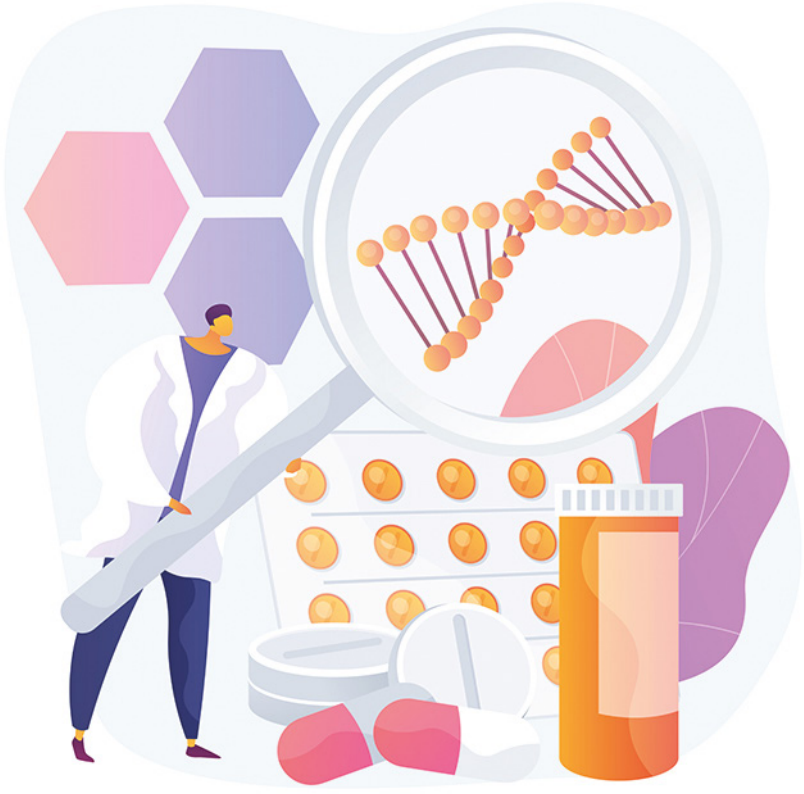
Dr. David Cano González.
IInstitute of Biomedicine of Seville, Hospitales Universitarios Virgen del Rocío /CSIC/University of Seville (Seville, Spain).
Member of SED Basic Experimental Diabetes Working Group.

From the Laboratory to the Clinic:

The Discovery of GLP-1 Analogues



In the vast landscape of medical science, there are discoveries that stand out not only for their health impact but also because of their intricate history of research and development. One of these milestones is the identification of the hormone GLP-1 (Glucagon-Like Peptide-1) and its subsequent application in the treatment of diabetes and obesity. In recent years, the media, and surprisingly, influencers and celebrities through social networks have popularized the drugs known as GLP-1 analogues. Nevertheless, the development process of these medications has been a long journey that spans decades of research, both in basic science to understand their molecular and cellular mechanisms and in pharmacology and clinical fields for their application in patients.

Since the early 20th century, it had been suggested that factors produced in the intestine influenced blood glucose levels by activating the secretion of the pancreas (even though insulin had not yet been discovered at the time, it was known that the pancreas was the main regulator of glucose levels in the bloodstream). However, this hypothesis lacked experimental support. In fact, in those years, attempts were made to treat diabetes by injecting intestinal extracts, but without success. It wasn't until 1964, with the development of methods to measure insulin in the blood, that it was demonstrated that oral glucose intake stimulated insulin secretion more than direct injection into the bloodstream. This phenomenon is known as the **incretin effect,** a physiological mechanism whereby the body, after food intake, "alerts" pancreatic beta cells to produce insulin in response to the imminent rise in blood glucose levels. The demonstration of the existence of the incretin effect marked the beginning of the search for the responsible intestinal hormones.

In 1971, **John Brown** at the University of British Columbia (Canada) identified the first incretin factor. Brown discovered that an intestinal hormone, known as **Gastric Inhibitory Peptide (GIP)**, originally associated with acid secretion in the stomach, induced the release of insulin in response to glucose. They proposed that this hormone should be called Glucose-Dependent Insulinotropic Polypeptide, a name that more accurately reflected its biological function. This finding opened new possibilities for the treatment of diabetes. Unfortunately, it was soon discovered that GIP had no effect on people »

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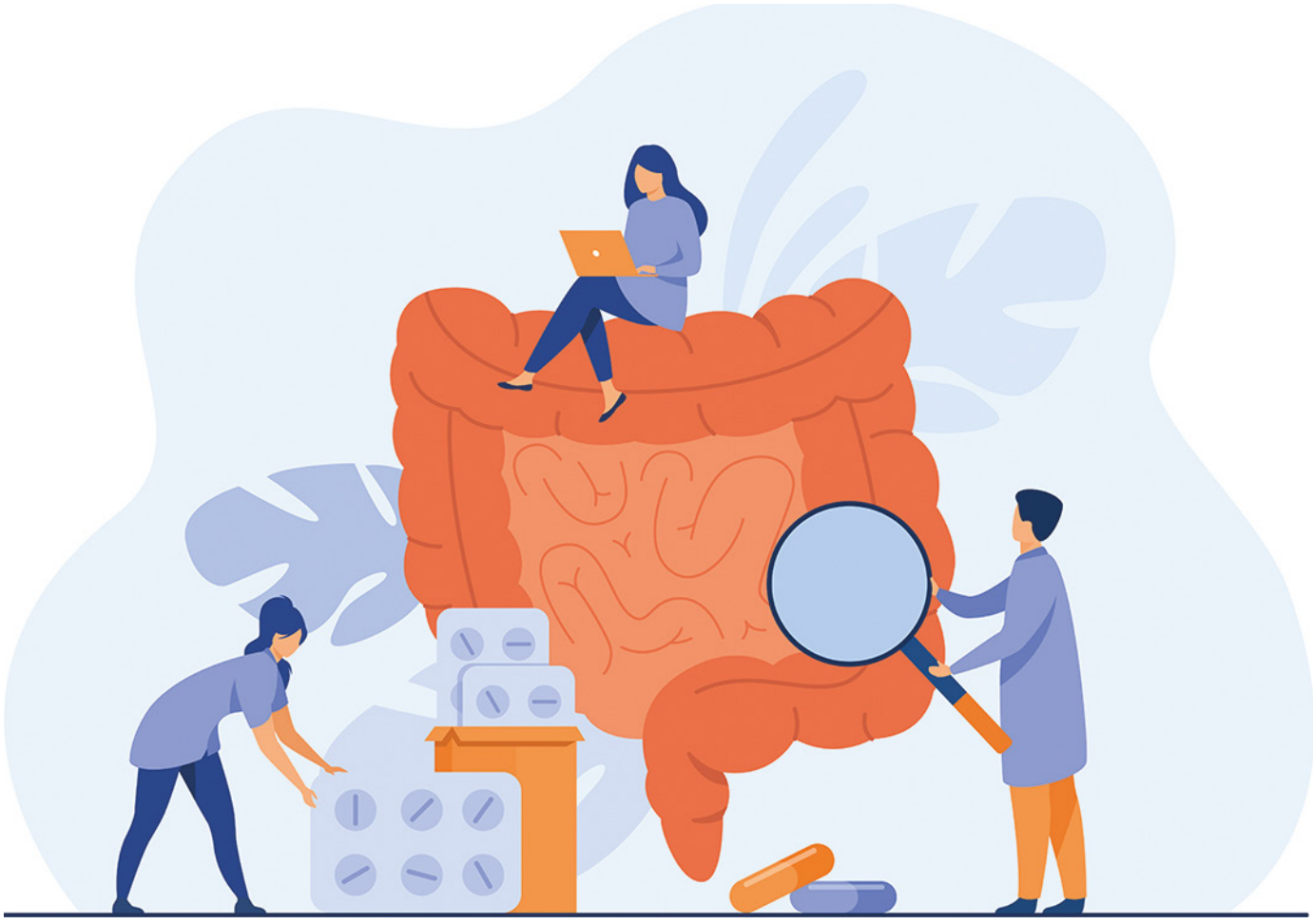

» with diabetes, and the therapeutic interest in intestinal hormones waned for many years.

However, it was suspected that there could be > 1 hormone with an incretin function, which triggered the research of other possible candidates. Among them, **Glucagon-Like Peptide-1 or GLP-1** stood out, known as the "intestinal glucagon." Former studies had pointed to the presence of a glucagon-like hormone produced in the intestine, which is similar to that generated by pancreatic alpha cells. However, its exact role in the body and its therapeutic potential were unknown at that time. In the early 1980s, **Joel Habener** at the Massachusetts General Hospital in Boston (United States) (considered one of the pioneers of GLP-1) used genetic engineering techniques, which were innovative at the time, to clone and sequence the gene that encoded GLP-1. Surprisingly, a few years later, Jens Holst at the University of Copenhagen and **Daniel Drucker, Svetlana Mostov, and Joel Habener in** Boston simultaneously demonstrated that GLP-1 induced insulin secretion in pancreatic beta cells. Subsequent studies conducted in humans confirmed the incretin effect of GLP-1, which, in fact, was more pronounced than that of GIP.

Initially, the discovery of GLP-1 was received with moderate enthusiasm and some skepticism from a therapeutic standpoint. After all, GIP had also shown an incretin effect but had not been »

ENTHUSIASM FOR GLP-1 DECLINED IN THE YEARS FOLLOWING ITS DISCOVERY DUE TO THE LIMITATION OF ITS THERAPEUTIC POTENTIAL CAUSED BY ITS SHORT HALF-LIFE IN THE BLOODSTREAM

» effective in treating diabetes. However, this perception changed dramatically when it became evident that, unlike GIP, GLP-1 had the ability to stimulate insulin secretion to almost normal levels in individuals with type 2 diabetes mellitus (T2DM). Additionally, another notable characteristic of GLP-1 was its ability to inhibit glucagon secretion, unlike GIP, which stimulated such secretion. Consequently, GLP-1 had the potential to regulate blood glucose levels in diabetic patients in 2 different ways: by inducing adequate insulin secretion and curbing the excess secretion of glucagon, which are key aspects of T2DM. These findings represented a milestone in our understanding of the molecular mechanisms underlying T2DM, opening a new therapeutic horizon with vast implications that could not have been foreseen at that time.

However, as is common in science, especially in medical research, these promising results were hindered when trying to apply them to patient treatment. Scientists observed that the effect of GLP-1 was short-lived, with a half-life of just about 2 minutes in the bloodstream. This meant that the hypoglycemic effect of GLP-1 in diabetic patients could only be achieved through continuous subcutaneous infusions, limiting its widespread therapeutic use, and enthusiasm for GLP-1 waned in the following years. Despite these challenges, several research groups continued their work, trying to elucidate the molecular mechanisms through which GLP-1 regulates blood glucose levels, and the processes involved in its rapid degradation in the bloodstream. In 1995, **Jens Holst's** group at the University of Copenhagen made a crucial discovery by identifying that GLP-1 was degraded by the enzyme **dipeptidyl peptidase IV (DPP-IV).** From this finding, they proposed that inhibiting this enzyme could be a new therapeutic option for treating T2DM. Three years later, they published a pioneering article, where they described **DPP-IV inhibitors** that prevented the degradation of GLP-1. They demonstrated that this protection resulted in increased insulin secretion in response to glucose. These results were fundamental in driving the clinical development of DPP-IV inhibitors, which were eventually approved for use in 2006. Since then, DPP-IV inhibitors such as vildagliptin and sitagliptin have been crucial components in treating T2DM.

The significance of these discoveries is reflected in the numerous awards received by these researchers, including the recent award of the Princess of Asturias Prize for Technical & Scientific Research 2024, shared with American Jeffrey M. Friedman, the discoverer of leptin, a hormone that controls appetite.

Simultaneously, researchers dedicated to discovering or synthesizing clinically effective GLP-1 analogues in the laboratory. These compounds are known as GLP-1 receptor agonists (GLP-1RAs). In 1992, **exendin-4** was isolated, a peptide extracted from the saliva of a lizard, known as the Gila monster (Heloderma suspectum), which demonstrated the ability to induce insulin secretion similar to GLP-1. An important advantage from a clinical application perspective was that exendin-4 was not degraded by the DPP-IV enzyme. From this finding, a synthetic version of this peptide, known as **exenatide,** was developed. After several years of clinical trials, its clinical use was approved in 2005, becoming the **first GLP-1RA marketed for the treatment of T2DM.** Another therapeutic alternative was the development of modified versions of GLP-1 designed to be more stable and have a longer half-life in the human body. These analogues retained the ability to stimulate insulin secretion and suppress glucagon, but with improved efficacy and reduced susceptibility to enzymatic degradation by DPP-IV. One of the first to be developed was **liraglutide,** a variant of GLP-1 bound to a palmitic acid chain. This modification provided partial resistance to DPP-IV and reduced elimination through renal filtration, significantly increasing its half-life in the bloodstream to approximately 12 hours, making it suitable for daily administration as a treatment. Liraglutide was approved in 2010, and since then, other GLP-1RAs, such as **dulaglutide** and **semaglutide** (approved in 2014 and 2017, respectively), have been developed with an even longer half-life. These analogues have already become important tools in managing diabetes today. For more information on the use of GLP-1RAs in the treatment of diabetes, the reader can find an excellent review in the **February issue of this year's journal.**

Since the first clinical trials were conducted with liraglutide in diabetic patients, it was observed that GLP-1RAs, in addition to improving glycemic control, in many cases induced **weight loss.** Although this result might be surprising from a clinical perspective, it was not as surprising to researchers »

SINCE THE FIRST CLINICAL TRIALS EVER CONDUCTED ON LIRAGLUTIDE IN DIABETIC PATIENTS, IT WAS OBSERVED THAT GLP-1 RAS, IN ADDITION TO IMPROVING GLYCEMIC CONTROL, ALSO INDUCED WEIGHT LOSS IN MANY CASES

» in the field of GLP-1. Decades of intensive research since the discovery of GLP-1 revealed that this intestinal hormone has effects on many other organs besides the pancreas. In fact, GLP-1 receptor molecules have been identified in various organs and cell types, including the heart, blood vessels, immune cells, and the brain, among others, suggesting that GLP-1 could also have effects on these organs. Several experimental studies have confirmed this hypothesis. One of the best-established extrapancreatic effects of GLP-1 at the experimental level is its influence on the central nervous system, including the regulation of appetite and satiety, which was already described in animal models in 1996. On the other hand, it is well-established that GLP-1RAs inhibit gastric and intestinal motility, leading to a delay in gastric emptying and, as a result, a slowdown in nutrient absorption. This link between GLP-1 and reduced food intake made GLP-1RAs a promising treatment for obesity. In fact, in 2014, the use of a GLP-1 RA (liraglutide) was approved for the first time in the United States specifically for the treatment of obesity.

Clinical studies have supported the safety and efficacy of GLP-1RAs in the treatment of diabetes and obesity, which has led to their widespread adoption in clinical practice. However, GLP-1RAs continue to surprise. Recent studies have revealed that, in addition to improving glycemic control and reducing body weight, these drugs appear to have beneficial effects on the cardiovascular system. The **cardiovascular protection** of GLP-1RAs seems to be the result of a myriad of direct and indirect effects on various organs, including anti-inflammatory capability, vasodilatory effect, improvement of endothelial function, prevention of atherosclerotic plaque formation, increased contractility and heart rate, reduction of epicardial fat, protection vs ischemic heart damage, improvement of fatty liver, enhancement of renal function, and improvement of insulin resistance in the liver, muscle, and fat, among others. Although many of these extra-pancreatic effects of GLP-1 RAs have been demonstrated mainly in animal models and therefore require validation in high-quality clinical trials, their broad spectrum of action makes them attractive therapeutic options for treating comorbidities associated with diabetes and obesity.

In recent years, GLP-1RAs have gained popularity not only in the medical community but also in popular culture. Social media and mainstream media have helped spread information about these drugs, leading to greater interest and awareness regarding the treatment of diabetes and obesity. However, this popularization has also led to a certain trivialization in some cases, where GLP-1RAs are promoted as quick fixes for weight loss without adequately addressing lifestyle and dietary changes. This trivialization presents significant challenges for health care professionals and public health educators as they try to combat the spread of misinformation and promote responsible use of these drugs.

In conclusion, the discovery of the GLP-1 hormone and the development of GLP-1RAs have transformed the landscape of diabetes and obesity treatment. What began as basic research in molecular biology has led to innovative therapies that improve the quality of life for millions of people worldwide. It is crucial to recognize the significant advances made while responsibly addressing the dissemination of information about these drugs, ensuring their proper use, and avoiding the trivialization of serious medical conditions. Ultimately, the future of GLP-1 analogs looks promising, with ongoing research that could further expand their clinical applications and improve health on a global scale. D

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