

The expanding role of incretin-based therapies: how much should we expect?

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The increasing prevalence of type 2 diabetes mellitus (T2DM) worldwide and its combination with other pathologies including obesity, arterial hypertension, and dyslipidemia make this disorder one of the most significant challenges of the 21st century. Although multiple classes of antidiabetic drugs are available, more than half of the patients with T2DM still do not achieve optimal glucose control owing to the progressive nature of T2DM requiring stepwise therapy intensification and suboptimal compliance to diet and lifestyle measures as well as side effects of most antidiabetic drugs, in particular, hypoglycemia and weight gain. An urgent need for safer and more effective treatments has stimulated the development of several novel classes of antidiabetic drugs in the last decade with promising new molecules still emerging (Mraz *et al.* 2009). In contrast to the traditional glucocentric view, the focus has shifted toward a more complex approach emphasizing the importance of the beneficial effects of novel antidiabetics on multiple cardiovascular risk factors (Skyler *et al.* 2009). The discovery of incretin-based therapies has markedly improved our possibilities of T2DM treatment, owing not only to their good antidiabetic efficacy but also to other positive effects such as reduction of body weight and blood pressure and improvement of dyslipidemia as well as their potential neuroprotectivity and cardioprotectivity. In this miniseries, we have put together four reviews from leading research groups in the field focusing on some of the most intensively discussed effects of incretin-based therapies beyond the improvement of glucose control.

The incretins are peptide hormones released from the small intestine during meal absorption that stimulate insulin secretion from pancreatic β -cells and reduce excessive secretion of glucagon by pancreatic α -cells, thus improving two important defects of T2DM (Holst *et al.* 2008). Of the two currently known incretins, glucagon-like peptide 1 (GLP1) and glucose-dependent insulinotropic

polypeptide, only therapies based on the effects of the former are used in clinical practice. Two approaches have been adopted based either on the prolongation of the half-life of endogenous GLP1 by blocking its degradation by dipeptidyl peptidase 4 (DPP4) (DPP4 inhibitors) or on the stimulation of GLP1 receptor (GLP1R) with compounds resistant to DPP4 degradation (GLP1R agonists).

One important effect of GLP1 and GLP1R agonists observed in both preclinical and clinical studies was the reduction of food intake and body weight, which makes these medications rather unique within the antidiabetic armamentarium. In the first review of this miniseries, van Bloemendaal *et al.* (2014) discuss the effects of GLP1 and GLP1R agonists on appetite and body weight, focusing on their potential energy balance-regulating effects in the CNS. Although the fact that GLP1 and GLP1R mimetics have consistent acute effects on hunger and satiety has been known for some time, the underlying mechanisms are still only partially understood. They may include the well-documented delayed gastric emptying as well as potential direct effects in the CNS. The mechanism behind the effects is complex and clearly differs among the short-acting and the long-acting GLP1R agonists. These findings suggest that other components such as the direct action of long-acting GLP1R agonists might be in place.

Cardiovascular side effects have been a major concern of several antidiabetic and antiobesitic medications, eventually leading to the withdrawal of a number of drugs from the market. Therefore, the antidiabetic medications are currently being intensively scrutinized for cardiovascular safety. Preclinical and small clinical studies have shown that GLP1 has numerous beneficial effects on the cardiovascular system, including the reduction of blood pressure, the improvement of lipid profile, the amelioration of endothelial dysfunction, and

even direct cardioprotection in the experimental models of ischemia/reperfusion. The first clinical studies suggesting the effects of GLP1R agonists on ischemic preconditioning have recently been published. The important topic of cardiovascular effects of incretin-based therapies and their potential underlying mechanisms is covered in the review by Angeli & Shannon (2014).

Although T2DM certainly presents a huge global threat to mankind, neurodegenerative diseases are beyond all doubt a global peril to the aging population. It has been demonstrated more than a decade ago that insulin resistance is by far not limited to peripheral tissues such as the liver, the muscle, and the fat, but that it is also occurs in the brain (Bruning *et al.* 2000). Along this line, T2DM increases the risk of neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease. GLP1Rs are widely distributed within the brain, and experimental studies have suggested that they may also protect against neurodegeneration by multiple mechanisms. This important topic is the focus of the review by Dr Holscher (2014), one of the pioneers in this field.

The topic of the final review of the miniseries is the pancreatic safety of incretin-based therapies. Some pre-clinical studies have indicated that chronic GLP1R activation may stimulate the proliferation of pancreatic β -cells and thus increase β -cell mass, providing hope that this approach may potentially alter the natural progression of T2DM (Sturis *et al.* 2003). On the contrary, other studies have raised concerns that chronic use of incretin-based therapies may increase the risk of pancreatitis and pancreatic cancer (Matveyenko *et al.* 2009). The discussion has been further stimulated by the publication of human morphological data pointing to increased pancreatic ductal proliferation in patients treated with incretin-based therapies (Butler *et al.* 2013). Although the methodology described in the latter paper has been widely criticized, the potential pancreatic side effects of incretin-based therapies remain certainly an open and widely discussed topic. The difficult task of reviewing this subject has been undertaken by Lamont & Andrikopoulos (2014).

In summary, it is certainly safe to say that incretin-based therapies have markedly broadened our armamentarium of antidiabetic therapies. Nonetheless, as with all novel therapies, the potential hopes as well as fears can only be clarified by carefully performed clinical trials. In the meanwhile, we sincerely hope that our miniseries on incretin-based therapies can help both the researchers and the clinicians to better understand this rapidly evolving field.

Declaration of interest

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