

# Liraglutide as a Potentially Useful Agent for Regulating Appetite in Diabetic Patients with Hypothalamic Hyperphagia and Obesity

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## Abstract

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Hypothalamic hyperphagia and obesity are characterized by a lack of satiety and an abnormally high appetite that is difficult to control. We herein report the cases of two patients with hypothalamic hyperphagia and obesity with MRI-detectable hypothalamic lesions. These patients suffered from diabetes mellitus associated with an abnormal eating behavior and weight gain. Liraglutide was successfully used to treat their diabetes mellitus and suppress their abnormal appetites. Glucagon-like peptide-1 analogues, including liraglutide, are promising treatment options in patients with hypothalamic hyperphagia and obesity, as these agents enhance the hypothalamic input of the satiety signal, which is lacking in such patients.

**Key words:** GLP-1, hypothalamus, hyperphagia, obesity, satiety

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## Introduction

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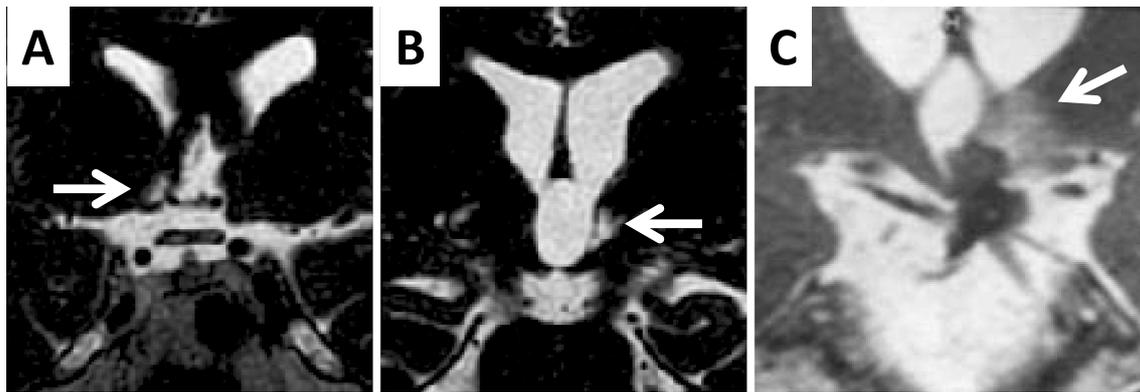
Hypothalamic hyperphagia and obesity are typically observed in patients with a history of extensive suprasellar surgery of hypothalamic tumors. Similar clinical manifestations are noted in patients with hypothalamic inflammatory disorders, head injuries and cerebral aneurysms (1), especially when the ventromedial hypothalamus, paraventricular nuclei and/or arcuate nucleus are involved (2). Patients with hypothalamic hyperphagia exhibit an excessive caloric intake and unusual food-seeking behaviors (2).

Similar phenotypes of hyperphagia and obesity have been shown to be induced in rodents by the selective destruction of the paraventricular nucleus (3) and dorsomedial nucleus (4), as well as the selective deletion of brain-derived neurotrophic factor neurons in the ventromedial nucleus and dorsomedial nucleus (5). These findings indicate that the hypothalamic nuclei are important in controlling appetite (1).

In order to control the whole-body weight, the hypothalamus receives afferent messages from the adipose tissue, gastrointestinal tract, liver and pancreatic beta cells and sends

efferent messages to the same organs as well as the muscles (1). With respect to the afferent signals, gut hormones are known to play a pivotal role in relaying information regarding the body's nutritional status to appetite-controlling centers within the central nervous system (CNS), such as the hypothalamus and brainstem (6). In patients with Prader-Willi syndrome, a genetic disorder that can result in hypothalamic obesity (1), it has been shown that the peripheral energy status is inefficiently sensed by the hypothalamus, as the secretion of pancreatic polypeptide, a gut hormone secreted by L cells in the intestines, is impaired (7). The serum level of ghrelin, another appetite-promoting gut hormone that is secreted primarily from the stomach, has also been reported to be inappropriately increased in both fasting and postprandial states (2).

Glucagon-like peptide-1 (GLP-1) is a product of the glucagon gene that is produced in the L cells of the intestinal mucosa. The level of GLP-1 is known to increase in the blood in response to the ingestion of lipids or carbohydrate-containing foods (8). Its chief action is insulinotropic in pancreatic beta cells in a glucose-dependent manner, while its many other actions include the glucose-dependent sup-



**Figure 1.** Hypothalamic injuries in the present two patients. Multiple high-intensity lesions were detected in the right (A) and left (B) ventral hypothalamus (arrow) on brain MRI in Case 1. A similar high-intensity lesion was noted in the left ventral hypothalamus on MRI in Case 2 (C). T2-weighted images of a coronal section without the use of contrast-enhancing medium are shown.

pression of glucagon production, a reduction of appetite and food intake and a delay in gastric emptying (9, 10).

GLP-1 analogues have recently been used as antidiabetic agents, and the improvement of the beta-cell function in patients with type 2 diabetes mellitus (DM) has been reported after three years of treatment with exenatide, a GLP-1 analogue (11). Some of the anorexic actions of GLP-1 appear to be mediated by the direct activation of the GLP-1 receptor in the CNS in addition to activation of the vagal nerve (12). However, the efficacy of GLP-1 analogues in treating hypothalamic hyperphagia and obesity is largely unknown.

We herein report the cases of two DM patients with hypothalamic pituitary injury in whom the GLP-1 analogue liraglutide was effective not only in treating their DM, but also in suppressing their abnormal appetites.

## Case Report

### Case 1

A 38-year-old man began treatment with the self-injection of liraglutide to treat DM. His past medical history was marked by a traumatic brain injury at 18 years of age when he fell from a rooftop and became comatose due to an acute subdural hematoma that required surgery. Postoperatively, he began engaging in abnormal eating behaviors, including eating in secret. His body weight increased by 17 kg over the next six years, and he developed DM [HbA1c: 8.9% (National Glycohemoglobin Standardization Program (NGSP))]. He was admitted to our hospital at 24 years of age, at which time he was advised to improve his lifestyle factors and reduce his body weight. However, once he was discharged, he found it very difficult to correct his eating habits, and his body weight increased to 100 kg by 25 years of age.

The patient was admitted to our hospital two more times with diabetic symptoms, including extreme thirst, polyuria and weight loss. At 31 years of age, he was also diagnosed

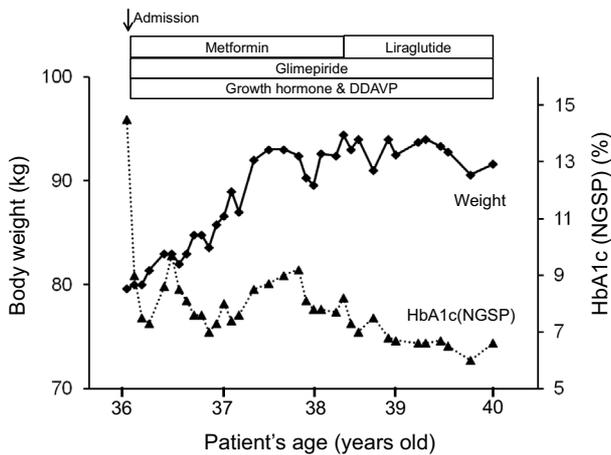
as having diabetes insipidus due to low urine osmolarity and an inappropriately low antidiuretic hormone level, and treatment with d-arginine vasopressin was started. Left optic nerve atrophy and bilateral sensory hearing difficulty were also noted, and brain MRI detected a suspected brain injury in the bilateral hypothalamus (Fig. 1A, B).

It was difficult to achieve good control of the patient's DM using several antidiabetic agents. He was subsequently readmitted to our hospital at 36 years of age due to marked hyperglycemia with an HbA1c level of 14.5%. While his diabetes was being treated, a severe adult growth hormone (GH) deficiency was detected due to a poor response to GH on an insulin tolerance test (0.189 pg/mL after stimulation) and a GH releasing peptide (GHRP)-2 stimulation test (0.1401 pg/mL after stimulation). GH replacement therapy was therefore initiated. There was a slight and temporary reduction in the patient's body weight after discharge; however, his body weight increased again due to overeating, and his DM worsened. Before we initiated liraglutide treatment, his HbA1c was 8.0% under treatment with 1 mg of glimepiride and 750 mg of metformin.

After liraglutide therapy (0.3 mg a day) was started, the patient's appetite decreased, and he lost 3 kg of body weight (from 94 kg). His DM has remained well controlled, with a level of HbA1c of around 6.5% under treatment with 0.9 mg of liraglutide and 1 mg of glimepiride for two years (Fig. 2).

### Case 2

A 71-year-old man was referred to our hospital due to panhypopituitarism and central diabetes insipidus. He had been diagnosed as having a cerebral aneurysm in the ventral surface of the pons and was treated with clip-wrapping at 64 years of age. He developed aseptic meningitis at 66 years of age and was treated with dexamethasone. He subsequently noticed thirst, polyuria and polydipsia, including an increased frequency of nocturia (around 5 times), and his polydipsic symptoms gradually progressed.



**Figure 2.** Clinical course in Case 1. The changes observed in the patient's body weight (left vertical axis) and HbA1c (NGSP) level (right vertical axis) after the last admission are shown. The administered medical treatments are presented at the top of the panel. Growth hormone and DDAVP were deficient hormones administered in this case. DDAVP indicates d-arginine vasopressin.

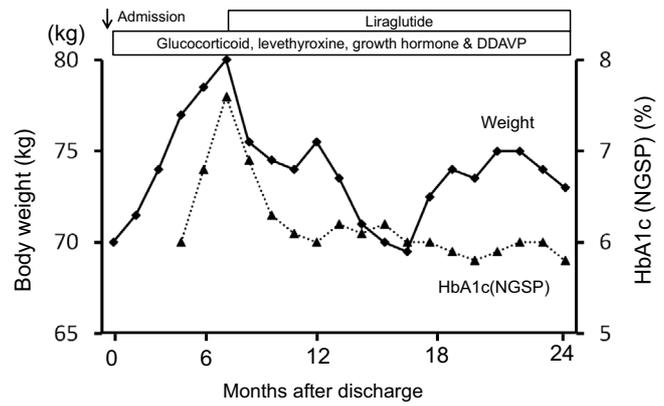
On pituitary MRI, no high signals were identified in the posterior lobe, and the entire pituitary was observed to be thin. There was no response of antidiuretic hormone on a hypertonic fluid loading test (data not shown). The patient's anterior pituitary function indicated panhypopituitarism for all anterior hormones. We also observed hypothalamic lesions on MRI (Fig. 1C).

We treated the patient with each deficient hormone, and he was discharged. However, his appetite increased remarkably, and he began eating more than twice what would be considered normal, including midnight snacking. Within two months, his body weight increased 6 kg from 74 kg, and his HbA1c level increased from 5.8% to 7.6%. We initiated treatment with 0.3 mg of liraglutide, and his appetite decreased within one week. The liraglutide dose was subsequently increased to 0.6 mg, and his appetite further decreased. In addition, he regained a sense of satiety and his weight decreased by 5 kg within four weeks. He ultimately lost 11 kg of body weight from 80 kg over a six-month period. His diabetes has remained well controlled (HbA1c around 6%) under treatment with 0.3 mg of liraglutide for more than two years, with a moderate increase in body weight (Fig. 3).

## Discussion

We herein described two patients with DM in whom liraglutide effectively treated diabetes. The liraglutide treatment was also effective in suppressing the abnormal appetites of both patients. Both cases involved a hypothalamic pituitary injury, which was considered to be the probable etiology of each patient's abnormal appetite.

The pathophysiological mechanisms by which humans develop hypothalamic hyperphagia and obesity are not yet fully understood. In addition to the abnormally enhanced ap-



**Figure 3.** Clinical course in Case 2. The changes in the patient's body weight (left vertical axis) and HbA1c (NGSP) level (right vertical axis) after admission are shown. The administered medical treatments are presented at the top of the panel. Glucocorticoid, levothyroxine, growth hormone and DDAVP were deficient hormones administered. DDAVP indicates d-arginine vasopressin.

petite observed in individuals with hypothalamic hyperphagia, several clinical manifestations have been identified, including leptin and ghrelin resistance, autonomic nervous system dysregulation (a decreased sympathetic activity and an increased parasympathetic activity), hyperinsulinemia and enhanced conversion of cortisol from cortisone (reviewed in refs. 2, 13). Therefore, simple lifestyle modifications, such as dietary restriction and exercise, are often ineffective.

A small number of patients with hypothalamic obesity are treated with sympathomimetics, somatostatin analogues, diazoxide plus metformin, triiodothyronine or sibutramine (2, 13). Some patients refractory to medical treatment have been reported to undergo surgical intervention, including bariatric surgery, gastric banding and laparoscopic truncal vagotomy (2, 13). The therapeutic outcomes of some of these approaches appear to be promising; however, the efficacy of these treatments remains inconclusive.

GLP-1 is known to have extrapancreatic actions, including a direct effect on the CNS to suppress appetite-mediating satiety signals (14). GLP-1 analogues are thus a logical choice for treatment in patients with hypothalamic hyperphagia and obesity. It has been shown that a GLP-1 analogue, exenatide, is effective in increasing satiety as well as improving diabetes in patients with Prader-Willi syndrome (15, 16). Very recently, a woman with a hypothalamic tumor treated with radiotherapy who developed hypothalamic obesity and diabetes was successfully treated with exenatide, as indicated by a decrease in both body weight and HbA1c as well as an improvement in her abnormal eating behaviors (17). Similarly, GLP-1 analogues have been successfully used to treat several patients with obesity and diabetes associated with hypothalamic tumors (18). We were also able to treat diabetes and suppress the abnormal appetites in our patients with hypothalamic hyperphagia caused

by traumatic hypothalamic injury and nonspecific inflammation. Therefore, it should be further researched which patients with hypothalamic hyperphagia and obesity are candidates for effective treatment with GLP-1 analogues.

Among the several pancreatic and extrapancreatic actions of GLP-1, we focus here on its action in the CNS in order to discuss the potential mechanisms accounting for the effectiveness of GLP-1 analogues in patients with hypothalamic hyperphagia and obesity. The mechanism(s) underlying the increase in satiety induced by GLP-1 analogues (14), which is lacking in these patients, is of significant interest.

It has been shown that the peripheral administration of GLP-1 decreases glucose metabolism in the human hypothalamus and brainstem (19), while a postprandial increase in the serum level of GLP-1 modulates the neuronal activity in some areas of the brain, including the hypothalamus (20), suggesting modulation of the satiety center in the brain by peripheral GLP-1. Similarly, in rats, it has been demonstrated that the peripheral administration of GLP-1 increases the expression of *c-fos*, an indicator of satiety, in the arcuate nucleus.

Furthermore, it has been documented that, in rats, the GLP-1 binding regions in the CNS are found primarily in the hypothalamus, thalamus, septal area, subfornical organ and area postrema (21, 22). Among these sites, GLP-1 receptors located in the subfornical organ and area postrema have been observed to interact with a peripherally administered GLP-1 receptor agonist following the injection of isotope-labeled GLP-1 (23). This observation can be accounted for by the fact the capillaries of these areas are known to lack the endothelial tight junctions associated with the blood-brain barrier (24). Meanwhile, the intracerebroventricular administration of GLP-1 results in a broad increase in the *c-fos* expression in the paraventricular nucleus, nucleus of the tractus solitarius and area postrema (25), resulting in a reduced caloric intake and weight loss in rodents (14, 26, 27). Although the precise role of GLP-1 neurons in the CNS has not been identified, it was recently demonstrated that GLP-1 neurons in the nucleus of the solitary tract process a satiety signal from an afferent input to the hypothalamus in rats (28), suggesting the anorexic properties of central GLP-1 signaling.

It has also been reported that the blood-brain barrier can not be crossed by peptide hormones, as evidenced by the absence of an antidiuretic hormone in the cerebrospinal fluid after its peripheral administration (29). This is also the case for GLP-1 (23). However, there appears to be an exception in which the permeability of the blood-brain barrier to pituitary hormones is increased in patients with hypothalamic pituitary tumors, particularly those associated with invasive pituitary adenoma (30).

These findings suggest, that in patients with hypothalamic lesions, peptide hormones, including GLP-1, may have a higher chance of directly accessing GLP-1 receptors beyond the blood-brain barrier, such as those located in the hypothalamus. This may also constitute an additional mechanism

augmenting the afferent signals of the peripheral energy status transmitted to the hypothalamus, thus suppressing appetite. In the present cases, we identified a bilateral hypothalamic injury in Case 1 and a unilateral injury in Case 2. The presence of an intact contralateral hypothalamus may explain the stronger clinical effect of the GLP-1 analogue observed in Case 2. Although we focused on disruption of the blood-brain barrier to explain the effectiveness of GLP-1 analogues in these patients, it may be also possible that the satiation network in the hypothalamus is somehow damaged in patients with hypothalamic hyperphagia and obesity. The influence of GLP-1 analogues on the satiation network may therefore be augmented in such patients. Hence, the accumulation of more cases is needed to elucidate the association between the clinical effects of GLP-1 and the extent of hypothalamic injury.

Taken together, the past and present findings suggest that GLP-1 analogues, including liraglutide, are effective in regulating appetite and improving DM in patients with hypothalamic hyperphagia and obesity is due to an increase in afferent signals to the hypothalamus, potentially including the improved access of GLP-1 analogues to the GLP-1 receptors in the CNS. We hypothesize that GLP-1 analogues are promising agents for regulating an abnormal appetite in patients with hypothalamic disorders.

**The authors state that they have no Conflict of Interest (COI).**

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