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Understanding incretins

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The 'incretin effect' is the physiological phenomenon observed following ingestion of glucose that results in plasma insulin concentrations almost twofold greater than those measured after a comparable intravenous (IV) glucose stimulus [1]. This phenomenon proves that the gastrointestinal tract is pivotal in regulating insulin secretion and glycaemia. It is now understood that the incretin effect is due to two hormones, glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP).

Incretin hormones in health

Intestinal nutrient stimulates secretion of GLP-1 and GIP. GLP-1 has potent pancreatic and gastrointestinal effects, such as stimulating insulin and suppressing glucagon secretion, as well as slowing gastric emptying and reducing gastric acid secretion (Fig. 1). GIP also stimulates insulin secretion, but the effects on glucagon and gastric emptying are less predictable and unlikely to substantially contribute to the glucose-lowering effects (Fig. 1) [1].

Of particular relevance to the potential clinical use of incretin hormones, the insulinotropic effects of GLP-1 are glucose-dependent—i.e. at blood glucose concentrations below 4 mmol/l islet cells are unresponsive to even pharmacological doses of these hormones (Supplemental Figs. 1A and 1B) and therefore administration of these hormones has the capacity to treat hyperglycaemia without causing hypoglycaemia [2].

Use of incretin hormones outside of the ICU

In ambulant patients with type 2 diabetes the insulinotropic properties of GLP-1 but not GIP are retained [3]. This has resulted in the GLP-1 receptor remaining the focus for drug development. However, GLP-1 (and GIP) is rapidly metabolised by the ubiquitous enzyme dipeptidyl-peptidase 4 (DPP-4) with plasma half-lives of minutes [4]. Novel GLP-1 receptor agonists resistant to DPP-4 degradation that require only intermittent injection are now available (drugs such as exenatide, lixisenatide and liraglutide). Inhibitors of DPP-4 that protect endogenous GLP-1 and GIP from degradation, and can be

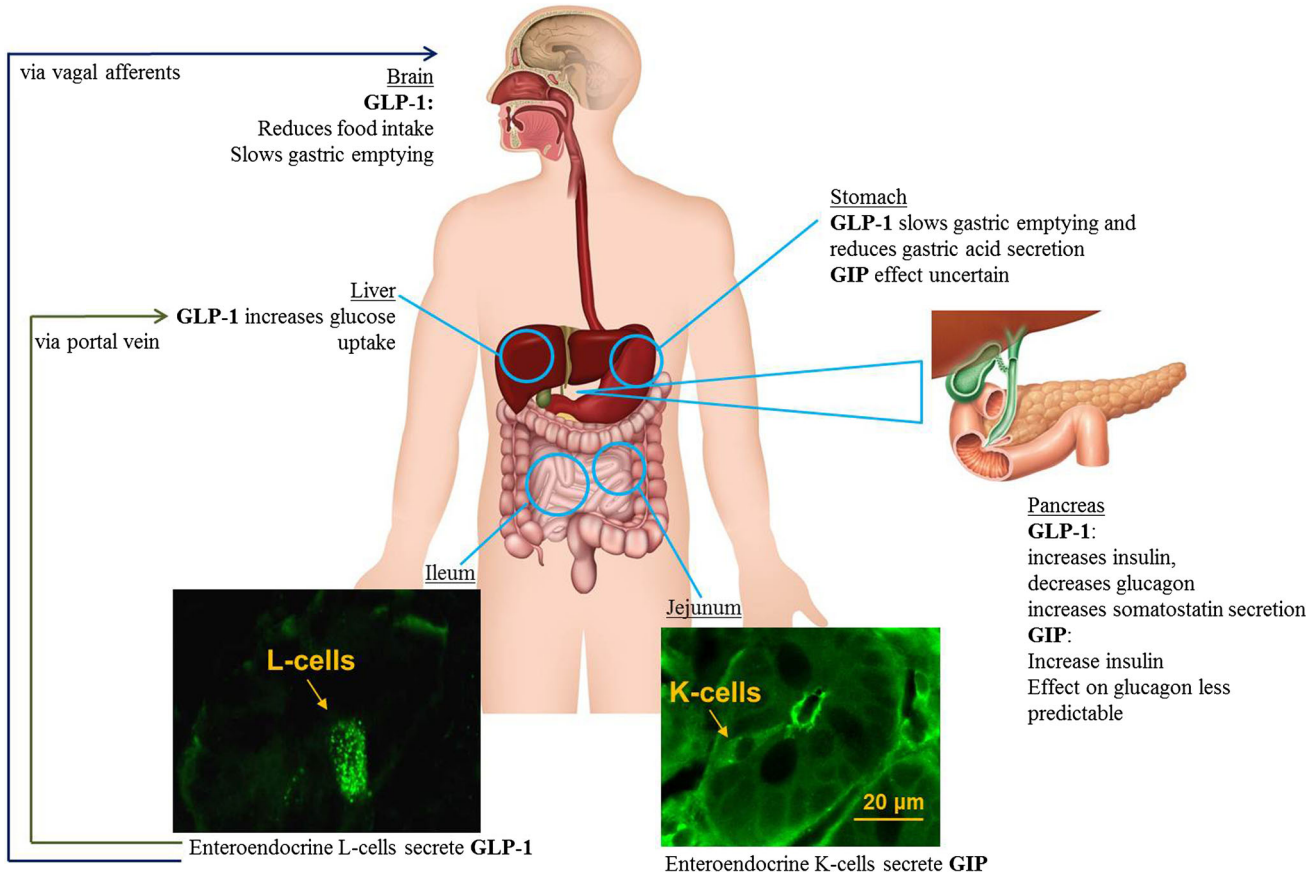

Fig. 1 Secretion and effects of incretin hormones. Enteroendocrine cells are immunopositive for glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Nutrient stimulates secretion leading to effects on the gastrointestinal system via endocrine and centrally mediated effects

administered orally, were subsequently developed that similarly lower blood glucose (drugs such as sitagliptin, vildagliptin and saxagliptin) [4]. These GLP-1 agonists and DPP-4 inhibitors have now been incorporated into routine clinical use in the management of patients with type 2 diabetes [5]. Furthermore, owing to effects on gastric emptying and secretion, pre- and pilot clinical studies suggest that GLP-1 agonists and DPP-4 inhibitors may also improve intestinal absorption in patients with short bowel syndrome [6].

Rationale to use GLP-1 in the critically ill

IV administration of insulin is effective in lowering blood glucose but is associated with significant rates of hypoglycaemia and substantial glycaemic variability. There is increasing evidence that in the critically ill the last two domains of glycaemia may be more harmful than hyperglycaemia per se [7, 8]. In ambulant patients with type 2 diabetes glucose-lowering regimens of GLP-1 agonists potently lower blood glucose and reduce glycaemic variability with no risk of inducing hypoglycaemia [1, 2, 4]. On the basis of these properties, further study of the use of GLP-1 in the critically ill was warranted.

Concerns about using GLP-1 in the critically ill

In ambulant diabetics GLP-1 agonists may cause substantial nausea and vomiting. However, these adverse effects are more prominent when commencing treatment using intermittent subcutaneous administration of a GLP-1 agonist rather than IV administration of the synthetic peptide [9]. GLP-1 also potently slows gastric emptying and slower gastric emptying may increase enteral feed intolerance and gastro-oesophageal reflux and, thereby, aggravate ventilator-associated complications in the critically ill. Proof-of-principle studies were therefore undertaken.

Proof-of-principle studies in the critically ill

Similar to effects observed in ambulant patients with type 2 diabetes GLP-1 has potent glucose-lowering properties when administered to critically ill patients [10–12]. GLP-1 also slows gastric emptying in the critically ill, but only when the baseline emptying rate is relatively 'normal' and not when it is already delayed [12]. Moreover, the slowing of gastric emptying appears to be attenuated (at least in health) during prolonged (24 h) infusion of GLP-1 [13]. Accordingly, slower gastric may be less problematic during prolonged IV infusion in the critically ill. Studies to evaluate the effects of prolonged GLP-1 receptor stimulation on enteral feed tolerance, reflux events and ventilator-associated complications in the critically ill are therefore still required. In terms of the proprietary compounds the GLP-1 agonist exenatide has been administered to patients in a cardiac ICU with a reduction of blood glucose concentrations observed [14]. However, nausea occurred frequently in patients receiving exenatide. The majority of studies have focussed on the use of GLP-1 as a stand-alone therapy, but its use may also be in combination with insulin. Using a relatively small sample Galiatsatos and colleagues recently compared GLP-1 and placebo, as add-on treatment to insulin, and reported that GLP-1 reduced glycaemic variability [15].

Future directions

Further studies are required to determine whether (a) the intact peptide or GLP-1 agonists (or a DPP-4 inhibitor) are the agent of choice and (b) GLP-1 should be used as a stand-alone therapy—this would require identifying patients that have the capacity to respond to this regimen—or administered in combination with insulin.

Conclusions

There are limitations with the use of insulin to treat hyperglycaemia in the critically ill. Treatment with GLP-1 is appealing as its use does not cause hypoglycaemia and may reduce variability. Whilst it is far too premature to recommend the clinical use of GLP-1 preliminary data are promising and further studies are eagerly awaited.

Conflicts of interest AMD and PBJ have no conflicts of interest to declare.

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