Review Article

Hypothalamic neuroinflammation induced by obesity and the effect of Liraglutide

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ABSTRACT

Recently, significant attention has been given to the effects of obesity-inducing neuroinflammation on the hypothalamus, particularly the activation of glial cells and neurodegenerative sequences. Understanding how high-fat diets provoke neuroinflammation is essential to propose preventative or management strategies combined with medication interventions such as liraglutide. Scientific studies related to obesity and high-fat diet (HFD) in adult humans and rodents and published in PubMed, Science Direct, and ClinicaTrials.gov in the past ten years have been reviewed. The focus has been placed on studies (A) investigating HFD and obesity effects on neuroinflammation and glial cell activation. (B) The effect of liraglutide intervention on neuroinflammation induced by obesity in the hypothalamus. A total of 90 articles fit the inclusion criteria and were included. Findings revealed that induced obesity by HFD is associated with neuroinflammation in the hypothalamus, specifically microglial activation and oxidative stress, and the cellular and molecular mechanisms for this injurious effect are discussed in the review. On the other hand, liraglutide shows promising neuroprotective, anti-inflammatory, and anti-apoptosis activities that help manage neurodegenerative diseases. Obesity influences multiple aspects of neuroinflammation in the hypothalamus, including increasing blood-brain barrier permeability, inducing oxidative stress in ER, activating glial cells, and insulin and leptin resistance. It also highlights the consequences of HFD, not only in inducing obesity but also in altering neural integrity. Finally, liraglutide is neuroprotective and limits the initiation of neuroinflammation; therefore, it could be an encouraging therapy for the management of neurodegenerative diseases.

Keywords: Gliosis, High fat diet, Hypothalamus, Liraglutide, Neuroinflammation, Obesity

Introduction

Obesity is now recognized as a challenging global health burden, has approached pandemic dimensions, affected various categories, and correlated to several diseases' complications [1-4]. Its pathogenesis emerges from an interplay between genetic predispositions and environmental factors that results in a dysfunctional immune response, including cell infiltration, dysregulation of inflammatory mediators, which all create low-grade inflammation that affects numerous tissues, including the central nervous system (CNS) [5]. Hence, obesity is recently concomitant with increased incidence of metabolic syndrome and degenerative CNS diseases, all of which share a general neuroinflammatory component such as demyelination, losing long white matter tracts, leptin, and insulin resistance [6-9].

The hypothalamus has consistently attracted attention because of housing anorexigenic pro-opiomelanocortin /cocaine and amphetamine-regulated transcript (POMC/CART) neurons and the orexigenic Agouti-related protein/ neuropeptide Y (AgRP/NPY) neurons in the paraventricular hypothalamic nucleus (PVN). It is fundamental in regulating food intake, food-seeking behavior, weight control, and energy hemostasis [10-12]. Therefore, any destruction of the PVN or activation of glial cells

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(Gliosis) caused by hypothalamic inflammation leads to overeating, insulin and leptin resistance, and obesity [8, 13].

Recently, several studies have shown that high-fat diets (HFD) are neurotoxic. The major neuropathological hallmarks are impairment of blood-brain barrier (BBB) function, dysfunction in endothelial cells and astrocytes, reduction in the transport function of the hypothalamic cells, and rising levels of reactive oxygen species (ROS). Generally, HFD (40–70% fat) alters CNS by affecting different signaling pathways in the hypothalamus, the cranial nerves (vagus nerve), and the choroid plexus. It induces oxidative stress and reduces the number of polydendrocytes and tanycytes in the brain [14, 15]. Moreover, HFD of 60% kcal from fat can increase immune cell entry into the hypothalamus and cortex and induce neuroinflammation [16].

Additionally, exposure to HFD for weeks can increase IgG-or in the ARC, induce the release of proinflammatory cytokines from microglia, astrocytes, and perivascular macrophages. Also, it impairs mitochondrial and neuronal functions, stimulates arcuate mediators including TNF-α, nuclear factor (NF)-κB pathway through activation of Toll-like receptor -4 (TLR-4) pathway, upregulates interleukin-6 (IL-6) expressions, and alters pathways of feeding behavior and energy expenditure [13, 17-19]. A high-fat diet rich in long-chain saturated fatty acids is the worst; it alters CNS homeostasis via increasing macrophage infiltration and proinflammatory activity and decreases the functions of the hypothalamus and supporting cells, such as oligodendrocytes [13, 20]. On the other hand, one research revealed that a high-fat diet could promote better cognitive function in Alzheimer's disease in the short term by limiting brain atrophy and improving BBB function but not amyloid-beta levels [21].

It has been known that both hypothalamic-pituitary-adrenal (HPA) axis and the Gut-brain axis of glucagon-like peptide-1 (GLP-1) exchange signals via the vagal nerve, thereby regulating various physiological functions, including gastric motility and digestion, appetite, and energy metabolism. In contrast, any hypothalamic inflammation or dysregulation in these axes will be associated with metabolic dysfunctions, leptin plus insulin resistance, and upper-body obesity [19, 22, 23].

GLP-1 receptors (GLP-1R) are expressed throughout the central nervous system, and GLP-1 protein may cross the blood-brain barrier [24]. Glucagon-like peptide-1 (GLP-1) agonists have a remarkable potent anti-inflammatory effect due to their ability to inhibit NF-kB pathways, upregulate NAD-dependent deacetylase sirtuin-1 (SIRT1) expression, reduce cortical Aβ1–42 levels, and down-regulate pro-inflammatory factors including cytokines (TNF-α) and (TLR2, TLR4) receptors [25, 26]. Recently, Long-acting glucagon-like peptide-1 (GLP-1) agonists such as liraglutide have shown convincing neuroprotective effects beyond anti-diabetic and obesity. A dose of 25 nmol/kg, intraperitoneally (i.p), given once daily, can activate anti-apoptotic pathways and restrict the damaging effects of free radicals against type 2 diabetes, stroke, and Alzheimer's disease [27-30].

Liraglutide showed some surprising benefits against brain insulin resistance induced by obesity via inhibiting hypothalamic insulin resistance induced by HFD since HFD increases the content of saturated acyl-CoA species in the hypothalamus and activates local inflammatory signals, thus causes a failure inappropriately regulating food intake [31, 32].

This review focuses mainly on recent studies investigating the neuro-inflammatory consequences of obesity on the hypothalamus: Gliosis, activation of microglia cells, proinflammatory cytokines, and endoplasmic reticulum (ER) oxidative stress. In particular, the ability of a high-fat diet to induce neuroinflammation and mechanisms in which liraglutide may change the negative neural impact of HFD beyond its anti-obesity activity **(Table 1)**.

Table 1. Effect of High Fat Diet and Liraglutide on Hypothermic Neuroinflammation

Study	Species	Sample	Diet Protocol	Diet Duration	Liraglutide intervention	Molecules analyzed and results	Mechanism(s) for neuroinflammation
Kreutzer *et al.*, 2017	Human	**G1**:57 obese **G2**: 54 non-obese control subjects **Test:** MRI & Spectroscopy **Tissue:** hypothalamus **Design**: Cohort	NA	NA	NA	**Increased:** - JNK - MC4R - Gliosis - CNS Inflammation **Decreased:** - Parasutterella sp. in the gut - Mean HOMA-IR	Polymorphisms in the JNK Gene & the MC4R Gene Increase the Individual Susceptibility to Gliosis Association with MBH inflammation and gliosis in obese humans
Samara *et al.*,2020	Human	**Study 1:** **G1**:25 obese human G2:21 non-obese **Study 2:** **G1**:18 obese human G2: 41 non-obese **Test:** MRI	NA	NA	NA	**Increased:** loss of long white matter tracts	Demyelination/remyelination, associated with persistent neuroinflammatory process induced by obesity

Baufeld *et al.*, 2016	Human C57BL/ 6 mice	**Human**: 12 obese, 9 non-obese **Tissue:** hypothalamus, frontal cortex brain autopsies **Test:** Iba1 and GFAP immunoassay **Animal:** C57Bl/6 J 60 mice, age: 100–120 days	**Animals:** HFD (60 % kcal % fat LFD (10 % kcal % fat)	divided groups: 3 days, 4 and 8 week (LFD or HFD) 16 weeks (HFD) 20 weeks (HFD)	NA	**Increased** - Gliosis - Bodyweight - Serum leptin level - GFAP-positive astrocytes - Interleukin-1b (Il1b) **Decreased** IL-6, IL-1β, CXCL1 and TNFα for LFD	- Microglia activation Downregulation of microglia-specific genes involved in sensing microenvironmental alterations,
Dalvi *et al.* 2017	Mice	C57BL/6 12mice aged 10-to-12-week-old	HFD: 60% kcal fat (5.49 kcal /g Ad-libitum standard rodent chow diet	8 to 20 weeks	NA	**Increased:** - Heat-shock protein 70 - Neurotrophic factor TNF-α expression in NPY/AgRP - ER stress genes - GFAP-positive astrocytes **Decreased:** - IκBα and NF-κB levels - TNF-α expression	TNF-α expression in the NPY/AgRP neurons causes exhaustion of hypothalamic-protective mechanisms and development of chronic inflammation, appetite, and neuropeptide dysregulation
Zhuang *et al.*, 2017).	Mice	Four-week-old C57BL/6J 10 mice (18 ± 1 g)	HFD, 45% fat, 10g/kg of AA) Low-fat diet (LFD,10% fat) as control 10weeks inducing obesity then 15weeks, 2 groups on 2 diets	10weeks 15weeks	NA	**Increased:** - Leptin, and insulin resistance - circulating level of LPS - NF-κB signaling **Decreased:** - adiponectin level - microbial richness - AGRP mRNA level	TLR4-NF-κB pathway induces insulin resistance. Serotonin triggers hypothalamic leptin resistance via microglia accumulation. reduction AGRP/ neuro-peptide Y reduces expression POMC and leptin receptor
de Bona *et al.*, 2019	Mice	30 Swiss mice age: 40 days old, weighing 30-40 g,	HFD: lipids 59%, lard based, kcal: 1000.028, high in saturated fat NFD: Carbohydrate69%, kcal: 1000.028	10-week for each group HFD and NFD	NA	**Increased** - IL-1β levels - lipid peroxidation Oxidative damage in the hypothalamus **Decreased** GSH level in the hypothalamus - complex I, II, and IV activity - IL-10 level	- Increased expression of proinflammatory cytokines and markers of apoptosis A high-fat diet compromises BBB integrity, facilitating the entry of immune cells into the CNS increased generation of ROS impairs mitochondrial function
Cansell *et al.*, 2021	Mice	C57Bl/6J 20 mice weight: (20–25 g) age: 8-week-old CX3CR1eGFP/eG220 mice age:9–10 week-old	HFD (4,494.5 kcal/kg with 40.9% from fat) Ad-libitum (3,395 kcal/kg 13.5% fat)	single meal	NA	A single high-fat meal increases serum levels of endotoxins, but not those of cytokines, chemokines and TGs A single high-fat meal increases serum levels of endotoxins, but not those of cytokines, chemokines and TGs single high-fat meal increases serum levels of endotoxins, but not those of cytokines, chemokines and TGs **Increased:** - endotoxins - Inflammatory- response - GFAP expression microglial remodeling in ARC - Microglial marker Iba1 **Decreased:**	Promotion of LPS trafficking over the intestinal epithelium to the hypothalamus Modulation of mRNA levels of neuropeptides involved in The regulation of energy imbalance by reduction of Anorexigenic peptide POMC Activation of NPY/AgRP neurons through TNFα and ER stress signaling

					- Anorexigenic peptide POMC AgRP and CART hypothalamic gene expression	
Barreto-Vianna *et al.*,2016	Mice	Sixty male C57BL/6 mice At 3 months of age	HF, 50% energy from lipids, 14% proteins, and 26% carbohydrates—5.0 kcal/kg) Chow: 10% lipids, 14% proteins, and 76% carbohydrates—3.8 kcal/kg);	8 weeks.	liraglutide (200 lg/kg, twice daily, SQ	**HFD:** - Resistance to insulin &leptin - Microgliosis - Bax/Bcl2 ratio in the ARC. **Liraglutide**: Activation POMC/ CART in the ARC. - Leptin sensitivity Decreases microgliosis & Bax/Bcl2 ratio.	Liraglutide: Stimulate the insulin release from the pancreas, Reversed the resistance to exogenous leptin Stimulates the activity of the melanocortin system in neurons, which leads to hypophagia. Increases Anti-apoptotic signals. This effect is crucial since obesity increases the susceptibility to neurodegenerative diseases
Liao *et al.*, 2019	Rats	36 Sprague-Dawley rats,	HFD 45% energy from fat After 12 weeks 36 DIO rats were randomly divided into three groups	HFD group and an LFD group as the control for 12 weeks	200 µg/kg, SQ, twice daily	**HFD** - IL-1β, IL-6, TNF-α - SOCS3 - Decreased POMC/ CART - Density of microglia - Decreased Bcl2 **Liraglutide** - Microglia polarization to M2 - Decreased SOCS3	Liraglutide: blockade of NF-κB and p38 MAPK pathways in LPS-activated microglia Decreases SOCS3, and decreased neuronal apoptosis and microgliosis Liraglutide inhibits the M1 phenotype The reduction in microglial activation - The reduction release of proinflammatory cytokines inhibits the NF-κB pathway and down-regulates mitogen-activated protein kinase kinase

Abbreviations: ARC: arcuate nucleus, Bax/Bcl2: B-cell associated X protein/ B-cell lymphoma 2, BECN-1: Beclin-1 is a protein, CART: cocaine- and amphetamine-regulated transcript, CNTF: Ciliary neurotrophic factor, ER: Endoplasmic reticulum, GFAP: Glial fibrillary acidic protein, HFD: High fat diet, Hsp72: Heat shock 70 kDa protein 1, Iba1: Ionized calcium binding adaptor molecule 1, IKBKB: Inhibitor Of Nuclear Factor Kappa B Kinase Subunit Beta, IKBKE: Inhibitor Of Nuclear Factor Kappa B Kinase Subunit Epsilon, IL-1,6,10: Interleukins 1,6,10, LC3: Microtubule-associated protein 1A/1B-light chain 3, LFD: Low fat diet, MC4R:Melanocortin 4 receptor, MRI: magnetic resonance image, NA: Not available, NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells, NPY/AgRP: neuropeptide Y/ Agouti-related protein, p38 MAPK: p38 mitogen-activated protein kinases, POMC: Pro-opiomelanocortin, ROS: Reactive oxygen species, SFA: saturated fatty acid, SOCS3 or SOCS-3: Suppressor of cytokine signaling 3, SQ: Subcutaneous, SQSTM1: Sequestosome 1, TLR4:Toll Like Receptor 4, TNF- α: Tumor necrosis factor, ULK1: Unc-51 Like Autophagy Activating Kinase 1.

Materials and Methods

Search strategy and data sources

This present review's relevant data were collected by searching literature published in PubMed, Science Direct, and ClinicaTrials.gov between January/2021 and April /2021. The research terms included: Gliosis, High fat diet, Hypothalamus, Liraglutide, Neuroinflammation, and Obesity.

Selection of published studies (inclusion/ exclusion criteria)

The main inclusion criteria were published reviews, clinical trials, and cross-over designs, cohort studies, case reports, investigating neuroinflammation induced by obesity and the neuroprotective effects of liraglutide. Selected full-text articles of preclinical and clinical studies on humans and animals that have been published within 10 years were included, and references from included original papers were reviewed to identify further eligible studies. Based on the research strategy, 90 appropriate articles were selected from around 162 articles that were investigated. Selected articles were categorized in main headings "Gliosis and Activation of microglia in the hypothalamus: key factors for neuroinflammation and obesity", "Endoplasmic reticulum (ER) oxidative stress, and proinflammatory cytokines induced by obesity: markers for hypothalamic neuroinflammation", and "The Effect of Liraglutide on Hypothalamic Neuroinflammation Induced by Obesity".

After the final screening, 10 articles were excluded for specific reasons, including insufficient information (n= 3), cell line and tissue culturing (n=2), non-mechanistic reviews (n =3), and no comparison group included in the trial (n= 2). The exclusion criteria were non-English language studies, abstracts, conference proceedings, letters, and clinical trials published over 10 years. On the other hand, ClinicalTrials.gov was searched for ongoing registered clinical trials, and inclusion and exclusion criteria were identical to selecting published studies.

Data collection

Findings were extracted from articles by one researcher and independently checked for accuracy by two supervisors. Data summarized in one table titled "Effect of High Fat Diet and Liraglutide on Hypothermic Neuroinflammation" which was divided into a group of columns entitled as follow: Study, Species, Sample, Diet Protocol and Duration, Liraglutide intervention, Molecules analyzed and results, and Mechanism(s) for neuroinflammation, and a figure titled "The effect of HFD induced obesity and liraglutide on hypothalamic neuroinflammation"

Gliosis and activation of microglia in the hypothalamus: key factors for neuroinflammation and obesity

The brain's innate immune system, including neurons, glial cells (astrocytes, oligodendrocytes, and microglia), macrophages, and dendritic cells (DCs), are essential neuroprotective cells. The activation of this system under acute conditions in CNS can provide an inflammatory protective response. However, chronic exposure to internal or external injurious stimuli results in degenerative inflammation. Glia cells constitute more than 50% of the CNS mass, and they have a high level of interaction with neurons, and microglia are the most abundant brain innate immune cells and comprise ~10–15% of all glial cells [33, 34]. Microglia plays an essential role in regulating homeostatic balance in normal CNS by clearing cell wastes, unnecessary neurons and synapses, and neuronal precursors such as amyloid plaques. Also, it plays a role in the restoration of hemostasis in the injured CNS because of the highly dynamic interaction between microglia/macrophages and their constant ability of phagocytosis [35, 36].

Microglia have high metabolic flexibility and sensitivity to changes in the CNS microenvironment. Rapid activation during aging or injurious conditions characterized by changes in morphological (small somata and long), Intracellular Ca2+ signaling, and functional signatures enable them to estimate an inflammatory response [33, 37]. In chronic inflammation such as obesity/diabetes and their pathological consequence, dystrophic and degenerating neuronal processes often act as significant operators of microglial pathological activation. Gliosis is a non-specific reactive change of glial cells in response to any damage in the central nervous system (CNS), and this response involves the proliferation of several different types of glial cells. Obesity increases the migration of peripheral immune cells into the CNS and stimulates gliosis. At the same time, it increases sympathetic neuron-associated macrophages (SAM) and deletes methyl CpG binding protein 2) (Mecp2) in brown adipose tissue (BAT). Additionally, it increases the neuropeptide Y (NPY) in CNS and induces hypothalamic proinflammatory cytokine expression and proinflammatory signaling (NF-κB), in which all these combined mechanisms result in neurodegeneration [38].

Regarding high-fat diet-induced obesity, the activation of microglia in the arcuate nucleus (ARC) of the hypothalamus and accumulation of IgG within microglia begin to develop as early as two weeks after exposure to a high-fat diet [18, 39]. Research revealed that chronic exposure to a high-fat diet, particularly diets rich in saturated fat, contributes to obesity-associated gliosis and astrocytic process plasticity. The neurogenic inflammation occurred because of increased oxidative stress in neurons, promoted mitochondrial and leptin signaling dysfunction in oligodendrocytes, and increased gene expression of microglial markers (glial fibrillary acidic protein [GFAP] and Iba1, which causes myelin disturbances and hypothalamic neuropathy [38, 40]. Studies also showed that the glial cells are particularly affected by saturated fatty acids (SFAs) diet due to heterogeneity and neurogenic neuroinflammation during degenerative conditions [41].

More significantly, neonatal high-fat diet feeding seems to raise plasma glucose levels associated with microglial activation in the hypothalamus in weeks [42, 43].

Indeed, reactive morphological and functional changes that characterized microglia activation increase inflammatory cytokines, nitric oxide, and reactive oxygen species (ROS). Mechanistically, it has been reported that the chemokine CX3CL1 (fractalkine) and TLR4 are highly expressed in mice's hypothalamus after weeks to months of exposure to high-fat diets [44-47]. Also, High-fat diets induce bone marrow-derived monocytic cell accumulation, activate IKKB/NF-κB and JNK pathways, leading to endoplasmic reticulum stress that contributes to obesity and glucose intolerance. On the other hand, low-to standard fat diets reduce microglial activation and revoke hypothalamic inflammation. Important to note that in some studies, hypothalamic inflammation had been detected within 24 to 72 h after the intervention of HFD, there was a positive relationship exists between the number of hypothalamic microglia activated and the obese phenotype [15, 18, 47].

Diet-induced microgliosis has been recognized in human and laboratory models of neurodegenerative diseases such as Alzheimer's disease, Parkinson's and provides a potential mechanistic link between obesity/type 2 diabetes and accelerated cognitive and memory decline. In contrast, pharmacological inhibition of microglial activation in obese associated with the prevention of obesity-associated cognitive decline [48].

The role of gut microbiota in neuroinflammation and the progression of neurodegenerative diseases has been lately highlighted. The consumption of HFD aggravates gut microbial and plays a role in developing diet-induced hypothalamic microgliosis and activating peripheral immune cells. Mechanisms include: activating Toll-like receptor 4 on microglial cells and release of inflammatory cytokines, up-regulating GPR41 and GPR109A that increases hypothalamic inflammation, activation of the vagal system, which affects neuropsychological functions and producing short-chain fatty acids that can influence gene expression and inflammation within CNS [49, 50].

Endoplasmic reticulum (ER) oxidative stress, and proinflammatory cytokines induced by obesity: markers for hypothalamic neuroinflammation

The activation of TLR-4 by a high-fat diet (60% calories from fat) promotes IKB kinase/nuclear factor _B (NF-κB) pathway and JNK. This pathway elevates the inflammatory response, apoptosis, amyloidogenesis, and age-related behavior in CNS activates gliosis (astrocytes and microglia) and macrophages towards the inflammatory M1 phenotype and suppresses innate immune receptors. In addition, these pathways activation leads to an increase in cytokines, such as tumor necrosis factor (TNF)-a, interleukin (IL)-6, interleukin (IL)-1_, chemokines, and other

pro-inflammatory factors [42]. The inflammatory mediators and ER oxidative stress magnify each other effects and cause further dysfunction of the insulin and leptin signaling pathway in the hypothalamus, causing more metabolic dysfunctions.

It has been found that chronic exposure to palmitate induces NPY mRNA levels, the expression of TNF-α, heat-shock protein 70 (HSP70), and CNTF in the hypothalamus [20]. TNF-α regulates synaptic plasticity, astrocyte-induced synaptic, sleep, and learning and memory strengthening in healthy conditions. However, under pathological circumstances, it is highly released by microglia and astrocytes and induces neuroinflammation by elevating amyloid-beta (Aβ) plaque and BBB disruption. In addition, the western diet (high-fat, high-glycemic-index) can increase the permeability of the blood-brain barrier. The diet increases circulating levels of amyloid-β (Aβ), thus contributing to blood-brain barrier damage via reduced gene expression of tight junction proteins. This leakage makes the hypothalamus sensitive to inflammation markers that are circulating, like the TNF and cytokines IL-1_ that can initiate central inflammation [10, 21, 51].

A chronic high-fat diet leads to POMC/CART neurons loss in the hypothalamus, thus altering neuronal control of appetite, energy expenditure, and caloric intake, which cause a vicious obesity circle. Consumption of HFD for eight weeks significantly increases heat-shock protein 70 and ciliary neurotrophic factor, which in contrast can be revered by low-normal fat diets in 20 weeks Belsham [20].

Basic levels of autophagy are important in maintaining energy homeostasis, body weight, and the functionality of the hypothalamic neuron. Chronic exposure to a high-fat diet leads to reduced autophagy activity in POMC neurons, resulting in excessive food intake. Moreover, it induces the downregulation of autophagic proteins such as JNK and Bax, which control stress and activates IκB kinase β responsible for the inactivation of the NF-κB transcription factor [52, 53].

The effect of liraglutide on hypothalamic neuroinflammation induced by obesity

Glial cells, including microglia, are highly dynamic, and glial activation prioritizes oxidative energy and glucose utilization, plasticity, and maintenance of neural circuits. This response induces proinflammatory gene transcription and the release of reactive oxygen species (ROS), which serve as an innate first-line defense to infection. However, cytotoxic with net negative outcomes on memory, cognitive ability, weight control, and food intake in diseases appear with extended chronic inflammatory conditions such as obesity, stroke, and neurodegenerative disorders. Chronic inflammation is responsible for provoking neural injury via increasing levels of soluble CX3CL, which stimulate recruitment of macrophages, lymphocytes, and B cells to CNS, leading to the production of a pathogenic IgG antibody that increases inflammatory cytokines and promotes polarization of M2 macrophages to the proinflammatory phenotype [15, 47, 54].

Efficient insulin signaling in the mediobasal hypothalamus blocks gluconeogenesis, glia activation, central inflammation, and vagal innervation/stimulation [45]. On the other hand, in obesity, insulin/ leptin resistance in the mediobasal hypothalamus results from hetero-dimerization of Toll-like receptors 1 and 2 (TLR1 and TLR2) homo-dimerization of Toll-like receptor 4 (TLR4) and pathological activation of the IKK/NF-κB axis. IKK/NF-κB has constitutive activity in the hypothalamus. It can be activated by different effectors, including molecular patterns associated with pathogens (PAMPs), molecular patterns associated with damage (DAMPs), chemokines, cytokines and neurotransmitters that modulate synaptic plasticity, neurotransmission, and neuroprotection [42, 55]. In addition, it is associated with elevated endoplasmic reticulum oxidative stress, neuroinflammation, apoptosis independent of neurodegeneration, and mechanical disturbances linked to satiety and hunger [14, 45, 56].

In the brain, liraglutide modulates the phosphorylation of neuronal IRS-1 serine and AKT and GSK-3 β levels and enhances synaptic plasticity, thus improving cognition [32, 57]. Moreover, it regulates neurogenesis in the brain and facilitates the differentiation of neuronal stem cells via the MAPK pathway; it inhibits neuron apoptosis by increasing the levels of the survival factors B-cell lymphoma 2, Bcl-XL through the PI3K/AKT pathway and decreases the phosphorylation of τue protein and accumulation of amyloid-β and prevent amyloid plaques [30, 58, 59].

Liraglutide controls feeding behavior, body weight, and glucose metabolism via directly linked mechanisms to CNS. It inhibits hypothalamic proopiomelanocortin (POMC) and Neuropeptide Y/Agouti-related peptide (NPY/AgRP) neurons through post-synaptic GABAA receptors. It enhances the activity of pre-synaptic GABAergic neurons that requires both TrpC5 subunits and K-ATP channels and indirectly increases excitatory tone to POMC neurons. Moreover, it increases the cocaine- and amphetamine-stimulated transcript neuropeptide messenger ribonucleic acid and directly activates arcuate POMC neurons via TrpC5 channels, sharing a similar mechanistic pathway adipose-derived peptide leptin [60, 61].

For immunomodulation and microglial activation, liraglutide inhibits NF-κB (Nuclear Factor-κB) with PI3K/AKT pathway activity, decreases proinflammatory cytokines' secretion, diminishes the microgliosis by decreasing Bax/Bcl2 ratio, thus helps in counteracting the obesity neurodegenerative impact, and reduces the accumulation of intracellular ROS in microglia. On the other hand, it increases levels of AKT, which decreases the levels of GSK-3 β and reduces oxidative stress. It ameliorates AGEs-induced oxidative stress in ER, cell death in astrocytes, reverses the AGEs mediated reduction in intracellular cyclic AMP (cAMP) levels, protein kinase A (PKA) activity, and the phosphorylation of the cAMP response element-binding (CREB) protein, and increases the production of anti-apoptosis Bcl-X. Hence, liraglutide contributing to cell survival and inhibition of apoptosiss [30, 38, 62].

There is a direct linear association between hypothalamic microgliosis, ARC microglial density, and obesity [47, 63]. Liraglutide reduces weight, suppresses apoptosis, and diminishes microgliosis. Furthermore, it inhibits LPS-induced M1 microglial polarization and promotes microglial polarization to the M2 phenotype, diminishing inflammatory cytokine expression and reducing the damaging factors of hypothalamic reconstruction. Also, it acts on activated microglia, inhibits the Notch-1 signaling pathway, and down-regulates the negative regulator Hes-1, inhibiting the NF-κB and Jun NH2- terminal kinase (JNK)/p38 MAPK signaling, and down-regulates mitogen-activated protein kinase [48, 64] **(Figure 1)**.

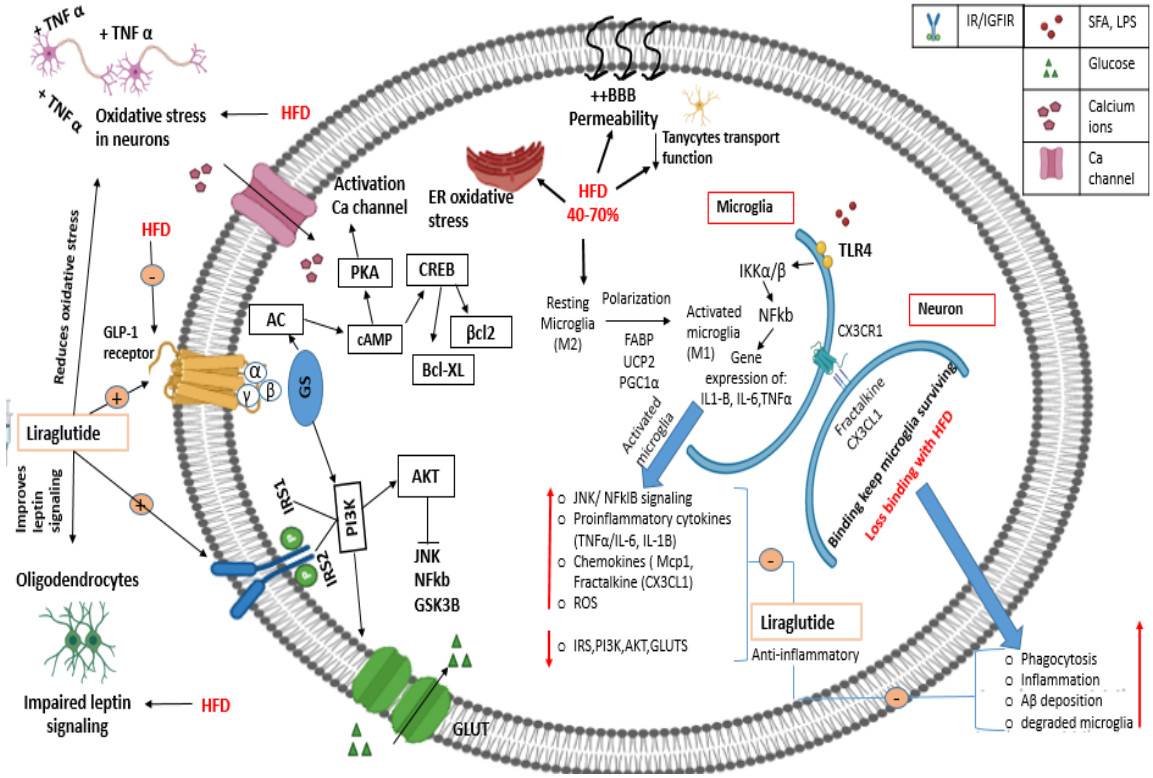

Figure 1. The effect of HFD induced obesity and liraglutide on hypothalamic neuroinflammation

Obesity-induced by a high-fat diet (HFD) of 40-70% results in increased levels of circulating fatty acids, lipopolysaccharide (LPS), and inflammatory mediators, leading to altered homeostasis in many organs, including the central nervous system (CNS). The CNS can be affected through different communication pathways that alter the blood-brain barrier, hypothalamus, glial cells such as astrocytes, oligodendrocytes, and microglia. Due to anatomic position, microglial cells of the arcuate nucleus are sensitive to LPS and SFAs from the HFD because high-fat diets activate TLR4 Toll-like Receptor 4 (TLR4) in the microglial membrane. These receptors use uncoupled protein 2 (UCP2) as a source of energy, and the process is regulated by fatty-acid-binding proteins (FABP) and Peroxisome proliferator-activated receptor-gamma coactivator (PGC-1α), resulting in activation of microglia and switching to inflamed M1-phenotype. Furthermore, activation of TLR4 receptors lead to IKK (IKKα/β) downstream and activation of NF-κB that provokes the gene expression of (interleukins IL1-B and IL-6, and tumor necrosis factor-alpha (TNFα). The activated microglia increases JNK/NFkl3 signaling, expression of pro-inflammatory cytokines (TNFα/IL-6, IL-1B), and chemokine levels such as Mcp1 and Fractalkine (CX3CL1), and reactive oxygen species (ROS) production, while inhibits Insulin Receptor Substrate (IRS) proteins, Phosphatidylinositol-3-kinase (PI3K)/ Protein kinase B (Akt) pathway, and GLUTS activity. Fractalkine (CX3CL1) is a unique adipocytokine, abound membrane protein in an OFF signal in a healthy matter, and keeps microglia in a surveying state. With chronic high fat consumption, the expression of fractalkine and CX3CR1 is reduced; in contrast, the bounded form is released as soluble protein following proteolytic cleavage, thus causing inflammation, inducing phagocytosis, increasing (amyloid-beta) Aβ deposition, and stimulating migration of inflammatory cells to CNS. HFD inhibits the activity of glucagon-like (GLP-1) receptors. Insulin can cross the blood-brain barrier (BBB) and activates insulin receptor (IR) or insulin-like growth factor-1 receptors (IGF-1R) expressed in neurons. Liraglutide crosses the BBB and activates GLP-1R present in the brain, initiating positive control on cell metabolism and energy homeostasis pathways. The activation sequences include Adenyl cyclase (AC), cyclic adenosine monophosphate (cAMP); Protein kinase (PKA), which consequently activates calcium channels, increases Ca2+ entry to cells, and contributes to cell growth, repair, and regeneration. On the other hand, activation of cAMP response element-binding protein (CREB) leads to increased Bcl: B-cell lymphoma production, the ratio between Bcl-XL to Bcl-2 determines the activity of apoptosis in CNS, and liraglutide increases the production of anti-apoptosis Bcl-X, thus contributing to cell survival, inhibition of apoptosis. It also activates Glucose

transporter (GLUT), therefore enhances glucose intake by CNS and inhibits C-Jun N-terminal kinase (JNK), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), Protein kinase B (Akt), and Glycogen synthase three betas (GSK-3b) via PI3K/Akt pathway. Therefore, liraglutide has anti-inflammatory activity in the hypothalamus, can reduce oxidative stress in neurons, regulates synaptic growth and repair, improves leptin signaling oligodendrocytes, and counteract the effects of HFD on microglia and microglial activation.

Conclusion

Obesity influences multiple aspects of neuroinflammation in the hypothalamus, including increasing blood-brain barrier permeability, inducing oxidative stress in ER, activating glial cells, and insulin and leptin resistance. This effect highlights the significance of HFD, not only in inducing obesity but also in altering neural integrity. It leads to the hypothesis that diet in conjunction with pharmaceutical intervention can limit the initiation of neuroinflammation. Liraglutide has encouraging neuroprotective, anti-inflammatory, and anti-apoptosis effects and has a promising future in managing neurodegenerative diseases.

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