White paper

IAPP (Amylin), a gut-brain axis hormone involved in metabolic regulation

The islet amyloid polypeptide (IAPP) also known as amylin, is an anorexic neuroendocrine hormone co-secreted with insulin. This molecule has been shown to be deficient in individuals with diabetes and to play an important role in glucose homeostasis.

What is IAPP?

IAPP is a neuroendocrine hormone encoded by chromosome 12 in human [1]. This molecule is produced and stored in pancreatic β-cells together with insulin. IAPP is co-secreted with insulin by the β-cells of the pancreas in response to nutrient stimuli such as glucose, arginine, fatty acids, and plays a major role in regulating blood glucose levels, food intake, and body mass [1; 2; 3]. IAPP synthesis and excretion from the pancreas are like insulin, with low levels during fasting and increased levels after a meal [1; 3]. It has been described that Insulin-to-IAPP co-secretion ratio is consistently maintained at approximately 10:1 to 100:1 [1]. The circulating half-life of endogenous IAPP is short and has been described as < 20 min [1; 2].

While it is predominantly produced and secreted by the pancreas, IAPP is also synthesized in lower quantities within other cell types and tissues, like: enteroendocrine cells in the gastrointestinal tract, pulmonary tissue, the central nervous system -CNS- and specific brain regions [1; 2; 3].

This 37-residue -long hormone (~4 kDa) has as main physiological functions: delay gastric emptying, regulate satiety, and control glucose homeostasis [3; 4; 5]. IAPP is derived from an 89 residue pre- pro-IAPP protein, processed into a 67 residue pro- IAPP, and subsequently to a mature biologically active 37 amino acid protein monomer through cleavage by prohormone convertase 1/3 (PC1/3), prohormone convertase 2 (PC2), and carboxypeptidase-E [2]. (Figure 1). Once the mature hormone is secreted it interacts with receptors, being the three most important variants of amylin receptors determined by the type of RAMP molecule resulting in AMY_1, AMY_2, and AMY_3 [3]. (Figure 2).

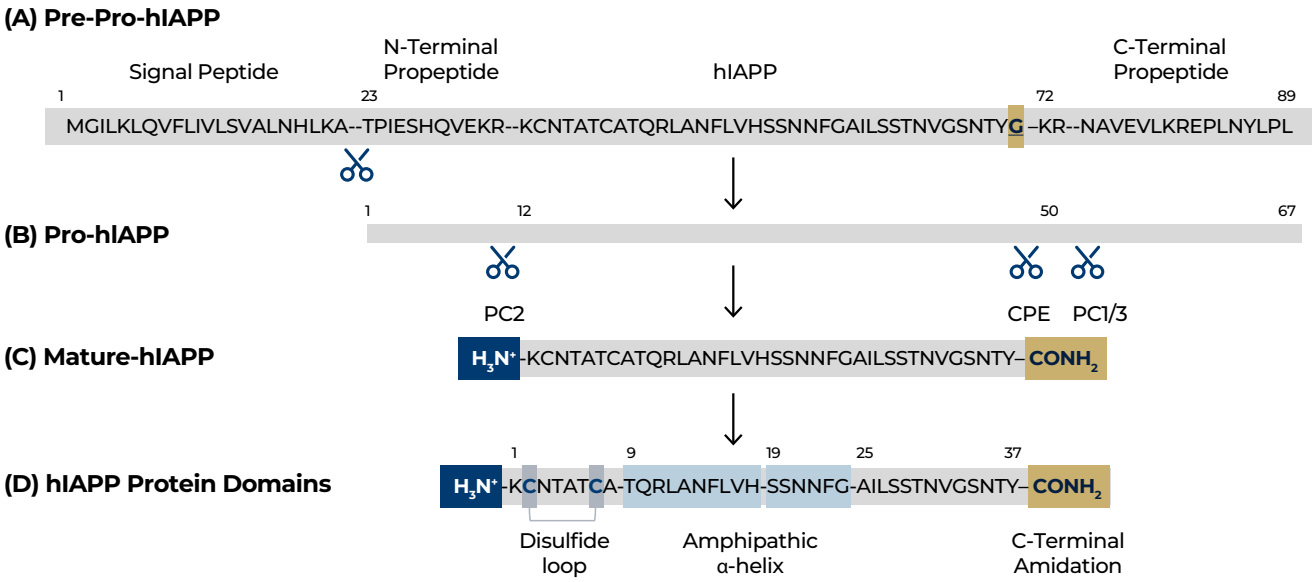

Figure 1. Processing of the human IAPP. (A) The 89 amino acid pre- pro- hIAPP having the signal peptide from residue 1 to residue 22 is cleaved. (B) The 67 residue pro- hIAPP peptide is cleaved by PC2, PC1/3 and CPE to a mature 37 residue hIAPP. (C) Mature hIAPP. (D) Mature hIAPP showing a disulfide bond (green) between cysteine 2 and cysteine 7, amphipathic α- helix (highlighted in dark green) and C- terminal helix amidation.

Modified from: Muhammad, T., Pastore, S. F., Good, K., Yu, W. H., & Vincent, J. B. (2025). The role of amylin, a gut-brain axis hormone, in metabolic and neurological disorders. FASEB bioAdvances, 7(3), e1480.

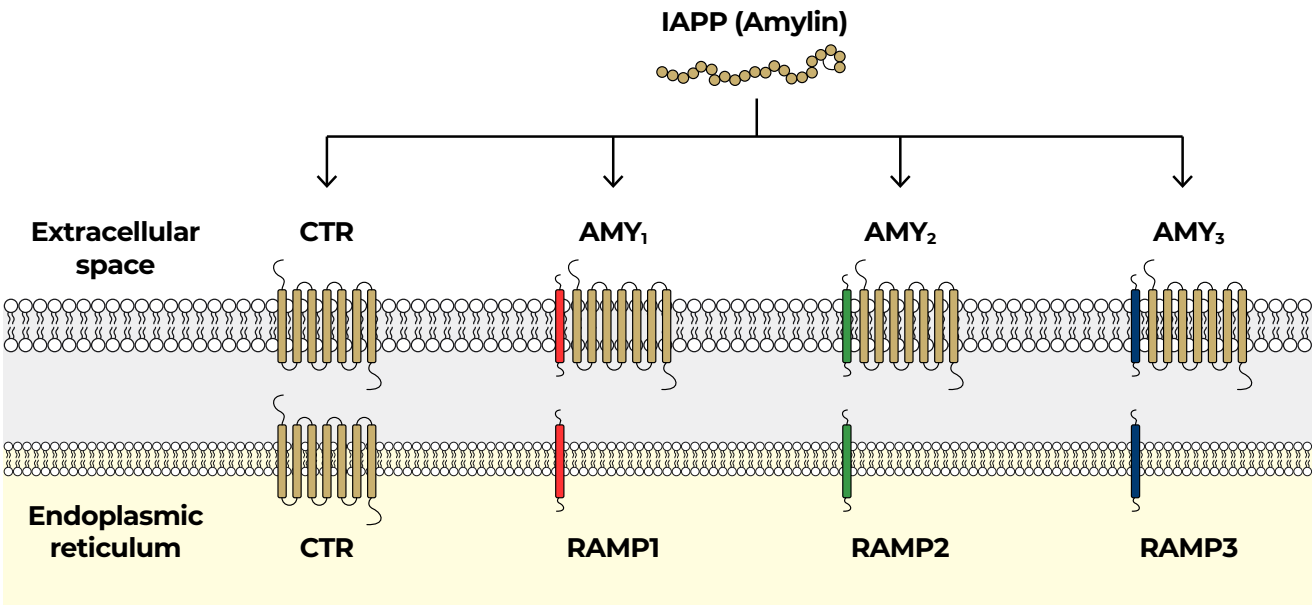

Figure 2. Schematic representation of the complex relationship between the calcitonin receptor (CTR), the receptor activity-modifying proteins (RAMP), and three main amylin receptors (AMY1, AMY2, and AMY3). RAMP enhances the susceptibility of the CTR for IAPP.

Modified from: Eržen, S., Tonin, G., Jurišić Eržen, D., & Klen, J. (2024). Amylin, Another Important Neuroendocrine Hormone for the Treatment of Diabesity. *International journal of molecular sciences*, *25*(3), 1517.

Physiological functions of IAPP

IAPP is known to influence satiation, inhibit glucagon secretion after meals (postprandial secretion), slow gastric emptying, and reduce digestive enzyme secretion via both peripheral and central mechanisms [2; 3].

It has been shown that IAPP suppresses postprandial glucagon secretion indirectly and directly through its effect on pancreatic α-cells and reduces hepatic glucose mobilization after nutrient ingestion [3]. It slows gastric emptying and pancreatic enzyme secretion, lowering glucose levels in the circulation and directly targets different structures in the central nervous system by the activation of noradrenergic neurons [2; 3].

Muhammad *et al.* refer on their 2024 review to the concept of "homeostatic eating control", where it is possible to differentiate two types of signals: adiposity signals, which are related to long-term body fat regulation, and meal-associated signals that respond to food intake [2]. Similarly, studies have shown that IAPP may improve leptin sensitivity in obesity [2; 3] where leptin, a hormone secreted by the adipose tissue, signalizing the level of triglycerides in the adipose tissue, often becomes less effective [2; 3].

IAPP has been implicated in broader actions, such as playing a role in lipid metabolism by potentially modulating chylomicron uptake, opposing glycogen synthesis and activating glycogenolysis and glycolysis (indirectly affecting liver metabolism) and being involved in neurocognition. Moreover, IAPP has been suggested to be involved in blood pressure regulation, impairing endothelium-dependent relaxation responses suggesting IAPP-induced hypertension, and modulating bone remodelling and formation (in animal models) [1]. See Figure 3.

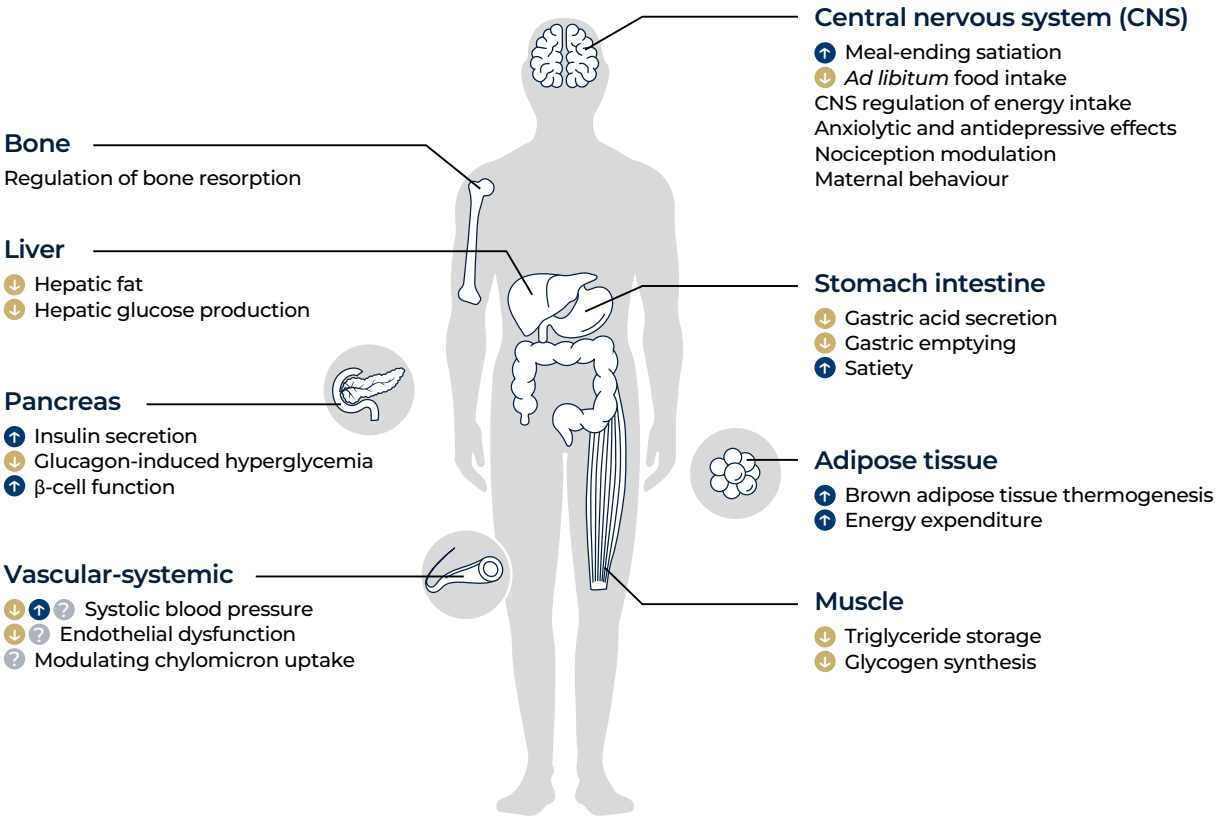

Figure 3. Organ-specific physiological actions of IAPP. Golden arrows indicate decreased levels/activity, blue arrows show an increase, and question marks indicate areas that are not yet fully understood.

Modified from: Volčanšek, Š., Koceva, A., Jensterle, M., Janež, A., & Muzurović, E. (2025). Amylin: From Mode of Action to Future Clinical Potential in Diabetes and Obesity. Diabetes therapy: research, treatment and education of diabetes and related disorders, 16(6), 1207–1227.

All these actions have been described and implicated in multiple disorders. Metabolic disorders such as obesity, type 1 and 2 diabetes mellitus, gestational diabetes. Neurological disorders like Alzheimer's and Parkinson's disease, cerebrovascular dementia, depression and alcohol use disorder, and other related disorders as bone metabolism, polycystic ovary syndrome and cardiac dysfunction [2].

References

1. *Amylin: From Mode of Action to Future Clinical Potential in Diabetes and Obesity.* **Volčanšek, Š., Koceva, A., Jensterle, M., Janež, A., & Muzurović, E.** s.l. : Diabetes therapy : research, treatment and education of diabetes and related disorders, 2025, Vols. 16(6), 1207–1227.
2. *The role of amylin, a gut-brain axis hormone, in metabolic and neurological disorders.* **Muhammad, T., Pastore, S. F., Good, K., Yu, W. H., & Vincent, J. B.** s.l. : FASEB bioAdvances, 2025, Vols. 7(3), e1480.
3. *Amylin, Another Important Neuroendocrine Hormone for the Treatment of Diabesity.* **Eržen, S., Tonin, G., Jurišić Eržen, D., & Klen, J.** s.l. : International journal of molecular sciences, 2024, Vols. 25(3), 1517.
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