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Review

Amylin-mediated control of glycemia, energy balance, and cognition

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HIGHLIGHTS

- Amylin is physiologically relevant for glycemic and energy balance control.
- Amylin receptor agonists reduce blood glucose, feeding, and body weight.
- Amylin may reduce cognitive and neurodegenerative symptoms in Alzheimer's disease.
- Amylin may exert anti-psychotic effects.
- Amylin-based pharmacotherapies may provide benefit to metabolic/cognitive outcomes.

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ABSTRACT

Amylin, a peptide hormone produced in the pancreas and in the brain, has well-established physiological roles in glycemic regulation and energy balance control. It improves postprandial blood glucose levels by suppressing gastric emptying and glucagon secretion; these beneficial effects have led to the FDA-approved use of the amylin analog pramlintide in the treatment of diabetes mellitus. Amylin also acts centrally as a satiation signal, reducing food intake and body weight. The ability of amylin to promote negative energy balance, along with its unique capacity to cooperatively facilitate or enhance the intake- and body weight-suppressive effects of other neuroendocrine signals like leptin, have made amylin a leading target for the development of novel pharmacotherapies for the treatment of obesity. In addition to these more widely studied effects, a growing body of literature suggests that amylin may play a role in processes related to cognition, including the neurodegeneration and cognitive deficits associated with Alzheimer's disease (AD). Although the function of amylin in AD is still unclear, intriguing recent reports indicate that amylin may improve cognitive ability and reduce hallmarks of neurodegeneration in the brain. The frequent comorbidity of diabetes mellitus and obesity, as well as the increased risk for and occurrence of AD associated with these metabolic diseases, suggests that amylin-based pharmaceutical strategies may provide multiple therapeutic benefits. This review will discuss the known effects of amylin on glycemic regulation, energy balance control, and cognitive/motivational processes. Particular focus will be devoted to the current and/or potential future clinical use of amylin pharmacotherapies for the treatment of diseases in each of these realms.

Contents

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1. Introduction

One commonly observed feature in the pancreas of individuals with type 2 diabetes mellitus (T2DM) is the presence of insoluble amyloid aggregations, or deposits of protein folded in β-sheets, in the islets of Langerhans. Although the precise mechanisms by which these deposits develop are still not entirely clear, initial identification of amyloid in the pancreas of diabetic patients dates back to the early 1900s [1]. Later reports confirm the presence of pancreatic amyloid deposits in the islets of humans [2,3], non-human primates [4,5], and cats [6,7] with diabetes. Characterizing the composition of the amyloid aggregations took decades, but eventually it was determined that the amyloid comprised a previously unknown 37-amino acid peptide, which was termed islet amyloid polypeptide (IAPP) [8,9] or, less commonly, diabetes-associated peptide [10].

Intriguingly, although aggregated IAPP is a prominent feature in pancreatic tissue from diabetic individuals, IAPP was also found in normal pancreatic islets [9]. This suggested that IAPP might have an important role in the normal endocrine function of the pancreas. Later research provided evidence that IAPP itself is not inherently cytotoxic, supporting the notion that it may have physiologically relevant effects under normal conditions. Rather, the process of IAPP aggregation disrupts normal cellular function and can induce cell death [11,12]. As researchers began to uncover physiological effects of IAPP in non-disease states, thus demonstrating roles for the peptide beyond its association with pathophysiological amyloid deposits, it was renamed amylin [13–15], which remains the most commonly used name today.

Indeed, we now recognize that amylin has important neuroendocrine functions in glycemic regulation (see [16–18] for review). Amylin is co-secreted with insulin from the pancreatic β-cells in response to nutrient stimuli during a meal, and suppresses postprandial blood glucose levels [18–23]. The beneficial glycemic effects of amylin led to the development and subsequent clinical usage of an FDA-approved amylin analog, pramlintide, as an adjunctive therapy for the treatment of diabetes mellitus [24,25]. However, amylin also has potent effects on energy balance, and acts within the brain to reduce food intake and body weight [26,27]. It is important to note that the energy balance and glycemic effects of amylin are dissociable under carefully controlled experimental conditions [28]. Collectively, these metabolic effects of amylin have brought attention to this peptide as a leading candidate for the development of new pharmacotherapies for the treatment of obesity and diabetes [27,29–32].

Recent research has brought to light a putative novel role for amylin in processes related to cognition, including possible ameliorative effects on neurodegenerative and psychotic disorders [33,34]. Although this area of research is still relatively new, the notion that amylin-based pharmacotherapies could be used for treatment of such disorders is already being considered [35]. Here, an overview of amylin's roles in glycemic regulation, energy balance control, and cognitive processes will be provided. In addition, the current and potential future clinical use of pharmaceuticals targeting the amylin system to treat disorders related to each of these realms will be discussed.

2. Glycemic regulation

Normal glycemic regulation involves coordinated physiological effects that maintain adequate levels of available glucose; the specific responses required depend on the energy status of the individual. Simply put, when a human or non-human animal is fasted, glycemic regulation primarily entails the conversion of stored energy to readily usable energy (e.g., conversion of liver glycogen to glucose), a process initiated by the pancreatic hormone glucagon. When a non-human animal or human is actively consuming or has recently consumed food, a different set of responses is required to control the influx of glucose from the food while suppressing the endogenous production of glucose from glycogen. Amylin is released during the feeding/fed state in response to nutrient entry into the gastrointestinal tract. Accordingly, amylin and amylin receptor agonists reduce postprandial blood glucose levels and improve glycemic control in humans and in non-human animal models [18]. The mechanisms by which this occurs, and the current use of amylin-based drugs for the treatment of diabetes mellitus, will be discussed in this section.

2.1. Amylin-mediated control of blood glucose levels in normoglycemic individuals

When a human or other animal eats, amylin is released with insulin from pancreatic β-cells [18–23]. The roles of amylin and insulin for glycemic regulation have been suggested to be complementary [16,18], rather than a direct functional interaction. The effects of insulin on blood glucose levels are well known; this hormone facilitates transport of glucose from the bloodstream into peripheral tissues such as skeletal muscle (recently reviewed in [36]). However, blood glucose levels are influenced not only by the transport of glucose into tissue, but also the entrance of glucose from ingested food into the bloodstream. This side of the equation is controlled in part by amylin, which slows gastric emptying [37,38], thereby delaying and controlling the entry of nutrients/glucose into the small intestine and subsequently into circulation. This effect can be observed when plasma amylin is experimentally increased to levels comparable to those normally observed in a postprandial state [39].

The available evidence indicates that amylin may act centrally to inhibit gastric emptying. In one study [40], subdiaphragmatic deafferentation was carried out in rats according to the procedure of Walls and colleagues [41], which eliminates vagal afferent signaling while maintaining a portion of vagal efferent communication. This manipulation did not impact the ability of amylin to suppress gastric emptying in the animals [40], suggesting that the effect may be mediated by direct action in the brain. The area postrema (AP), a nucleus in the caudal hindbrain that is important for the physiological and behavioral effects of amylin [30,42], may be one important central site of action for the effects of amylin on gastric emptying. Lesions of the AP appear to diminish the ability of amylin to suppress gastric emptying (reviewed in [43]). However, the neural mechanisms by which amylin might act in the AP to impact gastric emptying are unclear. The dorsal vagal complex of the hindbrain, comprising the AP, the nucleus of the solitary tract (NTS), and the dorsal motor nucleus of the vagus (DMV), plays a critical role in the neural control of gastric emptying (reviewed in [44,45]). Briefly, the NTS integrates relevant neural and humoral signals, including direct vagal input, and sends this information to the DMV. Gastric-projecting preganglionic neurons in the DMV then provide autonomic control over gastric emptying (reviewed in [45]). It is clear that the AP projects to the NTS [46] and that peripheral amylin induces cFos in both of these nuclei [47]. To speculate, amylin may act in the AP, or