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Of mice and men: incretin actions in the central nervous system

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ABSTRACT

Incretins have risen to the forefront of therapies for obesity and related metabolic complications, primarily because of their efficacy and relatively few side effects. Importantly, their efficacy in altering energy balance and decreasing body weight is apparently through actions in the central nervous system (CNS); the latter may have implications beyond obesity per se, i.e. in other disease states associated with obesity including CNS-related disorders. Here, we first describe the role of the CNS in energy homeostasis and then the current state of knowledge in terms of incretin physiology, pathophysiology and efficacy in preclinical and clinical studies. In the future, more clinical studies are needed to fully map mechanistic pathways underlying incretin actions and outcomes in the human CNS. Additionally, future research will likely lead to the discovery of additional novel incretins and/or more efficacious medications with less side effects through the improvement of current compounds with properties that would allow them to have more favorable pharmacokinetic and pharmacodynamic profiles and/or by combining known and novel incretins into safe and more efficacious combination therapies leading ultimately to more tangible benefits for our patients.

Contents

Abbreviations: AD, Alzheimer's Disease; AgRP, agouti-related peptide; AKT, Protein kinase B; BAX, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma 2; BDNF, brain-derived neurotrophic factor; CART, cocaine- and amphetamine- related transcript; CNS, central nervous system; CREB, cAMP-response element binding protein; DM, type 2 diabetes; DPP4, dipeptidyl peptidase 4; fMRI, functional magnetic resonance imaging; GDNF, glial cell-derived neurotrophic factor; GIP, gastric inhibitory peptide or glucose-dependent insulinotropic peptide; GIPR, GIP receptor; GLP-1, glucagon-like peptide 1; GLP-1R, GLP-1 receptor; MAPK, mitogen-activated protein kinase; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MMSE, mini-mental state exam; NAcc, nucleus accumbens; NPY, neuropeptide Y; NTS, nucleus of the tractus solitarius; OFC, orbitofrontal cortex; PD, Parkinson's Disease; PI3K, phosphatidylinositol 3-kinase; POMC, pro-opiomelanocortin; RCT, randomized-placebo controlled trial; SN, substantia nigra; TMTB, Trail Making Test-B; TrkB, Tropomyosin receptor kinase B; US, United States; VTA, ventral tegmental area.

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Obesity is a global health epidemic which affects approximately a third of United States (US) Americans and has a similar prevalence in other westernized countries [1–21]. Obesity can lead to or exacerbate other metabolic diseases, such as type 2 diabetes, liver and renal diseases, cancers, and cardiovascular diseases, leading to about 300,000 deaths each year [22,23]. Considering the rising healthcare costs to treat obesity and its comorbidities, effective treatments are increasingly needed.

To understand and treat obesity, it is critical to understand how the brain integrates environmental and internal inputs to influence appetite, ingestive and exercise behaviors. Indeed, the central nervous system (CNS) is critical for regulating energy homeostasis and, in turn, body weight. Herein, we will first discuss the basic physiological systems at play in the CNS before discussing a new critical hormonal pathway important for the treatment of obesity, i.e. incretins, and what is currently known in terms of the actions of incretins in the CNS.

1. CNS mechanisms of eating behaviors

Current research implicates primarily five CNS systems in the regulation of eating and weight [24]. Beyond the homeostatic system, frequently studied in rodent models, the reward, emotion/memory, attention, and cognitive control systems are also key regulators of energy intake and expenditure especially in humans; the fact that many of these cannot be directly studied in rodents highlights the need for more translational/clinical studies.

The homeostatic system in the brain is primarily based in the hypothalamus, which integrates signals from the periphery into the CNS and regulates functions important for survival such as temperature, eating behavior etc. [25–32]. This system may be most critical for humans in states of starvation as it is rarely implicated in studies with obese humans [24,33,34]. Notably, other cognitive systems feed into the hypothalamus, and the hypothalamus itself may be indirectly controlled by other CNS centers in terms of appetite and eating in humans [24]. These differences highlight the importance of human studies, as rodents have a more simplistic regulation of eating behaviors and may not directly correlate with human CNS findings. Regardless, on the basis of experiments in rodents, the hypothalamus contains two primary classes of neurons which regulate energy intake and expenditure [35]. In the arcuate nucleus of the hypothalamus, pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART) neurons decrease energy intake and increase energy expenditure, while agouti-related protein (AgRP) and neuropeptide Y (NPY) neurons do the opposite [35]. These neurons respond to hormones from the periphery (leptin, ghrelin, incretins) to communicate with the rest of the brain. Given its potentially limited role in humans, however, other, higher cognitive areas may be more important to study.

The reward system, consisting primarily of dopaminergic neurons which project from the ventral tegmental area (VTA)/substantia nigra (SN) to the nucleus accumbens (NAcc), striatum, and orbitofrontal cortex (OFC), is frequently hypothesized as a potential cause for obesity and studied in both rodents and humans [36–56]. Observations of lower dopamine receptor availability in the striatum led to the hypothesis that a hyposensitivity to reward leads individuals to seek highly palatable and rewarding but unhealthy foods and thus become obese [57–61]. Other studies have shown an increased response of the reward system, particularly NAcc and OFC, to food cues, suggesting a hyperresponsivity to food cues and a potential disconnect between expected and actual reward which could then lead to increased seeking of rewarding foods and the development of obesity [62–66]. The reward system also interacts with higher cognitive systems to alter food intake.

Emotion and memory systems also modulate eating behaviors. Depression, anxiety, joy, and anger have all been shown to increase appetite and decrease diet quality [67–72]. The amygdala has repeatedly been shown to be altered in response to food cues, particularly in cases of obesity [73–78]. Similarly, memory may play a role in eating behaviors, interacting with many other brain areas, such as the insula, hypothalamus, and OFC [79–82]. Obesity and memory are likely involved in a cycle where increasing obesity leads to impaired memory which can in turn contribute to increased obesity [83–86].

Attention networks, which include the parietal and visual cortices, are implicated in obesity as obese individuals show attentional bias for food cues, particularly for highly palatable but less nutritious food cues [87–90]. There is also evidence that increased activation of attention-related brain areas corresponds with later weight gain, even in normal weight individuals [66,91]. Thus, there are interactions between attention to food cues and weight status in humans.

Finally, the cognitive control system is an executive system that includes response inhibition, such as stopping oneself from selecting higher calorie and less nutritious food items [24]. Cognitive control is implemented primarily by the prefrontal cortex, including the dorsolateral prefrontal cortex, pre-supplementary motor cortex, and cingulate cortex [92]. Obesity has been linked to poorer inhibitory control and alterations in activations of these areas related to eating behaviors [93–106]. Whether obesity could be caused by or whether it causes poorer inhibitory control remains to be determined.

2. Incretins

Incretins were originally discovered and studied in relation to their actions on glycemia. Initially, gut extracts were shown to reduce urinary sugar levels in patients who had diabetes [107]. The substrates within gut extracts were later purified and named “incretin” by LaBarre in 1929 [108], defined as a gut hormone that stimulates the release of pancreatic hormones. However, it was not until after radioimmunoassays (RIAs) were developed in the 1960s that scientists were able to further study and define incretins, which are now known for their actions to glucose-dependently secrete insulin. As such, they were originally studied for their role in lowering blood sugars and treating diabetes.

Glucagon-like peptide 1 (GLP-1) and gastric inhibitory polypeptide, also known as glucose-dependent insulinotropic polypeptide (GIP), are the currently known incretins, molecules which are secreted by the gut in response to food intake and which regulate insulin and further appetitive behaviors and digestion. Both GLP-1 and GIP are cleaved and inactivated by dipeptidyl peptidase 4 (DPP4) [109,110]. Currently, GLP-1 agonists, which increase GLP-1 past physiological to pharmaceutical levels, and DPP-4 inhibitors, which increase both GLP-1 and GIP at physiological levels in circulation, are being used as treatments for diabetes and/or obesity and differences in outcomes may be related to the resultant physiological or pharmacological levels (Fig. 1). More recently, studies on incretins have been extended to other neurological conditions and disorders (Table 1).

2.1. Incretins: GIP

GIP is secreted by K cells in the small intestine and causes pancreatic islets to secrete insulin in a glucose-dependent manner [111,112]. It binds the GIP receptor (GIPR), which is a G-protein coupled receptor, and it is cleaved by DPP4 quickly after secretion [110,113,114]. GIP levels rise rapidly after ingestion of a mixed meal and respond more to the ingestion of glucose or proteins versus fat [115,116]. Medications that mimic GIP are currently in various stages of the approval process, although none have yet been approved for use in humans.

2.2. Preclinical studies on GIP

GIPR are expressed in the cerebral cortex, hippocampus, olfactory bulb and anterior olfactory nucleus, lateral septal nucleus, subiculum, inferior colliculus, and inferior olive in rats [117,118]. Activation of GIPR in the hippocampus by *n*-acetylated-GIP enhances synaptic plasticity, while blocking of GIPR by a GIP antagonist [(Pro3)GIP] impairs memory in mice [119,120]. In addition, chronic GIP infusion results in faster proliferation of progenitor cells in the hippocampus and dental

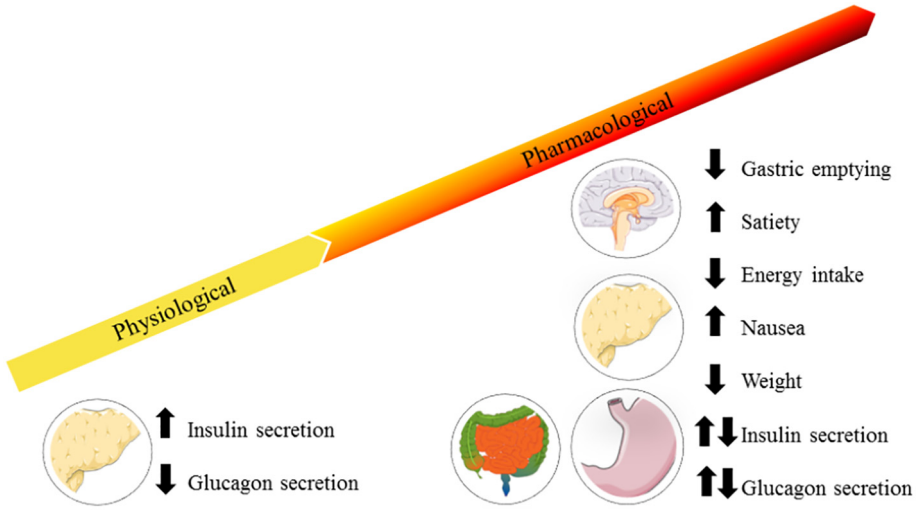

Fig. 1. Physiological and pharmacological effects of incretins, particularly GLP-1 analogues. At physiological levels, incretins increase insulin secretion and decrease glucagon secretion through actions on the pancreas. At pharmacological levels, they appear to also impact weight and appetitive behaviors in other organs, especially the brain or central nervous system (CNS). The illustrations were downloaded from https://smart.servier.com/.

gyrus [117,121], while anti-GIP vaccination results in higher apoptotic rates of hippocampal cells in rats [120].

Neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease (PD), have been linked to desensitization of the insulin receptor and type 2 diabetes. Therefore, GIP analogues in combination to GLP-1 analogues, currently approved for diabetes, represent potential therapeutic strategies for neurodegenerative disorders, if both their function as insulin sensitizers and their previously described beneficial effects in brain function are confirmed in humans. In a mouse model of AD the long-lasting GIP analog D-Ala(2)GIP was found to have neuroprotective and regenerative properties as evidenced by the preservation of synaptic plasticity and the reduction in cognitive decline, amyloid plaque formation, inflammation and oxidative stress in the cortex even at advanced disease stages [122,123]. A triple GLP-1/GIP/glucagon receptor agonist injected daily for 2 months restored the abnormalities in memory associated with AD via reduction of pro-apoptotic and increase in anti-apoptotic signaling as well as promotion of neurogenesis in the dentate gyrus [124]. In a mouse model of PD, chronic administration of a GIP analog (D-Ala2-GIP-glu-PAL) prevented the motor dysfunction and the loss of dopaminergic neurons in the substantia nigra pars compacta (SNc), while decreasing inflammation, oxidative stress, lipid peroxidation and expression of a-synuclein in the SN and striatum [125]. Dual GIP/GLP-1 agonists reversed motor impairment (as per motor coordination and muscle strength tests) and decreased dopamine synthesis, while inducing expression of the Glial Derived Neurotrophic Factor more efficiently than liraglutide, a GLP-1 agonist, alone in a mouse model of PD [126]. However, both drugs reduced inflammatory response to a similar extent [126] (Table 1).

GIP receptor activation in the brain could also potentially play a role in management of Huntington's disease. Administration of D-Ala^{2}GIP, a GIP receptor agonist, to a rodent model of Huntington's improved abnormalities in locomotor activity, movement and neuromuscular coordination as well as short-term episodic memory associated with the disease [127]. The above effects were mediated by decreased lipid peroxidation in brain and restoration of antioxidants and monoamines, i.e. norepinephrine, epinephrine, serotonin, dopamine and their metabolites, in striatum [127]. These studies will need to be expanded into human populations.

2.3. Clinical studies on GIP

To the best of our knowledge, GIPR have not yet been studied in the human brain nor have any drugs which specifically target the actions of GIP been studied in the human CNS. DPP4 inhibitors increase GIP levels and thus may partially reflect the administration of GIP. Notably, there are drugs in development for use in humans which may target GIP, such as the triple GLP-1/glucagon/GIP agonist HM15211 currently in Phase I clinical trials, and thus, future studies may examine effects of GIP in the human CNS.

2.4. Incretins: GLP-1

GLP-1 stimulates insulin secretion from pancreatic islets after it is secreted by the L cells of the lower intestine and colon [128,129]. GLP-1 binds to the GLP-1 receptor (GLP-1R), a G-protein coupled receptor which is found in the pancreas and brain of humans and rodents [130–132]. Like GIP, it is also cleaved rapidly by DPP4 [110,113,114]. Eating mixed meals, glucose, proteins, or fats stimulates rapid GLP-1 secretion from the intestines [115,129]. GLP-1 analogues have been developed by various companies for the treatment of diabetes (exenatide, liraglutide, lixisenatide, albiglutide, dulaglutide, and semaglutide) and more recently for the treatment of obesity with or without diabetes (liraglutide, others potentially forthcoming).

2.5. Indirect incretin actions: DPP4 inhibition

Since DPP4 would normally cleave GLP-1 and GIP after their release, inhibition of DPP4 causes prolonged activity of GLP-1 and GIP at physiological levels [133]. As the inhibition of DPP4 would effectively have the actions of increasing the availability of the active forms of GLP-1 and GIP after a meal, the medications which have these actions effectively act on the same mechanisms as above. However, the effects on glycemia and other studied outcomes tend to be less dramatic [134,135], as the levels of GLP-1 and GIP are at physiological and not pharmaceutical levels (unlike with GLP-1 analogues). We would expect that this would extend to human CNS findings, but the research on cognition is limited. Regardless, several DPP4 inhibitors have been approved for the treatment of diabetes (sitagliptin, vildagliptin, saxagliptin, linagliptin, alogliptin).

2.6. Preclinical studies on GLP-1

GLP-1R is expressed in the CNS of rodents and particularly highly in the area postrema and subfornical organ [136]. A high level of expression has also been observed in some hypothalamic nuclei (paraventricular nucleus, dorsomedial hypothalamic nucleus and

Table 1
Effects of incretin-modifying medications on neurodegenerative disorders.

Disease features	Incretin-based medication	Medication effect	Rodent model	References
Alzheimer's disease (AD)				
b-Amyloid protein plaque formation	D-Ala(2)GIP	↓amyloid plaque formation	Mouse model of AD	Duffy et al., 2013, Faivre et al., 2013 [122,123]
	Liraglutide, exendin-4	↓levels of amyloid-beta protein precursor and mature peptide	Triple transgenic AD mice with and without streptozocin-induced diabetes Mouse model of AD Amyloid beta protein induced AD mouse model Double transgenic mouse model of AD db+/db + male mice	Perry et al., 2003, Li et al., 2010, Gengler 2012, Qi et al., 2016, Chen et al., 2017, Holubova et al., 2019 [163–168]
	Exenatide	↓deposition of beta amyloid in the hypothalamus	Insulin resistant male Wistar albino rats	Gad et al., 2016 [174]
	Linagliptin, saxagliptin, sitagliptin	↓ amyloid beta	Double transgenic mouse model of AD Mouse model of AD Streptozotocin-induced diabetic rat model of AD	D' Amico et al., 2010, Kosaraju et al., 2013, Kosaraju et al., 2017 [206,211,213]
	Vildagliptin	↓ expression of amyloid precursor protein	Rat model of diabetes and AD	Khalaf et al., 2019 [209]
Tau protein hyperphosphorylation	Liraglutide, exendin-4	↓ phosphorylated tau protein levels	db+/db + male mice Triple transgenic AD mice with and without streptozocin-induced diabetes. Triple Transgenic mouse model of AD Amyloid beta protein induced AD mouse model Double transgenic mouse model of AD Mouse model of AD	Perry et al., 2003, Li et al., 2010, Gengler et al., 2012, Kosaraju et al., 2013, Qi et al., 2016, Chen et al., 2017, Kosaraju et al., 2017, Holubova et al., 2019, Khalaf et al., 2019 [163–168,206,209,211]
	Linagliptin, vildagliptin, saxagliptin		Mouse model of AD	
	Sitagliptin	↑tau phosphorylation	OLETF (Otsuka Long Evans Tokushima Fatty) diabetic rats	Kim et al., 2012 [214]
Gliosis and inflammation	Liraglutide	↓ activation of glial cells	Mouse model of AD	Long-Smith et al., 2013 [169]
	Exenatide	↓microglial cell expression	Insulin resistant male Wistar albino rats	Gad et al., 2016 [174]
	Exendin-4	↓oxidative stress	Adult male Wistar albino rats	Abdelwahed et al., 2018 [178]
	Linagliptin	↓inflammation and oxidative stress in the cortex	Mouse model of AD	Duffy et al., 2013, Faivre et al., 2013, Kosaraju et al., 2017 [122,123,206]
	D-Ala(2)GIP		Mouse model of AD	
Impaired neurogenesis	Liraglutide	Promoted neurogenesis in the hippocampus	Mouse model of AD	McClean et al., 2010, Gengler et al., 2012, McGovern et al., 2012, Parthsarathy and Holscher, 2013, Wang et al., 2013, Lennox et al., 2015 [165,170–173,215]
	GLP-1/GIP/glucagon receptor agonist		Double transgenic mouse model of AD	
	Val(8)GLP-1		C57B/16 mouse brain	
	Sitagliptin		male C57Bl/6 J mice	
	Linagliptin	Enhanced differentiation of interneurons and neuroplasticity in the piriform cortex	Goto-Kakizaki rats	Lietzau et al., 2018 [200]
	Vildagliptin	↓ apoptosis of neuronal cells in the hippocampus	rat models of DM	Ma et al., 2018, Zhang et al., 2018 [207,208]
	GIP analogue	faster proliferation of progenitor cells in the hippocampus and dental gyrus	C57Bl/6 mice	Nyberg et al., 2005, Faivre et al., 2012 [117,121]
Impaired synaptic plasticity	liraglutide	Protected against diabetes-induced abnormalities in hippocampal synapses	Young Swiss TO mice Streptozotocin-induced mouse model of DM	Porter et al., 2010, Kong et al., 2018 [179,180]
	Val(8)GLP-1	Enhanced synaptic plasticity in the hippocampus and protected against amyloid-beta- induced synaptic dysfunction	Double transgenic mouse model of AD Wistar rats	McClean et al., 2010, Gengler et al., 2012, Wang et al., 2013 [165,170,171]
	exenatide	activated brain-derived neurotrophic factor (BDNF)- Tropomyosin receptor kinase B (TrkB) neurotrophic axis in the hippocampus, important for synaptic plasticity	Mice with B6;129 genetic background	Bomba et al., 2018 [177]
	Lixisenatide	Counterbalanced the AD-like deficits in synaptic plasticity	Adult male Sprague–Dawley rats	Cai et al., 2014, Cai et al., 2017 [175,176]
	Vildagliptin	Improved hippocampal synaptic plasticity when combined with either decreased caloric intake or SGLT-2 inhibitor	High fat diet fed Wistar rats	Pintana et al., 2016 [199]
	n-acetylated-GIP	Enhances synaptic plasticity	Male Wistar rats	Gault et al., 2008, Tian et al., 2010 [119,120]
	D-Ala(2)GIP, *n*-acetylated-GIP	Preserved synaptic plasticity	Mouse model of AD	Nyberg et al., 2005, Faivre et al., 2012, Duffy et al., 2013, Faivre and Holscher, 2013 [117,121–123]
Memory deficits	Liraglutide	Improved memory and learning	db+/db + male mice Triple Transgenic mouse model of AD Amyloid beta protein induced AD mouse model Double transgenic mouse model of AD	Perry et al., 2003, Li et al., 2010, Gengler et al., 2012, Qi et al., 2016, Chen et al., 2017, Holubova et al., 2019 [163–168]

Table 1 (*continued*)

Disease features	Incretin-based medication	Medication effect	Rodent model	References
	Exenatide	Improved long-term memory and learning	Mice with B6;129 genetic background	Bomba et al., 2018 [177]
	Exendin-4	Improved learning, spatial working memory and locomotor activity	Diabetic rats	Abdelwahed et al., 2018 [178]
	Lixisenatide	Counterbalanced the AD-like deficits in spatial memory	Adult male Sprague–Dawley rats	Cai et al., 2014, Cai et al., 2017 [175,176]
	GLP-1/GIP/glucagon receptor agonist	Restored abnormalities in memory	Double transgenic mouse model of AD	Tai et al., 2018 [124]
	Vildagliptin	Improved memory, learning and cognitive decline and ↑ hippocampal mitochondrial function	Wistar rats	Pintana et al., 2013 [186,187,217]
	Saxagliptin	Improved memory	Streptozotocin-induced diabetic rat model of AD	Kosaraju et al., 2013 [211]
	Sitagliptin	Increased BDNF and hippocampal mitochondrial function; improved working memory and learning; protective against development of memory impairments and cognitive decline	Double transgenic mouse model of AD Diabetic Sprague-Dawley rats Male NIH/OlaHsd mice Mouse model of AD	D'Amico et al., 2010, Sakr 2013, Gault et al., 2015, Dong et al., 2019 [212,213,215,216]
Cognitive decline	Liraglutide	Improved cognitive function	Young Swiss TO mice on high fat diet	Porter et al., 2010, Kong et al., 2018 [179,180]
	Exenatide	Improved cognitive function (as per the eight-radial arm maze task)	Insulin resistant male Wistar albino rats	Gad et al., 2016 [174]
	Exendin-4	↑ expression of BDNF gene and protein levels, associated with cognitive improvement	Adult male Wistar albino rats	Abdelwahed et al., 2018 [178]
	Vildagliptin	attenuated high-fat diet induced cognitive decline	High fat diet fed Wistar rats	Sa-Nguanmoo et al., 2017 [198]
	Linagliptin D-Ala(2)GIP	↓the cognitive decline	Mouse model of AD Female triple transgenic mouse model of AD	Duffy and Holscher, 2013, Faivre and Holscher, 2013, Kosaraju et al., 2017 [122,123,206]
Parkinson's disease (PD)				
Dopaminergic neuron loss	(Val8) GLP-1-glu-PAL	↑the anti-apoptotic Bcl-2 and ↓the pro-apoptotic BAX; ↑ tyrosine hydroxylase levels, thus prevented the reduction in the dopaminergic neurons	1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model of PD	Zhang et al., 2015 [182]
	Semaglutide	counterbalanced the reduction of tyrosine hydroxylase levels, ↓ inflammation and lipid peroxidation and prevented apoptosis in the substantia nigra and striatum	MPTP mouse model of PD	Zhang et al., 2018 [181]
	Sitagliptin	↑ striatal and nigral dopamine, BDNF and dendritic spine density	Rotenone model of PD	Badawi et al., 2017 [184]
	Dual GIP/GLP-1 agonist	Reversed decreased dopamine synthesis; ↓expression of the Glial Derived Neurotrophic Factor (GDNF); ↓inflammation	Mouse model of PD	Yuan et al., 2017 [126]
	D-Ala2-GIP-glu-PAL	prevented the loss of dopaminergic neurons in the substantia nigra pars compacta; ↓ inflammation, oxidative stress and lipid peroxidation in the SNc and striatum	Mouse model of PD	Li et al., 2017 [125]
↑ a-synuclein	D-Ala2-GIP-glu-PAL	↓ expression of a-synuclein in the SNc and striatum	Mouse model of PD	Li et al., 2017 [125]
Motor dysfunction	(Val8) GLP-1-glu-PAL	Prevented motor abnormalities (as per the Rotarod, open field locomotion and swim test)	MPTP mouse model of PD	Zhang et al., 2015 [182]
	Exendin-4	↓L-dopamine induced dyskinesias	6-Hydoxydopamine lesioned rat	Abuirmeileh et al., 2012 [183]
	Saxagliptin	Improved motor control and performance	Adult male Wistar rats	Nassar et al., 2015 [218]
	Sitagliptin	Improved memory task performance and motor performance	Rat model of PD	Li et al., 2018 [219]
	Dual GIP/GLP-1 agonist	Reversed motor impairment (as per motor coordination and muscle strength tests); ↑expression of the GDNF; ↓inflammation	Mouse model of PD	Yuan et al., 2017 [126]
	D-Ala2-GIP-glu-PAL	Prevented motor dysfunction	Mouse model of PD	Li et al., 2017 [125]
Huntington's disease				
Movement disorders Cognitive disorders	D-Ala2GIP	↓lipid peroxidation in brain and restoration of antioxidants, monoamines and metabolites in striatum ➔improved locomotor	Rat model of Huntington's disease	Verma et al., 2018 [127]

(*continued on next page*)

Table 1 (*continued*)

Disease features	Incretin-based medication	Medication effect	Rodent model	References
		activity, movement, neuromuscular coordination and short-term episodic memory		

AD, Alzheimer's disease; db+/db+, diabetic; BAX, beta cell lymphoma 2 associated X protein; Bcl-2, beta cell lymphoma 2; BDNF, brain-derived neurotrophic factor; DM, type 2 diabetes; GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide 1; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; PD, Parkinson's disease activated; TrkB, Tropomyosin receptor kinase B.

arcuate nucleus), the thalamus (ventral thalamic nuclei, paraventricular nucleus, zona incerta, nucleus reuniens, parasubthalamic nucleus, reticular thalamic nucleus, posterior thalamus, parafascicular thalamus and precommissural area), the periaqueductal grey, the mammillary recess, the central nucleus of the amygdala and the caudal hippocampus [136,137]. One study suggested that the piriform and cingulate cortices may express GLP-1R in mice and rats, unlike the rest of the neocortex [136,138].

Central administration of GLP-1 analogues, such as exendin-4, a GLP-1R agonist, inhibits food intake and food rewarding in rodents [139–141]. GLP-1 achieves the above effects by targeting both the homeostatic (hypothalamic nuclei, nucleus of the solitary tract) and hedonic (VTA, Nacc) systems respectively via its receptors and relevant neuron projections throughout the CNS [142–145]. Interestingly, exendin-4 and liraglutide do not only reduce food reward, but also broader tests of reward, reinforcing behavior and locomotor hyperstimulation associated with drugs such as amphetamine, cocaine, alcohol and nicotine by acting on the mesolimbic dopamine system in mice, which suggest a potential role of GLP-1 in management of drug addiction [146–149]. Knowledge of the CNS effects of GLP-1 analogues is expanding across neurological conditions and neurodegenerative disorders.

Various neurotransmitters and neurons are involved in GLP-1-related appetite and body weight regulation, as evidenced by rodent studies. Administration of liraglutide in lean rats decreased meal size and frequency, total food intake, and body weight [150,151]. Intrahypothalamic liraglutide administration for 28 days decreased body weight and fat mass, possibly through increasing expression of the melanocortin 4 receptor gene [152]. Additionally, liraglutide has also been shown to stimulate serotoninergic neurons in dorsal raphe and thus could also act through enhancing the action of serotonin on the hypothalamic serotonergic ($5\text{-}HT_{2A}$) receptors [153]. Liraglutide twice daily for 8 weeks activated the POMC and CART neurons in the arcuate nucleus of the hypothalamus, increased leptin sensitivity, reduced microgliosis and restored the imbalance in pro-apoptotic to anti-apoptotic factors ratio induced by obesity in mice [154]. Injection of exendin-4 either systemically or into the hypothalamic paraventricular nucleus blunted the acyl ghrelin-induced and acyl ghrelin plus NPY-induced increase in respiratory exchange ratio in adult male rats, suggesting an interplay between GLP-1 and ghrelin in the hypothalamus [155].

Liraglutide has been shown to affect energy metabolism in rodents in an age- and duration-dependent manner, changing the activity of complexes I, II, III and IV and creatine kinase in the prefrontal cortex, cerebellum, hippocampus, striatum, hypothalamus and posterior cortex in young vs. adult rats after a single liraglutide shot compared to daily administration for 7 days [156]. Furthermore, liraglutide enhanced the expression of anti-inflammatory markers (interleukin-10, transforming growth factor β, and arginase 1) and decreased reactive gliosis in the hippocampus of pregnant rats subjected to food restriction [157].

Exendin-4 enhanced the ability of neurons to repair DNA damages caused by oxidative stress in a rat model of ischemia [138]. Liraglutide also demonstrates neuroprotective effects when administered to rats after occlusion of the middle cerebral artery, as evidenced by the improved behavioral scores (as per the modified Bederson's test), microvessel density and endothelial cell proliferation, the decrease in size of infarct and reactive oxygen species production as well as upregulation of vascular endothelial growth factor in the cortex [158–160]. The aforementioned beneficial effects were possibly mediated by activation of the phosphatidylinositol 3-kinase (PI3K)/Protein kinase B (AKT) and mitogen-activated protein kinase (MAPK) pathways and are irrespective of glycemic control in rats with diabetes [159,161]. In a rat model of global cerebral ischemia-reperfusion administration of lixisenatide, 1 h and 24 h after reperfusion enhanced the expression of cerebral endothelial nitric oxide synthase and vascular endothelial growth factor [162].

Exendin-4 and liraglutide administered centrally or peripherally in db/db diabetic mice or a mouse model of AD with or without diabetes decreased levels of amyloid-beta protein precursor and mature peptide, a pathognomonic feature of AD, as well as brain phosphorylated tau protein levels, improving learning and memory [163–168]. In addition, liraglutide improved amyloid plaque load and associated abnormalities in insulin signaling, while reduced activation of glial cells in a mouse model of AD after 8 weeks [169]. Furthermore, liraglutide and Val(8) GLP-1, a GLP-1 analog with long half-life, enhanced synaptic plasticity in the hippocampus after 3 weeks of treatment, while Val(8)GLP-1 protected against amyloid-beta- induced synaptic dysfunction and intracellular calcium overload in rats [165,170,171]. Acute and chronic treatment with liraglutide promoted neurogenesis in a mouse model of AD [172], while (Val8)GLP-1 promoted neurogenesis and proliferation of neuronal cells in the dentate gyrus of the hippocampus, without affecting learning and memory after acute and 3-week administration in mice [173].

Exenatide improved cognitive function on the eight-radial arm maze task, as well as decreased the percentage of microglial cell expression and the deposition of amyloid beta in the hypothalamus when administered in insulin-resistant male rats for 8 weeks [174]. Lixisenatide counterbalanced the AD-like deficits in spatial memory and synaptic plasticity as a result of amyloid beta protein injection in rats [175,176]. In addition, activation of Akt-MAPK1/2 signaling pathway and inhibition of the amyloid beta protein-induced intracellular rise of calcium by injection of lixisenatide into the hippocampus seem to confer neuroprotective and cytoprotective effects in the hippocampal cells derived from adult male rats [176].

Exenatide administered for 2 months improved long-term memory, without affecting energy metabolism in brain, and activated brain-derived neurotrophic factor (BDNF)- Tropomyosin receptor kinase B (TrkB) neurotrophic axis in the hippocampus, suggesting that exenatide might play a protective role in the cognitive decline associated with aging [177]. Exendin-4 in diabetic rats improved locomotor activity and spatial working memory compared to untreated rats after 30 days [178]. In addition, they had decreased brain tissue malondialdehyde levels, a marker of oxidative stress and enhanced expression of BDNF gene and increased protein levels, a factor whose decrease is associated with cognitive dysfunction in diabetes [178]. Liraglutide for 28 days conferred a similar protection against diabetes-induced abnormalities in hippocampal synapses, improved cognitive function and enhanced autophagy via the activated protein kinase/mammalian target of rapamycin pathway [179,180].

Semaglutide administered once daily for 7 days improved 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced motor defects, counterbalanced the reduction of tyrosine hydroxylase levels, reduced

the inflammation and lipid peroxidation and prevented apoptosis in the SN and striatum in a mouse model of PD in an equal or superior fashion than liraglutide [181]. In addition, (Val8)GLP-1-glu-PAL administered once daily in an MPTP mouse model of PD prevented the associated motor abnormalities (as per the Rotarod, open field locomotion and swim test) and the reduction in the dopaminergic neurons (i.e. enhanced the levels of tyrosine hydroxylase) in the SN as well as increased Beta cell lymphoma-2 (Bcl-2) and decreased Beta cell lymphoma-2 associated X protein (BAX) after 8 days [182]. Exendin-4 progressively decreased L-dopamine induced dyskinesias co-administered with L-dopamine for 7 days in rats, potentially allowing for the same therapeutic effect in PD but with fewer side effects [183]. In conclusion, the anti-inflammatory, anti-apoptotic and neurotrophic properties of GLP-1 analogues could potentially help slow or prevent the progression of PD [184].

In mouse models of epilepsy, pretreatment with liraglutide for 33 days reduced the severity of seizures and behavioral abnormalities, by decreasing oxidative stress and restoring the brain levels of various neurotransmitters, namely gamma aminobutyric acid (GABA), glutamate, dopamine, norepinephrine, and serotonin and hippocampal BDNF levels [185,186]. In addition, liraglutide once daily decreased the associated oxidative stress and chronic inflammation as evidenced by the increased levels of the anti-apoptotic Bcl-2 and decreased levels of the pro-apoptotic BAX in mitochondria as well as lower numbers of activated microglial cells and astrocytes and lower levels of Tumor Necrosis Factor-α and Interleukin-1ß in the hippocampus respectively [187]. This may suggest that GLP-1 analogues could be helpful in treating seizures and epilepsy.

2.7. Preclinical studies on DPP4 inhibition

Administration of linagliptin, a DPP4 inhibitor, after transient cerebral ischemia in db/db mice, restored cognitive decline and atrophy in hippocampus and cortex, as well as decreased oxidative stress and reactive microgliosis, highlighting the potential importance of DPP4 inhibitors in counteracting the cognitive impairment after vascular complications due to diabetes [188]. Linagliptin has also been suggested to be neuroprotective by marginally decreasing stroke volume and significantly increasing number of surviving neurons by 30% when administered chronically in rodents before the incidence of stroke, but not acutely after the stroke [189]. In a recent mouse study, linagliptin improved cognitive outcomes after ischemic brain injury by increasing the brain levels of the stromal cell- derived factor-1α, a DPP4 substrate [190]. In addition, pretreatment with vildagliptin, another DPP4 inhibitor, resulted in a dose-dependent neuroprotection by decreasing the area of infarction and the loss of neurons and exerting antioxidant and anti-apoptotic effects in rats subjected to left middle cerebral artery occlusion, a model of stroke [191]. Alogliptin has also been shown to have a neurovascular protective effect in a mouse model for stroke, preventing cerebral infarction and improving markers of neurovascular health [192]. Similarly, alogliptin administration before focal ischemia in rodents showed decreased volumes of infarction and less severe stroke-induced neurological deficits scores [193]. Sitagliptin also showed neuroprotective effects in a mouse model of brain trauma through activation of the cAMP-response element binding protein (CREB) system [194] and decreased hippocampal injury cause by transient ischemia in rodents with diabetes [195]. Sitagliptin also improved working memory and markers of inflammation in mice exposed to chronic cerebral hypoperfusion [196].

Vildagliptin also significantly improved insulin sensitivity and reduced the number of reactive oxygen species in the brain of high-fat diet fed rats deprived of testosterone by bilateral orchiectomy [197]. Nevertheless, the drug failed to correct the decline in cognitive function and defects in synaptic plasticity in the hippocampus associated with the lack of testosterone [197].

Furthermore, vildagliptin for four weeks improved mitochondrial function, insulin signaling, apoptosis in brain, thus attenuating high-fat diet induced cognitive decline in obese insulin-resistant rats, albeit leaving synaptic plasticity in the hippocampus unchanged [198]. However, when vildagliptin was combined with either decreased caloric intake or SGLT-2 inhibitor for 4 weeks, improved hippocampal synaptic plasticity was observed in male obese, insulin resistant rats [199].

Diabetes reduces neurogenesis in the main olfactory bulb and neuroplasticity (as per the number and differentiation rate of calbindin+ interneurons) in the piriform cortex, in addition to causing defects in the ability to detect odors and formation of olfactory memories in rats [200]. Administration of linagliptin for 16 weeks enhanced differentiation of interneurons and neuroplasticity in the piriform cortex, leaving the rest of the diabetes-induced abnormalities unchanged [200]. Linagliptin for 4 weeks decreased diabetes induced neovascularization possibly via inhibition of endothelin-1 in the brain of diabetic Goto-Kakizaki rats [201]. Sitagliptin also protected the proliferation of neural progenitor cells in a rodent model of type 2 diabetes without obesity, where this is usually impaired [202].

Linagliptin for 3 weeks exerted neuroprotective effects in mice with cuprizone-induced demyelination, as evidenced by the improved outcomes in behavioral and motor tests, and decreased demyelination and oxidative stress [203]. Sitagliptin protected against cisplatin-induced neurotoxicity in rats and improved performance on locomotor and Rotarod tasks, likely through actions in the cerebellum [204]. Sitagliptin also increased the GLP-1/GLP-1R effect on GABAergic transmission in a rodent model for febrile seizures [205], which may indicate a therapeutic potential.

Treatment with linagliptin for 8 weeks ameliorated the cognitive decline associated with AD in a mouse model of AD by decreasing amyloid beta, tau phosphorylation, as well as inflammation in the brain possibly via increasing levels of GLP-1 and GIP in the brain [206]. In addition, administration of vildagliptin in rat models of type 2 diabetes decreased the hippocampal neuron apoptosis, and thus, improved the cognitive decline associated with diabetes via activation of the Akt/p-glycogen synthase kinase 3β (GSK3β) signaling pathway [207,208]. Additionally, vildagliptin reduced the expression of amyloid precursor protein and phosphorylated tau in a rat model of diabetes and AD [209]. Saxagliptin was also shown to have a protective role in rodents with insulin resistance and D-galactose-induced dementia [210] and caused attenuation of amyloid beta, tau phosphorylation and improved memory in rodents with AD along with increased GLP-1 in the hippocampus [211]. Similarly, sitagliptin improved performance on memory tasks and increased BDNF in a rodent model of AD [212]. Sitagliptin was also shown to improve memory impairments and decrease amyloid beta in a mouse model for AD [213]. However, in another study, sitagliptin was shown to increase tau phosphorylation in rats with OLETF type 2 diabetes, which could worsen AD [214].

In high-fat-diet mice without AD, sitagliptin also improved memory and hippocampal neurogenesis suggesting it may be protective against the development of memory impairment and cognitive decline [215]. Similar results were seen in rodents with type 2 diabetes who were given sitagliptin and showed improvements in working memory and reduced adiponectin levels [216]. Both sitagliptin and vildagliptin showed improved memory/learning and increased hippocampal mitochondrial function in rodents with diet-induced obesity and insulin resistance [217].

Saxagliptin was also shown to improve motor control and performance in a rodent model of PD [218]. Along similar lines, sitagliptin improved memory task performance in rodents with PD as well as increased BDNF and dendritic spine density [219]. Sitagliptin has also been shown to increase motor performance and striatal and nigral dopamine in a mouse model of PD [184].

2.8. Clinical studies on GLP-1

GLP-1R has have been found in the parietal cortex, hypothalamus, and area postrema of humans [132]. Several studies have also investigated the effects of GLP-1 analogues in the human CNS using fMRI (Fig. 2). Liraglutide at doses approved for diabetes (1.8 mg) and exenatide, which is currently approved for diabetes, have been shown to decrease reward-related activations in areas including the insula and putamen to food cues in the short-term, before weight loss, after a single dose [220,221], for 10 days [222], or for 17 days [132]. Liraglutide (1.8 mg) at 17 days was also shown to decrease attention-related parietal cortex activations to highly desirable (high calorie or high fat) food cues [132]. In a longer-term study, no difference in brain activations between liraglutide (1.8 mg) and insulin to food cues was observed in a longer-term study of 12 weeks [222,223], but this did not include a placebo control and weight loss had occurred in the liraglutide group. More recently, in a study of liraglutide at doses approved for obesity (3.0 mg), no differences in brain activations to food cues were seen between liraglutide and placebo at 5 weeks (Farr et al., Under Review). However, when weight loss was controlled, a counter-regulatory increase in reward-related orbitofrontal cortex was observed (Farr et al., Under Review). This may indicate early CNS mechanisms which lead to later weight loss plateaus with liraglutide. Similarly to findings with MRI, a positron emission study (PET) of brain glucose metabolism showed that single dose exenatide increased metabolism in areas related to reward including the orbitofrontal cortex, cingulate cortex, and thalamus, as well as the emotion and attention related systems including the limbic system, frontal and parietal lobes, insula, and putamen [224]. To conclude, GLP-1 analogues have effects on the reward and attention systems in humans, but the dose and time interactions need to be further evaluated.

Less evidence is available for the effects of GLP-1 analogues on general cognition. In patients with executive function impairments defined by Trail Making Test-B (TMTB) score, an open-label pilot of 4 weeks showed that liraglutide improved TMTB score as well as improved a composite test score, which combined results from the Digit Symbol Substitution, Rey Auditory Verbal Learning, and Stroop (cognitive control) tests [225]. In a 17-day randomized, controlled trials of 20 patients with type 2 diabetes without known cognitive impairments, liraglutide (1.8 mg) did not alter spatial working memory, verbal memory, stop signal task (cognitive control), intra/extra-dimensional set shift, or spatial span outcomes [132]. In the 35-day randomized, controlled trial of 20 patients with obesity without known cognitive impairments, liraglutide (3.0 mg) did not impact spatial working memory, verbal memory, intra/extra-dimensional set shift, or spatial span outcomes, but liraglutide did increase the proportion of successful stops on the stop signal task (a task of cognitive control) (Farr et al., Under Review). Larger studies would be needed to further determine any dose and/or time relationships between liraglutide and cognition.

GLP-1 analogues are now being tested in humans for their use with AD. A small randomized, placebo-controlled trial on liraglutide showed benefits for brain glucose metabolism though without changes in cognition at 26 weeks [226]. A larger trial with liraglutide is currently underway to determine whether this may be able to treat AD [227]. Exenatide has also shown efficacy at treating PD in small trials [228,229], suggesting mechanisms in the dopamine pathways. Follow up showed continued benefit on the motor scale and dementia ratings in the absence of the medication for the group which had been exposed to exenatide for 12 months but had not taken exenatide for an additional 12 months [230]. A current study is also examining whether exenatide might help patients with alcohol dependence and results will be coming in the future [231]. Future studies should expand on potential cognitive changes/benefits with liraglutide and exenatide as well as the other GLP-1 analogues, which may have similar effects.

2.9. Clinical studies on DPP4 inhibition

Limited information is known about the effects of DPP4 inhibitors in the human brain. Although to our knowledge no studies have yet examined how these medications act in the CNS with MRI, some studies have shown cognitive improvements. Six-month sitagliptin treatment showed fewer declines on the Mini-Mental State Examination as compared to metformin [232]. Data from a cognitive substudy for the MMSE is currently underway for lingliptin with results expected this year [233]. Future research should expand on this research into the realms of eating behaviors as well as other cognitive outcomes and disorders.

2.10. Incretin based therapies targeting obesity and related disorders

Treatments for obesity are still in the stages of relative infancy. The first and most common treatment for obesity is lifestyle intervention, which reduces caloric intake and increases the amount of exercise, with little to modest improvements in BMI and obesity-related comorbidities [234]. Medications to treat obesity are somewhat more effective, with 3–9% weight loss over lifestyle interventions alone but are prescribed in addition to and not instead of lifestyle interventions [235]. The most effective treatment for obesity is currently bariatric surgery, which has more potential side effects, as it is a highly invasive procedure, although it results in 17–35% weight loss across studies versus 5–10% in control groups [236]. This is comparable to weight loss with very low calorie diets, which achieve weight loss of up to 20%, but weight loss with very low calorie diets is usually unsustainable and has a relatively short period of benefit [237]. Thus, bariatric surgery is frequently studied as the most effective therapy currently available, and some combination medications of incretins with other gut peptides are currently in preclinical and clinical studies based on these findings [238].

Similar to the way hypertension was originally treated in the early 1950s [239], research into the mechanisms which make bariatric surgery effective at reducing weight have revealed a large increase in gut-secreted peptides and particularly the incretins [240], acknowledging their importance not only for diabetes but also for obesity. More specifically, postprandial GLP-1, GLP-2, glucagon, oxyntomodulin and fasting glicentin levels rise after bariatric surgery, while GIP levels decrease, leading to remarkable weight loss independent metabolic improvement [241–249]. In addition, incretin-based therapies, like liraglutide [250], semaglutide [251], and albiglutide [252], improve cardiovascular outcomes and are approved for patients with cardiovascular disease, while other GLP-1 analogues are currently being assessed for their potential reno- and cardioprotective properties [15,253]. These additional health benefits, together with the advances in pharmacology which have enabled the oral administration of incretin based therapies, like semaglutide, will enhance the position of these drugs in the treatment armamentarium for type 2 diabetes and obesity [254]. Although research on the mechanisms of bariatric induced weight loss has resulted in the development of only GIP and GLP-1 analogues thus far, this may and/or has already resulted in other, novel incretin or incretin-like markers being developed for obesity.

3. Quo vadimus

A lot has been learned over the past few years about incretin physiology. This newly found knowledge has been successfully translated into novel therapeutics offering tangible benefits to our patients and opening novel and highly promising paths for further improvements and even more benefits in the future.

At this point, we may have to raise a really fundamental question, however, and that is why are we not making even more significant and faster strides towards the discovery and development of novel anti-obesity medications? [255] Is it because biological mechanisms

play a relatively small role in comparison to environmental and other factors contributing to the obesity epidemic, as some have proposed? The effectiveness of bariatric surgery as well as the discovery and successful use of incretins in the clinic, in addition to lifestyle modification, proves that biological mechanisms do play a significant role as originally envisioned with the discovery of leptin in humans [256–265].

If this is the case, the next question would be whether we are utilizing the most appropriate experimental models for the study of obesity pathogenesis and discovery of new medications for use in humans? CNS studies highlight the differences between the usually exploited experimental model, i.e. the rodent models for the study of obesity, and the resultant rodent brains vs. the human brain, i.e. the brain of the species of interest. For instance, although many hypothalamic neuropeptides had been identified on the basis of studies in rodents as promising candidates for drug development in humans many have failed to reach approval as potential pharmacotherapies for obesity in humans. In this context, although rodent studies have focused on the presence of GLP-1R in hypothalamus and nucleus of the tractus solitarius (NTS) but not the cortex, initial human studies have shown more cortical locations and activations for GLP-1R and GLP-1 agonists, which are in need of further evaluation. Thus, we need to be reminiscent that, although both rodent studies similar to observational studies in humans are important in raising hypotheses, it is a deep understanding of human physiology and pharmacology principles as well as rigorous translational research and clinical proof-of-concept studies that can lead to the development of new compounds to be tested in clinical trials for efficacy and then improved through further interventional studies in humans.

Translational human CNS-focused studies with incretin-based therapeutics are, to-date, limited, and more clinical studies are needed to fully capture the activity and mechanisms underlying the actions of incretins in the human brain. These data also highlight the need for more human/clinical studies in the area of energy homeostasis and drug discovery/pharmacotherapy of obesity. To make progress in addressing new problems such as obesity, which is the epidemic of the 21st century, and its comorbidities, we need to agree upon and make a conscious decision that new paradigms are needed. Similarly, a new focus on human studies and moving away from funding primarily physiology studies or in-depth mechanistic studies of animal/rodent models, which may or may not be fruitful, given differences among mouse, rat, primate, and human brains, is also absolutely necessary.

Further, developing better tools to study neurocognitive aspects of the energy homeostasis regulation in humans, developing better neuroimaging techniques to be used more often in human studies, and carefully monitoring and assessing parameters which play a role in alterations of energy homeostasis in humans is of paramount importance. In addition, novel targeted and untargeted studies in humans, such as studies of the multiome [266], are needed to further define the pathways regulating energy homeostasis in humans. The availability of big data (really large number of variables per subject in relation to the number of subjects in the study) to be collected and/or currently available in biobanks and population databases which can now be analyzed through the use of novel artificial intelligence and generalized adversarial network analytical tools offer additional opportunities to be leveraged [266]. Integrating the analysis of as many data as reasonably possible, while realizing and to the extent possible, addressing limitations in the analysis and conclusions drawn on the basis of observational data collected for other purposes, is absolutely essential for novel pathways important in humans to emerge and/or for the integration of known pathways, environmental, biological, psychosocial etc. to be fully integrated. All the above, and subsequently proof-of-concept physiology studies and finally small interventional clinical trials in humans, will be needed for the field to move significantly forward.

4. Conclusions

The incretin system has proven to be highly useful in terms of their effects on glycemia and body weight. As research continues to expand into other potential indications and to delve into a deeper understanding of underlying mechanisms and actions in CNS, we anticipate that we will not only learn more about the mechanisms through which they may alter energy homeostasis and glycemia but also other disease states

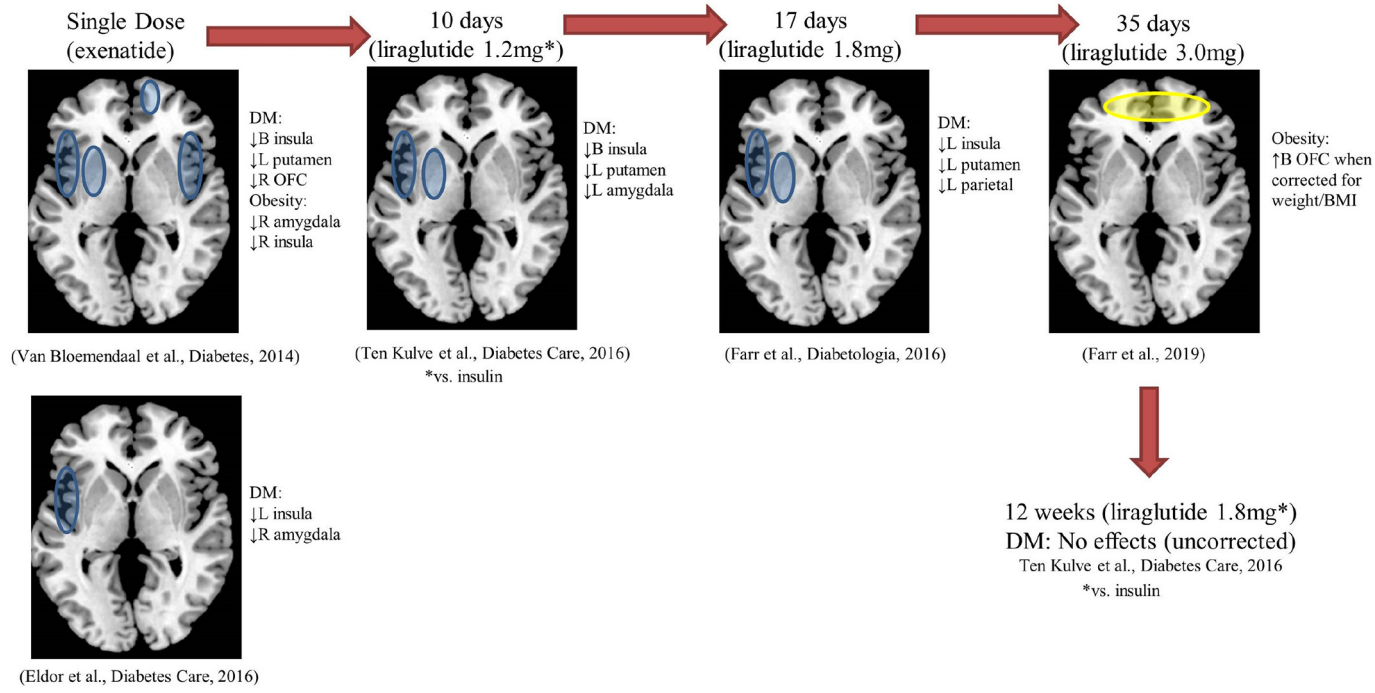

Fig. 2. Results from imaging studies examining GLP-1 analogues (exenatide and liraglutide) over time. Note that the results used slightly different imaging and evaluation parameters. Blue color indicates area of decreased activation; yellow indicates area of increased activation. All studies used placebo comparator unless otherwise noted. B, bilateral; L, left; R, right; OFC, orbital frontal cortex; DM, patients with type 2 diabetes.

such as non-alcoholic fatty liver disease (NAFLD), cardiometabolic diseases, and neurodegenerative disorders. Progress in terms of our understanding of how incretins work has led to finding and developing as therapies safer and more efficacious incretins with improved pharmacokinetic (e.g. modified incretins through replacing certain amino acids, use of better linkers that prolong half-lives) and pharmacodynamic profiles (e.g. more lipophilicity that allows better CNS penetration) leading to more effective treatments for obesity and metabolic conditions. Thus, expanding preclinical and clinical research to other CNS areas outside of the hypothalamus as well as studying other members of the incretin family and/or other CNS-acting molecules (e.g. melanocortins which act downstream of leptin and may bypass tolerance due to mutations in the pathway between the leptin receptor and the melanocortin receptors) is expected to provide an array of opportunities for developing novel pharmaceuticals and to thus advance both science and patient care. Future research should also study these current and to-be-developed molecules in healthy subjects as well as clinical samples of populations with metabolic and neurodegenerative disorders to better delineate their functions and mechanisms of action in the CNS in humans.

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Declaration of Competing Interest

The authors have nothing to disclose.

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