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Amylinergic control of food intake

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Abstract

Amylin is a pancreatic B-cell hormone that plays an important role in the regulation of nutrient fluxes. As such, amylin reduces food intake in laboratory animals and man, slows gastric emptying and it reduces postprandial glucagon secretion. Amylin deficiency which occurs concomitantly to insulin deficiency in diabetes mellitus, may therefore contribute to some of the major derangements associated with this disorder (hyperphagia, excessive glucagon secretion, accelerated rate of gastric emptying). The described actions of amylin all seem to depend on a direct effect of amylin on the area postrema (AP). As to amylin's satiating effect, the physiological relevance of this action is underlined by studies involving specific amylin antagonists and amylin-deficient mice. In the AP, amylin seems to modulate the anorectic signal elicited by CCK. Subsequent to AP activation, the amylin signal is conveyed to the forebrain via distinct relay stations. Within the lateral hypothalamic area, amylin diminishes the expression of orexigenic neuropeptides such as orexin and MCH. Whether these effects contribute to amylin's short term satiating action remains to be determined. Recent studies suggest that amylin may also play a role as a long-term, lipostatic signal, especially when other feedback systems to the brain are deficient. Obese, leptin-resistant Zucker rats which are hyperinsulinemic and hyperamylinemic, were chronically infused with the amylin antagonist AC 187. AC 187 significantly elevated food intake in obese Zucker rats while having no effect in lean controls. This indicates that at least under certain conditions, chronic blockade of endogenous amylin action may lead to an increase in food intake and/or body weight. As mentioned, the site and mechanism of action for peripheral amylin to reduce food intake seems to be well established. It is less clear how centrally administered amylin reduces food intake although it is well known that 3rd ventricular administration of amylin produces a very strong and long-lasting anorectic action. Amylin receptors have been described in various hypothalamic nuclei but the endogenous ligand of these receptors remains to be investigated. The same holds true as to the physiological relevance of the anorectic effect seen after central amylin administration.

Keywords: Amylin; Area postrema; CNS pathway; Refeeding; Amylin knockout mouse

1. Introduction

Amylin, or islet amyloid polypeptide (IAPP), was first isolated from pancreatic amyloid deposits. These typically occur in human type 2 diabetes mellitus, in feline diabetes mellitus, and in insulinomas in dogs, cats and humans [1]. Amylin, however, is also a physiological product of pancreatic B-cells from where it is co-secreted with insulin. Shortly after its discovery, amylin was shown to reduce food intake in rats and mice and numerous experiments confirmed these original findings. The anorectic action of amylin appears to be one important factor in amylin's overall role to control the influx of nutrients into the circulation. Apart from amylin induced anorexia, amylin's actions to reduce gastric acid secretion, to limit the rate of gastric emptying, and to diminish pancreatic glucagon and digestive enzyme secretion are other factors that serve the same purpose [reviewed in 2,3]. Interestingly, all these effects seem to be mediated by a direct action on the central nervous system by interaction with area postrema (AP) neurons. Due to these actions, amylin is considered a necessary and complementary factor to insulin in the control of nutrient flux by regulating nutrient appearance and the postprandial glucose concentration [3]. These actions are also the basis for the use of amylin analogs as pharmaceutical drugs in the treatment of type 2 diabetes mellitus.

The best investigated function of amylin and the focus of this review is its role as a hormone contributing to meal-ending satiation [reviewed in 2,4]. However, amylin is among the more interesting hormones affecting food intake because in addition to the immediate effect of amylin to control meal size, several

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studies suggest that amylin may also be involved in the long-term control of food intake and body weight. Hence, amylin shares characteristics similar to the established adiposity signals leptin and insulin [5,6].

2. Regulation of amylin synthesis and secretion

It is likely that the pancreatic B-cells constitute the main source for circulating and postprandially released amylin [7]. Pancreatectomized cats have virtually no meal-induced release of amylin and no postprandial increase in blood amylin levels [unpublished]. In rats, meal intake results in a marked four- to fivefold increase in the plasma amylin concentration. This increase is correlated to the size of the ongoing meal and occurs in less than 5 min after meal onset. The meal-induced increase in pancreatic amylin secretion is believed to be the basis for the satiating effect of endogenous amylin (see below).

Due to their co-synthesis in pancreatic B-cells and co-localization in the same secretory vesicles, insulin and amylin are normally co-secreted upon activation with the appropriate stimuli, i.e., nutrients, incretin hormones, or neural input [8,9]. Under physiological conditions, the secretions of amylin and insulin occur at a ratio of approximately 1:100 which is reflected by a similar ratio of peripheral amylin: insulin plasma levels in the fed state. Under fasting conditions, the peripheral amylin levels are about 10% those of insulin which reflects the slower clearance of amylin versus insulin. However, dissociation from this fixed ratio in amylin versus insulin secretion is possible, e.g. in human obesity, various rat models of obesity (see also "Amylin as an adiposity signal"), diabetes mellitus, pancreatic cancer, and pharmacological intervention (e.g. dexamethasone) where amylin is over-secreted relative to insulin [9–11]. The underlying mechanism(s) for this dissociation from the physiological ratio and the possible functional significance for the regulation of nutrient fluxes and of food intake are unknown at present.

3. Characterization of amylin's effects on food intake as a satiating signal

Amylin shares the typical characteristics of satiating hormones such as cholecystokinin (CCK) which are involved in the control of meal size [12]. As outlined, amylin is released during food ingestion, and it dose-dependently reduces meal size. Further, after intraportal or intraperitoneal injection amylin has a rapid onset and brief duration of action [13]. However, during chronic amylin infusion [14,15], amylin not only reduced food intake by decreasing average meal size, but in some studies it also reduced meal number by increasing the duration of the intermeal interval. Similarly, amylin increases the latency to eat under certain experimental conditions [13]. The latter effects may be taken as evidence that amylin also has an effect on postprandial satiety. However, neither chronically elevated amylin levels nor an acute increase in amylin prior to meal onset mimics the natural situation because physiologically, amylin is acutely released during, but not before a meal. Therefore, the best characterized function of amylin is to reduce meal size and it remains to be investigated whether amylin also has an effect on postprandial satiety [reviewed in 4,16]. The latter could e.g. be tested by administering amylin towards meal ending or in the intermeal interval.

The anorectic action of amylin appears to be specific. It has been shown repeatedly that amylin does not reduce feeding by producing a conditioned taste aversion or by an unspecific effect (e.g. via a reduction in drinking) [13,17,18]. Even at doses 100× to 300× higher than the minimal effective dose of peripheral amylin (0.5 μg/kg), it did not produce a conditioned taste aversion response.

The lowest dose of exogenous amylin that produced a significant reduction in feeding yielded plasma amylin levels that were about two-times higher than the concentrations measured postprandially [19]. Hence, strictly spoken physiological amylin concentrations that occur at the end of a spontaneous meal have not yet been shown to reduce feeding. This may however be related to different kinetics of the blood amylin concentration after exogenous amylin delivery rather than endogenous secretion because the course of amylin concentration may possibly be as important as the peak amylin concentration.

The most important argument indicating that amylin is a physiological regulator of meal size is provided by studies showing that peripherally or centrally delivered amylin antagonists produce an effect opposite to that of amylin, i.e., an increase in eating, mainly via a meal size effect [20,21]. In the latter study [21], the amylin antagonist AC 187 was infused directly into the area postrema (see following paragraph).

4. Primary site of action mediating the satiating effect of amylin

Amylin binding sites have been described in various CNS locations involved in the regulation of food intake, and amylin is known to cross the blood brain barrier via specific transport systems [22,23]. The exact role of many of these receptor sites and of the specific transport systems is unknown, however. Experimental evidence clearly supports the idea that the anorectic effect of peripheral amylin is mediated by direct humoral action on the area postrema (AP) in the hindbrain [e.g., 15,21,24]. Hence, blood borne amylin acts via a brain site where it has easy access to the receptor neurons due to the lack of a functional blood brain barrier in the AP. As mentioned, the effects of amylin to reduce the rate of gastric emptying and pancreatic glucagon secretion also seem to depend on the AP.

Experimental evidence supporting a pivotal role of the AP to mediate amylin's anorectic action is provided by behavioral studies that have shown repeatedly that after acute but also chronic peripheral administration, amylin's effect is abolished in rats with lesions in the AP/NTS region [15,24]. In contrast, none of the techniques used to block nerval afferent information from the periphery to the brain was able to abolish the anorectic action of peripheral amylin [25–27]. The importance of the AP for mediating the anorectic effect not only of exogenous, but also of endogenous amylin was demonstrated in that an infusion of amylin into the AP potently reduced feeding whereas infusion of the amylin antagonist AC 187 increased food intake due to an increase in meal size. AC 187 infused into the AP also reduced the anorectic effect induced by a peripheral amylin injection. These