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Review

Effects of Liraglutide Combined with Normal Fat Diet on Neural and Thermogenic Activities of 5' - AMPK in the Hypothalamus

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Abstract. *Background:* Medical nutrition therapy is essential in managing and preventing diseases, and liraglutide plays a critical role in controlling weight and modulating the effectiveness of 5' AMP-activated protein kinase (5'-AMPK) in the hypothalamus. On the other hand, the neural effects of liraglutide and 5'-AMPK are negatively altered by a high-fat diet (HFD); in addition to that, it remains unclear how normal-fat diets combined with liraglutide could counteract the HFD effect. *Objectives:* To investigate the effects of a high-fat versus normal diet on the neural and thermogenic activities of liraglutide and 5' –AMPK in the hypothalamus. *Methods:* We searched the available literature for studies published in PubMed, Science Direct, and ClinicaTrials.gov between November/2020 and January /2021, and we included controlled clinical trials based on the animals' model issued in the past six years. *Findings:* A total 101 out of 250 articles included in our search, and findings revealed that high-fat diets negatively influence liraglutide and 5'-AMPK in the hypothalamus. In contrast, a normal-fat diet could reverse this negative influence if combined with a dose of 1.8-3 mg/kg of liraglutide for up to 16 weeks. *Conclusion:* High-fat diets counteract the activity of liraglutide and 5'-AMPK in controlling food intake and energy hemostasis in the hypothalamus. Furthermore, we didn't find adequate studies examined the effect of combining a normal-fat diet with liraglutide on 5'-AMPK in the hypothalamus; hence, our concern was reviewing and predicting the possible effect of normal-fat diets.

Key words: liraglutide, hypothalamus, 5'-AMP-activated protein kinase, high fat diet, obesity

Background

For years now, obesity has a significant focus as a modern health challenge. As a chronic disease, it has a notable role in causing many metabolic diseases, including diabetes, and inducing neuroinflammation (1-3). The prevalence of obesity has dramatically increased in middle-aged individuals by more than 30% over the past thirty years. More importantly, females and patients with type 2 diabetes are the highest affected groups (3-5). No single factor defines obesity, and research supports the theory of multiple factorial dysfunctions where pathogenesis results from a long-term interplay between hereditary, genetic, immune, and environmental risk factors. Its pathogenesis process is complex and shares various dysfunctional pathways with metabolic conditions such as type 2 diabetes mellitus. Both conditions share specific features such as leptin resistance, insulin insufficiency and resistance caused by beta-cell dysfunction, and high oxidative stress and inflammation in different organs (5,6). Furthermore, the consequences of obesity are serious. Hormonal and neural signaling disturbances can cause cardiovascular diseases (7), increase the risk of cancer in multiple organs (8), and alter memory and cognitive skills (9-11).

Recently, numerous antidiabetics have been investigated to evaluate their effect on weight control and obesity management. One of the most important groups is glucagon-like peptide-1 (GLP-1) agonist. Newly, GLP-1 agonists revealed remarkable outcomes in reducing nerve cell loss and improving neuron sensitivity to insulin (12,13). Also, GLP-1 agonists diminish peripheral and central inflammation by decreasing interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha) and increasing the secretion of insulin and adiponectin in different organs (14,15). Therefore, they are considered neuroprotective medications and can be used to manage hypothalamic obesity and neurogenerative diseases.

Liraglutide is a long-acting GLP-1 agonist with better control of food intake, weight, insulin, and glucagon than other agents. It stimulates both thermogenesis in brown adipose tissue and the brain. It stimulates pro-opiomelanocortin neurons/cocaine- and amphetamine-regulated transcript (POMC)/CART) in the hypothalamic ventromedial nucleus (VMH) while inhibits neuropeptide Y/Agouti-related protein (NPY/AgRP) neurons and potassium ATP channels of the arcuate nucleus resulting in reducing appetite and suppression. Moreover, regarding effects on gastrointestinal activity, liraglutide suppresses hedonic feeding behaviors via slowing gastric emptying and reducing apolipoprotein C-III expression (16-21).

5'-AMP-activated protein kinase (5' -AMPK) is one of the most important kinases for energy regulation peripherally and in the central nervous system. It regulates the sympathetic system activity in brown and white adipocytes and the thermogenesis process in different brain regions, particularly in the ventromedial nucleus hypothalamus [22]. On the other hand, any reduction in 5' -AMPK levels or activity in peripheral tissues such as the liver and adipose tissue would mainly cause glucose intolerance, diabetes, and obesity (23,24).

Liraglutide modulates the activity of 5' -AMPK in the central nervous system and peripheral organs by activating the phosphatidylinositol 3-kinase (PI3K)/protein kinase B pathway. This modulation changes autophagy in cells affected by high glucose levels, inhibits tumor proliferation factors, stimulates lipids oxidation, and upregulates insulin signaling, in which liraglutide playing a role in reducing weight and inflammation (25-28).

Studies have recently shown that chronic consumption of a high-fat diet (HFD) (>40% kcal) could cause glucotoxicity and lipotoxicity in pancreatic cells, leading to many metabolic dysfunctions. It has been recognized that HFD alters many metabolic pathways, including gut-brain communication, satiety, leptin, and insulin signaling. HFD reduces the activity of GLP-1 receptors and hindbrain GLP-1 receptor expression, consequently limiting the acute anorexic response to liraglutide and increases food intake and weight. Moreover, it could increase lipid oxidation and lower the 5'-AMPK's peripheral activity by up to 50% (29,30).

To our concern, obesity and related metabolic diseases oblige enormous nutritional and medical challenges in different medical sectors. The effect of HFD on the activity of liraglutide and 5'-AMPK in human peripheral tissues, such as adipose tissue and muscles, is obvious. However, liraglutide reduces insulin resistance and decreases lipid profile values in blood, even with fat diets supplying 60-80% of total daily calories. It enhances autophagy, increases glucose transporter 1 (GLUT 1), and increases 5' -AMPK phosphorylation in muscles by 50% (31,32). Our concern in search directed toward investigating the effects of combining high or normal fat diets with liraglutide on neural activity 5' -AMPK in the human hypothalamus.

Material and method

Protocol, 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 November/2020 and January /2021. The research terms included: liraglutide, GLP-1 agonist, hypothalamus, Brain, Neuroprotective, 5' –AMPK, thermogenesis, and low to normal fat diet, high fat diet, and obesity.

Selection of published studies (Inclusion/ Exclusion criteria)

The main inclusion criteria were published clinical trials and cross-over designs investigating the effects of high and normal-fat diets and liraglutide on 5' -AMPK neural and thermogenic activity, mainly in the hypothalamus other brain regions of animal models. Selected full-text articles of preclinical and clinical studies that have been published within 5-6 years were included, and references from included original papers were reviewed to identify further eligible studies. Based on the research strategy, 101 appropriate articles were selected from around 240 articles that were investigated. Selected articles were categorized in main headings "Effects of High-Fat Diet, Liraglutide on the Neural Activity of 5' –AMPK in Hypothalamus, and Other Brain Regions", "Effects of HFD, Liraglutide on the Thermogenic Activity of 5' –AMPK in Hypothalamus, and Other Brain Regions", and "Effect of Adding Normal-Fat diet to Liraglutide regimen on 5' –AMPK Activity in Hypothalamus and Other Brain Regions.

After the final screening, 21 articles were excluded for specific reasons, including study design (n = 8), insufficient information (n= 4), cells and tissue culturing (n=2), liraglutide is used in combination with other antidiabetic drugs (n=5), no comparison group included in the trial (n = 2). The exclusion criteria were non-English language studies, abstracts, conference proceedings, letters, case reports, and clinical trials published over six 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 which was divided into a group of columns entitled as follow: study material, study samples, brain tissue locations, a summary of results and mechanisms describe the effects of liraglutide and HFD on the neural and thermogenic activity of 5' –AMPK in the hypothalamus and other brain regions, authors, and final year of publication. Data regarding the effect of a normal-fat diet on liraglutide activity was summarized in a figure titled: Summary for the effects of GLP-1 agonist (liraglutide) with normal-fat diet on the neural and thermogenic activity of 5' –AMPK.

Effects of High-Fat Diet, Liraglutide on the Neural Activity of 5' –AMPK in Hypothalamus, and Other Brain Regions

Food intake and energy hemostasis are physiologically well balanced. Hemostasis is regulated through complicated neural pathways, including peripheral-central-hormonal activities (33) that control specific neurons in different brain regions such as the hypothalamus, brain stem, cortico-limbic system, amygdala, basal ganglia, and frontal- partial lopes. HFD of 60% disrupts the vagal signaling of several gastrointestinal hormones such as cholecystokinin and serotonin (34-36). This disruption causes changes in normal gastrointestinal flora, thus suppressing GLP-1 hormone secretion from enteroendocrine cells. Also, It negatively correlates to gut permeability and inflammation resulting in early insulin and leptin resistance in vagal nerves with high hyperphagia and negative consequences (37,38).

Additionally, a HFD contributes to peripheral and central neuroinflammation via impairing the phosphorylation of 5'–AMPK, mitogen-activated protein, and extracellular signal-regulated kinases, in which all rise energy intake behavior in the hypothalamus and brain (39-41). Generally, fat diets can increase thiobarbituric acid reactive substances that indicate lipid peroxidation and lower brain eicosapentaenoic acid. Most recent studies revealed that high-fat diets activate glial cells, including microglia and astrocytes in the hypothalamus and hippocampus, and decrease the serotonin and glutamate-glutamine ratio in the hippocampus leading to cognitive decline, dementia, and neurodegenerative disorders (39,42-44). Changes in feeding behavior in individuals with obesity induced by a HFD are another negative issue mainly accompanied by oxidative stress and mitochondrial dysfunction in the brain cortex. This

dysfunction causes disturbances in energy balance, and reducing brain-derived neurotrophic levels, which is a major contributor to brain plasticity and reduced levels, leads to depression (45).

The American Diabetic Association recommends choosing glucose-lowering medications for overweight or obese patients with type 2 diabetes based on their impact on weight control and obesity management (46). Besides GLP-1 agonist (Liraglutide) positive action on insulin secretion with minimal hypoglycemic effect, it has newly show anti-appetite, anti-inflammatory, neuroprotection, and anti-apoptosis activities (47). Peripherally, GLP-1 agonist, particularly in liver and adipocytes, decreases the liver's triglyceride synthesis, reduces adipocyte size in visceral regions and in some subcutaneous, and increases fatty acid β-Oxidation in the skeletal muscle. At the same time, it delays gastric emptying rate and gut transit time in the gastrointestinal tract, thus reducing food absorption, and positively modulates the composition of the gut microbiota, which plays an important role in immunity and inflammation (48-50).

Liraglutide controls the expression of 5'–AMPK in the hypothalamus and other regions in the brain. It inhibits phosphorylation of 5'–AMPK in the nucleus tractus solitarius and stimulates a mitogen-activated protein kinase. Thus, it suppresses food intake and reduces the high intake of glucose into the lateral hypothalamus, while in skeletal muscles, it decreases ectopic intramyocellular fat deposition (28,51). Furthermore, liraglutide has a good influence on short and long-term appetite regulation in primary controlling neural regions, including the partial cortex, medulla oblongata. It induces neuroprotection via stimulation of autophagy and the transcription factor forkhead box-O3 (p-FOXO3) expression in spinal neurons (2,12).

Interestingly, long-term administration of liraglutide enhances AMP kinase/ peroxisome proliferator-activated receptor-γ coactivator 1a signaling, responsible for fatty acid oxidation and regulation of mitochondrial function (52).

Endogenous GLP-1 hormone has a short duration of activity. It is rapidly degraded after secreted from the nucleus tractus solitarius, and this decreases proglucagon-derived peptides (PGDPs) levels which is essential for glucose regulation and food reward behavior, and hypophagia. Thus, any reduction in (PGDPs) levels will further decrease circulating levels of GLP-1, impaired glucose homeostasis, and aggravate food reward behavior (53-55). In comparison, liraglutide inhibits food motivation by 30 %. (51)

Compared to endogenous GLP-1, long-duration agonists such as liraglutide have a more prolonged effect by crossing the blood-brain barrier. In the brain, nuclei and receptors affected are the periventricular and lateral hypothalamus, medial nucleus tractus solitarius, melanocortin 3/4 receptors in the hindbrain, and the hippocampus (56-58).

Recently, research has revealed that liraglutide reduces neuroinflammation in the hypothalamus and hippocampus induced by a HFD, and its effect is significant with diets that contain fatty-acid such as palmitate (59,60). Also, it is promoting learning and memory functions in the hippocampus in health and traumatic injury (61). Recently a study showed that an injection of GLP-1 agonist directly into the arcuate nucleus could reduce hepatic glucose production and glucose uptake by cells, especially neurons (62). Furthermore, Long-term administration of intrahypothalamic liraglutide could enhance the phosphorylation serine S845 postsynaptic glutamatergic receptors, thus controlling appetite, food intake, and reducing body weight 8% (22,63,64).

In the hippocampus, liraglutide regulates the capacity of gamma-aminobutyric acid (GABA) signaling of cornu ammonis pyramidal neurons; thus, it helps in activating memory and learning (65). Moreover, liraglutide activates the cyclic adenosine monophosphate response element-binding protein (cAMP/PKA/CREB) pathway in astrocytes. Its anti-inflammatory activity due to activation of (cAMP/PKA/CREB) pathway prevents the lipopolysaccharide-induced release of interleukin-1β and promotes anti-inflammatory cytokines, such as interleukin-10 (IL-10). Indeed, it reduces oxidative stress, glutamate excitatory toxicity induced cell death in neurons and enhances the frequency of spontaneous excitatory postsynaptic currents (47,66).

Effects of High-Fat Diet, Liraglutide on the Thermogenic Activity of 5'–AMPK in Hypothalamus, and Other Brain Regions.

5'–AMPK a good metabolic sensor that regulates caloric intake in different peripheral organs such as the liver, adipocytes, and muscles. In the central nervous system, it selectively chooses between carbohydrates or fat metabolism in the paraventricular hypothalamus (67,68), and any changes in sympathetic firing to brown and white adipocytes could negatively alter thermogenesis activity of 5'–AMPK. Lately, it has been observed that the administration of thyroxine could reverse this alteration (69,70). Other mechanisms in which 5'–AMPK controls adaptive thermogenesis, food intake, and autophagy include activation of corticotropin-releasing hormone, releasing neuropeptides such as α-melanocyte-stimulating hormone, and agouti-related-peptide expressing neurons (AgRP) that all increase sympathetic tone to adipose tissue (24,68,71).

The loss of GLP-1 receptors on the dorsomedial hypothalamic nucleus cell membrane due to obesity diminishes brown adipocyte thermogenesis activity, decreases the activity of GLP-1 agonist, and increases adiposity (72,73). As early mentioned, liraglutide stimulates POMC/CART neurons while inhibits GABA transmission in neurons, and this regulates energy signals homeostasis and thermogenesis activity of 5'–AMPK in the central nervous system and peripheral tissues(74). Liraglutide provokes weight loss throughout various molecular mechanisms starting from the controlling enzymes and kinases of the hypothalamic ventromedial and the paraventricular hypothalamus, which regulate thermogenic browning of white adipocytes (16,72,74). Also, liraglutide could change the activity of the 5'–AMPK by inducing the expression of uncoupled protein 1 (UCP1) in brown adipocytes. It inhibits ghrelin-stimulated neuronal signals, reducing food intake, and interacts with 5'–AMPK activity on orexigenic action of ghrelin[16]. Furthermore, it decreases mitogen-activated protein kinase (MAPK) activation and modulates intestinal intra-inflammatory lymphocytes (75). In conclusion, liraglutide is an effective antidiabetic used in weight control (76), increases hypothalamic Glp1recepter expression, and activates systems that have an important role in regulating energy homeostasis (63,77).

Worth mentioning that the activation of GLP-1 receptors by liraglutide in the lateral hypothalamus activates orexin. This neuropeptide regulates sleep and appetite, modulates 5'–AMPK activity, stimulates brown and white adipose tissue thermogenesis, and significantly increases uncoupled proteins 1&3 that produce more thermal energy production in adipocytes (16). Furthermore, liraglutide induces white adipose tissue browning via upregulating soluble guanylyl cyclase and protein kinase G (50,77,78). Recent investigations showed that treating obese individuals with liraglutide (3 mg daily) for five or more weeks could decrease glucose and energy intake and carbohydrate oxidation. A 30 nmol/kg/day concentration of liraglutide in blood could activate white adipocytes' browning, increase energy expenditure, and activate the 5'–AMPK energy expenditure in the liver and adipocytes. On the other hand, a HFD counteracts all previous effects and decreases energy expenditure (59,70,80).

Additionally, resting energy expenditure for obese patients can be decreased within 12 weeks if liraglutide is combined with lower daily energy intake or low caloric diets (81). The efficacy appears to be more when the medication is administered intra-hypothalamic rather than subcutaneous. At the immune level, liraglutide increases the expression of invariant natural killer T cells, which increases fibroblast growth factor 21 (FGF21) and induces thermogenic browning of white fat. Finally, it could inhibit the migration of human lymphocytes and prevent the recruitment of pro-inflammatory macrophages in tissues, thus reducing inflammation and its cosequances (72,82). Therefore, liraglutide could be a potential anti-inflammatory effect and can be used not only for obesity treatment but also for prevention at subclinical levels.

High-fat diets induce cytokines' secretion, such as nitric oxide and tumor necrosis factor, which interfere with insulin signaling in adipocytes, and increase glucose uptake resulting in adipocyte dysfunction and insulin resistance (83). Furthermore, a HFD alters the hypothalamic function and cellular proteins involved

Table 1. A summary of Neural and Thermogenic Effects of High-Fat Diet, and Liraglutide on Brain Regions Including Hypothalamus

Studies material	Studies Groups and Samples	Summary of Effects	References	Country
High fat diet (60% kcal from fat) High fat : 62.2 kcal% fat, 19.6 kcal% carbohydrate, and 18.2 kcal% protein) for 28 days High fat diet (40% fat J/J, 29% protein J/J, 31% carbohydrate J/J). AMPK Modulators	**Studies Groups** Male C57BL/6J mice Weanling female C57BL/6 mice Male Wistar rats **Samples** hypothalamus Brain (cerebral cortex, hippocampus)	**High fat diet:** • decreases level of adiponectin, dysregulation of leptin, and Glu/Gln ratio in hippocampus • Increases levels of TNF-α, oxidative stress, and inflammation both in peripheral tissues and in the hypothalamus after 1 week of treatment. • reduces hypothalamic AMPK activation, decreases pAMPK/AMPK and Glc in the hippocampus, and alters in fatty acid oxidation • are lipotoxic, decreases BDNF expression, alters food intake, energy balance, body weight and HOMA index • increases dopamine level, glutamate, IL-6 and IL-12 proinflammatory cytokines hippocampal cell apoptosis • Activates of AMPK inhibits ACC, resulting in a reduced of malonyl-CoA and leading to activation of CPT1c in these CRH neurons, thereby increasing food consumption • alters phosphoglucomutase-1 (PGM1), triosephosphate isomerase and phosphoglycerate mutase 1 both involved with the regulation of the glycolytic pathway • it is neurotoxic via the polyol pathway, changing intracellular tonicity and increasing toxic AGEs which in combination with a HFD promote microglial reactivity • switch from excitatory (glutamatergic) to inhibitory (GABAergic) neurotransmission that may disturb the tight balance between the orexigenic and anorexigenic networks that control appetite regulation and energy homeostasis • increases birth weight, decreases lean body mass percent • newborn off sprin exhibit reduced hypothalamic POMC mRNA and increased NPY signaling (PVN NPY1R) and NPC proliferation	(Alvarez-Crespo et al. 2016; Feillet-Coudray et al. 2019; de Lartigue 2016; Lizarbe et al. 2019; Madsen et al. 2019; Martínez-Sánchez et al. 2017; Raider et al. 2017)	USA Korea Japan Spain UK Italy Saudi Arabia
liraglutide (100 μg/kg-3mg) subcutaneously and intraperitoneally antibodies: AMPK, phosphorylated, AMPK	**Studies Groups:** diabetic men and women of age 34–95 years) Sprague–Dawley rats Male diabetic db/db mice **Samples:** hypothalamus medulla oblongata parietal cortex tissues Astrocytes and microglia	**Liraglutide:** • decreases attention to highly palatable foods, deactivate parietal cortex, lowers fasting blood glucose in diabetic mice • reduces the cavity of necrotic tissue and the loss, promotes autophagy and autophagic flux via the AMPK-FOXO3 signaling pathway • increases the number of dopaminergic neurons in substantia nigra, and restores the AMPK/PGC-1a signaling • Restores AGEs-induced ROS production and cell death, and inhibits the AGEs induced secretion of the proinflammatory cytokines TNF-α and IL-1β. • prevents lipopolysaccharide induced release of IL-1β by astrocytes, and activates MC3/4R	(Farr et al. 2016; Kaineder et al. 2017; Secher et al. 2014; Zhang et al. 2019; Zhou et al. 2019)	USA PRC

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liraglutide (SQ or IT High fat (40%) high-fat (HF, 50% energy from lipids, 14% energy from proteins and 26% energy from carbohydrates—5.0 kcal/kg).	**Studies Groups** activated iNKT cells in obese mice Male Sprague Dawley rats KKAy mice Glp1r-knockout (KO) and age-matched wild-type (WT) male mice on a C57/BL6J **Samples** hypothalamus blood intestine brainstem microglia astrocytes hippocampus	**High Fat Diet with Liraglutide:** • HFD induces inflammation, leptin and insulin resistance, increase in IL1b, loss of hippocampal synaptic proteins, and activates microglia and astrocytes in the hippocampus causing microgliosis, increase in brainstem preproglucagon (PPG) expression, and saturated fatty acid diet is associated with an inflammatory response in the hypothalamus which all these effects decreased after administration of liraglutide (Neuroprotective). It activates the central anorectic pathway, improving metabolism and reducing reactive microgliosis in the hypothalamus. • Liraglutide reduces obesity in HFD-fed mice, decreased body weight gain by approximately 13.3% ($P < 0.001$), intrahypothalamic liraglutide treatment induced a significant body weight loss from day 9 to day 28 and a significant loss in adipose tissue depots (iWAT, iBAT) after 28 days compared with subcutaneous liraglutide treatment. Liraglutide induced WAT browning via sGC-dependent pathway, can activate human iNKT cells, induces FGF21, thermogenesis, and weight loss, decrease the respiratory exchange ratio (RER), and inducts β-oxidation. • Inhibition of NPY gene expression by GLP-1 is involved in the sympathetic control of BAT thermogenesis. Liraglutide stimulates the melanocortin system other than POMC/α-MSH. It triggers the white fat browning in mice, and up-regulation of brown fat marker genes stimulates mitochondrial biogenesis in WAT. Liraglutide upregulates the soluble guanylyl cyclase (sGC) and protein kinase G I (PKGI). Liraglutide change the structure and composition of gut microbiota in both obese and diabetic rats, mainly Firmicutes, Bacteroidetes, Tenericutes, and Proteobacteria	(Barreto-Vianna, Aguila, and Mandarim-de-Lacerda 2017; Barreto-Vianna, Aguila, and Mandarim-De-Lacerda 2016; Davies et al. 2015; Drucker 2018; Martínez-Sánchez et al. 2017; Oh et al. 2016; Swick et al. 2015)	USA PRC Austria Switzerland Brazil

in neurogenesis, synaptogenesis and causes hypothalamic astrocytosis and microgliosis in the hypothalamus, responsible for many neurodegenerative diseases and energy metabolism disturbances (84,85).

Besides, it increases expression of phosphodiesterase 4A5 and its phosphorylation activation process which suppresses the cAMP/PKA pathway, results in sort of a depression behavior, inflammation induced by lipopolysaccharide (LPS), and reverses the excitatory effects of orexin and melanin in neuron (86-88).

Effect of Adding Normal-Fat diet to Liraglutide regimen on 5' –AMPK Activity in Hypothalamus and Other Brain Regions.

Some human studies revealed that although low-carbohydrate diets are popular for weight loss, fat diets containing 30% of fat or less share comparable results with low carbohydrate diets on weight loss and hemoglobin parameters A1c (HbA1c) (89,90). Given what was previously discussed regarding the importance of liraglutide in controlling obesity, and the adverse effects of a HFD on the nervous system on the action of hypothalamic enzymes, especially 5'–AMPK and its activity on thermogenesis and neural activity, it is expected that normal-fat diets can play the role of improved contrast. Some clinical studies have discussed the role of a normal-fat diet, but unfortunately, research has focused only on the effects of HFD or liraglutide's effectiveness as a drug; thus, scrutiny in this area is still available, and more research could open the gate for greater understanding.

A dose of 1.0-1.8 mg/kg of liraglutide with a normal-fat diet promotes weight loss (91,93), induces a reduction in overall caloric intake (91,94). Liraglutide could reduce visceral adipose tissue by 15.3% (95), and a normal-fat diet helps to improve b-cell function and enhance insulin sensitivity (96). As the negative effect of a HFD on 5'–AMPK in brain regions and other body tissues has been clarified in previous sections, specific positive effects of using a normal-fat diet could be expected.

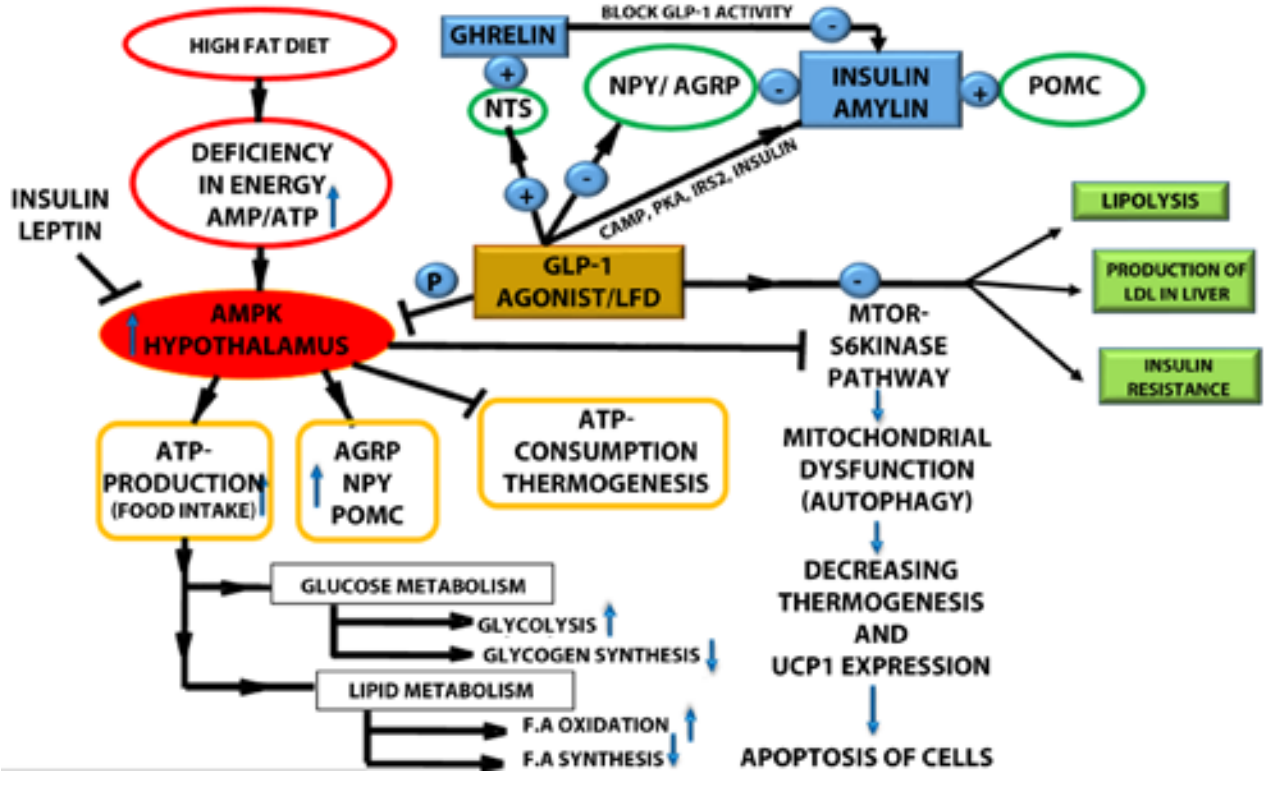

Figure 1. Summary for the effects of glucagon-like peptide-1 agonist (liraglutide) with low-fat diet on the neural and thermogenic Activity of AMPK

Figure 1 summarizes the main predicated neural and thermogenic effects for hypothalamic 5'–AMPK if the normal fat diet is a part of liraglutide intervention. Generally, a normal-fat diet could enhance the liraglutide effect on 5'–AMPK in the brain and other tissues, induce glycogen synthesis, reduce lipolysis and fatty oxidation, and even provide an anti-tumor effect (97,98). Liraglutide improves cognitive ability by decreasing phosphorylated 5'–AMPK, and phosphorylated Akt expression in the brain (99-100). Moreover, liraglutide upregulates the autophagy process and avoids lipotoxicity in tissues such as the liver by increasing 5'–AMPK levels (101).

Finally, it should be mentioned that conducting the before-mentioned clinical studies on humans is difficult due to tissue specificity and 5-AMPK examined and related ethical issues for obtaining a tissue sample for analysis. Therefore, experiments on animal models were selected to be a comparable template determining the effectiveness of liraglutide and high-fat diets on 5-AMPK effectiveness in the hypothalamus and predicting the effect of normal-fat diets.

GLP- 1 agonist (liraglutide), combined with a low to normal fat diet (20-30%), can stimulate GLP-1 receptors on the membranes of adipose tissues, liver, and pancreas. It downstream lipolysis and low-density lipoproteins in the liver, and decreases insulin resistance in peripheral and central nervous systems. Also, this activation enhances β-cells proliferation in pancreatic cells, protects β-cells against apoptosis by increasing the insulin growth factor receptor autocrine loop activity and decreasing the expression of uncoupled protein1. Also, the activation promotes pre-adipocyte differentiation, and reduces adipogenic and lipogenic genes' expression and cytokine and chemokines production in different organs, including the brain. It enhances lipolytic markers in human adipose tissue, increases glucose uptake, and decreases adipocyte hyperplasia. Regarding the neural effects of liraglutide, it has a neuroprotective and synaptic plasticity promoting activities in the hypothalamus and hippocampus on different levels such as learning and memory functions via activating cAMP/ Protein kinase (PKA)/pCREB pathway, and pro-opiomelanocortin (POMC) The injection of liraglutide into the arcuate nucleus reduces hepatic glucose production, and stimulation of the hypothalamic paraventricular nucleus controls food intake; in conclusion, liraglutide may inhibit the motivation for food by 30 %

Conclusion

Many antidiabetic agents are being used in obesity management. Liraglutide activates neural centers in the hypothalamus and hindbrain and controls appetite and food intake. 5-AMPK stimulates energy production in peripheral tissues, improves metabolic status, and modulates uncoupled proteins. On the other hand, HFD counteracts all previously mentioned effects. Through the literature, no adequate studies showed the effect of a low to normal-fat diet on liraglutide and 5-AMPK in the brain, so our concern was to review the possible action of normal-fat diets on the activity of liraglutide on hypothalamic 5-AMPK. Low to normal-fat diets with 30% could enhance liraglutide activity on 5-AMPK, metabolism processes such as glycogen and fatty acids synthesis, increasing thermogenesis and expression of UCP1, and reducing side effects of liraglutide using a lower dose combined with a normal-fat diet regimen.

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