

Upper Silesian Center of Children's Health in Katowice, Poland

# The role of amylin in glucose homeostasis regulation and possible future usage in adolescents with type 1 diabetes



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## Abstract

Amylin is a polypeptide hormone, which is produced mainly in pancreas and released along with insulin. It has got numerous actions affecting glucose homeostasis regulation. At present more and more studies show the usefulness of amylin analogue — pramlintide as an adjunctive treatment with insulin in type 1 as well as in type 2 diabetes.

The data come also from the adolescent population. Through its influence on glucagon secretion and gastric motility amylin can help in easier maintenance of "near-normoglycemia" state in patients with diabetes. It is a promising new agent in diabetes treatment.

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**key words:** diabetes, glucose homeostasis, amylin analogue

Amylin (IAPP, islet amyloid polypeptide), one of the less known pancreatic hormones, has been lately attracting more and more attention. It is produced in beta-cells of pancreas along with insulin and C-peptide and in smaller amounts also in the stomach and in the dorsal root ganglia of the spinal cord. Amylin consists of 37 amino acids [1, 2]. It is a proteolysis product of a precursor particle — proamylin. Its gene is localized on the 12 chromosome. The secretion of amylin is stimulated by the food ingredients like glucose and arginine.

The definite role of amylin in maintaining the homeostasis hasn't been fully elucidated yet, but some of the conducted studies have led to a number of notions [1, 3–11]. Amylin decreases glucose concentration by:

- suppression of endogenous glucagon secretion and subsequent;
- reduction of post-meal hepatic glucose production;
- slowing down gastric emptying;
- central satiety regulation;
- which leads to decrease in postprandial glucose level (Table 1).

In normal conditions during the meal, appearance of food in gastro-intestinal tract increases the secretion of insulin, amylin and the glucagon-like peptide (GLP-1). When the food gets to the stomach and intestine, glucose and amino acids are being released into the blood

stream. In respond, beta-cells of pancreas secrete insulin and amylin. The latter limits glucose appearance while the former promotes glucose removal from the circulation. The insulin and amylin secretion is glucose concentration-dependent and becomes completely inhibited with serum glucose level at 60 mg/dL (3.3 mmol/L).

Amylin is a glycogen synthesis and glucose expenditure modulator in the skeletal muscles. It has an effect on insulin-resistance state induction in that tissue and probably also in the liver. In normal metabolism amylin can act in concert with insulin in order to switch the place of carbohydrates bioavailability from glycogen to the adipose tissue reserves by making the skeletal muscles relatively insulin resistant. The dose of insulin needed to stimulate carbohydrate metabolism in the adipose tissue concurrently stays unchanged.

Amylin affects glucagon secretion, i.e. inhibits the amino acid-stimulated secretion and decreases endogenous glucose production in the postprandial period [12, 13]. While discussing the issue one should mention the differences in glucagon response depending on the type of the stimulus, which was confirmed by the experimental studies. This results in different secretion of glucagon in patients with diabetes and accompanying beta-cell dysfunction. The release of glucagon in these patients, in response to hypoglycemia, is usually preserved or sometimes decreased, while the amino acid-stimulated secretion can be aggravated. This phenomenon is caused by the lack of alpha-cell suppression following the beta-cell function deficit. Moreover, amylin inhibits post-meal glucagon secretion via acting through the CNS.

The insulin and amylin release is regulated not only by the glucose concentration but also by the incretin effect.

Furthermore, amylin slows down the gastric emptying. These mechanisms contribute to the glucose level regulation and its concentration maintenance in the blood during the postprandial period below 140 mg/dL (7.8 mmol/L).

Amylin is thought to be an anorectic hormone as it prevents the hunger appearance, which can also affect the glucose homeostasis [14].

**Table 1.** Characteristics of amylin and pramlintide effects

- |  |
|--|
| • Amylin — physiological effects   |
| — Suppression of endogenous glucagon production (especially in the postprandial state) |
| — Reduction in postprandial hepatic glucose production                                 |
| — Reduction in gastric emptying time   |
| — Centrally mediated induction of satiety  |
| — Reduction in postprandial glucose levels   |
| • Pramlintide — effects in type 1 and type 2 diabetes mellitus                         |
| — Reduction in prandial glucose  |
| — Reduction in HgA <sub>1c</sub>   |
| — Reduction in prandial glucagons  |
| — Slowed gastric emptying  |
| — Weight loss  |

In type 1 diabetes the insulin and amylin secretion is almost absent. In type 2 diabetes the situation is different, which depends on the phase of the disease and beta-cell destruction grade. As the disease develops, the beta-cell dysfunction progresses along with the insulin and amylin secretion decrease. The disturbances of insulin secretion rhythm go usually together with similar amylin secretion changes.

Insulin, amylin and GLP-1 secretion is thought to be the key, leading to postprandial hyperglycemia, which is found in diabetic patients. The amylin and GLP-1 deficit causes stomach emptying acceleration followed by increased glucose absorption into the blood stream with a subsequent elevation of post-meal glycemia. Moreover, the glucagon secretion increases, which effects in up-regulated glucose production in the liver [15].

In type 1 diabetes of the autoimmune background there is a parallel lack of insulin and amylin [16–18]. The amylin deficit can elevate the risk of severe post-insulin hypoglycemia. These numerous actions of amylin in glucose homeostasis regulation and in other fields have led to the attempts of applying it in diabetes therapy as an adjunctive treatment.

In some of the physiological actions of amylin and the actions of its analogue — pramlintide in diabetic patients have been compiled (Table 1).

Most of the reports deal with using amylin and its analogues in the treatment of type 2 diabetes. It is connected with the positive actions in terms of postprandial hyperglycemia and its anorectic potential. However, there is an increasing body of evidence stating that the amylin use as a therapy supporting insulin action in type 1 diabetes of the autoimmune origin, can be beneficial. Pramlintide is an amylin analogue, which has already found its place in diabetes treatment [7, 19–23]. Additionally, within the last two years some reports about pramlintide use in adolescents with diabetes appeared [24, 25].

The intensive insulin therapy and sustaining the “near normoglycemia” state in patients with type 1 diabetes is frequently connected with the increased risk of hypoglycemia and also with weight gain. Insulin treatment suppresses glucagon secretion and as a result, it decreases endogenous glucose production. The introduction of amylin as an adjunctive treatment could help to prevent that kind of threats. Combining insulin therapy with pramlintide allows to treat diabetes in more physiological manner [8, 26–30]. Some authors believe however, that pramlintide in combination with insulin improves glycemia control in patients with diabetes but also increases the risk of hypoglycemia. Not all authors share that point of view [19, 21, 28, 31].

Kruger and Gloster [32] point at a positive role of pramlintide in regulation of glucose inflow into the blood

stream through the inhibition of glucagon secretion in post-meal period and also through the influence on the gastrointestinal motility. These authors suggest that pramlintide use, as an agent supporting the insulin therapy, either in type 1 or type 2 diabetes, decreases glycosylated hemoglobin and does not rise the risk of hypoglycemia.

Morrero et al. [33] analyzed, by means of questionnaire, the result of 29-week observation of patients with type 1 diabetes. The patients were treated either with multiple injections of insulin or with constant subcutaneous insulin infusion (CSII). In 130 subjects pramlintide as an adjunctive treatment was used and 136 received placebo. In the pramlintide group a significant body weight loss and the insulin requirement decrease were noted. HbA<sub>1c</sub> as an indicator of the metabolic control was similar in both groups.

Ratner et al. [34] presented the results of a multicenter study of 651 patients with diabetes, who were treated with pramlintide in addition to insulin. They noticed a positive effect of this therapy on the metabolic control of the disease. Levetan et al. [26] followed the subjects with type 1 diabetes treated with CSII and pramlintide. They revealed that the addition of pramlintide as an adjunctive agent led to the significant improvement in glycemia profile and decrease of the levels of glucagon and triglycerides. Similar positive effects of pramlintide on the glycemia control in type 1 diabetic patients are reported by other authors [4, 35].

Stadler et al. [36] conducted an interesting study in 11 type 1 diabetic patients. They assessed the beta-cell function after successful kidney-pancreas transplant. These authors stated that the increased insulin secretion is accompanied by the similar changes in amylin release. They concluded that amylin concentration can be an indicator of beta-cell function in patients after the transplant.

Whitehouse et al. [31] conducted a multicenter, randomized trial in a group of 480 patients with type 1 diabetes. They used pramlintide as adjunctive agent with insulin. In the group that received amylin analogue a significant HbA<sub>1c</sub> decrease was seen when comparing to the placebo group. The authors emphasize good tolerance of the drug.

Baron et al. [37] highlight, as particularly useful, applying GLP-1 apart from amylin for the supporting insulin therapy.

The synthetic analogues of these hormones are at present available for clinical use [38]. However, they were not being used in Poland so far.

The role of amylin is also interesting in terms of obesity. In obese people hyperamylinemia, very often hyperglycemia and an increased corticosteroid secretion are a frequent finding. An additional phenomenon to hyper-

amylinemia, is an amylin resistance. Hence applying amylin treatment can break this resistance and, as studies show in obese people, can lead to glycemia normalization and weight loss.

Apart from the carbohydrate metabolism and glucose homeostasis, amylin reveals also some other actions, such as effect on bone tissue metabolism. It inhibits the osteoclastic activity allowing the normal bone rebuild process (i.e. the osteocytes resorption by osteoclasts with subsequent rebuilding the bone tissue by osteoblasts). Hence it can be used in osteoporosis treatment, also in patients with type 1 diabetes. Some reports about amylin having a role in endothelial damage appeared lately. It is probably connected with some gene mutation [39].

All these different actions of amylin point at its usefulness in an adjunctive therapy with insulin in patients either with type 1 or type 2 diabetes [40–43]. Not only does the lack of insulin occur in diabetes but also there is an amylin and GLP-1 deficit. That leads to over-expression of glucagon in postprandial period and acceleration of stomach emptying, which is followed by a post-meal glycemia increase. Hence amylin and GLP-1 agents usage can positively affect gluco-regulation.

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