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Editorial

INNOVATIVE THERAPIES IN TYPE 2 DIABETES: THE DREAM OF THE FUTURE

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Motto:

*"*I think that any life which merits living lies in the effort to realize some dream, and the higher that dream is, the harder it is to realize.*"*
Eugene O'Neill, *The Unknown O'Neill: Unpublished or Unfamiliar Writings of Eugene O'Neill*

The unprecedented progress in medicine, like in all other sciences, is also present in the recent years in the field of diabetology. We presented in a recent paper the main information regarding the pathophysiology of type 2 diabetes mellitus (T2DM) and how specific knowledge in this field evolved during the last years [1]. Nevertheless, clinicians mostly see pathophysiology as a practical mean to understand spontaneous evolution of a specific disease and to identify new and better ways for treating it. Therefore, we aimed now to analyze T2DM from the recently opened perspectives in its therapy. Newly introduced medications in this field tend to act upon multiple pathophysiological mechanisms, and some of them influence the comorbid conditions frequently associated with T2DM.

Glucagon-like peptide 1 (GLP-1) receptor agonists efficiently reduce HbA_{1c} by increasing the β-cell insulin secretion in a glucose-dependent manner, and therefore have a reduced risk of inducing hypoglycemia. They also inhibit the α-cell glucagon secretion (and thus reduce the hepatic glucose output), reduce body weight by decreasing appetite and delay gastric emptying, with favorable consequences on postprandial hyperglycemia. Moreover, they exert beneficial effects on other cardiovascular risk factors such as dyslipidemia, high blood pressure and endothelial dysfunction and it is hoped they will preserve beta cell function on the long term [2,3].

Given the multiple positive effects of GLP-1 receptor agonists, the high interest shown by

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different pharmaceutical companies in developing new agents in this class becomes easily understandable [4]. Soon after the first GLP-1 receptor agonist, exenatide (AstraZeneca; administered either twice daily or once weekly), was introduced, other compounds reached the market: liraglutide (Novo Nordisk; once daily), lixisenatide (Sanofi; once daily), albiglutide (GlaxoSmithKline; a GLP-1 receptor agonist developed by fusioning a human GLP-1 dimer with recombinant human albumin and administered once weekly) [5,6] and dulaglutide (Eli Lilly; a GLP-1 analog associated with a Fc fragment of human antibodies, administered once weekly) [7,8]. Other molecules in different development stages are: efpeglenatide (Hanmi Pharmaceutical; an exendin-4 analog conjugated to a non-glycosylated human Fc fragment, now in phase IIb studies for once weekly or once monthly administration) [9], and semaglutide (Novo Nordisk; a GLP-1 receptor agonist with once weekly subcutaneous or oral administration – the latter formulation entering phase 3 clinical studies in the near future) [9-12]. Studies using a subcutaneously implanted osmotic pump to release exenatide at a slow and constant rate during one year are also under way [13,14].

As to dipeptidyl peptidase 4 (DPP-4) inhibitors, 5 compounds are approved at present in the United States and/or in Europe: sitagliptin, saxagliptin, alogliptin, linagliptin and vildagliptin. Other members of this class such as anagliptin, teneligliptin and gemigliptin are approved for clinical use in some Asian countries. All DPP-4 inhibitors are administered once daily, except for vildagliptin, which requires twice-daily dosage [15]. Omarigliptin (Merck Sharp & Dohme), a once-weekly administered DPP-4 inhibitor, is in the phase of clinical studies [16,17].

Sodium-glucose co-transporter (SGLT)-2 inhibitors proved their efficacy not only in decreasing glycemia and HbA_{1c}, but also in improving some other cardiovascular risk factors. They lower blood pressure (due to the natriuretic effect induced by the SGLT-2 inhibition) and body weight (due to losing approximately 280 kcal/day by glycosuria) [18]. Some of these compounds already started to be successfully used in clinical practice in the United States and/or in Europe: dapagliflozin (AstraZeneca), canagliflozin (Janssen) and empagliflozin (Boehringer Ingelheim / Eli Lilly). The last recently produced a great impact in the reunited fields of cardiology and diabetology, as it was proven to reduce the rate of cardiovascular events in a specific outcome trial [19]. Other SGLT-2 inhibitors are approved only in Japan or still in the phase of clinical trials: tofogliflozin (Chugai Pharma), ipragliflozin (Astellas Pharma), luseogliflozin (Taisho Pharmaceutical), ertugliflozin (Merck / Pfizer) [20].

Besides inhibiting SGLT-2, canagliflozin also seems to have a mild inhibitory effect on SGLT-1, but without clinical significance. Meanwhile, another compound (LX4211 – sotagliflozin; Lexicon Pharmaceuticals) is in research at present. LX4211 inhibits both SGLT-2 and SGLT-1 and determines an increased glucose excretion rate in the urine, higher levels of circulating GLP-1 and lower intestinal absorption of glucose [21-23]. Preliminary study results suggest that dual inhibition of SGLT-2 and SGLT-1 might offer some advantages compared to the mere inhibition of SGLT-2 [20,23].

Newer drugs to stimulate insulin secretion are also under research. Thus, activation of free fatty acid receptors (FFAR), naturally occurring on the surface of pancreatic β-cells, by synthetic ligands, only stimulates insulin secretion when glucose concentrations are high, hence with a low risk for hypoglycemia. The insulin-secreting mechanism involved by the activation of these

receptors is scarcely known, but seems to differ from the pathway used by GLP-1 receptor agonists [24,25]. One of these FFAR activators, fasiglifam (TAK-875; Takeda Pharmaceuticals), induced a significant HbA_{1c} decrease, but studies were interrupted due to its hepatotoxicity [26]. Studies using other similarly acting compounds are ongoing.

Newer approaches also center on classical molecules such as metformin. Being placed by all T2DM guidelines on the first therapeutic step, metformin became the most used antihyperglycemic drug. Nevertheless, its mechanism of action is still insufficiently known, but supposedly involves multiple pathways. Metformin is mostly absorbed in the upper part of the small bowel. Its plasma levels poorly correlate to the antihyperglycemic effects, thus proving that metformin also has a pre-systemic effect: as it concentrates in the L-cells of the small intestine, metformin stimulates the release of GLP-1 and peptide YY [4,27].

Delayed-release metformin (Metformin DR; Elcelyx) is a new slow-release metformin preparation, which is not absorbed in the upper part of the small bowel, hence exerting its action mainly locally, in the distal part of the small intestine, on the entero-endocrine L-cells. Trials results showed an increased efficacy in reducing HbA_{1c}, although plasma levels of metformin were reduced [27]. These low plasma concentrations might allow using the new metformin preparation in patients with impaired renal function [4].

Besides thiazolidinediones, other compounds acting upon intra-cellular structures were identified in the last years. MSDC-0602 acts on the same mitochondrial targets as thiazolidinediones, by modulating pyruvate entry into the mitochondria and regulating pyruvate oxidation [28,29]. MSDC-0602 proved to have the same efficacy on reducing HbA_{1c} as 45 mg/day pioglitazone, but with lesser hydro-saline retention and weight gain [30].

Pyruvate dehydrogenase kinase inhibitors recently entered the attention of researchers in T2DM-targeted therapies. Pyruvate dehydrogenase catalyzes pyruvate oxidation into acetyl-coenzyme A and carbon dioxide. Four pyruvate dehydrogenase kinase isoenzymes exist, each having a tissue-specific distribution. Muscular isoenzyme inhibition increases pyruvate oxidation into the muscle and reduces liver delivery of lactate and alanine (both precursors of gluconeogenesis), while inhibition of the liver isoenzyme directly reduces gluconeogenesis. Both compounds are, for the moment, in the phase of pre-clinical studies [4,31].

Protein tyrosine phosphatase 1B inhibitors are also in a pre-clinical research phase. They motivate their utility by counterbalancing the reduced insulin receptor tyrosine phosphorylation found in patients with T2DM [32,33].

Fibroblast growth factor (FGF)-21 has a protein structure, is produced in the liver and determines an increased sensitivity to insulin. A FGF-21 analog, LY2405319 (Eli Lilly), was proven to reduce both glycemic levels and serum lipid fractions [34,35].

Chronic inflammation in the adipose tissue is another pathophysiological mechanism contributing to hyperglycemia in T2DM. Its causes include adipocyte hypoxia, but also intervention of free fatty acids and glucose metabolites, such as diacylglycerol, ceramides and reactive oxygen species [36,37]. Therefore, anti-inflammatory therapy was suggested to improve insulin sensitivity. Poor results of studies with such compounds might be explained by the multiple pathways leading to inflammation, the inhibition of a single mechanism being unable to induce clinically significant results [38].

T2DM also features high circulating levels of glucagon and an increased liver sensitivity to glucagon. GLP-1 receptor agonists and DPP-4 inhibitors are thought to inhibit endogenous glucagon secretion, hence reducing the glucose output from the liver. Somatostatin-induced reduction of glucagon levels was shown to decrease hepatic glucose production and to lower fasting glycemic levels [4]. These arguments led to research upon glucagon receptor antagonists, at present in the phase of animal models studies [39-41].

Other hopes in the field of innovative therapies for T2DM are linked to glucokinase activators and acetyl-coenzyme A carboxylase inhibitors. Glucokinase is the enzyme that activates phosphorylation of free glucose after it enters the cell. In β-cells, a specific glucokinase is the rate-limiting step for insulin secretion, while another glucokinase increases glycogen synthesis and decreases the glucose output in the liver. However, studies using glucokinase activators revealed only a small and fading out effect of these compounds [42-44]. Acetyl-coenzyme A carboxylase catalyzes the carboxylation of malonyl-coenzyme A on the pathway towards free fatty acids synthesis, known to determine hepatic and muscular insulin resistance. Inhibition of acetyl-coenzyme A carboxylase determines an increased sensitivity to insulin, low concentrations of free fatty acids and glucose, and an improved lipid profile [45-47].

The list of future hopes for T2DM therapy also extended in the last years to other compounds with a potential antihyperglycemic effect: activation of protein deacetylase sirtuin (SIRT)-1 by SRT 3025, AMP-activated protein kinase (AMPK) activators, modulators of gut microbiota, ranolazine, glycogen phosphorylase inhibitors, glycogen synthase activators, etc. [4,48]. Nevertheless, next years will decide which of these potential drugs can and will successfully be used for treating diabetic patients. At this moment, even after all progresses of the last decades, we are still far from reaching the high dream of perfection in the field of T2DM therapies.

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