Mini Review

Amylin, Food Intake, and Obesity

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Abstract

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Amylin, also known as islet amyloid polypeptide, identified in 1987, is a naturally occurring hormone, released by the β cells of the pancreas and consists of 37 amino acids. Amylin seems to decrease food intake through both central and peripheral mechanisms and indirectly by slowing gastric emptying. The mean basal amylin concentration is higher in obese than in lean human subjects. The amylin response to oral glucose is also greater in obese subjects, whether or not they have impaired glucose tolerance. The elevated amylin levels in obesity may lead to down-regulation of amylin receptors and lessen the impact of postprandial amylin secretion on satiety and gastric emptying. Amylin administration may overcome resistance at target tissues, delay gastric emptying, and have potential for inducing weight loss in obese individuals.

Key words: food intake, amylin, gastric emptying, satiety, weight loss

Introduction

Overweight [body mass index, $\geq$25 kg/m^2], which includes the obese subset (body mass index, $\geq$30 kg/m^2), is the most common nutritional disease in the United States, affecting more than half of the population. The crude prevalence was 59.4% for men, 50.7% for women, and 54.9% overall (1). The treatment of obesity, even with comprehensive multidisciplinary approaches, including drugs, is difficult; patients generally lose only 10% to 15% of their baseline body weight, reaching a plateau after 4 to 6 months of weight loss, and then begin to regain (2). A better understanding of the etiology and pathophysiology of obesity is essential to develop more effective preventive and therapeutic measures. More knowledge about the function of amylin, a recently discovered peptide that is elevated in obese individuals, may lead to better treatment of obesity. Although amylin has multiple actions, including inhibiting secretion of glucagon and insulin, as well as that of lipase and amylase, this review focuses on the relationship between amylin, obesity, and food intake.

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History of Amylin

Early in the 20th century, two independent researchers (3,4) described hyalinosis of the pancreas in patients with diabetes mellitus. Amyloid deposits were observed, with the major protein component isolated much later in 1987 and identified as the peptide amylin (5,6). Since then, there have been many studies on the role of amylin in the development of insulin resistance and diabetes (7). Amylin has been experimentally administered in diabetic patients to improve glycemic control (8,9). Other studies of amylin in animals and humans have shown both a direct inhibitory effect on food intake and an indirect effect by slowing gastric emptying (10,11).

Amylin Composition and Synthesis

Amylin, a naturally occurring hormone, also termed islet amyloid polypeptide, consists of 37 amino acids, amidated at the C-terminal. Amylin is produced through gene expression on chromosome 12. It is transcribed as an 89-amino-acid prepolypeptide, which is cleaved to form the mature peptide in the β cells of the pancreas, where it is stored along with insulin and C-peptide in the same granules (5). Amylin is a normal product of β cells and is co-released with insulin in a molar ratio of $\sim$1 to 100 in healthy non-diabetic subjects in response to nutrient stimuli (carbohydrate- and protein-containing meals) (12,13). The amylin to insulin molar ratio is alterable as seen in dexamethasone-treated rats that exhibit an increased ratio (14). Amylin residence time in the plasma is longer than insulin and similar to C-peptide (15), although amylin has a faster clearance rate than insulin by the kidneys (16). Because body weight and adiposity influence kinetic parameters and overall levels of insulin and amylin (13), the molar ratio of amylin to insulin is a good indicator of relative amylin deficiency (17).

Amylin has a disulfide bridge in the region between amino acids 2 and 7, and a region between amino acids 20 and 29 is responsible for amyloid formation in humans and cats (18,19). In most other animals, amylin has no propensity to form amyloid (18,20) even with an amyloidogenic sequence, as in the dog. The dog, unlike humans and cats (21), also does not develop type 2 diabetes.

Amylin circulates in the plasma at concentrations of 5 to 30 pM/L in normal subjects (11), with a mean of 3.4 ± 0.7 pM in lean subjects and 4.7 ± 0.9 pM in obese subjects with normal glucose tolerance. For obese subjects with impaired glucose tolerance, lower values of 4.0 ± 0.3 pM were observed, and for those with type 2 diabetes, 3.7 ± 1.1 pM (17,22). The stimulated amylin response to an oral glucose tolerance test is higher in obese subjects, whether they have impaired glucose tolerance or not. The highest amylin response to a glucose load has been observed in women during normal pregnancy or gestational diabetes, the next highest in obese subjects, and virtually no response in patients with insulin deficiency due to type 1 or late type 2 diabetes (23).

Effects on Food Intake

Meal termination and satiety may be partly due to the release of gastrointestinal peptides and pancreatic hormones (24,25). Preclinical data with amylin and clinical data with pramlintide (a human amylin analogue) support a role for amylin in satiety. Pramlintide administration led to sustained weight loss when given for up to one year to type 1 and type 2 diabetic patients at doses resulting in plasma concentrations close to those in non-diabetic humans (26–28). The weight change in type 1 was −0.5 kg for the 30/60 μg pramlintide four-times daily and in type 2, −1.5 kg for the 150 μg pramlintide three-times daily, as compared with +1.0 kg for the placebo group.

In addition, amylin diminished insulin-induced feeding in mice without affecting the insulin induced hypoglycemia (29). Amylin injection inhibited food intake in both food-deprived and nonfood-deprived mice whether they were diabetic or not (29). Amylin also reduced food intake when given to either genetically obese (*ob/ob*) and lean (*ob/c*) mice, or to diabetic obese (*db/db*) and lean (*db/c*) mice over a wide age range of 4 to 22 months (30). Central bolus infusion of amylin (100 pmoles into the third ventricle) significantly decreased 24-hour food intake by over 30% in rats (10). The effect persisted over the subsequent week after discontinuation of amylin, without compensation in food intake. Body weight and retroperitoneal fat-pad weight were significantly reduced in the amylin-treated rats (10). In contrast, when amylin antagonist AC 187 was administered to rats, food intake (31), and total body fat increased by ~30%, but not body weight (32). Activation or inhibition of area postrema, a circumventricular organ outside the blood brain barrier, by amylin and its antagonist (AC 187) produce or inhibit anorexia respectively. The stimulatory effect is apparently mediated through formation of second messenger cGMP (33).

The role of serotonergic, histaminergic, and dopaminergic systems was recently studied. Amylin may induce anorexia through its effect on brain serotonin by increasing the transport of the precursor tryptophan into the brain (34) to inhibit feeding by serotonin action in the paraventricular nucleus. Serotonin in rats reduces the size and duration of meals as well as the rate of eating, but does not affect the latency to feed or meal frequency, suggesting increased satiation rather than reduced hunger (35). Amylin's anorectic effect is through stimulating histamine H1 receptors and not by enhancing endogenous histamine release, as indicated by the anorectic effect being absent in mice lacking functional H1 receptors (36). Additionally, the anorectic effect of amylin was attenuated in rats treated with dopamine D_2 (2) receptor antagonists (37). Amylin also inhibits stimulation of feeding by the potent hypothalamic neuropeptide Y (NPY). When male Sprague Dawley rats received 1 nmol of NPY through a intracerebroventricular cannula, subsequent dosing with amylin resulted in dose-dependent inhibition of NPY-induced feeding (38). Furthermore when rats received daily doses of 0.5 nmol of amylin, 30 minutes before the dark phase, for 6 days, food intake and ultimately body weight were significantly reduced. These rats lost 17.3 ± 6.1 g, whereas their control counterparts gained 7.7 ± 5.1 g. In spite of the reduced food intake, NPY was not elevated, suggesting that amylin may regulate NPY production or release (38).

A number of gastrointestinal peptides reduce food intake by stimulating ascending vagal fibers. Whereas truncal vagotomy blocks inhibition of food intake by cholecystokinin (CCK), somatostatin, and glucagon, it does not block inhibition by amylin (30). One mechanism by which amylin appears to reduce food intake is by augmenting the actions of other peptides such as CCK, glucagon, and bombesin, all of which also increase amylin secretion. However, the CCK antagonist L-364718 did not attenuate amylin's reduction of food intake, suggesting that amylin does not produce its effect through the release of CCK (30). Instead it appears to be the converse, that the anorectic effects of CCK and bombesin depend partly on the presence of amylin or its near cousin, the calcitonin gene-related peptide (CGRP) (38). Amylin is ~50% homologous to the 37-amino-acid neuropeptide α- and β-CGRP (39), which all act on a family of related G protein-coupled receptors. Both CGRP and amylin peptides have nearly identical N- and C-terminal regions and the disulfide bridge between amino acids 2 and 7 (40). In contrast to amylin, which is only expressed by the β cell of the pancreas, CGRP is expressed in many tissues, such as the brain, spinal cord, thyroidal C cells and pancreatic islets, and is a potent vasodilator, involved in regulating blood flow (40). When amylin action is blocked with a

CGRP receptor antagonist, the anorectic effects of CCK and bombesin are also attenuated in rats (38).

There is evidence to support a role for endogenous amylin in regulating body weight and food intake. Combined amylin and CCK, each at sub-threshold doses, is twenty fold more potent in inhibiting food intake in rodents than when administered separately (41). Both amylin and CCK are naturally secreted in response to mixed meals. Furthermore, there is a 23% to 29% increase in body weight in *amylin* gene knockout mice (31). Finally, unlike lithium chloride, amylin's suppressive effect on food intake is not aversive. Amylin may peripherally produce anorexia by inhibiting nitric oxide, a major regulatory agent in the gastrointestinal tract, because L-arginine, a precursor for nitric oxide, partly reverses the effect of amylin on food intake (42–44).

Gastric Emptying

The rate of gastric emptying plays a major role in blood glucose homeostasis in normal subjects by controlling the delivery of carbohydrate to the small intestine. Of peptides known to be secreted in response to ingested carbohydrate, amylin and glucagon-like peptide-1 have been reported to inhibit gastric emptying at near-physiological concentrations (43,45). A subcutaneous injection of amylin produced a dose-related slowing of gastric emptying in both diabetic and control rats, in greater magnitude than other gut peptides (46). The rate of gastric emptying of carbohydrate-containing liquids in humans is normally regulated at ~2 kcal/min (8.36 Joules/min) as a result of feedback from mucosal receptors in the small intestine (47). The rate of gastric emptying accounts for 34% of the variance in peak plasma glucose after a 75-g oral glucose load in normal subjects (48). The benefit of ingesting soluble fiber on glycemic control in type 2 diabetes probably reflects retardation of gastric emptying and slower intestinal carbohydrate absorption (49).

With the consequent accumulation of food in the stomach and greater gastric distension, amylin may result in earlier meal termination by slowing gastric emptying. The presence of specific binding sites for amylin have been reported in the stomach fundus (50). The major brain sites regulating gastric motility are the dorsal vagal complex of the brainstem, composed of the nucleus tractus solitarius, dorsal motor nucleus of the vagus, and area postrema. These regions receive information from visceral afferents and integrate the information to regulate efferent nerve activity to the stomach (51). Amylin-like receptors have been found in two locations in the hindbrain of the rat, the area postrema and the nucleus accumbens (52). Amylin no longer inhibited gastric emptying after subdiaphragmatic vagotomy in rats (53) or after surgical ablation of the area postrema (54). Gastric emptying became accelerated in amylin deficient BB rats (55,56) and in rats treated with amylin antagonists (57).

In a randomized, double-blind placebo-controlled crossover study, delayed gastric emptying of both solid and liquid meals after infusion of pramlintide was reported in men with type 1 diabetes with amylin-deficiency (11). A similar effect was observed in early type 2 diabetic subjects, who were relatively hyperamylinemic (58), and in normal healthy subjects (59). In support of amylin's effect on gastric emptying, infusion of pramlintide (50 μg h-1) had no effect on plasma glucose when glucose was infused intravenously rather than given orally (60). Interestingly, amylin no longer slowed gastric emptying during hypoglycemia, induced by exogenous insulin. Thus, the feedback mechanism which beneficially restricts nutrient availability by slowing gastric emptying during normoglycemia and hyperglycemia is appropriately blocked during hypoglycemia (61).

Amylin to Treat Obesity

In animal and human studies, it has been found that amylin delays gastric emptying and decreases food intake. Obese subjects exhibit hyperamylinemia, and their elevated amylin levels may cause down-regulation of amylin receptors. Obese subjects often experience hyperglycemia and increased corticosteroid secretion (9), both of which enhance amylin secretion in response to a meal, which could lead to amylin resistance. Amylin administration to obese individuals may have the potential to promote weight loss by delaying gastric emptying and inhibiting food intake, and overcoming resistance at the target tissues.

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