investigated the protective role of melatonin against adipose hepatic metabolic compared to the obese group don't treat with melatonin, melatonin administration significantly improved insulin resistance in the obese with melatonin group.

Animals receiving melatonin have higher liver glycogen levels, which reduce blood sugar, according to the study, high-fat diet-induced diabetes in mice improved with an intra-peritoneal injection of 10 mg/kg melatonin, which also increased hepatic glycogen and reduced liver steatosis **(Shieh *et al.*, 2011)**.

Melatonin enhances gluconeogenesis as result to its role signal transducer and activator of transcription 3 (STAT3) phosphorylation and silent information regulator 1 (SIRT1) expressing **(Chen *et al.*, 2019)**.

Moreover, melatonin promotes glucose uptake skeletal muscle of mouse by activating the insulin receptor substrate 1- (IRS1-PI3K-PKCζ) pathway **(Ha *et al.*, 2006)**. As well as activation of the cyclic adenosine monophosphate (cAMP) to prevent insulin resistance in rats **(Teodoro *et al.*, 2014)**.

2.3. High-fat diet effect on cognition and brain

Previous investigations have proved that the brain is sensitive to dietary of essential fatty acids (EFAs) and led to a remarkable thought that changes in membrane composition may alter the metabolic properties of neurons, whether changes in dietary fat composition could have a significant impact on membrane composition and neuronal function **(Dyer and Greenwood, 1988)**. The Central Nervous System consists of a number of distinct brain areas that are involved in controlling memory and learning processes, however, the hippocampus has a prominent function, dorsal hippocampus appears to be largely linked to cognition, while emotion, effect and stress bind in the ventral hippocampus, this region is unique in that its anatomical activities are divided along the dorso-ventral axis **(Fanselow *et al.*, 2010)**. Both the dorsal and ventral gyrus of the hippocampus, known collectively as the dentate gyrus (DG), are sites of postnatal hippocampal neurogenesis (hNG), action paves the way for the maturation of nascent neurons, which eventually become integrated into the hippocampus circuitry and contribute to its function **(Bortolotto *et al.*, 2014)**, there is a considerable body of evidence that demonstrates that when postnatal

hippocampal neurogenesis is deregulated, it contributes to cognitive impairment as well as changes in mood. Neuroplasticity is known to be negatively affected by chronic over-nutrition, which reduces the amount of new adult neurons in the hippocampus formation and decreases proliferating cells **(Lindqvist et *al*., 2006)**.

The Western diet (rich in fat and sugar) has been linked to memory problems as well **(Abdulwahid, 2019; Francis and Stevenson, 2013)**. Studies have shown that a diet containing mostly Saturated fat acids (SFAs) and Trans fatty acids (TFAs) is inked with a higher the level risk for Alzheimer's disease **(Granholm *et al*., 2008)**. It has been shown in the past that cognitive decline can be brought on by a prolonged rise of oxidative stress brought on by either one's diet or by genetic abnormalities **(Nagai *et al.*, 2003)**.

Several remarkable beliefs regarding beliefs regarding a relationship bind fatty acids and performance cognitive or dementia have been postulated, these hypotheses include mechanisms involving atherosclerosis, impacts on brain development, thrombosis, membrane function, inflammation and deposition of beta amyloid **(Kalmijn, 2000; Leyane *et al.*, 2022)**. Amyloid deposition and cognitive function in

mice were studied in the context of a chronic high- fat meal, as were the brain transcriptase and lipidome, increases in amyloid plaques and declines in cognitive function were both observed in patients who underwent HFD,high-fatt diet considerably influenced the brain's levels of (24) lipid sub species. As a result of this integrated approach, the CNS is shown to respond to HFD in a variety of ways **(Nam *et al*., 2017)**. At a young age, a nutritious diet has been linked to better cognitive outcomes, however, a fed heavy in processed components and added sugar has been linked to lower language, school success and nonverbal thinking in adolescents **(Nyaradi *et al*., 2013)**. Over consumption of food has also been linked to shrinkage of the brain in humans and preclinical animals, according to many studies **(Luciano *et al*., 2017)**.

Moreover, a high intake of lipids has been linked to cognitive decline and an increased risk of dementia, according to both epidemiological and experimental investigations, according to the findings, an HFD enhanced the oxidative stress, inflammation, and activation of Nuclear factor $_{\text{kappa}}$ B-cell (NF-$_{k}$B) in the rat cerebral cortex, raising the possibility that the high fat diet increases the risk of dementia **(Zhang *et al*., 2005, 2010; Tan and Norhaizan,**

2019). The dentate gyrus of the hippo campus freshly produced cell count was drastically reduced after seven weeks of HFD without any neuronal loss, high fat diet also reduce the level of brain derived neurotropic factor (BDNF) in the hippocampus and increased level Malondialdehyde (MDA) **(Park *et al.*, 2010)**.

High fat diets at last impair or decline learning and memory in adult rats by influence disrupt cognitive function and plasticity of neuronal and the growth of the brain's neurons **(Asadbegi *et al.*, 2017)**. A rise in serum corticosterone may be a cause of the disruption of hippocampal neurogenesis that has been linked to a high dietary fat intake, Brain derived neurotropic factor levels in the hippocampal hippocampus and the number of dentate gyrus cells that had just been generated was both significantly reduced after seven weeks of HFD **(Park *et al.*, 2010)**. Chronic ingestion of high levels of saturated or unsaturated fat can also cause given cognitive impairment **(Yeh *et al.*, 2022)**. Although more research is needed to pinpoint the neurobiological mechanisms causing this impairment, preliminary data points to the consumption of saturated fatty acids linked to high-fat diets, as well as insulin resistance and glucose intolerance, as potential contributors

(Winocur and Greenwood, 2005). Spatial memory loss and cell death in the hippocampus can be caused by a high fat diet **(Asadbegi *et al.*, 2017)**. There is no doubt that a person's overall health, neuronal function, memory, and ability to learn and remember are strongly influenced by their lifestyle and diet throughout their lives **(Parletta *et al.*, 2013)**.

Moreover, unbalanced production of reactive oxygen species (ROS) and the body's own antioxidants is thought to functional a significant turn in the neurotoxicity caused by a high fat diet, Cell death occurs because of hydroxyl radical formation, lipid peroxidation, and apoptosis when exposed to oxidative stress **(Ganji *et al.*, 2017)**. Neuro-behavioral disorders are a conditions, damage or dysfunction of the brain that result in changes in behavior or cognition, while being widely known that obesity has adverse effects on brain function in humans and rodents, what is lacking is an understanding of the underlying mechanisms **(Winocur and Greenwood, 2005)**. However, the Consumption of a low carb high fat meal results in neuroinflammation and may play a part in the emergence of neurodegenerative illnesses including Parkinson's and Alzheimer's **(Mattson, 2003)**. Sugar and fat rich diets have been shown to impair spatial memory and working memory in rats as well as mice

(Morales-Delgado *et al*., 2018; Davis *et al.*, 2020) and in male and female **(Garcia-Serrano *et al.*, 2022)**. Consumption of diet have fat and refined sugar lowers learning, hippocampal brain derived neurotropic factor and neural plasticity in rats, which confirms the association between high fat food consumption and cognitive impairment **(Molteni *et al*., 2002)**.

Sharma have shown that brain neurochemistry is changed in a region-specific manner in response to HFD over consumption **(Sharma and Fulton, 2013)** which could lead to behavioral impairment. For instance, striatal and mesolimbic Dopamine signaling in rodents is altered after chronic (three months) intake of HFD **(Akter *et al.*, 2020)**. Furthermore, high fat diet impairs fatty acids receptor mediated signalling pathways leading to memory deficits **(Del Olmo and Ruiz-Gayo, 2018)**. The gauge of population spikes (PS) and decline of field excitatory post synaptic potentials (fEPSP) are both altered by chronic high-fat diet (HFD) in mice, which in turn decreases hippocampal long-term potentiation (LTP) in the dentate gyrus granular cells **(Karimi *et al*., 2013)**. Furthermore, exposing to HFD for 5 weeks and leading to working and references memory impairment due to impairment of remarkable down

regulation in hippocampal neurotransmitter synthesizing enzymes in rats **(Abdulwahid, 2019)**.

Thought process dependent on in situ inflammation eating high fat diets has been shown to reduce leptin and insulin signaling, which may cause neurons to die and synaptic inputs to be reduced in the lateral hypothalamus and the arcuate nucleus, according to research **(Dalvi *et al.*, 2017)**. Astrocytes appear to be susceptible to HFD, as are neurons morphology. The hypothalamus is where most of the study has been done **(Chowen *et al.*, 2016)**, however, the hippocampus has received far less attention. In this regard, it was discovered that high fat intake from weaning onwards was linked to both (longer and less numerous) astrocyte prolongations and reversible activation of the microglia in the hippocampus **(Cano *et al.*, 2014; Hao *et al.*, 2016; Abdulwahid, 2019)**, the amount of glial fibrillary acidic protein positive astrocytes in obese rats receiving a similar diet decreased **(Gzielo *et al*,. 2017; Del Olmo and Ruiz-Gayo, 2018)**, and no obese high body weight mice receiving a comparable dietary intervention from weaning demonstrated a high level of Ionized calcium binding adaptor molecule 1 (Iba1) positive microglia cells **(Vinuesa *et al.*, 2016)**.

The effect was only seen in the dorsal hippocampus, not the ventral, and was associated with lower expression levels of the brain derived neurotropic factor in the dorsal hippocampus **(Chiazza *et al.*, 2021)**. Taking the results of each study together, now it has been well understood concerning the possible influence of a high calorie nourishment on brain, specifically the dorsal hippocampal neuroplasticity (**Chiazza *et al.*, 2021)**. The development of cells that express the protein double cortin (DCX), which is necessary for neuronal differentiation and migration, is a critical phase in postnatal hippocampus neurogenesis **(Ayanlaja *et al.*, 2017)**. (DCX+) cells are lowered by chronic over nutrition in murine models **(Han e*t al.*, 2019)**, and these negative effects are more severe at younger ages and may be region specific **(Vinuesa *et al.*, 2016; Ferreira *et al*, 2018)**. Additionally, some of these changes take place prior to a large weight gain **(Bortolotto *et al.*, 2019)**. The hippocampus' importance to learning and memory performance has been increasingly recognized in recent years **(Manns and Eichenbaum, 2006)**, growing concern has been expressed about its susceptibility to obesity and obesogenic diets. In particular, hippocampal-dependent memory deficits were observed in animals fed high-fat or high-sucrose diets

over extended periods of time **(Stranahan *et al.*, 2008)**. It's interesting that some research on adult rodents and people found that just a few days of an obesogenic diet are enough to have an impact on hippocampus functioning **(Spencer *et al.*, 2017)**.

Bad diets and obesity lead to certain conditions, like diabetes type II, metabolic and cardiovascular syndromes, each such factor plays a part in cognitive impairment caused by diet and/or obesity **(Freeman *et al.*, 2014)**. A high fat diet induces brain damage including oxidative stress, insulin resistance, cerebral cortex, inflammation, changes in vascularization and breaching blood brain barrier integrity and causes mitochondrial dysfunction and cognitive impairment **(Freeman *et al.*, 2014)**.

High fat diet can lead to memory loss that is dependent on the hippocampi following prolonged consumption for longer four weeks **(saiyasit *et al.*, 2020)**. Although there are still many unanswered questions regarding how HFD affects hippocampal function, it is known that a diet have high fat consumption affects emotional abilities and cognitive through a number of distinct mechanisms, including : signals of inflammation, like immune cell recruitment with

activation glial cell **(Pistell *et al.*, 2010)**, manly mitochondrial malfunction and anomalies in cellular bio energetics **(Carraro *et al.*, 2018)**, deterioration of synaptic plasticity **(Liu *et al.*,2015)**, raise permeability and alteration of brain blood barrier **(Kanoski *et al.*, 2010)**.

Rodents fed a diet of high fat over a lasting a long time showed neurobehavioral and neuroimmunological alterations linked to obesity. It has been shown that HFD patients have peripheral inflammation, which can signify brain-based issues. Additionally, HFD promotes the production of reactive oxygen species in the periphery, which results in oxidative stress and brain dysfunction, impairing learning and memory. Alterations in spatial memory and hippocampus expression have been linked to chronic high fat diet eating over three to six weeks **(Ajayi *et al.*, 2021)**.

2.3.1. Elevated plus-maze (EPM) for anxiety.

In order to evaluate anxiety in rats, **(Handley and Mithani, 1984)** first described the Elevated plus Maze, which was later verified by Pellow and colleagues in 1995. This device is a four- armed maze with two open arms crossing in the center and two closed arms that are walled in and elevated off the ground **(Pellow *et al.*, 1985)**. The EPM

is a test that evaluates whether rats exhibit anxiety like behavior, due to its face, construct, and predictive validity, it has been the most widely used task to evaluate anxiety in animal models (rats, etc.), it has also been used to characterize the brain regions and mechanisms behind anxiety related behavior, as well as to evaluate the anxiolytic and anxiogenic effects of pharmaceutical agents, drugs of abuse, and hormones **(Walf *et al.*, 2009)**. The elevated plus maze is a test that assesses anxiety in lab animals and is typically conducted on rodents as a general research tool for neurobiological anxiety studies as well as a screening test for potential anxiolytic or anxiogenic substances **(Kraeuter *et al.*, 2019)**. The model relies on the subject's shown thigmotaxic tendencies and fear of open areas **(Treit *et al.*, 1993)**. Because of its nervousness, the animal spends more time in the EPM's confined arms, the test does not include any aversive stimuli that could cause the subject to the freeze, startle, or flee from the situation **(Lezak *et al.*, 2017)**.

2.3.2. Barnes Maze test (BM)

This maze was employed to assess cognitive deficits in learning and memory of rats. According to some researchers, Barnes Maze is similarly heavily dependent on the

hippocampus (**Barnes, 1979)**. Although lesion studies have shown that the prefrontal cortex and striatum are likely more engaged in reversal learning tasks **(de Bruin *et al.*, 1994)**. The Barnes maze ability is utilized to test spatial memory, Most Barnes maze protocols start with a habituation phase where the rat is introduced to tecosystemtem and chore, followed by a training phase where the rat receives numerous trials to gain the knowledge the task, and a probe (memory) phase where the rat is tested after 24h, to see if they can recall what they had previously learned **(Gawel *et al.*, 2019)**. The main difference between BM and (MWM) Morris water maze is that the former is on a dry table, while the latter involves swimming, thus, the advantage of BM is that the stress which results from swimming in opaque water in the MWM is avoided **(Othman *et al.*, 2022)**. Performance in BM has been used to assess spatial learning, and memory **(Sunyer *et al.*, 2007)**, particularly in dorsal hippocampus (dH) because it is involved in spatial memory processing **(Bannerman *et al.*, 2014)**. There may be a benefit to the Barnes Maze over the Morris Water Maze for people who have difficulty swimming because of obesity or other metabolic problems brought on by a high fat diet **(Pitts, 2018)**, confounding elements related to stress responses may

be avoided if the Barnes Maze is utilized instead of the Morris Water Maze. As at least one study has demonstrated, while stress hormone levels are up during both tests (Barnes and Morris Water Mazes), test performance only correlates with stress hormone levels during the Morris Water Maze, the stress response is substantially stronger during this test **(Harrison *et al.*, 2009; Benjamin Chun-Kit Tong, 2017)**.

2.4. High -fat diet and pro- inflammatory cytokines

In both rats and humans, the spleen is a critical organ for the initiation of immune responses and the production of the majority of inflammatory cytokines; Spleens also play a role in immune regulation and in maintaining an anti-inflammatory immunological environment **(Lori *et al.*, 2017)**. During lipopolysaccharide induced end toxemia, tumor necrosis factor alpha that has recently been produced is released by the spleen into the liver. It leaves the liver and enters the blood stream, where it becomes the primary source of tumor necrosis factor-Alfa (TNFα) in end toxemia **(Tracey, 2007)**. Tumor necrosis factor defines as a critical cytokine that can variety of harmful effects, including the production of other pro inflammatory cytokines and the

infiltration of macrophages **(Tracey, 2007)**. As a result, it is not apparent if a meal rich in fat causes increase in Tumor necrosis factor Alfa in the spleen, that get both lipopolysaccharide and fatty acids target the same receptor toll -like receptor 4 (TLR4), they hypothesize that excessive ingestion of diet high fat may enhance TNF generation in the spleen **(Rocha *et al.*, 2016)**. Tumor necrosis factor is the key protein associated with obesity and plays a very essential function in regulating body fat metabolism, and relevant research demonstrates that obesity is commonly accompanied by chronic inflammation and the emergence of oxidative stress in patients **(Suo and Wang, 2015; Wu *et al.*, 2016)**. Obesity can significantly raise tumor necrosis factor; researchers believe that natural immunity and low-grade inflammation are the primary causes of this occurrence at present time **(Liu and Liu 2012)** in the article **(Wu *et al.*, 2016)**.

A high-fat diet also raises plasma levels of TNF, a cytokine linked to vascular damage and insulin resistance, given that the TNF induced increase in the expression of the enzyme phosphatase and tension homologue decreases act signaling and, as a result, nitric oxide (NO) production TNF, a cytokine that aids in insulin resistance and vascular

dysfunction, is also produced in greater quantities in the blood when eating a high-fat diet, given that TNF decreases act signaling and subsequently nitric oxide (NO) generation by up regulating the expression of the enzyme phosphatase and tension homologue **(da Costa *et al.*, 2017)**. Consumption of fat is linked to an increase in leptin levels and the formation of fat cells in the body **(Schaffler *et al.*, 2007; Song and Choi, 2016)**. Leptin also stimulates the generation and movement of white blood cells in the bone marrow, so acting on the immune system, in addition, it enhances the production of pro inflammatory cytokines such as TNF, as well as the adherence and phagocytosis of macrophages, and it boosts the proliferation of T cells **(da Silveira *et al.*, 2009; Santos *et al.*, 2019)**. Another research has demonstrated that obesity reduces blood supply to adipose tissue, resulting in hypoxia, which initiates an inflammatory response **(Zeyda and Stulnig, 2007)**. Obesity and a high-fat diet cause adipocyte hypoxia, which ultimately leads to adipocyte cell death Roden and Shulman as a result, macrophages are attracted in, and pro-inflammatory cytokines are released **(Roden and Shulman, 2019)**. Obesity and insulin resistance are specifically associated with an elevated and rice in

classically activated pro-inflammatory M1 macrophages and effector T cells in adipose tissue of mice **(Mathis, 2013)**.

2.5. Effect of high- fat diet on Dopamine

Motivation, reward, punishment, energy expenditure and working memory are all functions of dopamine (DA), which has been recognized as an important neurotransmitter in brain function **(Cools, 2008)**. Dietary consumption is influenced by dopamine, dopamine- related brain circuits can be modulated by food intake, particularly of pleasant dietary items, however, increased dietary fat intake has been linked to a decrease in dopamine signaling, which may lead to an increase in calorie intake to compensate for this decreased dopamine **(Vucetic and Reyes, 2010; Hryhorczuk *et al.*, 2016; Joshi *et al.*, 2020)**. As a neurotransmitter, dopamine regulates food intake. Several studies have shown that a lack of dopamine causes to eat excessively **(Goyal *et al.*, 2020)**. Food cravings, emotional over eating, and preference for high fat foods have all been linked to sensitivity to reward in humans **(Davis *et al.*, 2007)**. Insulin's ability to regulate dopamine uptake in the nucleus accumbens (NAc) is notably hindered by saturated fat, this is because saturated fat reduces the expression of dopamine transporter on the cell surface

and so declines dopamine uptake **(Patel *et al.*, 2019)**. Dopamine release and absorption are modulated by peripheral signals such as insulin and leptin, which influence food intake **(Coccurello and Maccarrone, 2018)**. The development of dopaminergic neurotransmission is impacted by insulin induced neuronal insulin resistance, as insulin enhances dopamine transport activity and delicately controls the firing of dopamine neurons **(Stouffer *et al.*, 2015)**. A significant portion of the modern diet and natural rewards contain carbohydrates and fats, so in the brain reward system which can alter the dopamine signaling **(Fritz *et al.*, 2018; Fernandes *et al.*, 2020)**, can lead to overeating and obesity if the internal homeostatic process, which balances (appetite / satiety), is disturbed **(Zimmerman and Knight, 2020)**. One of the neurotransmitters involved in processing rewards, such as the enjoyable elements of eating, is dopamine **(Volkow *et al.*, 2011)**, as a result of inflammation, synaptic dopamine may be reduced and eating patterns may be altered. Dopamine cell bodies that extend to the striatal complex from the ventral tegmental area (VTA) and substantial nigraparcompacta (SNc) are the primary origins of the dopamine system **(Gerfen and Bolam, 2016)**. Dopamine neurons in the SNc are normally associated with motor

control, but dopamine neurons in the ventral striatum that project to the ventral tegmental region have been connected to reward processing **(Morales and Margolis, 2017; da Silva *et al.*, 2018)**. However, investigations showed that the dorsal striatum projecting SNc neurons can also be linked to the desire to eat and movet **(Lee *et al.*, 2020)**. Evidence suggests that a high fat diet decreases dopaminergic activity in the brain. This is thought to exacerbate obesity by encouraging binge eating as a way to make up for the reduced dopamine **(Tellez *et al.*, 2013)**.

Extensive high fat food access and lent virus mediated suppression of striatal dopamine 2 receptors in rats resulted in the development of compulsive like food seeking, consistent with some of the data from humans **(Johnson and Kenny, 2010)**. Both the basal level of dopamine and the dopamine release in response to food or amphetamines are reduced by eating high fat cafeteria style diets **(Geiger *et al.*, 2009)**. Neurotransmitter malfunctions in the brain cause symptoms such as motor and cognitive behavioral abnormalities in various neurodegenerative disorders **(Banerjee *et al.*, 2020; Moini *et al.*, 2021)**. A key neurotransmitter, dopamine, is involved in the regulation of the feed eating reward circuit, along with emotional

responses and motor activity **(Conde Rojas *et al.*, 2020)**. Reduced motor activity, abnormal changes to the food reward circuitry, impaired motor and sensory balance, are all caused by loss and disappearance of dopaminergic neurons in the brain **(Bissonette and Roesch, 2016)**. It has been demonstrated that eating a high-fat diet can disrupt dopaminergic pathways and result in motor and behavioral deficiencies, although it is unknown how long chronic HFD exposure is necessary to have these consequences **(Han *et al.*, 2021)**. Dopamine, a neurotransmitter that is critical for controlling appetite, has been shown to cause pathological overeating when it is suppressed **(Goyal *et al.*, 2020)**. The neurotransmitter dopamine plays a crucial function in eating management, according to numerous types of research, reduction of dopamine causes pathological overeating **(Goyal *et al.*, 2020)**.

2.6. Effect of high-fat diet on Leptin

The action of leptin on weight is mediated by leptin receptors in the hypothalamus, which are highly expressed in the body **(Morioka *et al.*, 2016)**. As well as to reducing hunger, Leptin also boosts energy expenditure **(Considine *et al.*, 1996; Zeng *et al.*, 2015)**. People and animals who are

obese are resistant to leptin's main effects, obesity induced leptin resistance has been demonstrated in the scientific literature **(Sáinz *et al.*, 2015)**.A study by **(Kalra *et al.*, 1999; Handjieva-Darlenska and Boyadjieva, 2009)** was conducted to investigate the effect of a consumption high fat on plasma leptin levels and adiposity not (rather than) body weight, the rat's consumption diet rich in fat showed a significant increase in leptin, moreover, small amounts of leptin are also released by cells in the stomach epithelium and the placenta, although adipocytes are the primary source of leptin expression. Human and rodent obesity raises levels of leptin, an adipocyte derived hormone **(Çakır *et al.*, 2022)**. Adipose tissue hormones such as leptin are affected by the nature of one's diet **(Leobowitz *et al.*, 2006; Würfel *et al.*, 2022)**. Leptin resistance is developed in rodents fed a high-fat diet, which reduces the vagal afferent nerve's (VAN) ability to respond, It in turn decreases nutrient absorption and energy excess storage from the high-fat, high-calorie diet **(Huang *et al.*, 2021)**.

As a result, why obesity is not always associated with high blood pressure may be explained by the dual function of leptin and the modulation of vascular tone **(Lembo *et al.*, 2000; Lobato *et al.*, 2012; da Silva *et al.*, 2020)**. There are

specific leptin receptors (Ob-Rb type) located in the vascular endothelium that allows leptin to regulate vascular tone in addition to its role in regulating energy storage **(Leung and Kwan, 2008)**.

It is important to understand the Western diet induced metabolic changes because of its direct link to GUT afferent information and appetitive behavior, Chronic high fats diet feeding is a common cause of disturbed leptin signaling in the hypothalamus, which leads to the state of hyperphagic obesity and leptin resistance **(Velloso and Schwartz, 2011; de Lartigue, 2016)**. According to research, the raised leptin levels in plasma that occurs during high fat diet inter venations have a dual effect, as it is for both the development and learning and memory of brain consolidation**(Guo and Rahmouni, 2011)**. In contrast, leptin resistance brought on by hyper leptinmia appears tube linked to deficits at brain hippocampal-dependent memory or rats behaviors, whereas, leptin resistance evoked by **(Van Doorn *et al.*, 2017)**. Adult mice with cognitive impairments who spontaneously produce too much amyloid precursor protein benefit from leptin therapy **(Farr *et al.*, 2006; Calió *et al.*, 2021)**. The leptin receptor (db/db) inactivation mutation has been linked to cognitive deficits in mice, according to some researchers

(Dinel *et al.*, 2011; Du *et al.*, 2020). Leptin targets various cell types in the CNS and has a significant impact there thanks to leptin receptors **(Scott *et al.*, 2009)**. It was established that microglia might express the leptin receptor and release inflammatory cytokines when stimulated by leptin **(Tang *et al.*, 2007)**. In contrast, Leptin injection to the ventral hippocampus reduced conditioned location preference for food, lengthened the time it takes to run for food, and inhibited the formation of new memories increased delay to run for food and suppression of memory consolidation were observed after leptin injections to the ventral region of the hippocampus **(Kanoski and Davidson, 2011; Kanoski *et al.*, 2011)**.

2.7. Melatonin

Melatonin N-acetlyl 5methoxytryptamin, isolated for first time from pineal glands of bovine **(Lerner *et al.*, 1958; Venegas *et al.*, 2012)**, is an endoneurohormone derived from tryptophan **(García-Bernal *et al.*, 2021)**. Melatonin have different physiological operations, like immune responses, circadian rhythms, appetite, mood regulation, anxiety, cardiac function and sleep**(Comai and Gobbi, 2014; Tan *et al.*, 2015; Ma *et al.*, 2020)**. Melatonin also affects the aging

operation and ovulation pubertal, neutralizes free radicals and regulates pressure that was recorded by many studies Pandi-Perumal and his team,(2008); Carretero and team (2009), these are just a few of its additional functions **(Claustrat and Leston, 2015)** and another article record melatonin function by **(Tchekalarova *et al.*, 2022)**. The lack of melatonin linked to a wide range of health problems, including neurodegenerative illnesses, circadian rhythm and mood disorders deprivation, diabetes type two and pain **((Hardeland, 2012; Comai *et al.*, 2014)**. The pineal gland produces melatonin in reaction to darkness **(Srinivasan *et al.*, 2009)** and other studies by **(Peuhkuri *et al.*, 2012; Tan *et al.*, 2016)**. Some health problems, such as obesity, diabetes, hypertension, and respiratory diseases, can be linked to sleep deprivation **(Kuvat *et al.*, 2020)**, this is because sleep deprivation has a negative impact on biological and physiological processes **(McEwen, 2016; Yin *et al.*, 2017)**. It's no coincidence that melatonin secretion occurs just as sleep propensity, as well as core body temperature, alertness, and performance, are all on the decline **(Pandi-Perumal *et al.*, 2008; Borbély *et al.*, 2016)**. Hippocampal neurons directly respond to melatonin's effects on memory formation **(Chang *et al.*, 2021)**, there are anti-nociceptive,

anti-depressant, anxiolytic, anti-neophobic, and locomot or activity regulating effects of melatonin by **(Uz *et al.*, 2005) and Mantovani and his collogues (2006)** other **(Chen *et al.*, 2014; Fenton-Navarro *et al.*, 2021)**. Melatonin plays important roles in neurogenesis, neuroprotection, preservation of oxidant anti-oxidant equilibrium, modulation cardio vascular, control the diabetes and system of immune **(Muñoz-Jurado *et al.*, 2022)**. It direct is doing antioxidant anti apoptotic impacts on cells as well as impacts on tissues and organs **(Onaolapo *et al.*, 2016)**. However, during the day darkness does not raise melatonin production, while during the night exposure to light causes a reduction of melatonin, the light suppression mechanisms and circadian rhythm are both intercede through the Supra chiasmatic nucleus (SCN) **(Kasi Ganeshan, 2019; Guan *et al.*, 2022)**.

Sleep disorders such as insomnia, epilepsy, ischemia injury, and neuropsychiatric diseases have all been linked to low levels of the sleep hormone melatonin, which may also say in the formation of cataracts, aging, and retinitis **(Singh and Jadhav, 2014; Davis, 2019)**. It became later eventually revealed to be present or generated in extra pineal areas like the epidermis, lymphocytes, bone marrow cells, platelets, gastro intestinal tract, retina and Hadrian gland **(Tordjman**

***et al.*, 2017)**. Rather than being stored, the neurohormone melatonin is secreted directly into the bloodstream, where it can travel throughout the body and penetrate tissues **(Masters *et al.*, 2014)**. Melatonin is synthesized in a distinct diurnal pattern, at night secretory peak, during the day with low levels **(Pevet and Challet, 2011)**, the production of melatonin by the pineal gland during the night time is carefully controlled by the clock of the supra chiasmatic nucleus (SCN) and is hindered via the illumination circumstances **(Hull *et al.*, 2018)**. The shoot of inhibitory γ-amino butyric acid (GABA)by retinal ganglion cells, which emerge to the supra chiasmatic nucleus in the hypothalamus by light, drives activity in the circuit governing melatonin synthesis and release **(Kalsbeek *et al.*, 1999; Bedrosian *et al.*, 2013)**. Previous research has indicated that melatonin influences sleep, gastrointestinal mediators like ghrelin and leptin, adiposity and weight regulation of the body **(Zanuto *et al.*, 2013)**, melatonin may also be regulating the syndrome of metabolic, glucose homeostasis, and hazard of diabetes **(Konturek *et al.*, 2011)**. Melatonin can bind to hemoglobin and albumin in the blood stream **(Li and Wang, 2015; Wang *et al.*, 2018)**, Melatonin is not retained when it is produced; instead, it is released into the CSF and peripheral circulation

(attached to albumin). The liver is responsible for melatonin metabolism, where it is mostly converted to 6-hydroxymelatonin and conjugated to 6-sulfatoxymelatonin before being excreted in the urine **(Aulinas, 2019)**. Melatonin's half-life in human blood is around 40 minutes **(Ma *et al.*, 2005)**. A reliable indicator of melatonin secretion is the 6-sulfatoxymelatonin measurement **(Bojkowski *et al.*, 1987; Foroughinia *et al.*, 2020)**. Extremely low melatonin toxicity **(Adriaens *et al.*, 2006; Galano *et al.*, 2011)**. Mitochondria effect and influence physiological via Melatonin **(Reiter *et al.*, 2003; Marón *et al.*, 2020)**. By improving the flow of electrons in the inner mitochondrial membrance, melatonin protects the morphological of cell membrane, boosting the activity of antioxidant enzymes, scavenging free radicals and workable functional aspects **(García *et al.*, 2020; Fan *et al.*, 2020)**. Two G-protein receptors that have high affinity are known as melatonin receptor one and melatonin receptor two which activated by melatonin **(Dubocovich and Markowska, 2005)**. The melatonin receptor (MTandMT2) cause the adenylate cyclase to inhibit and control a number of cellular and physiological operation in target cells, such as reproductive and metabolic activities neuronal firing, cell proliferation, immunological

responses, and arterial vasoconstriction **(Ng *et al.*, 2017; Nikolaev *et al.*, 2021)**. The Meynert nucleus, the supra schismatic nucleus, the Para ventricular nucleus, the peri ventricular nucleus, the supr aoptic nucleus, a mammillary bodies, the nucleus accumbens, the sub stantianigratubero mammillary nucleus, and the retina are all locations where MT1 is found **(Dubocovich and Markowska, 2005)**, while the hippo campus, the SCN, and the retina, on the other hand, are the primary sites of MT2 expression **(Ng *et al.*, 2017)**. The cerebellar cortex, pineal gland, cerebral glial cells, neurons and thalamus express both receptors **(Brunner *et al.*, 2006; Samanta, 2022)**.

Finally, Melatonin is emitted by extra pineal sources, with the largest levels being released by the skin and gut **(Pan *et al.*, 2022)**, the retina, testicles, ovary, placenta, glial cells, and lymphocytes are additional extra pineal sources **(Tan *et al.*, 2010)**. However, although pinealectomy is known to disrupt melatonin rhythm, melatonin released from extra pineal sources hsanegligible impact on plasma melatonin circadian oscillation **(Pelham, 1975)**. Melatonin is secreted by the extra pineal regions, where it stays and mostly serves as an antioxidant in these tissues **(Tan *et al.*, 2010)**.

Typically produced of melatonin in the initial year of a person's life, its production begins at a very poor amount before the age of three months, steadily increases until it reaches its highest level between the ages of one and three years, and then begins to gradually decrease until full adulthood **(Waldhauser *et al.*, 1993)**. Melatonin is discovered for be highly produce between three to four in the morning **(Claustrat and Leston, 2015)**. Blood borne melatonin is found in milk, cerebrospinal fluid, semen, pre-ovulatory follicles, saliva, amniotic fluid and urine **(Reiter *et al.*, 2016)**. Levels of Melatonin in the blood suggest that the pineal gland is functioning actively **(Reiter *et al.*, 2016)**. Since melatonin is hydrophilic and lipophilic via nature, it has the advantage of being able to cross the barrier of brain **(Pardridge and Mietus, 1980)**.

2.7.1. Melatonin synthesis

The ability of the pineal gland for absorb a lot amount of tryptophan and produce a lot of melatonin in response to darkness may be explained by this **(Masters *et al.*, 2014; Xie *et al.*, 2022)**. Melatonin is quickly free fired to circulation after production so that it can reach to target both central tissue and peripheral; the location and types of melatonin

receptors determine the effects of melatonin **(Tordjman *et al.*, 2017)**. The pineal gland converts an important amino acid tryptophan, into melatonin, the hormone of darkness, melatonin is produced out of a many step process **(Wurtman *et al.*,1964)**, first step, formation of 5hydroxytryptophan by hydroxylation of tryptophan by tryptophan 5hydroxylase, then by L-aromatic amino acid decarboxylase decarbxylated it to 5hydroxytryptamine (Serotonin).

Serotonin also consider important neurotransmittor so it is Nacetylated by Timezyme or it's known as arylalkylamine Nacetyltransferase, (this enzyme limited rate in this step for melatonin formation or synthesis) to form Nacetylserotonin which is converted to Nacetyl5methoxytryptamine (melatonin) by Nacetyl serotoninOmethyl transferase (ASMT), also called hydroxyindoleOmethyltransferase or (HIOMT) **(Ren *et al.*, 2017)**.

In the brain, **(Carampin *et al.*, 2003; Cardinali, 2019)** melatonin by formamidase is oxidized to N1-acetyl-N2-formyl-5-methoxykynuramine (AFMK), another metabolically melatonin is N1-acetyl-5-methoxy-kynuramine (AMK) **(Hirata *et al.*, 1974; Kelly et al., 1984)**. Both AFMK, and AMK the melatonin metabolism are present in

the brain, AFMK was first discovered in brain of rat at 1974 by **(Hirata *et al.,* 1974)**. Moreover, AFMK and AMK can be generated by ultra violet radiation pathways or enzymatic and free radical **(Tan *et al.,* 2000)**, so they considered antioxidants with the ability to scavenge free radicals **(Hardeland *et al.,* 2012)**.

In the form of sulphate and glucuronide 6-hydroxy melatonin excreted in urine **(Isidorov and Nazaruk, 2017)**, so when 6hydroxy melatoninsulphate is found in urine that associate with the melatonin level in plasma **(Arendt *et al.,* 1985)**.

Since the methylation step in the conversion of N-acetyl serotonin to melatonin requires folate, folate deprivation in rats reduces the production of melatonin in the body **(Fournier *et al.,* 2002)**. Additionally, vitamin B6 is critical for tryptophan decarboxylation and boosts pineal gland melatonin release not in adults, but in babies **(Munoz-Hoyos *et al.,* 1996)**. When norepinephrine binds in pinealocytes to adrenergic 1 receptors, it increases the synthesis of cyclic AMP (cAMP), which in turn leads to the production of N-acetyltryptamine (NAT), so Norepinephrine initiating melatonin synthesis **(Tan *et al.,* 2010)**.

2.7.2. Melatonin as anti-inflammatory agents

Melatonin is a hormone that has a variety of qualities, such as antioxidant, and immunomodulatory activities, melatonin reduces tumor necrosis factor, which has been shown to be helpful in a number of inflammatory autoimmune disorders so its consider as anti-inflammatory **(Tyagi *et al.*,2010)** by many researchers **(Huang *et al.*, 2019; Muñoz-Jurado *et al.*, 2022)**.

The capacity of melatonin to prevent oligodendroglia damage may be due to a number of actions that it has through its receptors: Production of free radical scavengers by activated microglia **(Mohan *et al.*, 1995)**. The pro-inflammatory cytokines are decreased expression as a result of improved membrane fluidity, decreased edema and polymorph nuclear cell infiltration into damaged tissue, prevention of nuclear factor-$_k$B translocation to the nucleus, and other factors that are important in the inflammatory response by binding to DNA **(Mayo *et al.*, 2005)**.

Melatonin lowers inflammatory harm by blocking NF-kB and transcription factors which in cells can reduce additional ROS generation and may be helpful in the treatment of inflammatory diseases, Melatonin and AFMK

reduced TNF production in peripheral monocytes and COX-2 and iNOS expression in macrophages, Melatonin on the other hand, were shown by macrophages to be easily oxidized by them to AFMK. AMK, like its predecessors AFMK and melatonin, has been shown to reduce the expression of COX-2 in macrophages, and reduce COX-2 and iNOS activation that promotes pro- inflammatory cytokine release, are inhibited by melatonin's anti-inflammatory properties **(Bonnefont-Rousselot and Collin, 2010)**. Furthermore, its anti-inflammatory effects are likely due to an interaction with particular binding sites in lymphocytes and macro- phages, which melatonin interacts with directly **(Esposito *et al.*, 2010)**. AFMK and AMK have recently been shown to detoxify reactive species and protect tissues from reactive intermediate damage **(Galano *et al.*, 2013; Iwan *et al.*, 2021)**.

Melatonin may also influence astrocyte reactivity or death by increasing the astrocytes' anti-oxidative defenses **(Calabrese *et al.*, 2004)**. In a variety of CNS diseases, astrocytes become stimulated, this triggers the induction of iNOS **(Bolaños *et al.*, 1997; Tran *et al.*, 2021)**. Melatonin's anti-inflammatory effects are achieved by its ability to reduce cyclooxygenase activity and NF-$_{kappa}$B binding to DNA,

hence reducing the production of proinflammatory signals (Cox) **(Deng *et al.*, 2006; Jiménez-Rubio *et al.*, 2012)**.

2.7.3. Melatonin antioxidant

As anti-oxidative therapy melatonin is widely used **(Magri and Petriccione, 2022)**. Melatonin can electron donor because its electron rich aromatic indole ring therefore its antioxidant and free radical scavenging make it significantly reduce oxidative stress **(Tan *et al.*,2015)**, mitochondrial electron 4 transport chain efficiency is increased because of its little size and nature properties are amphiphilic. In (Parkinson's and Alzheimer's) disease models, melatonin protects degenerative alternating in the central nervous system while lowering free radicals that can cause damage to DNA **(Baydas *et al.*, 2003; Cardinali, 2019)**, as a result, melatonin has positive effects such as activation of antioxidant enzymes **(Tomás-Zapico and Coto-Montes, 2005; Kurhaluk and Tkachenko, 2022)**, contributes to the safety against oxidative damage **(Tzoneva *et al.*, 2021; Madhu *et al.*, 2022)** and suppression of lipid peroxidation **(Ortega-Arellano *et al.*, 2021; Saidi *et al.*, 2022)**. Another important low molecular weight antioxidant, glutathione is stimulated by melatonin, and this is another important antioxidant that is not enzymatic **(Debnath *et al.*,**

2021). Melatonin works in conjunction escorted by else antioxidants, and it in mitochondria also high raise the adequate of the electron transport chain **(Bisquert *et al.*, 2018; Sunyer-Figueres *et al.*, 2020)**. In addition, it has been demonstrated that it can neutralize free radicals, such as nitric oxide, hydroxyl radicals, peroxyl radicals, singlet oxygen, peroxynitrite and hydrogen peroxide, it has been shown that melatonin suppresses the activity of NO synthase, in addition to its NO and peroxynitrite scavenging properties **(Moussa *et al.*, 2019; Kaur and Bhatla, 2022)**.

2.7.4. Effect of melatonin in body Wight

There is a well-established relationship between melatonin and body weight, Bartness *et al*., discovered in 1984 and reviewed by (**Wang *et al.*, 2020)**, therefore can see the low photoperiod leads to increased hamster weight, following pinealectomy, indicating a connection linking the pineal gland, melatonin, and fat mass, then research demonstrated the treatment by exogenous melatonin lead to lowered animal body weight **(Tamura *et al.*, 2021)**. In numerous animal studies, melatonin decreased weight growth and associated characteristics such as abdominal fat deposition, essentially in animals that consumption diet cause obesity **(Delpino and Figueiredo, 2021**). Studies have

shown that melatonin administration can help with weight loss, waist circumference, body mass index (BMI) **(Guan *et al.*, 2022)**. Ibrahim Ahmed and colleagues discovered the first favorable effect of melatonin on lipid and cholesterol profile, the overweight of diabetic and obese rats, long term dosing of melatonin can minimize weight growth **(Ibrahim Ahmed and Agaty, 2021)**. To restore youthful plasma melatonin levels it was shown that daily melatonin treatment in middle-aged rats decline plasma insulin, plasma leptin, visceral fat and body weight to more young levels **(Puchalski *et al.*, 2003)**. Models laboratory rodents are known for nightly activity so when melatonin levels endogenous are high they can eat, melatonin has no alteration in water intake but decreased body weight **(Obayemi *et al.*, 2021)**, and in mice fed a high fat diet the exogenous administration of melatonin was adequate to restore glucose tolerance and insulin sensitivity. Another study found that daily melatonin administration reduced the weight increase of HFD-fed rats compared to HFD rats that were not treated with melatonin **(Owino *et al.*, 2019)**.

Melatonin reduced inflammation brought on by the HFD, adipocyte hypertrophy, insulin resistance, and weight gain with enhanced energy expenditure, melatonin also

increase BAT to expression uncoupling protein 1 (UCP1) and produced heating, which helped with cold tolerance, notably, melatonin cause a changing metabolism of energy by to favored using fat **(Xu *et al.,* 2022)** at the same studied result show Melatonin boosted elevated expression of antioxidant enzyme in liver and white adipose tissue, the activity of hepatic SOD, nonetheless, it reduced the mRNA expression of NADPH subunits, which help to generate ROS in adipocytes and hepatocytes **(Xu *et al.,* 2022)**.

2.7.5. Effect of melatonin on the glycemic index

Inflammation, endoplasmic reticulum (ER) stress, oxidative stress and glucose metabolism dysfunction are all factors in the etiology of diabetic type 2 (**Alchemy *et al.,* 2021; Lima *et al.,* 2022)**. Melatonin has been shown to decrease hyperglycemia in rodents by increasing insulin sensitivity, inducing and promoting glycogen hepatic synthesis and pancreas to regenerate cell **(Kanter *et al.* 2006; Aierken *et al.,* 2022)**. The study by Guan, the obesity and melatonin (OBS+MLT) group's fasting plasma insulin was lower after melatonin administration than in the untreated obese group **(Guan *et al.,* 2022)**. Obese animals had insulin resistance as compared to control animals, as well Melatonin (OBS+MLT) significantly improved insulin

resistance compared to the group that was not given melatonin **(Obayemi *et al.*, 2021)**. Melatonin has been shown to influence glucose and energy homeostasis via modulating cyclic adenosine monophosphate and cyclic genuine monophosphate **(Stumpf *et al.*, 2008; Mühlbauer *et al.*, 2011)**, further supporting the idea that melatonin aids in bodily maintenance. Additionally, melatonin has been demonstrated to reduce glucose and cholesterol levels in pinealectomizedrats **(Obayemi *et al.*, 2021)** similar results the melatonin after eight week reduction in blood glucose and cholesterol lipid profile and inflammation and oxidative stress **(Farid *et al.*, 2022)**. In peripheral tissues, melatonin's effect on insulin resistance (IR), such as pancreas and adipose tissue **(Cuesta *et al.*, 2013)**, and skeletal muscle, twelve weeks of melatonin therapy for obese patients resulted in significant reductions in the IR index by stimulating the pancreas to regeneration β-cell **(Li *et al.*,2018; De Luis *et al.*, 2020)**.

By restoring the impact of insulin on the cardiovascular system, melatonin therapy enhances glucose metabolism in the case of pre-existing insulin resistance **(Kanter *et al.*, 2006)**. When melatonin is secreted by the body during the night, it has an adverse effect on insulin levels and the start

resistance of insulin **(McMullan *et al.*, 2013; Ivanov *et al.*, 2020)**, it has also been discovered that melatonin receptor gene polymorphisms are linked to IR **(de Luis *et al.*, 2020)**.

Melatonin contributes to the improvement of IR through (MT1) or by preventing mitochondrial malfunction, boosting ER stress, and enhancing hepatocytes linked to insulin resistance and T2DM **(Treister-Goltzman and Peleg, 2021)**. It increases insulin secretion by activating the phospholipase/IP3 pathway, which from organelles mobilizes Ca2+ with decreases insulin secretion by blocking the cAMP and cGMP pathways **(Bach *et al.*, 2005)**, both melatonin receptors act as a mediator for melatonin's effects on insulin secretion. Melatonin causes encourages the tyrosine phosphorylation of the insulin receptor and the creation of insulin growth factor **(Ha *et al.*, 2006)**.

When the internal circadian rhythm is disrupted, it causes glucose intolerance and insulin resistance **(Shi *et al.*, 2013)**, which can be alleviated by taking melatonin. As a result, the action on type2diabetes medication due to the existence of melatonin receptors on pancreatic islets of human **(Sharma *et al.*, 2015)**. While despite the widespread belief that melatonin disrupts glucose homeostasis by suppressing insulin production, an explanation for the mixed

findings has yet to be provided **(Karamitri and Jockers, 2019)**. Melatonin has also been shown to play a significant function in control both glucose metabolism and energy equilibrium in animal experiments **(Owino *et al.*, 2019**; **Xu *et al.*, 2022)**.\

2.7.6. Effect of melatonin on leptin

Melatonin receptors were recently discovered in adipocytes, which are where leptin is created, and both hormones, leptin and melatonin, play a significant part in the regulation of body mass and energy balance **(Alonso-Vale *et al.*, 2005)**. In addition to energy expenditure and energy intake, energy storage is crucial to energy balance and is regulated by a number of neuronal and endocrine variables including insulin, leptin, glucocorticoids, and grow thing hormone **(Buonfiglio *et al.*, 2018)**. Energy expenditure, energy storage and food intake are the three main components that make up energy balance, and melatonin plays a role in their control, moreover, in Syrian hamsters, melatonin was found to be a potent synchronizing agent for leptin release **(Chakir *et al.*, 2015)**. White adipocytes produce leptin and release it, and lack of melatonin is linked to increased body mass, metabolic syndrome, and diabetes **(Cipolla-Neto *et al.*, 2014)**. For example, Leptin binds to

receptors in the hypothalamic cell membrane and regulates the hypothalamic neurons that control appetite **(Kwon *et al.*, 2016; Cao *et al.*, 2022)**, Leptin secretion is influenced by adipose tissue fat content **(Wang *et al.*, 2021)**, and an excess of adipose tissue fat leads to an abnormal increase in leptin secretion **(Friedman, 2019; Hasani *et al.*, 2021)**, fat accumulation in adipose tissue increases as a result of sleep deprivation that mean melatonin decrease leptin due to decrease fat **(Hu *et al.*, 2022)**.

The blood brain barrier is crossed by the transporters that carry secreted leptin to the cerebrospinal fluid (CSF), an raise in leptin secretion in adipose tissue results in a decrease in leptin transport across the brain blood barrier, which has a saturation limit for bound leptin transporters **(Maffei and Giordano, 2021)**, excess leptin, saturating its transporters, and a lack of receptors or signaling in the hypothalamus are all contributing factors to leptin resistance **(Burguera *et al.*,2000; Banks, 2008; Suriagandhi and Nachiappan, 2022)**, due to increased food intake and decreased energy expenditure, a person with leptin resistance is more likely to become obese.

Changes in lifestyle can alter leptin secretion patterns, resulting in hormonal imbalances and a raise in ROS

production, which can lead to oxidative stress. Melatonin has been found to play an important role in energy metabolism and hormone regulation, including the signaling and secretion of leptin **(Suriagandhi and Nachiappan, 2022)**. As previously studied, melatonin has been shown to have a synchronizing effect with the metabolism in white adipocytes, which helps to reduce appetite and increase satiety signals in the central nervous system **(Kim *et al.*, 2020)**.

2.7.7. Effect of melatonin on dopamine

Melatonin appears to limit calcium influx into the excited nerve endings, hence inhibiting the release of dopamine that has been triggered **(Zisapel and Laudon, 1983)**. Melatonin has been shown to inhibit the release of dopamine in particular regions of the mammalian central nervous system (medulla-pons, hypothalamus, retina and hippocampus), melatonin can exacerbate symptoms in Parkinson's patients (due to its alleged interaction with the release of dopamine), it can ward off neurodegeneration as well (Due to its antioxidant capabilities and influences on mitochondrial function), it's possible that the melatonin-dopaminergic system interaction is crucial to the biological clock's nonphotic and photic synchronization along with the

striatum's fine-tuning of motor coordination; melatonin's antioxidant properties and interactions with other neurotransmitters may be helpful in treating dopamine-related disorders **(Zisapel, 2001)**. Melatonin stopped and ended dopamine transporter (DAT) expression was reduced in the rat hippocampus as a result of methamphetamine use **(Panmak *et al.*, 2021)**.

Dopamine content in the posterior pituitary decreased over the course of five weeks after daily melatonin administration, the reduction was greater than (50) %. it appears that melatonin has an inhibitory effect on the dopaminergic system of the neuro intermediate lobe, as evidenced by these findings **(Alexiuk and Vriend, 2009)**. Regulation of circadian rhythm disorders may become a novel target for therapeutic intervention since during the day melatonin levels drop and dopamine levels rise, while during the night melatonin levels rise and dopamine levels fall (**Shen *et al.*, 2017; Li *et al.*, 2020)**.

In hippocampus, melatonin reduced the dopamine transporter (DAT) protein expression decrease brought on by chronic amphetamine use, as well as in the ventral tegmental region (VTA), the decrease in mRNA expression **(Leeboonngam *et al.*, 2018)**.

The inhibition by melatonin of stimulated dopamine release from the male rat hypothalamus in vitro also exhibited a 24-h. rhythm, with a peak at five hours after lights-on and almost no inhibition 10 h. later in the day **(Zisapel *et al.,* 1985)**. Inhibition of dopamine release was associated with a significant increase in glutamate and aspartate release (**Exposito *et al.,* 1995)**.

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