Incretion therapy 2011: hype or reality?

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Introduction

Type 2 diabetes has assumed a pandemic prevalence. In the absence of metabolic control, life expectancy in patients with diabetes is reduced by a mean of 15 years, and morbidity in relation to vascular and neuropathic complications, some three- to fourfold. Adequate metabolic control remains elusive and worldwide, fewer than 40% of patients with diabetes achieve glycaemic targets. This poor outcome is attributable in part to the suboptimal, non-physiological glucose-lowering therapies that are currently available and in routine use. More specifically, effective glucose lowering is currently limited by the concurrent adversities of hypoglycaemia and weight gain.

Incretin system

It is well known that oral glucose is able to produce an endogenous insulin response that is some two-fold higher than intravenous glucose, suggesting that intestinal factors promote and amplify the secretion of insulin, ie. the “incretin effect”. It is also established that this incretin effect is deficient in subjects with obesity, pre-diabetes and overt diabetes. The recent molecular delineation of certain gut peptides that restore this incretin effect has offered therapeutic opportunities to address this abnormality. In this regard, glucagon-like-peptide 1 (GLP1) has emerged as a major incretin hormone. GLP1 is secreted from L-cells which are found in the highest concentration in the terminal ileum. However, the GLP1-secreting L-cells, as well as the G protein-coupled GLP1 receptors, are widely dispersed in the gut and also in the rest of the body.

Glucose homeostasis and the incretin system

Therapeutically, GLP1 levels can be enhanced endogenously by use of oral dipeptidyl peptidase-4 (DPP4) inhibitors, or exogenously by the injection of GLP1. The former are low-molecular-weight molecules that inhibit the DPP4 enzyme system selectively, which is responsible for the rapid inactivation of circulating GLP1, while the latter provide a prolonged agonistic function at the receptor. Therefore, GLP1 enhancers or mimetics are able to lower the glucose concentration by a number of unique mechanisms, including:

- Stimulating pancreatic beta cells (insulin secretagogue).
- Stimulating beta cells only in the presence of hyperglycaemia (glucose-dependent secretagogue function).
- Inhibiting alpha cell function (thereby reducing glucagon and hepatic glucose output).
- Stimulating beta cell neogenesis (thereby reversing the progressive decline in insulin secretory reserve).
- Delaying gastric emptying (thereby reducing postprandial hyperglycaemia and promoting both satiety and weight loss).
- Stimulating hypothalamic satiety (thereby promoting weight loss).

Summary

The incretin effect is deficient in patients with type 2 diabetes. This can now be restored therapeutically with a GLP1 enhancer or mimetic. The therapeutic benefits that follow are unique - the secretagogue action is glucose dependent (thus mitigating hypoglycaemia), hepatic glucose output is inhibited (thus fasting hyperglycaemia is reduced) and gastric emptying is delayed (thus postprandial hyperglycaemia is attenuated). Furthermore, the incretin effect includes important long-term benefits in regard to them promoting sustained weight loss and preserving beta cell secretory reserve.

Conclusion

The restoration of the incretin effect in type 2 diabetes is now achievable and associated with significant glycaemic and other metabolic improvements. Importantly, this integrated gluco-cardio-metabolic improvement is achieved safely and easily.