

Editorial

Drugs with incretin: a therapeutic alternative in type 2 diabetes mellitus

Fármacos con actividad incretina: una alternativa terapéutica en la diabetes mellitus tipo 2

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Some time ago, it has been proved that the oral ingestion of glucose causes a higher release of insulin than its intravenous route administration; since then the incretin concept has been stated, that supposed the existence of certain hormones or neurotransmitters that, released from the intestinal wall –in contact with food– would stimulate the pancreatic secretion of insulin.¹ Nowadays, several hormones are grouped under the term incretin, among which the GLP-1 (glucagon-like peptide-1) and the GIP (glucose-dependent insulinotropic peptide) are the principal ones.²

The GLP-1, secreted from the L cells (localized in the ileum and colon) and after the stimulus of nutrients as carbohydrates and fats, flows in plasma as GLP-1 (7-37) and GLP-1 (7-36 amide). Afterwards, it is degraded by the dipeptidyl peptidase-4 enzyme (DPP-4) and only a 25% reaches. In liver, a 40-50% is destroyed reaching a 10-15% of the initial secreted product systemic circulation only; its plasmatic half-life is of approximately 2 minutes. It has been proposed the possibility that

the insulin-secretory action of the GLP-1 can take place not only through endocrine route but also through a neurotransmitter mechanism by stimulation of afferent sensitive neurons connecting the intestinal wall, the liver and the hepatoportal region.³ The GIP, secreted by the K cells (located in the duodenum and the jejunum) in response to the ingestion of nutrients is likewise metabolized by the mentioned enzyme (DPP-4) and its plasmatic half-life is of 7 minutes.

The GLP-1 exerts diverse actions in the organism.^{2,4} On one side, synthesis and secretion increases, in response to glucose levels its activity is not accompanied by hypoglycemia. Experimentally, it seems to favor the differentiation the neogenesis of the pancreatic beta cell and inhibiting apoptosis; these data have not been confirmed on human beings. Moreover, it inhibits the glucagon secretion, depending likewise from the glycemia values, so it does not seem to influence in the contra-regulating function of this hormone regarding to hypoglycemia. It also delays the gastric emptying and diminishes the appetite sensation. It has also been described as a positive inotropic activity, and an arguable insulin-sensitizer activity. The GIP, independently of inhibiting the gastric acid secretion, shows functions similar to the ones exerted by the GLP-1, though it does not slow down the gastric emptying, it does not produce satiety or suppress the glucagon secretion.²

Reception date: January 14th 2008
 Acceptance date: January 14th 2008

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List of acronyms quoted in the text:

T2D: type 2 diabetes mellitus; DPP-4: dipeptidyl peptidase 4; GIP: glucose-dependent insulinotropic peptide; GLP-1: glucagon-like peptide-1.

In the type 2 diabetes mellitus (T2D)^{5,6} there is a moderate level of GLP-1 hyposecretion keeping mainly the insulinotropic effect. On the contrary, the GIP is secreted normally or hypersecreted, while the insulin-secretor effect is diminished. These alterations seem to be conditioned by the metabolic condition itself, though there are some data against it. Specifically, it has been proved the association among certain polymorphisms of the transcription factor TCF7L2 (with the risk of suffering T2D) and a lack of response of the pancreatic receptor to the GLP-1 insulin-secretory stimulus.⁷

The administration of GLP-1 has been proposed to correct the deficiency of incretin activity in T2D. Given its short half-life, the first experiences that confirmed a normalization of the glycemic levels were performed with native GLP-1 in a continuous intravenous⁸ or subcutaneous⁹ infusion. From these considerations, the approach of the therapeutic use of drugs with incretin activity was focused in a double direction: a) incretin-mimetic drugs or the GLP-1 receptor agonist resistant to the metabolic degradation and b) incretin-enhancer drugs or inhibitors of DPP-4.⁴

At present, within the group of incretin-mimetics, there is a clinical experience with a GLP-1 analogue (liraglutide) and with exenatide (a synthetic variety of exendin-4, obtained from saliva of the lizard *Heloderma suspectum*). Both present longer activity duration with regard to the native GLP-1 and are administered subcutaneously 1-2 times/day respectively. Initial studies have been performed about the use of a single weekly subcutaneous dose of long-acting exenatide, with good results.¹⁰ As regards to the DPP-4 inhibitors, the experience is focused on the vildagliptin and sitagliptin, active through oral route, 1-2 times/day.

From the performed different clinical studies,^{4,11} a series of results are deduced that remain mainly expressed in a recent meta-analysis.¹² The analysis groups 29 randomized and controlled trials with a minimum of duration

of 12 weeks, in which the efficacy of incretin-mimetics or inhibitors of DPP-4 versus placebo is compared as well as other hypoglycemic treatments, specially oral hypoglycemics, as monotherapy or combined therapy. A higher efficiency versus placebo is confirmed but not substantially lower than those of the hypoglycemic drugs, through in this last aspect contrary opinions came forth.¹³

It is evident that the administration of these drugs is followed by a decrease of basal and postprandial glycemia, as well as of an absence of hypoglycemia. The mean decrease of HbA_{1c} with incretin-mimetics and inhibitors of DPP-4 is of 0.97 and 0.74% respectively, though this decrease rate is conditioned to the basal values of HbA_{1c}. With the incretin-mimetics, corporal weight decreases between 1.4 and 4.8 kg. In relation to side effects, gastrointestinal disturbances have been documented, such as nausea and vomiting (20-30%) that usually eases off during the treatment. The DPP-4 inhibitors show a neutral effect on the weight, while unspecific upsets of scarce entity have been described (nasopharyngitis, headaches or urinary infections) as side effects. The higher metabolic efficiency (decrease of HbA_{1c}) and the existence of more side effects derived from the use of incretin-mimetics in comparison with the DPP-4 inhibitors seem conditioned by the fact that with the use of the first ones we reach pharmacology levels of GLP-1, while with the second ones we encounter the restoration of its physiological level as the DPP-4 proteolytic effect is inhibited.

In relation to therapeutic indication, the administration of drugs with incretin activity has been proposed in combined therapy with other oral antidiabetics, especially metformin. The possible role on the protection and regeneration of the pancreatic beta cell seems promising, though this circumstance has only been objectified in experimentation animals. Within this group of drugs, the following ones have been commercialized: exenatide (Byetta[®]), vildagliptin (Galvus[®]) and sitagliptin (Januvia[®]). Nowadays, in Spain, only the sitagliptin (Janu-

via[®]) is available, its use has been approved in combined therapy, associated with metformin, glitazone or sulfonylurea, or in triple therapy, together with metformin or sulfonylurea

In conclusion, the introduction of this new class of insulin-secreting agents with incretin activity constitutes an interesting alternative in the T2D treatment due to the absence of hypoglycemias, to the positive or neutral effect on the reduction of corporal weight and the potential protection of the beta cell. ■

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