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The Resurgence of Amylin

At the recent congress organized by the European Association for the Study of Diabetes (EASD), held in Madrid back in September 2024, many members of the Spanish Diabetes Society (SED) had the opportunity to attend. This allowed us to enjoy the presentation of new advances in diabetes, both in terms of understanding the disease and future treatments. One particular topic caught my attention, and I take this opportunity to delve into it—the prominence of a molecule for the treatment of diabetes and obesity. This molecule is amylin, which, together with GLP-1 and GIP receptor agonist drugs—already well known for their spectacular entry into the obesity market—seems to have an even stronger effect on weight reduction and diabetes control. Their synergistic action, meaning they are administered together, is superior to each drug used separately.

In summary, the explanation for these effects is that amylin acts on the satiety centers located in the brain to reduce food intake while improving glucose metabolism by delaying gastric emptying and inhibiting pancreatic glucagon secretion.

THERAPEUTIC HISTORY

Pramlintide is the first synthetic analog of amylin that was approved for the treatment of type 1 diabetes mellitus (T1DM) as an adjuvant to insulin and was later approved in the U.S. for the treatment of type 2 diabetes mellitus (T2DM), showing a 7.9% reduction in body weight. This analog has never been marketed in Europe, which is why it remains unfamiliar to us.

More recently, new amylin analogs with improved pharmacological profiles and great potential for weight reduction in obese patients have emerged. **Cagrilintide** is a long-acting amylin analog that, in a phase 2 clinical trial, demonstrated that its once-weekly subcutaneous administration resulted in a 10.8% weight reduction vs 9% with liraglutide treatment and 3% with placebo.

Other amylin-based molecules currently in early-stage clinical trials include long-acting amylin agonists combined with **GLP-1 analogs** and other enterohepatic hormones. In a 20-week phase 2 clinical trial, weekly cagrilintide in combination with semaglutide **(CagriSema)** showed a 15.6% reduction in body weight vs 5.1% with semaglutide alone, in people with diabetes and obesity. The mean HbA1c reduction with CagriSema was also greater vs cagrilintide alone (–2.2% vs –1.8% vs –0.9%, respectively). Currently, several phase 3 clinical trials are evaluating the safety and efficacy profile of CagriSema vs other analogs in people with obesity and T2D. Additionally, other oral GLP-1 and amylin co-agonists (amicretin) are being investigated in early-phase clinical trials. In conclusion, if we add the new results presented at the EASD24 congress to the list of studies, we anticipate that amylin will position itself as part of the new trend in treatments for both diabetes and obesity. Given that some European pharmaceutical companies are intensively researching the efficacy and safety of these molecules, we expect them to become available in our pharmacies as new treatment options in the near future ***(see Table 1)***.

BIOLOGICAL FUNCTIONS OF AMYLIN

Amylin is not a recent discovery; we have »

THE RESULTS PRESENTED AT THIS YEAR'S EASD CONGRESS INDICATE THAT AMYLIN WILL BECOME A KEY PLAYER IN NEW TREATMENTS FOR BOTH DIABETES AND OBESITY

NAME	MECHANISM OF ACTION	CLINICAL TRIAL PHASE	ADMINISTRATION	PHARMACEUTICAL COMPANY
CAGRISEMA*	Amylin RA	Phase 3	Subcutaneous, once a week	Novo Nordisk
CAGRILINTIDE	Amylin RA, GLP-1 RA	Phase 2	Subcutaneous, once a week	Novo Nordisk
AZD6234	Amylin RA	Phase 1	Subcutaneous, once a week	AstraZeneca
ZP8396	Amylin RA	Phase 1	Subcutaneous, once a week	ZealandPharm
AMYCRETIN	Amylin RA, GLP-1 RA	Phase 1	Oral, once a day	Novo Nordisk
DACRA	Amylin RA, Calcitonin RA	Phase 1	Not available	Eli Lilly

TABLE 1. Amylin RA (Amylin receptor agonist), GLP-1 RA (GLP-1 receptor agonist)
Treatment for diabetes with obesity

AMYLIN AND INSULIN WORK TOGETHER TO REGULATE METABOLISM

» known for decades that amylin is a hormone produced in the pancreas, alongside insulin. Amylin plays an important role in the regulation of glucose metabolism. It helps control blood sugar levels by delaying gastric emptying, which in turn reduces the rate at which glucose enters the bloodstream after meals. It also promotes satiety, which can help control appetite. Amylin and insulin work together to regulate metabolism. While insulin controls blood sugar by promoting the use of circulating glucose by different peripheral tissues and activating enzymes responsible for glucose metabolism, amylin regulates the flow of glucose from the digestive system to the bloodstream by delaying gastric emptying and suppressing glucagon secretion in the postprandial period, contributing to the inhibition of hepatic glucose production.

One of amylin's best-known actions is its **anorexigenic effect**. Weight reduction induced by amylin occurs through its action on the central nervous system. Once the amylin molecule binds to the receptor complex located in the brain's satiety-regulating centers, an anorexigenic signal is generated that induces satiety, reduces food intake, and consequently leads to significant weight loss in humans. This observation regarding body weight reduction has been therapeutically leveraged in patients with obesity through the use of amylin analogs, as we have discussed. Amylin analogs also act as **hypoglycemic agents** by reducing postprandial glucagon secretion and delaying gastric emptying, effects that, along with weight reduction through appetite control, represent a good alternative for the treatment of diabetes in individuals with obesity. Some of amylin's described actions counteract insulin's action in peripheral tissues. The biological action of amylin on the liver and skeletal muscle involves inhibiting some of insulin's anabolic actions in these tissues. Based on these observations, some studies suggest that an alteration in amylin regulation could be involved in the pathogenesis of **peripheral insulin resistance**. This effect would only make biological sense in the early stages of diabetes development in overweight or obese patients, where plasma amylin levels may be elevated alongside insulin.

Amylin in bone has been described as a growth factor that stimulates osteoblast proliferation and promotes bone formation. Finally, »

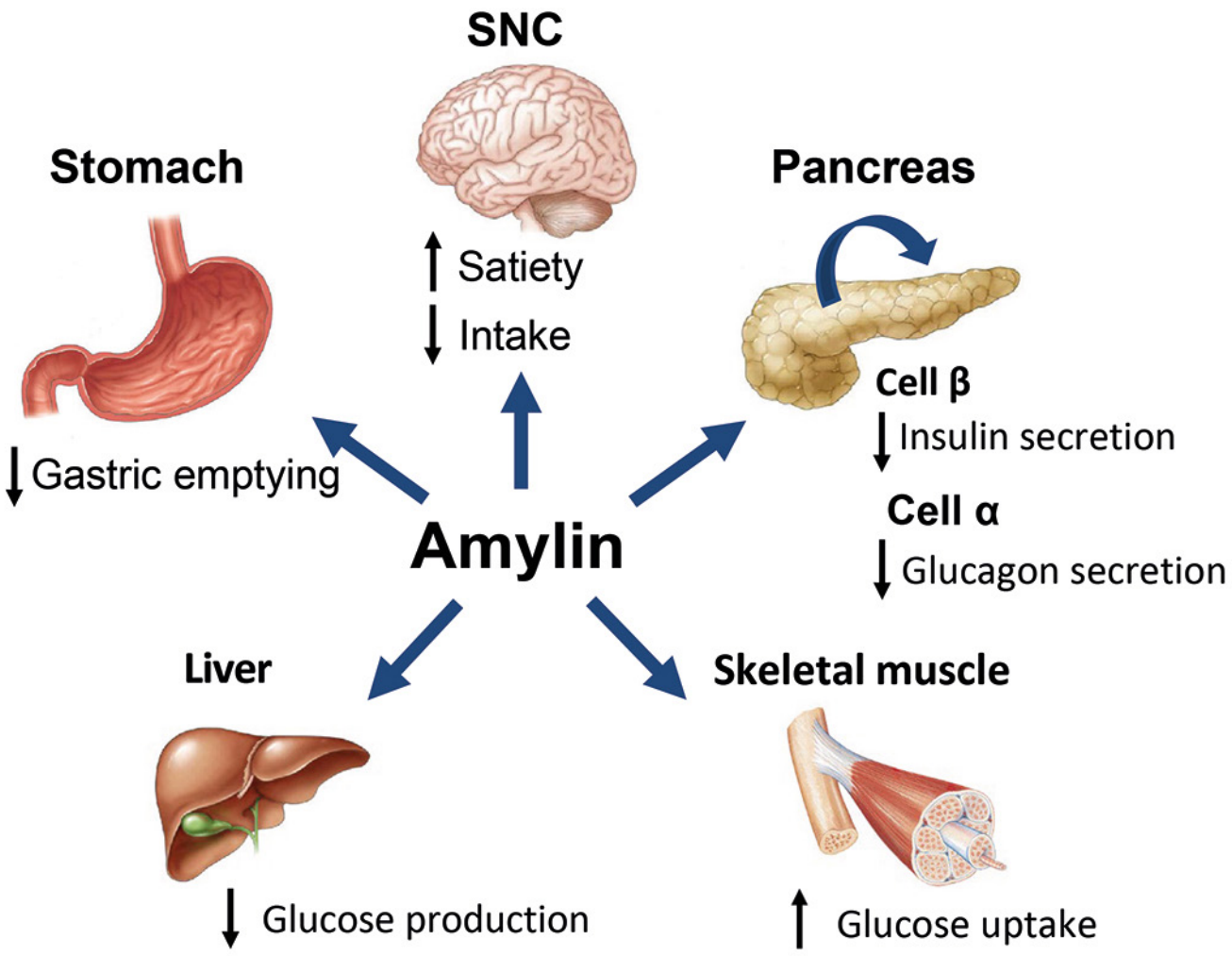


FIGURE 1. Biological actions of amylin on peripheral organs

» it has also been shown to generate proliferative signals on the beta cells themselves through autocrine mechanisms.

Pharmacological research efforts are focusing on the brain's mechanisms of action of amylin, particularly in neurons that regulate food reward and satiety behavior. The functional interaction of amylin with other hormones, such as leptin or insulin, on neuronal signaling pathways is being explored to open new therapeutic options not only for obesity but also for other neurological disorders. In particular, the therapeutic use of amylin or its analogs has highlighted possible effects in Alzheimer's disease and some psychotic disorders. It is expected that, along with clinical development, the eventual commercial availability of long-acting amylin analogs could improve the acceptance of this remarkable hormone for the treatment of some neurological disorders beyond the scope of diabetes and obesity ***(Figure 1)***.

TOXIC ACTIONS OF AMYLIN AND AMYLOID DEPOSIT FORMATION IN THE PANCREAS

Amylin was discovered in 1987 as the main protein component of the **amyloid deposits** present in pancreatic islets in patients with T2DM. Currently, the presence of these amyloid deposits is considered a pathological feature of this disease and bears some similarity to the amyloid deposits found in the brains of patients with Alzheimer's disease. We cannot say that they are identical, but we can say that both diseases share common pathogenic mechanisms. This fact has meant that for years, the study of amylin focused more on the toxic effects of amyloid deposits in the pancreatic islet and strategies to prevent them, rather than studying the biologi- »

AMYLIN WAS DISCOVERED WHEN IDENTIFIED IN AMYLOID DEPOSITS PRESENT IN THE PANCREATIC ISLETS OF PATIENTS WITH T2DM

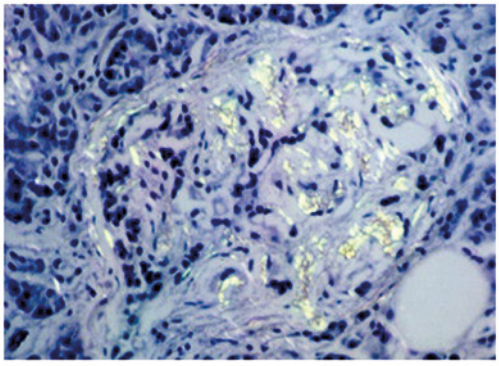
» cal effects it produces. Fortunately, its biological actions have been clarified, and new therapeutic opportunities for diabetes and obesity are emerging, as previously described. Nevertheless, amylin has structural characteristics that occasionally, and still without a clear cause, cause it to aggregate and form insoluble amyloid plaques that deposit in the pancreas *(Figure 2)*.

The progressive failure of β-pancreatic function, along with the loss of β-cell mass, are key factors in the manifestation of T2DM. One of the main factors involved in β-cell deterioration is the accumulation of amyloid substance deposits in the pancreatic islets, which is considered a hallmark of T2D. The process of fiber formation and aggregation to form amyloid **(amyloidogenesis)** is a common mechanism in other degenerative diseases like Alzheimer's disease or systemic amyloidosis.

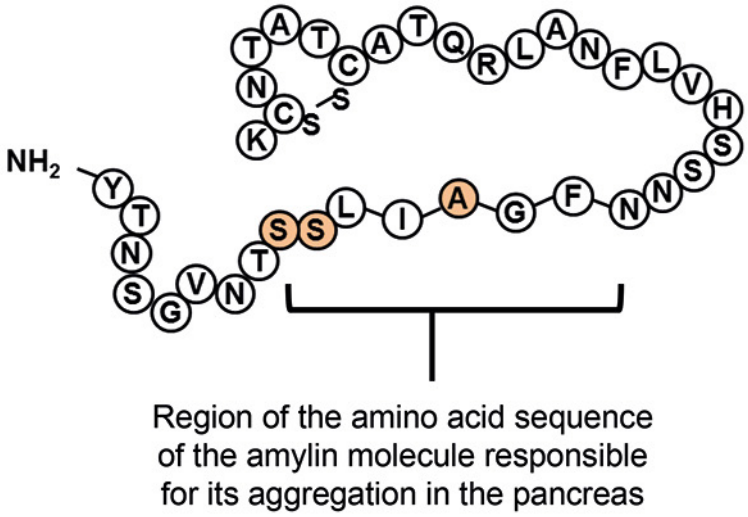
There are several hypotheses explaining the origin of amylin fiber aggregation in the context of T2DM. A widely accepted and logical hypothesis suggests that prolonged hyperglycemia leads to increased amylin synthesis and thus higher amylin concentrations within β-pancreatic cells. This phenomenon would facilitate its accumulation, eventually leading to cell death.

AMYLOID, INFLAMMATION, AND ANTI-INFLAMMATORY THERAPY IN T2DM

In recent years, several studies have shown that islet inflammation is a major cause of β-cell dysfunction in T2DM. Consequently, a lot of attention is being paid to the development of therapeutic strategies to target inflammation associated with the disease. This process involves the infiltration of inflammatory cells (macrophages) into the islet and an increase in the expression of molecules called pro-inflammatory cytokines. It has been suggested that amyloid in the islet promotes macrophage activation and the secretion of pro-inflammatory cytokines that are toxic to the cells. The fact that these pathways contribute to islet inflammation leads to the investigation of the possibility that they could serve as very promising therapeutic targets. D



Pancreatic islet of T2DM with refringent images demonstrating amyloid deposits



Region of the amino acid sequence of the amylin molecule responsible for its aggregation in the pancreas

FIGURE 2

CONCLUSIONS

Amylin is a hormone produced by beta cells and secreted alongside insulin. Its main actions include facilitating the reduction of blood glucose, inducing satiety, and delaying gastric emptying, among many other effects.

Amylin has been used for the treatment of T1DM and T2DM along with insulin. It has not yet been approved for use in Europe. Recent amylin analogs have proven highly effective in weight reduction and T2DM control. The association between T2DM and neurodegenerative disorders, particularly in elderly patients, could expand amylin's therapeutic use in the coming years.

The aggregation of amylin and the formation of amyloid deposits in the pancreatic islet is a characteristic feature of T2DM. The aggregation of amylin leads to inflammation of the pancreatic islet and alterations in β-cell function. Therapies designed to reduce islet inflammation and prevent amyloid aggregation in the pancreas of T2DM patients have generated great expectations for the recovery of insulin secretion function.

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