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Mini-review

The Hypothalamus and Hippocampus are Targets for New Drugs Controlling the Energy Balance and Treating Type 2 Diabetes Mellitus, Obesity, and Neurodegenerative Diseases

El Hipotalamo y el Hipocampo son Blancos de Nuevos Fármacos que Controlan el Equilibrio Energético y Tratan la Diabetes Mellitus Tipo 2, la Obesidad y las Enfermedades Neurodegenerativas

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SUMMARY: GLP-1 is an incretin secreted by intestinal cells and neurons in the brainstem, controlling glucose levels and food intake (appetite and satiety). Glucagon-like peptide type 1 receptor agonists (GLP-1RAs), as monotherapy or combined with other molecules, are indicated to treat type 2 diabetes mellitus (T2DM) and obesity because they act on the pancreatic beta-cell and insulin production and cause weight loss. However, the central action and neural pathways through which GLP-1Ras act must be better understood. Proopiomelanocortin (POMC) and neuropeptide Y (NPY) are critical neuropeptides intrinsically involved in the signaling pathway regulating appetite and satiety through GLP-1 and its agonists. Notably, the focus on combating obesity could be blocking the stimulation of orexigenic pathways and inhibiting anorexigenic pathways. Therefore, due to the high complexity of the neural circuits involved in appetite and satiety signaling and the multiple GLP-1RAs actions, more research still needs to be performed to elucidate these mechanisms. In addition, T2DM and obesity are associated with neuroinflammation and microglial activation, leading to a favorable environment for the development of neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease. In this case, the Hippocampus is the privileged target. In this text, we will review the main points related to the hypothalamic and hippocampal location and the activation pathways of POMC and NPY neurons that are targets of GLP-1RAs and have demonstrated an effective pharmacological treatment that has changed the perspective of the evolution of T2DM and obesity.

KEYWORDS: Hypothalamus; Hippocampus; POMC neurons; NPY neurons; GLP-1.

Abbreviations

AB, Beta-amyloid plaques;
ACTH, Corticotropin;
AgRP, Agouti-related protein;
AIF, Allograft inflammatory factor 1;
AMPK, AMP-activated protein kinase;
a-MSH, Alpha-melanocyte-stimulating hormone;
ARC, Arcuate nucleus;
BBB, Blood-brain barrier;
CA, Cornu Ammonis;
cAMP, Cyclic adenosine monophosphate;
CART, Cocaine-and amphetamine-regulated transcript;
CD68, Cluster of Differentiation 68;
CLIP, Corticotropin-like intermediate peptide;
CMS, Central melanocortin system;
CNS, Central nervous system;
DG, Dentate gyrus;
DPP-4, Dipeptidyl peptidase-4;
Ex-4, Exendin-4;
FGF-21, Fibroblast growth factor 21;
GABA, Gamma-Amino Butyric Acid;
GABAA, GABA receptor;
GDF15, Growth factor 21;
GFAP, Glial fibrillary acidic protein;
GIP, Gastric inhibitory polypeptide or glucose-dependent insulinotropic polypeptide;
GLP-1RA, GLP-1 receptor agonist;
IBA1, Ionized calcium-binding adapter molecule 1;
ICV, Intracerebroventricular;
IL-18, Interleukin-18;
IL-1B, Interleukin-1beta;
KATP, ATP-sensitive potassium channel;

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LepR, Leptin receptor;
MCP-1, Monocyte chemoattractant protein-1;
MCR, Melanocortin receptor;
MHC, Major histocompatibility complex;
NLRP3, NLR family pyrin domain containing 3;
NPY, Neuropeptide Y;
NTS, Nucleus tractus solitarius;
PC, Proprotein convertases;
POMC, Proopiomelanocortin;
PVN, Paraventricular nucleus;
PYY, Polypeptide YY;
T2DM, Type 2 diabetes mellitus;
TLR-4, Toll-like receptor-4;
TNF-a, Tumor necrosis factor-alpha;
TrpC5, Transient receptor potential canonical 5;
ULK1, Unc-51 like autophagy activating kinase 1;
VMH, Ventromedial nucleus;
Y1R, Neuropeptide Y receptor type1.

1. INTRODUCTION

Obesity has become a significant public health challenge, primarily associated with comorbidities such as type 2 diabetes mellitus (T2DM) and systemic arterial hypertension. Obesity's etiology involves multiple factors, but usually, the consumption of a diet high in fats and sugars (Spezani *et al*., 2020). The imbalance between energy intake and expenditure leads to energy accumulation in the subcutaneous and visceral fat, which is highly inflammatory (Boutari *et al*., 2023) (Fig. 1).

Visceral fat accumulation strongly correlates with a higher incidence of T2DM and increases the prevalence of fatty liver disease and the risk of cardiovascular outcomes (Cariou *et al*., 2021). Besides, obese people show raised production of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1B), contributing to insulin resistance and its consequences (Aguila *et al*., 2010; Rohm *et al*., 2022). In addition, cytokines target the central nervous system (CNS), resulting in neuroinflammation, microglia activation, hypothalamic dysfunction, and enhanced risk of developing neurodegenerative diseases with hippocampal involvement (Garcia-Serrano *et al*., 2022; Jangra & Tople, 2022).

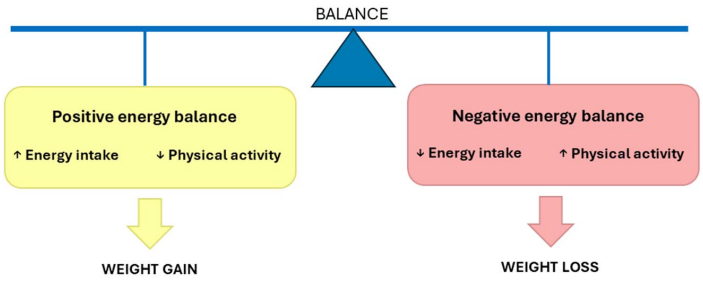

Fig. 1. Energy balance. Regular physical activity and reduced calorie intake result in a negative energy balance, leading to weight loss; otherwise, it is weight gain.

There are currently numerous possibilities for the treatment of obesity and its comorbidities:

1.1. Enteropancreatic hormones

a) Incretins

– Glucagon-like peptide type 1 (GLP-1) receptor agonists.
- Glucose-dependent insulinotropic polypeptide (GIP) receptor agonists.

b) Non-incretins

- Glucagon receptor agonists
- Amylin receptor agonists
- Polypeptide YY (PYY) receptor agonists

1.2. Non-enteropancreatic hormones

- Bimagrumab (myostatin blocker, a substance that inhibits the formation of muscle cells)
- Growth differentiating factor 15 (GDF15) receptor agonists (a cell stress-responsive cytokine member of the transforming growth factor-beta superfamily)
- Fibroblast Growth Factor 21 (FGF-21) receptor agonists (are potent metabolic regulators crucial in mediating the metabolic responses to fasting or starvation. It regulates fatty acid oxidation and ketogenesis and acts on glucose metabolism in white adipose tissue)

GLP-1 is mainly produced by the gut L-cells, especially in the ileum and colon, after food intake, but also secreted by the pancreas and certain areas of the brain, like the brainstem *nucleus tractus solitarius* (NTS) and hypothalamus (Singh *et al*., 2022b). GLP-1 has hypoglycemic action, stimulating insulin release, reducing glucagon secretion, and delaying gastric emptying (Nauck *et al*., 2021). Therefore, GLP-1 receptor agonists (GLP-1RAs) have been developed and are currently used for treating T2DM and obesity, resulting in weight loss (He *et al*., 2019).

GLP-1RA affects neuropeptide regulation involved in controlling food intake, such as proopiomelanocortin (POMC)/cocaine- and amphetamine-regulated transcript (CART) and neuropeptide Y (NPY)/Agouti-related neuropeptide (AgRP) (Abtahi *et al*., 2019) (Fig. 2).

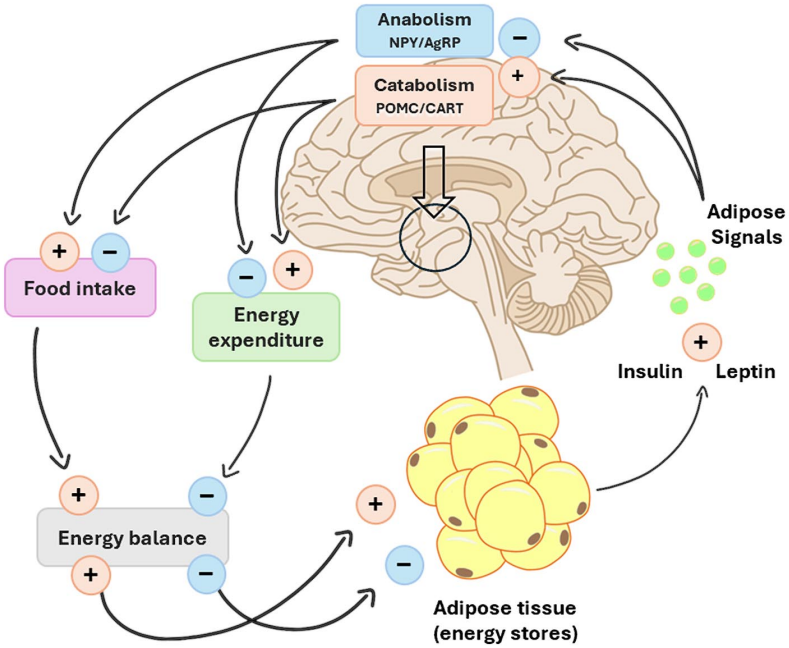

Fig. 2. Pathways and neuropeptides related to anabolism and catabolism in the hypothalamus (circle). Peptides such as leptin and insulin act as regulators of energy metabolism, signaling to the hypothalamus about energy stores and triggering anorectic pathways. Stimulation of POMC/CART neurons results in catabolic pathways activation, leading to lower energy intake and more significant energy expenditure. Stimulation of NPY/AgRP neurons leads to activation of anabolic pathways and fat storage.

2. HYPOTHALAMUS and energy homeostasis

The hypothalamus is essential in maintaining homeostasis by regulating physiological functions such as appetite, thirst, and temperature. Notably, the nuclei in the tuberal and supraoptic regions, such as the arcuate (ARC) and paraventricular (PVN), are directly involved in regulating appetite and food intake (He *et al*., 2019; Peterfi *et al*., 2021).

Complex systems in the body control the balance between appetite and satiety centrally through the signaling of neuropeptides and peripherally through the release of hormones and cytokines (such as GLP-1) that act as signals for food intake and energy storage in the form of fat. Peripheral signals reach the NTS via the vagus nerve, then the hypothalamus, where neuropeptide synthesis is regulated (Shan *et al*., 2019). In the ARC are the subpopulations of anorexigenic neurons that express the POMC/CART and the orexigenic neurons that express NPY/AgRP (Fig. 3).

Specific molecules such as GLP-1, ghrelin, leptin, and insulin stimulate the synthesis of POMC/CART and NPY/AgRP. GLP-1 inhibits the signaling of NPY/AgRP, suppresses appetite, stimulates POMC/CART, and promotes appetite (Abtahi *et al*., 2019; Singh *et al*., 2022b). Thus, the regulation of eating behavior coincides through the CNS and the gastrointestinal tract via the gut-brain axis, with the involvement of neuropeptides, hormones, and cytokines (Shobatake *et al*., 2019).

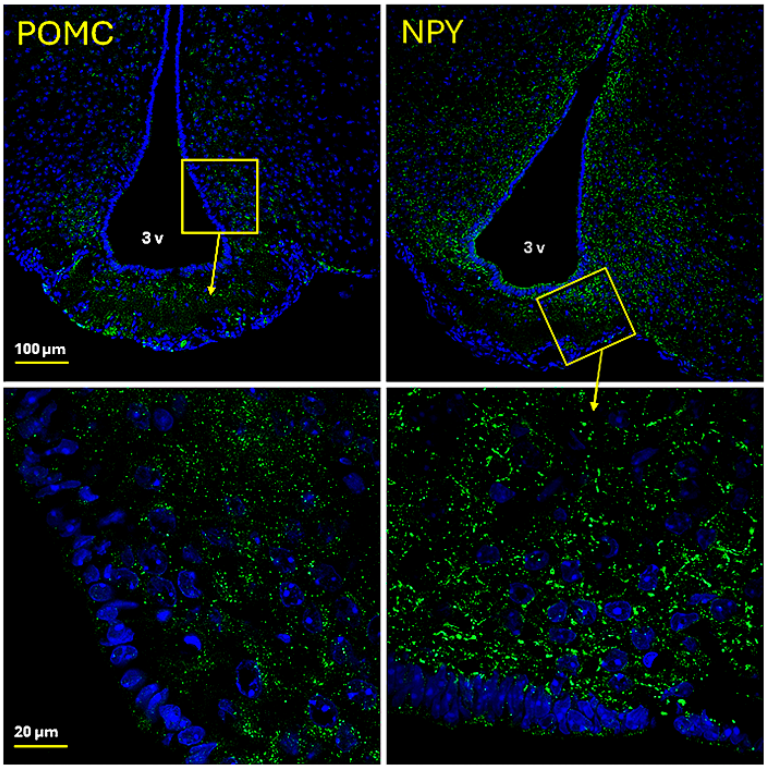

Fig. 3. POMC and NPY neurons were immunolabeled in the ARC. Representative images with low and high magnification. The activation of neurons expressing POMC and NPY neuropeptides was seen through immunofluorescence and confocal laser scanning microscopy (images provided by Spezani & Mandarim-de-Lacerda).

2.1. Proopiomelanocortin (POMC)

POMC is a protein that participates in various physiological processes, such as inflammation and stress response. Each specific tissue undergoes the action of proprotein convertases (PC), such as PC1/3, generating three different products. The hormone ACTH is one of the results of this proteolytic cleavage. Subsequently, it undergoes the action of PC2, resulting in the alpha-melanocyte-stimulating hormone (α-MSH) and the corticotropin-like intermediate peptide (CLIP) (Low *et al*., 2020) (Fig. 4).

Melanocortins (α-, β-, and γ-MSH) contain the amino acid sequence HFRW, which allows for greater specificity in binding to melanocortin receptors (MCR) (Low *et al*., 2020). In the hypothalamus and brainstem, neurons coexpress PC1/3 and PC2 and use melanocortins as neuromodulators of food intake and energy metabolism through binding to MC3R and MC4R (Low *et al*., 2020). The MC4R plays a critical role in anorexigenic signaling, as the absence of this receptor in neurons leads to weight gain (Peterfi *et al*., 2021).

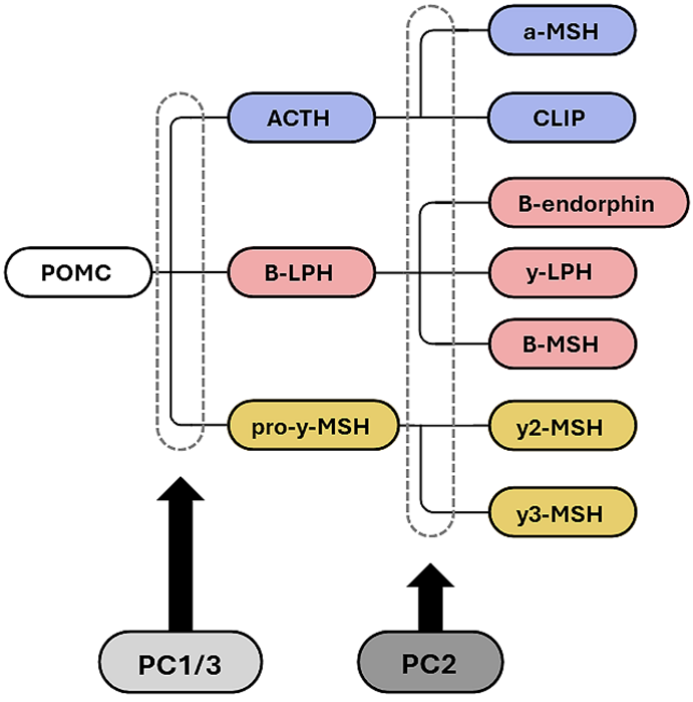

Fig. 4. Cleavage of POMC and its substrates. Various biologically active peptides, such as ACTH and a-MSH, are derived from the cleavage of POMC. The product of POMC cleavage directly depends on the tissue-specific proprotein convertase (PC). PC1/3 acts by generating ACTH, B-LPH, and pro-y-MSH. PC2 originates a-MSH and CLIP from ACTH, B-endorphin, y-LPH, B-MSH from B-LPH, and y2-MSH and y3-MSH from pro-y-MSH.

Evidence suggests the existence of POMC neuron subpopulations, as some of these neurons express GABAergic markers while others express glutamatergic markers (Biglari *et al*., 2021). Furthermore, specific POMC neurons have their activity stimulated by GLP-1. In contrast, others are stimulated by leptin, possibly due to the existence of POMC subtypes that express leptin receptors (LepR) and others that express GLP-1 receptors (GLP-1R) (Lee *et al*., 2023). In addition, there is a divergence regarding the anatomical distribution in the ARC of POMC subtypes and their respective anorexigenic signals (Biglari *et al*., 2021).

Some POMC neurons are also found in the NTS, playing a role in energy homeostasis, as the NTS is a receptor center for various afferent signals. However, despite playing a role in metabolism, this population is less studied due to its smaller quantity and difficulty in visualization with histochemical techniques. POMC neurons, just like those located in the ARC, are responsive to leptin, as the administration of peripheral leptin increases the immunolabeling of Fos protein, a transcription factor used as a marker of cellular activation (the detection of the Fos protein, a product of the cfos gene, within neurons is a standard procedure used in research to identify neurons and circuits within the brain that are active during certain situations, assuming that Fos expression is positively related to neuronal depolarization) (Georgescu *et al*., 2020).

One of the most essential neural systems involved in controlling food intake and maintaining body weight is the central melanocortin system (CMS). This system plays a vital role in regulating homeostasis, involving the participation of neurons that express melanocortin ligands and neurons that express melanocortin receptors (MCR). Melanocortin receptors exhibit significant diversity, with MC3R and MC4R being the most predominantly expressed in the brain and MC4R playing a crucial role in regulating energy homeostasis (Yang & Xu, 2020). This CMS signaling begins with the release of α-MSH, derived from the cleavage of POMC in neurons in the arcuate nucleus (first-order neurons), and the activation of melanocortin-4 receptors (MC4R) located in the neurons of the paraventricular nucleus (second-order neurons) (Sun *et al*., 2021) (Fig. 5). The activation of MC4R by α-MSH promotes appetite inhibition. In contrast, AgRP, released by AgRP neurons, stimulates food intake by activating MC4R, acting as an inverse agonist (Biglari *et al*., 2021).

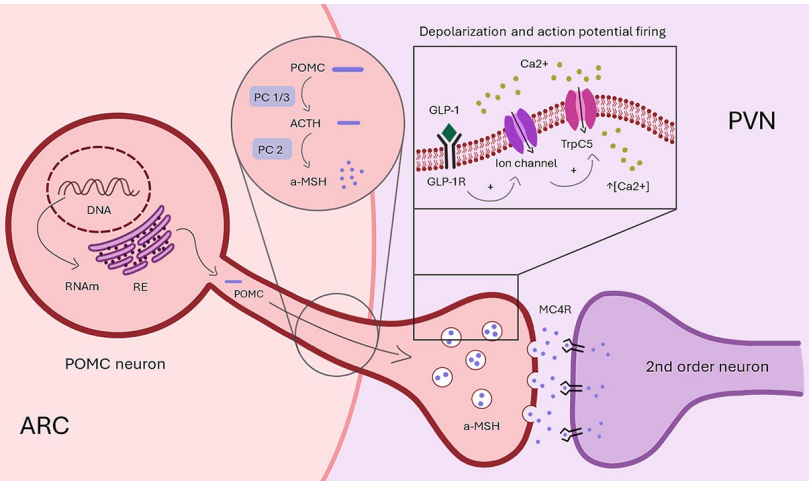

Fig. 5. Activation of POMC neurons and release of a-MSH. PC1/3 and PC2 carry out the cleavage of POMC into α-MSH by stimulating molecules such as GLP-1 and leptin, which promote an increase in intracellular calcium and the firing of the neuron's action potential. The axonal extensions of POMC neurons then release α-MSH in second-order neurons located in the paraventricular nucleus, which binds to melanocortin-4 receptors, promoting appetite inhibition and increased energy expenditure.

2.2. Neuropeptide Y

NPY is a neuropeptide expressed in neurons located in the ARC. It has an orexigenic function, activating energy metabolism by promoting more substantial food intake and less energy expenditure by binding its active form to hypothalamic Y1 receptors (Y1R). Besides, it stimulates the synthesis of fatty acids and fat deposition as an energy reserve, accumulating body fat and weight gain (Georgescu *et al*., 2020).

AgRP is another orexigenic peptide co-secreted with NPY and primarily increases food intake and decreases energy expenditure. The main signals for activating NPY/AgRP neurons are low blood sugar and the action of ghrelin. Insulin and leptin inhibit NPY/AgRP expression. The deletion of NPY in mice inhibits food intake (Rakhat *et al*., 2022).

Just like POMC, there are subpopulations of NPY that either express or do not express leptin receptors. Besides, NPY neurons also express AgRP in 80 % of the cases. Therefore, around 20 % of NPY neurons do not express AgRP (Lee *et al*., 2023).

3. HIPPOCAMPUS and memory

The Hippocampus is a significant brain structure involved in memory formation, spatial navigation, and learning. The main parts of the Hippocampus are (Fig. 6):

3.1. Dentate Gyrus (DG)

It is involved in the formation of new memories and the processing of spatial information. It receives input from the entorhinal cortex and projects to the CA3 region of the Hippocampus (Coelho *et al*., 2024; Huang *et al*., 2024).

3.2. Cornu Ammonis (CA) Regions

The Hippocampus is divided into several layers, such as CA1, CA2, CA3, and CA4. CA1 is responsible for consolidating and retrieving memories. It receives processed information from the CA3 and is a significant output region of the Hippocampus. CA2 is a less understood region but is thought to play a role in social memory (Oliva *et al*., 2016). CA3 is significant for pattern completion and the retrieval of stored memories. It receives inputs from the dentate gyrus and has a network of recurrent connections, making it essential for forming associative memories. CA4 is known as the hilus, near the dentate gyrus. It is involved in the transfer of information within the hippocampal circuit (Mercer & Thomson, 2017).

3.3. Subiculum

It is the primary output region of the Hippocampus. It connects to other brain parts, including the cortex and hypothalamus (Viellard *et al*., 2024). It involves spatial navigation, memory processing, and stress response (Baset & Huang, 2024).

3.4. Entorhinal Cortex

The entorhinal cortex does not anatomically participate in the Hippocampus proper. However, it is crucial for the hippocampal function (Nguyen *et al*., 2024). It is a significant input and output hub, sending sensory information to the Hippocampus and receiving processed information in return. The entorhinal cortex stands out as a critical brain region affected in the early phases of Alzheimer's disease, with some of the disease's pathological processes originating from this area, making it one of the most decisive brain regions in this neurodegenerative disease (Karimani *et al*., 2024).

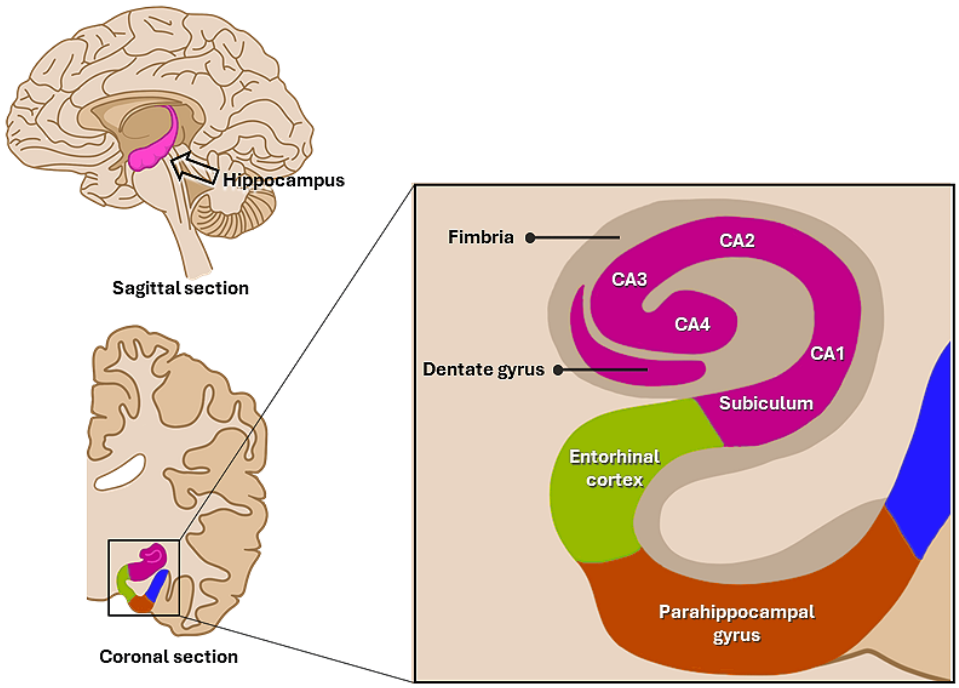

Figure 6. Schematic hippocampus drawing. The Hippocampus is located in the medial portion of the temporal lobe and can be divided into the cornu Ammonis (hippocampus proper) layers CA1, CA2, CA3, CA4, the Subiculum, and the Dentate gyrus. Additional structures, such as the Entorhinal cortex, also actively contribute to hippocampal functions. The Hippocampus is central to memory formation, learning, and spatial information.

4. NEURODEGENERATIVE DISEASES

The increase in inflammatory processes and insulin resistance in the central nervous system resulting from metabolic disorders such as obesity and diabetes is already correlated with neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease. There is a strong association between T2DM and Alzheimer's disease, which can be considered type 3 diabetes (Bharadwaj *et al*., 2017; Arnold *et al*., 2018; Amidfar *et al*., 2024). In these cases, there is an increase in the phosphorylation of the Tau protein (a microtubule-associated protein predominantly expressed in the neurons), a characteristic event of Alzheimer's disease (Di Lorenzo, 2024; Lantero-Rodriguez *et al*., 2024).

Microglia are specialized in phagocytosis in areas of neural injury or inflammation (Vianna *et al*., 2017; Thakkar *et al*., 2018; Hall *et al*., 2022) and play a crucial role in combating metabolic changes associated with obesity (Lin *et al*., 2023). They are reactive in response to pro-inflammatory factors such as those induced by a high-fat diet and the consequent reduction of functions in the hypothalamus (Dalvi *et al*., 2017).

The non-dopaminergic lesions in motor circuits are likely to contribute to the pathogenesis of Parkinson's disease (Halliday *et al*., 2005). Molecular mechanisms underlying the neuroprotective effects of GLP-1RAs in the laboratory and their potential therapeutic utility have particular relevance to Parkinson's disease and Parkinson's disease dementia (Athauda & Foltynie, 2016). Additionally, experimental Alzheimer's disease models demonstrate the loss of function of NPY/AgRP neurons and decreased responsiveness to appetite and appetite-related hormones, such as leptin, insulin, and ghrelin. Despite this, there is still a lack of studies in the literature demonstrating the supposed correlation between the higher incidence of Alzheimer's disease and the plasma concentrations of these hormones (Lopez-Gambero *et al*., 2022).

The deposition of beta-amyloid plaques in the CNS is also characteristic of Alzheimer's disease. However, the hypothalamus does not seem to be affected, with the Hippocampus being a more suitable location for depositing these plaques, leading to the activation of microglia and astrocytes and consequent hippocampal inflammation. The activation of hippocampal astrocytes directly interferes with the activity of hypothalamic neurons, as a negative correlation was observed between the expression of glial fibrillary acidic protein (GFAP), a protein indicative of astrocyte activation, and the expression of hypothalamic neuropeptides (Lopez-Gambero *et al*., 2021; Lopez-Gambero *et al*., 2022).

5. GLUCAGON-LIKE PEPTIDE TYPE 1

5.1 Glycemic control and neuroprotective effects

GLP-1 is a peptide derived from the cleavage of proglucagon and secreted by L cells in the intestine in response to nutrient stimulation after a meal (Sun *et al*., 2021), mainly after consuming foods rich in carbohydrates and fats (Singh *et al*., 2022b), and by a subpopulation of neurons in the NTS, located in the brainstem, where it acts as a neurotransmitter (Peterfi *et al*., 2021; Singh *et al*., 2022b). The function of glycemic control occurs through the incretin effect, stimulating insulin secretion in pancreatic beta cells to manage postprandial blood glucose levels (Chivite *et al*., 2021).

The action of GLP-1 occurs through its binding to G protein-coupled receptors, specifically GLP-1R, which are widely distributed across different cell types, such as pancreatic beta cells, cardiomyocytes, neurons, and in the vagus nerve (Abtahi *et al*., 2019; Singh *et al*., 2022b). After its release, GLP-1 is quickly inactivated by the action of the enzyme dipeptidyl peptidase-IV (DPP-IV), resulting in a half-life of approximately 1 to 2 minutes (Chivite *et al*., 2021; Hansen *et al*., 2021). Therefore, it is believed that endogenous GLP-1 primarily acts in a paracrine manner on the GLP-1R present in the celiac and gastric branches of the vagus nerve that innervates the intestine. The GLP-1R activation reduces food intake through glutamatergic signaling via the vagal-NTS, stimulating anorexigenic pathways (Shan *et al*., 2019).

The mouse's hypothalamus is the brain region with the highest density of GLP-1R, especially in the PVN and ARC, involved in the signaling pathways of appetite and satiety that receive axonal projections from GLP-1-producing neurons located in the NTS (Singh *et al*., 2022b) (Fig. 7). The GLP-1 intracerebroventricular administration increases intracellular calcium concentration in POMC neurons in the ARC, activating anorexigenic pathways through the enhanced activity of these neurons (Yermek *et al*., 2022).

Endogenous GLP-1 and its agonists are small molecules that can cross the blood-brain barrier (BBB), acting directly on the CNS through its connection with the GLP-1R. The BBB consists of glial cells, such as astrocytes, microglia, and some neurons. Therefore, activating glial cells during inflammation might affect BBB integrity. On the other hand, GLP-1 might mitigate microglial activation, contributing to the BBB integrity, reducing neuroinflammation, and maintaining tissue homeostasis (Shan *et al*., 2019). In a model of T2DM and obesity, Semaglutide mitigated the expression of genes related to neuroinflammation and microglial activation, such as MCP-1, TLR-4, IBA1, and CD68. Besides, Semaglutide also diminished gene expressions related to inflammasome complex activation, responsible for triggering inflammatory processes, such as the NLRP3, Caspase-1, IL-1B, and IL-18, thereby reducing neuroinflammation (Marinho *et al*., 2024).

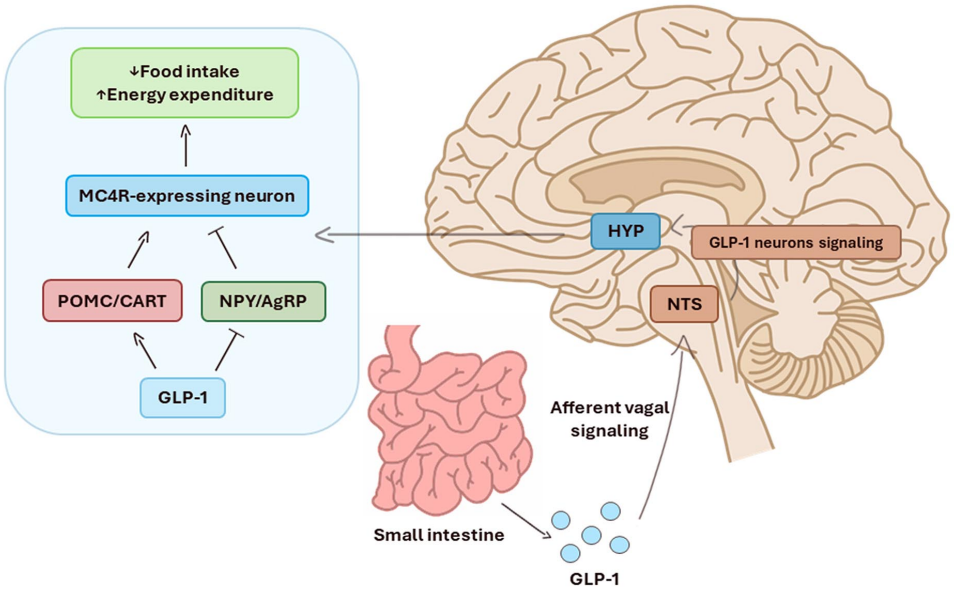

Fig. 7. Peripheral and central GLP-1 signaling. Peripherally secreted GLP-1 acts directly on the NTS and indirectly activates hypothalamic neurons, modulating circuits that regulate energetic balance. At the same time, GLP-1 can diffuse across the BBB and directly activate hypothalamic neurons. Reaching the ARC, GLP-1 stimulates POMC neurons and inhibits the activity of NPY/AgRP neurons. In the PVN, the product of POMC cleavage, a-MSH, binds to MC4R. The activation of these receptors leads to decreased food intake and increased energy expenditure.

5.2. GLP-1 receptor agonists

For effective therapeutic use of this peptide, GLP-1RAs have been developed (Table 1), which are resistant to the DPP-4 enzyme action, extending the GLP-1 effect in metabolism (Abtahi *et al*., 2019; He *et al*., 2019; Sun *et al*., 2021).

Exenatide was the first GLP-1RA developed from the study of the insulinotropic potential of exendin-4, a peptide found in the venom of the Gila monster (*Heloderma suspectum*), a species of venomous lizard (Furman, 2012). In 1993, GLP-1R cloned from human pancreatic islets showed that exendin-4 has a high affinity for these receptors, with approximately 53 % similarity to the GLP-1 molecule. Its binding to GLP-1R elevates intracellular levels of cAMP and stimulates insulin secretion (Thorens *et al*., 1993). Thus, a synthetic exendin-4 molecule Exenatide was developed to treat T2DM in 2005, administered subcutaneously twice daily (Kolterman *et al*., 2005; Furman, 2012).

Subsequently, other GLP-1RAs, such as Liraglutide, were developed to be administered daily via subcutaneous injection. Compared to Exenatide, Liraglutide shows 97 % similarity with endogenous GLP-1 and superior effects, with more significant reductions in hemoglobin A1c, fasting glucose, triglycerides, and free fatty acids (Ladenheim, 2015).

Liraglutide enhanced leptin sensitivity and diminished the microgliosis with a decreased Bax/Bcl2 ratio. Besides, Liraglutide activates central anorexigenic pathways, thereby diminishing the energy intake of obese mice and improving the metabolic parameters related to obesity. Liraglutide is a relevant neuroprotective agent that can decrease microgliosis and stimulate the anti-apoptotic pathway, significantly treating obesity and its comorbidities. Some benefits of liraglutide are independent of the weight loss, which usually accompanies the drug administration (Vianna *et al*., 2016).

Furthermore, palmitate intracerebroventricular infusion resulted in pronounced inflammation response in the Hippocampus, reactive microgliosis, and astrogliosis, with hypertrophied IBA1 immunoreactive microglia (Ionized calcium-binding adaptor molecule 1), also called allograft inflammatory factor 1 (AIF 1), is a well-established marker for microglia/macrophages), increased microglial density with ameboid shape, decreased number of branches and junctions and increased the major histocompatibility complex (MHC) II expression (Norden *et al*., 2016). Also, we observed an elevation in the pro-inflammatory cytokine levels TNF-α and IL6 in the Hippocampus of ICV palmitate-infused mice. Liraglutide induced the neuroprotective microglial phenotype, characterized by an increased microglia complexity (enlarged Feret's diameter, a measure of an object's size along a specified direction -- in general, it can be defined as the distance between the two parallel planes restricting the object perpendicular to that direction). Liraglutide also improved the number of cell junctions and processes and lower circularity, accompanied by a significant reduction in TNF-α and IL6 expressions. The study suggested that liraglutide is a suitable treatment against palmitate-induced neuroinflammation, which is characterized by reactive microgliosis and astrogliosis, as well as increased pro-inflammatory cytokines, which has been described as one of the primary causes of several pathologies of the CNS (Vianna *et al*., 2017).

Table 1. Current scenario of the GLP-1 receptor agonists.

Drug	Class	Structure	Status (approved for)	References
Albiglutide	GLP-1RA	GLP-1	T2DM (2014)	(Davis *et al*., 2015)
Cotadutide	Dual agonist	GLP-1/ Glucagon	In development (fatty liver?)	(Spezani *et al*., 2022)
Dulaglutide	GLP-1RA	GLP-1	T2DM (2014)	(Thompson *et al*., 2016)
Exenatide	GLP-1RA	GLP-1	T2DM (2005)	(Kolterman *et al*., 2005)
Liraglutide	GLP-1RA	GLP-1	T2DM (2009), Obesity (2014)	(Damholt *et al*., 2006; Pi-Sunyer *et al*., 2015)
Retatrutide	Triple agonist	GLP-1/GIP/ Glucagon	In development	(Dissanayake *et al*., 2024)
Semaglutide	GLP-1RA	GLP-1	T2DM (2017), Obesity (2021)	(Singh *et al*., 2022a)
Tirzepatide	Dual agonist	GLP-1/GIP	T2DM (2023), Obesity (2023)	(Dissanayake *et al*., 2024)

Dulaglutide is another GLP-1RA with 90 % similarity to endogenous GLP-1 and a superior effect to Exenatide, similar to Liraglutide (Thompson & Trujillo, 2016). Furthermore, Albiglutide, like Dulaglutide, another GLP-1RA approved for treating T2DM in 2014, is administered once a week, offering an advantage over previous GLP-1RAs (Davis *et al*., 2015; Thompson & Trujillo, 2016). About six years after the approval of the first GLP-1RA for treating obesity, in 2021, Semaglutide became the second agonist approved for weight maintenance (Davies *et al*., 2021; Singh *et al*., 2022a).

Combinations of the GLP-1 with other peptides were developed to enhance the management of these comorbidities, such as glucagon (GLP-1/Glucagon, Cotadutide) (Spezani & Mandarim-de-Lacerda, 2022) and GIP (glucose-dependent insulinotropic polypeptide, GIP/GLP-1, Tirzepatide) (Reis-Barbosa *et al*., 2024a; Reis-Barbosa *et al*., 2024b). Tirzepatide was approved in 2023 for treating T2DM and obesity, but Cotadutide remains in the study (Dissanayake & Somasundaram, 2024). Currently, triple agonism (GLP-1/GIP/Glucagon) is being developed (Retatrutide, Lilly Corporate Center, Indianapolis, IN, USA) (Harris, 2023; Sanyal *et al*., 2024).

In obesity, decreasing GLP-1RA in POMC neurons reduces satiety signals and weight gain by diminishing the action potentials in the neurons (Martine *et al*., 2023). GLP-1RAs act directly on POMC/CART (cocaine- and amphetamine-regulated transcript) and NPY/AgRP neurons and alter action potential frequencies, thereby inhibiting or stimulating the expression of these neuropeptides (Joly-Amado *et al*., 2014). The incubation of POMC/CART neurons with Liraglutide seems to stimulate excitatory synapses, while the incubation of NPY/AgRP stimulates inhibitory synapses (Dong *et al*., 2021).

A central component for the action of these agonists is the receptor TrpC5, which increases intracellular calcium and, consequently, releases neurotransmitters (He *et al*., 2019). POMC neurons with LepR that did not express TrpC5 fail to alter the resting membrane potential in response to Liraglutide, resulting in the absence of depolarization (Smith *et al*., 2019). POMC and NPY neurons seem to rely on TrpC5 to be influenced by GLP-1Ras. In addition, NPY also depends on ATP-sensitive potassium channels (KATP channels) (Dong *et al*., 2021) (Fig. 5).

The inhibition of GABAA receptors prevents the action of GLP-1RAs on NPY/AgRP neurons, suggesting that such agonists indirectly decrease the expression of NPY/AgRP by exciting presynaptic GABAergic neurons (Biglari *et al*., 2021). In POMC/CART neurons, GLP-1RAs appear to act directly and indirectly, as both the inhibition of GABAergic signaling and glutamatergic signaling did not prevent the action of these agonists (Chivite *et al*., 2021). Furthermore, increased c-Fos protein expression is also essential for neural activity activation (Abtahi *et al*., 2019). In mice, the cerebroventricular administration of Exendin-4 (Ex-4) increases the c-Fos expression in ARC and PVN neurons (Abtahi *et al*., 2019).

6. FINAL REMARKS

There is a high complexity in the neural circuits involved in appetite regulation, highlighting the interaction between peripheral and central signals mediated by neuropeptides and hormones. The role of GLP-1 on the GLP-1 receptors is essential in regulating eating behavior in the hypothalamus' ARC and PVN. Therefore, the anorexigenic and orexigenic pathways are modulated via POMC/CART and NPY/AgRP, respectively. Furthermore, GLP-1RAs, such as Liraglutide, Dulaglutide, or Semaglutide, strongly affect these pathways, reinforcing their therapeutic potential. However, the interaction between GLP-1 and other peptides, such as ghrelin, GIP, and leptin, highlights the complexity of regulating eating behavior.

The link between metabolic dysfunctions and neurodegenerative diseases, parallel to pursuing new therapeutic strategies to regulate food intake, stimulates a deeper understanding of the mechanisms involved. The new drugs in development usually combine GLP-1 with other peptides, such as GIP and glucagon. It is expected that this movement will continue, and more effective drugs, which can be administered for longer periods, are more affordable, and have fewer side effects, will become available.

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CONFLICT OF INTEREST STATEMENT

None of the authors has personal conflicts of interest and have not received payments for their work on this study.

FABIANO, M. M.; AGUILA, B. M & MANDARIM-DE-LACERDA, C. A. El hipotálamo y el hipocampo son albos de nuevos fármacos que controlan el equilibrio energético y tratan la diabetes mellitus tipo 2, la obesidad y las enfermedades neurodegenerativas.. *Int. J. Morphol., 43(1)*:182-193, 2025.

RESUMEN: El GLP-1 es una incretina secretada por las células intestinales y las neuronas del tronco encefálico, que controla los niveles de glucosa y la ingesta de alimentos (apetito y saciedad). Los agonistas del receptor de péptidos similares al glucagón tipo 1 (GLP-1RAs), como monoterapia o combinados con otras moléculas, están indicados para tratar la diabetes mellitus tipo 2 (T2DM) y la obesidad porque actúan sobre la célula beta pancreática y la producción de insulina y provocan pérdida de peso. Sin embargo, la acción central y las vías neuronales a través de las cuales actúan los GLP-1Ras deben comprenderse mejor. La proopiomelanocortina (POMC) y el neuropéptido Y (NPY) son neuropéptidos críticos que participan intrínsecamente en la vía de señalización que regula el apetito y la saciedad a través del GLP-1 y sus agonistas. En particular, el enfoque para combatir la obesidad podría ser bloquear la estimulación de las vías orexigénicas e inhibir las vías anorexigénicas. Por tanto, debido a la alta complejidad de los circuitos neuronales implicados en la señalización del apetito y la saciedad y a las múltiples acciones de los GLP-1RAs, aún es necesario realizar más investigaciones para dilucidar estos mecanismos. Además, la DM2 y la obesidad se asocian a la neuroinflamación y la activación de la microglia, lo que genera un entorno favorable para el desarrollo de enfermedades neurodegenerativas, como la enfermedad de Alzheimer y la enfermedad de Parkinson. En este caso, el hipocampo es la diana privilegiada. En este texto, revisamos los principales puntos relacionados con la localización hipotalámica e hipocampal y las vías de activación de las neuronas POMC y NPY que son dianas de los GLP-1RAs y han demostrado un tratamiento farmacológico eficaz que ha cambiado la perspectiva de la evolución de la DM2 y la obesidad.

PALABRAS CLAVE: Hipotálamo; Hipocampo; Neuronas POMC; Neuronas NPY; GLP-1.

REFERENCES

Abtahi, S.; Howell, E.; Salvucci, J. T.; Bastacky, J. M. R.; Dunn, D.P. & Currie, P. J. Exendin-4 antagonizes the metabolic action of acylated ghrelinergic signaling in the hypothalamic paraventricular nucleus. *Gen. Comp. Endocrinol., 270*: 75-81, 2019 (doi: 10.1016/j.ygcen.2018.10.008).

Aguila, M. B.; Santos, C. F.; Pinheiro, A. R. P.; Faria, T. S. & Mandarim-de-Lacerda, C. A. 2010. *Hepatic insulin resistance and nonalcoholic fatty liver disease.* In: Molière, J. & Gauthier, L., editors. Insulin resistance: symptoms, causes and treatment (book). Hauppauge, NY: Nova Science Pu. p 1-44.

Amidfar, M.; Askari, G. & Kim, Y. K. Association of metabolic dysfunction with cognitive decline and Alzheimer's disease: A review of metabolomic evidence. *Prog. Neuropsychopharmacol. Biol. Psychiatry, 128*:110848, 2024 (doi: 10.1016/j.pnpbp.2023.110848).

Arnold, S. E.; Arvanitakis, Z.; Macauley-Rambach, S. L.; Koenig, A. M.; Wang, H.Y.; Ahima, R. S.; Craft, S.; Gandy, S.; Buettner, C.; Stoeckel, L. E.; Holtzman, D. M. & Nathan, D.M. Brain insulin resistance in type 2 diabetes and Alzheimer disease: concepts and conundrums. *Nat. Rev. Neurol., 14*:168-81, 2018 (doi: 10.1038/nrneurol.2017.185).

Athauda, D. & Foltynie, T. The glucagon-like peptide 1 (GLP) receptor as a therapeutic target in Parkinson's disease: mechanisms of action. *Drug Discov. Today, 21*:802-18, 2016 (doi: 10.1016/j.drudis.2016.01.013).

Baset, A. & Huang, F. Shedding light on subiculum's role in human brain disorders. *Brain Res. Bull., 214*:110993, 2024 (doi: 10.1016/j.brainresbull.2024.110993).

Bharadwaj, P.; Wijesekara, N.; Liyanapathirana, M.; Newsholme, P.; Ittner, L.; Fraser, P. & Verdile, G. The Link between Type 2 Diabetes and Neurodegeneration: Roles for Amyloid-beta, Amylin, and Tau Proteins. *J. Alzheimers Dis., 59*:421-32, 2017 (doi: 10.3233/JAD-161192).

Biglari, N.; Gaziano, I.; Schumacher, J.; Radermacher, J.; Paeger, L.; Klemm, P.; Chen, W.; Corneliussen, S.; Wunderlich, C.M.; Sue, M.; Vollmar, S.; Klockener, T.; Sotelo-Hitschfeld, T.; Abbasloo, A.; Edenhofer, F.; Reimann, F.; Gribble, F.M.; Fenselau, H.; Kloppenburg, P.; Wunderlich, F.T. & Bruning, J.C. Functionally distinct POMC-expressing neuron subpopulations in hypothalamus revealed by intersectional targeting. *Nat. Neurosci., 24*:913-29, 2021 (doi: 10.1038/s41593-021-00854-0).

Boutari, C.; DeMarsilis, A. & Mantzoros, C. S. Obesity and diabetes. *Diabetes Res. Clin. Pract., 202*:110773, 2023 (doi: 10.1016/j.diabres.2023.110773).

Cariou, B.; Byrne, C. D.; Loomba, R. & Sanyal, A. J. Nonalcoholic fatty liver disease as a metabolic disease in humans: A literature review. *Diabetes Obes. Metab., 23*:1069-83, 2021 (doi: 10.1111/dom.14322).

Chivite, M.; Naderi, F.; Conde-Sieira, M.; Soengas, J. L.; Lopez-Patino, M. A. & Miguez, J. M. Central serotonin participates in the anorexigenic effect of GLP-1 in rainbow trout (*Oncorhynchus mykiss*). *Gen. Comp. Endocrinol., 304*:113716, 2021 (doi: 10.1016/j.ygcen.2021.113716).

Coelho, C. A. O.; Mocle, A. J.; Jacob, A. D.; Ramsaran, A. I.; Rashid, A. J.; Kohler, S.; Josselyn, S. A. & Frankland, P.W. Dentate gyrus ensembles gate context-dependent neural states and memory retrieval. S*ci. Adv., 10*:eadn9815, 2024 (doi: 10.1126/sciadv.adn9815).

Dalvi, P. S.; Chalmers, J. A.; Luo, V.; Han, D. Y.; Wellhauser, L.; Liu, Y.; Tran, D. Q.; Castel, J.; Luquet, S.; Wheeler, M. B. & Belsham, D. D. High fat induces acute and chronic inflammation in the hypothalamus: effect of high-fat diet, palmitate and TNF-alpha on appetite-regulating NPY neurons. *Int. J. Obes. (Lond),41*:149-58, 2017 (doi: 10.1038/ijo.2016.183).

Davies, M.; Faerch, L.; Jeppesen, O. K.; Pakseresht, A.; Pedersen, S. D.; Perreault, L.; Rosenstock, J.; Shimomura, I.; Viljoen, A.; Wadden, TA; Lingvay, I. & Group, S.S. Semaglutide 2.4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. *Lancet, 397*:971-84, 2021 (doi: 10.1016/S0140-6736(21)00213-0).

Davis, P. N.; Ndefo, U. A.; Oliver, A. & Payton, E. Albiglutide: A once-weekly glucagon-like peptide-1 receptor agonist for type 2 diabetes mellitus. *Am. J. Health Syst. Pharm., 72*:1097-103, 2015 (doi: 10.2146/ajhp140260).

Di Lorenzo, D. Tau Protein and Tauopathies: Exploring Tau Protein-Protein and Microtubule Interactions, Cross-Interactions and Therapeutic Strategies. *ChemMedChem*:e202400180, 2024 (doi: 10.1002/cmdc.202400180).

Dissanayake, H. A. & Somasundaram, N. P. Polyagonists in Type 2 Diabetes Management. *Curr. Diab. Rep., 24*:1-12, 2024 (doi: 10.1007/s11892-023-01530-2).

Dong, Y.; Carty, J.; Goldstein, N.; He, Z.; Hwang, E.; Chau, D.; Wallace, B.; Kabahizi, A.; Lieu, L.; Peng, Y.; Gao, Y.; Hu, L.; Betley, J. N. & Williams, K. W. Time and metabolic state-dependent effects of GLP-1R agonists on NPY/AgRP and POMC neuronal activity *in vivo. Mol Metab, 54*:101352, 2021 (doi: 10.1016/j.molmet.2021.101352).

Furman, B.L. The development of Byetta (exenatide) from the venom of the Gila monster as an anti-diabetic agent. *Toxicon, 59*:464-71, 2012 (doi: 10.1016/j.toxicon.2010.12.016).

Garcia-Serrano, A. M.; Mohr, A. A.; Philippe, J.; Skoug, C.; Spegel, P. & Duarte, J. M. N. Cognitive Impairment and Metabolite Profile Alterations in the Hippocampus and Cortex of Male and Female Mice Exposed to a Fat and Sugar-Rich Diet are Normalized by Diet Reversal. *Aging Dis., 13*:267-83, 2022 (doi: 10.14336/AD.2021.0720).

Georgescu, T.; Lyons, D.; Doslikova, B.; Garcia, A. P.; Marston, O.; Burke, L. K.; Chianese, R.; Lam, B. Y. H.; Yeo, G. S. H.; Rochford, J. J.; Garfield, A. S. & Heisler, L. K. Neurochemical Characterization of Brainstem Pro-Opiomelanocortin Cells. *Endocrinology, 161*, 2020 (doi: 10.1210/endocr/bqaa032).

Hall, M. B.; Habash, N. M.; Haas, N. A. & Schwarz, J. M. A method for the selective depletion of microglia in the dorsal Hippocampus in the juvenile rat brain. *J. Neurosci. Methods, 374*:109567, 2022 (doi: 10.1016/j.jneumeth.2022.109567).

Halliday, G. M.; Macdonald, V. & Henderson, J.M. A comparison of degeneration in motor thalamus and cortex between progressive supranuclear palsy and Parkinson's disease. *Brain, 128*:2272-80, 2005 (doi: 10.1093/brain/awh596).

Hansen, H. H.; Gronlund, R.V.; Baader-Pagler, T.; Haebel, P.; Tammen, H.; Larsen, L. K.; Jelsing, J.; Vrang, N. & Klein, T. Characterization of combined linagliptin and Y2R agonist treatment in diet-induced obese mice. *Sci. Rep., 11*:8060, 2021 (doi: 10.1038/s41598-021-87539-7).

Harris, E. Triple-Hormone Combination Retatrutide Induces 24% Body Weight Loss. *JAMA, 330*:306, 2023 (doi: 10.1001/jama.2023.12055).

He, Z.; Gao, Y.; Lieu, L.; Afrin, S.; Cao, J.; Michael, N. J.; Dong, Y.; Sun, J.; Guo, H. & Williams, K. W. Direct and indirect effects of liraglutide on hypothalamic POMC and NPY/AgRP neurons - Implications for energy balance and glucose control. *Mol. Metab., 28*:120-34, 2019 (doi: 10.1016/j.molmet.2019.07.008).

Huang, X.; Hu, S. S.; Zhang, Q. L.; Han, X. M.; Chen, Z. G.; Nie, R. Z.; Cao, X.; Yuan, D. H.; Long, Y.; Hong, H. & Tang, S. S. A circuit from lateral hypothalamic to dorsal hippocampal dentate gyrus modulates behavioral despair in mice. *Cereb. Cortex, 34*, 2024 (doi: 10.1093/cercor/bhae399).

Jangra, V. & Tople, J. Can Alzheimer's Disease Be Secondary to Type-2 Diabetes Mellitus? *Cureus, 14*:e31273, 2022 (doi: 10.7759/cureus.31273).

Joly-Amado, A.; Cansell, C.; Denis, R.G.; Delbes, A.S.; Castel, J.; Martinez, S. & Luquet, S. The hypothalamic arcuate nucleus and the control of peripheral substrates. B*est Pract. Res. Clin. Endocrinol. Metab., 28:*725-37, 2014 (doi: 10.1016/j.beem.2014.03.003).

Karimani, F.; Asgari Taei, A.; Abolghasemi-Dehaghani, M. R.; Safari, M. S. & Dargahi, L. Impairment of entorhinal cortex network activity in Alzheimer's disease. *Front. Aging Neurosci., 16*:1402573, 2024 (doi: 10.3389/fnagi.2024.1402573).

Kolterman, O. G.; Kim, D. D.; Shen, L.; Ruggles, J.A.; Nielsen, L. L.; Fineman, M. S. & Baron, A. D. Pharmacokinetics, pharmacodynamics, and safety of exenatide in patients with type 2 diabetes mellitus. *Am. J. Health Syst .Pharm., 62*:173-81, 2005 (doi: 10.1093/ajhp/62.2.173).

Ladenheim, E. E. Liraglutide and obesity: a review of the data so far. *Drug Des. Devel. Ther., 9*:1867-75, 2015 (doi: 10.2147/DDDT.S58459).

Lantero-Rodriguez, J.; Camporesi, E.; Montoliu-Gaya, L.; Gobom, J.; Piotrowska, D.; Olsson, M.; Burmann, I.M.; Becker, B.; Brinkmalm, A.; Burmann, B. M.; Perkinton, M.; Ashton, N. J.; Fox, N. C.; Lashley, T.; Zetterberg, H.; Blennow, K. & Brinkmalm, G. Tau protein profiling in tauopathies: a human brain study. *Mol. Neurodegener., 19*: 54, 2024 (doi: 10.1186/s13024-024-00741-9).

Lee, N. J.; Oraha, J.; Qi, Y.; Enriquez, R. F.; Tasan, R. & Herzog, H. Altered function of arcuate leptin receptor expressing neuropeptide Y neurons depending on energy balance. *Mol. Metab., 76*:101790, 2023 (doi: 10.1016/j.molmet.2023.101790).

Lin, L.; Basu, R.; Chatterjee, D.; Templin, A. T.; Flak, J. N. & Johnson, T.S. Disease-associated astrocytes and microglia markers are upregulated in mice fed high fat diet. *Sci. Rep., 13*:12919, 2023 (doi: 10.1038/s41598-023-39890-0).

Lopez-Gambero, A. J.; Pacheco-Sanchez, B.; Rosell-Valle, C.; Medina-Vera, D.; Navarro, J. A.; Fernandez-Arjona, M. D. M.; de Ceglia, M.; Sanjuan, C.; Simon, V.; Cota, D.; Rivera, P.; Rodriguez de Fonseca, F. & Suarez, J. Dietary administration of D-chiro-inositol attenuates sex-specific metabolic imbalances in the 5xFAD mouse model of Alzheimer's disease. *Biomed. Pharmacother., 150*:112994, 2022 (doi: 10.1016/j.biopha.2022.112994).

Lopez-Gambero, A. J.; Rosell-Valle, C.; Medina-Vera, D.; Navarro, J. A.; Vargas, A.; Rivera, P.; Sanjuan, C.; Rodriguez de Fonseca, F. & Suarez, J. A Negative Energy Balance Is Associated with Metabolic Dysfunctions in the Hypothalamus of a Humanized Preclinical Model of Alzheimer's Disease, the 5XFAD Mouse. *Int. J. Mol. Sci., 22*, 2021 (doi: 10.3390/ijms22105365).

Low, K.; Roulin, A. & Kunz, S. A proopiomelanocortin-derived peptide sequence enhances plasma stability of peptide drugs. *FEBS Lett., 594*: 2840-66, 2020 (doi: 10.1002/1873-3468.13855).

Marinho, T. S.; Fabiano, M. M.; Aguila, M. B. & Mandarim-de-Lacerda, C. A. Principal components analysis on genes related to inflammasome complex and microglial activation in the hypothalamus of obese mice treated with semaglutide (GLP-1 analog). *Brain Res., 1846*:149225, 2024 (doi: 10.1016/j.brainres.2024.149225).

Martine, F. F.; Reis, T.; Marinho, T. S.; Aguila, M. B. & Mandarim-de-Lacerda, C.A. Hypothalamic anorexigenic signaling pathways (leptin, amylin, and proopiomelanocortin) are semaglutide (GLP-1 analog) targets in obesity control in mice. *Life Sci., 313*:121268, 2023 (doi: 10.1016/j.lfs.2022.121268).

Mercer, A. & Thomson, A. M. Cornu Ammonis Regions-Antecedents of Cortical Layers? *Front. Neuroanat., 11*:83, 2017 (doi: 10.3389/fnana.2017.00083).

Nauck, M. A.; Quast, D. R.; Wefers, J. & Meier, J. J. GLP-1 receptor agonists in the treatment of type 2 diabetes - state-of-the-art. *Mol. Metab., 46*: 101102, 2021 (doi: 10.1016/j.molmet.2020.101102).

Nguyen, D.; Wang, G.; Wafa, T.; Fitzgerald, T. & Gu, Y. The medial entorhinal cortex encodes multisensory spatial information. *Cell Rep., 43*:114813, 2024 (doi: 10.1016/j.celrep.2024.114813).

Norden, D. M.; Trojanowski, P. J.; Villanueva, E.; Navarro, E. & Godbout, J. P. Sequential activation of microglia and astrocyte cytokine expression precedes increased Iba-1 or GFAP immunoreactivity following systemic immune challenge. *Glia, 64*:300-16, 2016 (doi: 10.1002/glia.22930).

Oliva, A.; Fernandez-Ruiz, A.; Buzsaki, G. & Berenyi, A. Spatial coding and physiological properties of hippocampal neurons in the Cornu Ammonis subregions. *Hippocampus, 26*:1593-607, 2016 (doi: 10.1002/hipo.22659).

Peterfi, Z.; Szilvasy-Szabo, A.; Farkas, E.; Ruska, Y.; Pyke, C.; Knudsen, L.B. & Fekete, C. Glucagon-Like Peptide-1 Regulates the Proopiomelanocortin Neurons of the Arcuate Nucleus both Directly and Indirectly via Presynaptic Action. *Neuroendocrinology, 111*:986-97, 2021 (doi: 10.1159/000512806).

Rakhat, Y.; Kaneko, K.; Wang, L.; Han, W.; Seino, Y.; Yabe, D. & Yada, T. d-Allulose Inhibits Ghrelin-Responsive, Glucose-Sensitive and Neuropeptide Y Neurons in the Arcuate Nucleus and Central Injection Suppresses Appetite-Associated Food Intake in Mice. *Nutrients, 14*, 2022 (doi: 10.3390/nu14153117).

Reis-Barbosa, P. H.; Aguila, M. B. & Mandarim-de-Lacerda, C.A. Tirzepatide, a dual receptor agonist of glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1, enhances beta-cell survival and maintenance markers in obese diabetic ovariectomized mice. *Diabetes Obes. Metab*., n/a, 2024a (doi: 10.1111/dom.15937).

Reis-Barbosa, P. H.; Marcondes-de-Castro, I.; Marinho, T. S.; Aguila, M. B. & Mandarim-de-Lacerda, C. A. The dual glucose-dependent insulinotropic polypeptide/glucagon-like peptide-1 receptor agonist tirzepatide effects on body weight evolution, adiponectin, insulin and leptin levels in the combination of obesity, type 2 diabetes and menopause in mice. *Diabetes Obes. Metab., 26*:4613-21, 2024b (doi: 10.1111/dom.15820).

Rohm, T. V.; Meier, D. T.; Olefsky, J. M. & Donath, M.Y. Inflammation in obesity, diabetes, and related disorders. *Immunity, 55*:31-55, 2022 (doi: 10.1016/j.immuni.2021.12.013).

Sanyal, A. J.; Kaplan, L. M.; Frias, J. P.; Brouwers, B.; Wu, Q.; Thomas, M. K.; Harris, C.; Schloot, N. C.; Du, Y.; Mather, K. J.; Haupt, A. & Hartman, M. L. Triple hormone receptor agonist retatrutide for metabolic dysfunction-associated steatotic liver disease: a randomized phase 2a trial. *Nat. Med., 30*: 037-48, 2024 (doi: 10.1038/s41591-024-03018-2).

Shan, Y.; Tan, S.; Lin, Y.; Liao, S.; Zhang, B.; Chen, X.; Wang, J.; Deng, Z.; Zeng, Q.; Zhang, L.; Wang, Y.; Hu, X.; Qiu, W.; Peng, L. & Lu, Z. The glucagon-like peptide-1 receptor agonist reduces inflammation and blood-brain barrier breakdown in an astrocyte-dependent manner in experimental stroke. *J. Neuroinflammation, 16*:242, 2019 (doi: 10.1186/s12974-019-1638-6).

Shobatake, R.; Itaya-Hironaka, A.; Yamauchi, A.; Makino, M.; Sakuramoto-Tsuchida, S.; Uchiyama, T.; Ota, H.; Takahashi, N.; Ueno, S.; Sugie, K. & Takasawa, S. Intermittent Hypoxia Up-Regulates Gene Expressions of Peptide YY (PYY), Glucagon-like Peptide-1 (GLP-1), and Neurotensin (NTS) in Enteroendocrine *Cells. Int. J. Mol. Sci., 20*, 2019 (doi: 10.3390/ijms20081849).

Singh, G.; Krauthamer, M. & Bjalme-Evans, M. Wegovy (semaglutide): a new weight loss drug for chronic weight management. *J. Investig. Med., 70*:5-13, 2022a (doi: 10.1136/jim-2021-001952).

Singh, I.; Wang, L.; Xia, B.; Liu, J.; Tahiri, A.; El Ouaamari, A.; Wheeler, M. B. & Pang, Z. P. Activation of arcuate nucleus glucagon-like peptide-1 receptor-expressing neurons suppresses food intake. *Cell Biosci., 12*: 178, 2022b (doi: 10.1186/s13578-022-00914-3).

Smith, N. K.; Hackett, T. A.; Galli, A. & Flynn, C. R. GLP-1: Molecular mechanisms and outcomes of a complex signaling system. *Neurochem. Int., 128*:94-105, 2019 (doi: 10.1016/j.neuint.2019.04.010).

Spezani, R. & Mandarim-de-Lacerda, C.A. The current significance and prospects for the use of dual receptor agonism GLP-1/Glucagon. *Life Sci., 288*:120188, 2022 (doi: 10.1016/j.lfs.2021.120188).

Spezani, R.; Silva, R. R.; Martine, F. F.; Marinho, T. S. ; Aguila, M. B. & Mandarim-de-Lacerda, C. A. Intermittent fasting, adipokines, insulin sensitivity, and hypothalamic neuropeptides in a dietary overload with high-fat or high-fructose diet in mice. *J. Nutr. Biochem., 83*:108419, 2020 (doi: 10.1016/j.jnutbio.2020.108419).

Sun, E. W.; Iepsen, E.W.; Pezos, N.; Lumsden, A. L.; Martin, A. M.; Schober, G.; Isaacs, N. J.; Rayner, C. K.; Nguyen, N.Q.; de Fontgalland, D.; Rabbitt, P.; Hollington, P.; Wattchow, D. A.; Hansen, T.; Holm, J. C.; Liou, A. P.; Jackson, V. M.; Torekov, S. S.; Young, R. L. & Keating, D.J. A Gut-Intrinsic Melanocortin Signaling Complex Augments L-Cell Secretion in Humans. *Gastroenterology, 161*:536-47 e2, 2021 (doi: 10.1053/j.gastro.2021.04.014).

Thakkar, R.; Wang, R.; Wang, J.; Vadlamudi, R.K. & Brann, D.W. 17beta-Estradiol Regulates Microglia Activation and Polarization in the Hippocampus Following Global Cerebral Ischemia. Oxid Med Cell Longev, 2018: 4248526, 2018 (doi: 10.1155/2018/4248526).

Thompson, A.M. & Trujillo, J.M. Advances in the treatment of type 2 diabetes: impact of dulaglutide. Diabetes Metab Syndr Obes, 9: 125-36, 2016 (doi: 10.2147/DMSO.S75452).

Thorens, B.; Porret, A.; Buhler, L.; Deng, S.P.; Morel, P. & Widmann, C. Cloning and functional expression of the human islet GLP-1 receptor. Demonstration that exendin-4 is an agonist and exendin-(9-39) an antagonist of the receptor. Diabetes, 42: 1678-82, 1993 (doi: 10.2337/diab.42.11.1678).

Vianna, ARB; Aguila, M.B. & Mandarim-de-Lacerda, C.A. Effects of liraglutide in hypothalamic arcuate nucleus of obese mice. Obesity (Silver Spring), 24: 626-33, 2016 (doi: 10.1002/oby.21387).

Vianna, ARB; Aguila, M.B. & Mandarim-de-Lacerda, C.A. Beneficial effects of liraglutide (GLP1 analog) in the hippocampal inflammation. Metab Brain Dis, 32: 1735-45, 2017 (doi: 10.1007/s11011-017-0059-4).

Viellard, J.M.A.; Melleu, F.F.; Tamais, A.M.; de Almeida, A.P.; Zerbini, C.; Ikebara, J.M.; Domingues, K.; de Lima,M.A.X.; Oliveira, F.A.; Motta, S.C. & Canteras, N.S. A subiculum-hypothalamic pathway functions in dynamic threat detection and memory updating. Curr Biol, 34: 2657-71 e7, 2024 (doi: 10.1016/j.cub.2024.05.006).

Yang, Y. & Xu, Y. The central melanocortin system and human obesity. J Mol Cell Biol, 12: 785-97, 2020 (doi: 10.1093/jmcb/mjaa048).

Yermek, R.; Wang, L.; Kaneko, K.; Han, W.; Seino, Y.; Yabe, D. & Yada, T. D-Allulose cooperates with glucagon-like peptide-1 and activates proopiomelanocortin neurons in the arcuate nucleus and central injection inhibits feeding in mice. Biochem Biophys Res Commun, 613: 159-65, 2022 (doi: 10.1016/j.bbrc.2022.04.027).

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