

## GHRELINOMA

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### ABSTRACT

Ghrelin is a 28 amino acid, acylated peptide mainly produced in the P/D1 neuroendocrine cells of the stomach wall. The peptide stimulates growth hormone release by acting on both the pituitary and hypothalamus, but also stimulates ACTH and prolactin as well as gastric acid secretion and intestinal motility. Ghrelin also increases appetite and food intake. Expression of ghrelin protein and mRNA has been identified in high percentages of gastric neuroendocrine tumors (NETs) but also intestinal and pancreatic NETs. Theoretically, a ghrelinoma could cause acromegaly, diabetes mellitus, diarrhea and gastric acid hypersecretion. Small numbers of cases with elevated plasma ghrelin have been reported. However, patients often have non-specific symptoms, that do not resemble the theoretical syndrome of a ghrelinoma. This suggests a low biological activity of these elevated ghrelin levels, which could be related to the ratio of acylated ghrelin and unacylated ghrelin. At this time the clinical relevance of hyperghrelinemia for NETs remains limited.

### GHRELIN

Ghrelin is a 28 amino acid, acylated peptide mainly produced in the P/D1 neuroendocrine cells of the stomach wall (1,2). It was discovered in 1999 by *Kojima* and colleagues as a ligand for the growth-hormone secretagogues receptor 1a (GHS-R1a), purified from rat stomach extract (1). Ghrelin expression has been found in multiple organs including the bowel, adrenal gland, thyroid,

ovary, testis, prostate, liver kidneys and myocardium (2-5). On top of this, ghrelin is produced in the central nervous system, particularly in the hypothalamus (6). Two isoforms of ghrelin can be found in equal amounts in the circulation: acylated ghrelin (AG) and unacylated ghrelin (UAG) (7). AG is formed when a hydroxyl group on one of UAGs serine residues is acylated by Ghrelin O-Acyltransferase (GOAT). The acylation allows AG to cross the blood-brain barrier and bind to the GHS-R1a and thereby stimulate growth hormone (GH) release in the pituitary and GHRH in the hypothalamus (8). Vice versa, GH infusion has been shown to decrease ghrelin levels (9). Other effects of ghrelin on the pituitary include stimulation of CRH dependent ACTH release, prolactin secretion and suppression of gonadotrophins (9). UAG does not bind to the GHS-R1a and was previously considered to be inactive, but currently both AG and UAG have been shown to influence glycemic regulation. When AG is administered to healthy individuals, insulin levels decline and plasma glucose levels increase. Coadministration of AG and UAG blunts the AG-induced alteration in insulin and glucose levels, suggesting UAG is an antagonist for AG (10). Ghrelin also has an important role in fasting. Plasma ghrelin levels rise preprandially and stimulates appetite, increases intestinal motility and gastric acid secretion (11). Acutely increased ghrelin levels stimulate lipolysis, however chronic administration of AG results in lipogenesis (12,13). Lastly, cardiovascular effects of ghrelin have been reported including vasodilation and an increased cardiac index and stroke volume (14). In Table 1 an overview of the effects of AG is provided.

Table 1. Effects of Ghrelin		
Site of action	Acylated ghrelin action.	Potential ghrelinoma symptoms
Pituitary	↑ GH secretion ↑ ACTH secretion ↑ PRL secretion ↓ LH in men/↓FSH and LH in women	Acromegaly Cushing syndrome Hypogonadism
Hypothalamus	↑ GHRH secretion ↑ CRH secretion ↓ GnRH pulse generator ↑ Food intake (via NPY) and appetite	<i>See pituitary</i>
Pancreas	↓ Insulin secretion (spontaneous and glucose stimulated) ↑ Glucose levels ↑ Glycogenolysis ↑ Glucagon secretion	Diabetes mellitus
Adipose tissue	↑ Lipogenesis (chronic) ↑ Lipolysis (acute)	Absence of cancer cachexia
Cardiovascular system	↑ Cardiac output ↑ Cardiac contractility ↓ Systemic vascular resistances ↑ Vasodilation	
Gastrointestinal system	↑ Gastric emptying ↑ Gastric acid secretion ↑ Gastric and intestinal motility	Gastric acid hypersecretion Diarrhea
Liver	↑ IGF-1	

Table modified from Motta G. et al; Natural and Synthetic Growth Hormone Secretagogues. Encyclopedia of Endocrine Diseases (27)

## GHRELIN AND NEUROENDOCRINE TUMORS

Based upon the physiologic effects of ghrelin one would expect that the clinical features of a ghrelinoma would include hyperglycemia (decreased insulin secretion) and GH excess with elevated IGF-1 and potentially features of acromegaly. Gastrointestinal symptoms could include hyperphagia and gastric acid hypersecretion (Table 1). The severity of these symptoms would probably also depend on the AG/UAG ratio. This complete syndrome has not been described in a patient to date, while tumor ghrelin immunoreactivity occurs frequently in neuroendocrine tumors (NETs) and in a small number of patients elevated plasma ghrelin levels have been found.

Expression of ghrelin protein and/or mRNA has been detected in a high percentage of gastric, intestinal and pancreatic NETs. Gastric NETs are regarded to derive from Enterochromaffin-Like (ECL) cells. They are classified as

type 1 if they are associated with atrophic gastritis. Type 2 gastric NETs are associated with a gastrin-producing neuroendocrine tumors (Zollinger-Ellison syndrome) and type 3 gastric NETs are sporadic (15). Ghrelin expression is lacking in ECL cells in physiological conditions (2), but in gastric NETs ghrelin is frequently expressed. Rindi and colleagues used immunohistochemistry to identify the ghrelin peptide in 86% of type 1, 67% of type 2, and 50% of type 3 gastric NETs (16). Also, high ghrelin expression can be observed within neuroendocrine hyperplasia of the stomach (associated with type 1 and 2 NETs). Despite the expression of ghrelin, these hyperplastic neuroendocrine cells are currently still regarded to derive from ECL cells as they display VMAT2 immunoreactivity, which is a specific marker for ECL cells (17). It is hypothesized that ECL cells secrete ghrelin in proliferative states, potentially under the influence of gastrin.

In the same study, eight intestinal NETs didn't express ghrelin immunohistochemically. Similar findings were reported by Papotti and colleagues, but they additionally detected ghrelin mRNA in 72% of intestinal carcinoids through *in situ* hybridization (18). These intestinal NETs were mostly negative for IHC suggesting that lower concentrations of ghrelin might be present, although below the detection limit of IHC or translation is absent. In pancreatic NETs, around 40% of tumors showed ghrelin immunoreactivity, whilst *in situ* hybridization revealed ghrelin mRNA in 68% of pNET, including non-functioning pNET, insulinoma, glucagonoma, and VIPoma (19,20). Normal pancreatic islet cells have also been demonstrated to express ghrelin peptide. The co-expression of ghrelin in a variety of NETs may also represent the common stem cell origin of the different enteroendocrine cell types (5).

Actual elevated plasma ghrelin levels in patients with a NET have only sporadically been measured (Table 2). In a study screening 26 patients with pNETs, mean plasma total ghrelin levels were similar between patients and healthy controls (20). However, plasma total ghrelin levels were elevated in a subset of 5 patients. These patients did not display features of acromegaly and mean body mass index of patients with hyperghrelinemia was similar to patients with normal ghrelin levels. Three other studies reported hyperghrelinemia in NET patients at a lower incidence of around 3% (total or acylated ghrelin; Table 2) (21-23). All patients with hyperghrelinemia had non-specific symptoms without evidence of GH excess or hyperglycemia. Again, mean plasma total ghrelin levels were similar in NET patients compared to controls and therefore ghrelin was found to be a poor screening tool for NETs (21,22).

**Table 2. Plasma Ghrelin Levels in Patients with Neuroendocrine Tumors**

	Patients screened	Mean total plasma ghrelin NET	Mean total plasma ghrelin controls	p value	Elevated ghrelin (number of patients, %)	Hyperghrelinemia : tumor type
Ekeblad (20)	pNET (n=26)	908 ng/L	952 ng/L	N.S.	5 (19.2%)	- pNET (n=2) - glucagonoma (n=1) - gastrinoma (n=2)
Corbetta (21)	pNET (n=24) siNET (n=10) gastric NET (n=6)	182 pmol/L	329 pmol/L	N.S.	1 (2.5%)	- pNET
Van Adrichem (22)	pNET (n=3) siNET (n=19) other (n=6)	62.9 pg/ml*	57.2 pg/ml*	p=0.66	1 (3.6%)	- siNET
Walter (23)	pNET (n=27) siNET (n=33) other (n=12)	NA	NA	NA	3 (4.2%)	- pNET - rectal NET - gallbladder NET

\*median acylated ghrelin. Abbreviations: N.S: Not significant; pNET: pancreatic neuroendocrine tumor; siNET: small intestinal neuroendocrine tumor.

Lastly, elevated ghrelin levels have been reported in three case reports. The first patient was a 60-year-old male, presenting with abdominal pain, weight loss, flushing and fatigue. There were no signs of diabetes mellitus or acromegaly. After being treated with a somatostatin analogue for four years and three cycles of temozolomide/capecitabine an elevated plasma total ghrelin level was measured. Four months later the patient

developed symptomatic endogenous hyperinsulinism and passed away another four months later (24). A second patient with a presacral NET was also diagnosed with a ghrelinoma based on elevated plasma total ghrelin levels (25). Symptoms included back pain and intermittent attacks of weakness, shivering, tachycardia, numbness and profuse perspiration. While AG levels were stable through the course of the disease total ghrelin levels increased tenfold

when the NET progressed. A third case report described a patient with a gastric NET with elevated total and acylated ghrelin. This patient reported frequent diarrhea and night sweats. During follow-up patient developed new-onset diabetes in the presence of normal IGF-1 levels (26).

In conclusion, while co-expression of ghrelin is a relative frequent finding in NETs, actual elevated plasma ghrelin levels has been described in small numbers of patients. The non-specific symptoms of a majority patients suggest limited biological activity of these elevated ghrelin levels, possibly related to the UAG/AG ratio. At this time the clinical relevance of hyperghrelinemia for NETs remains limited.

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