Milestone 22

Incretin drugs for glycaemic control

Over the past 15 years, drugs targeting the incretin hormones (Milestone 9), including glucagon-like peptide 1 (GLP1), have emerged as effective anti-hyperglycaemic agents. GLP1 is produced in the intestine and the brain in response to various stimuli, including food intake and bacterial metabolites, as well as immune and neuroendocrine mediators. The glucose-dependent postprandial release of GLP1 induces insulin secretion by pancreatic β-cells and suppresses glucagon secretion from pancreatic α-cells, which regulates glycaemia. Moreover, GLP1 modulates appetite by slowing gastric emptying and inducing satiety. However, these effects are short-lived because circulating GLP1 is quickly degraded by dipeptidyl peptidase 4 (DPP4) and has a half-life ≤5 minutes in circulation. Given the physiological role of GLP1 in glycaemic control, GLP1 receptor agonists (GLP1RAs) were developed as glucose-lowering agents to treat patients with type 2 diabetes (T2D). DPP4 inhibitors that prolong the half-life of endogenous GLP1 represent another approach to therapeutically target the incretin system.

GLP1RAs are peptide drugs that were developed as analogues of either human GLP1 or exendin 4, which is a salivary protein from the Gila monster lizard with ~50% homology to human GLP1. Human GLP1-based agents include albiglutide, liraglutide, dulaglutide and semaglutide, whereas exenatide and lixisenatide are based on exendin 4. These drugs are administered by subcutaneous injection, although an oral formulation of semaglutide is also available. One of the main differences between the two types of GLP1RA is their half-lives, which are shorter for exendin-4-based compounds. Various strategies have been developed to prolong the half-life of GLP1RAs, including binding the peptides to plasma albumin or conjugating them to the crystallizable fragment of IgG to delay drug clearance in the kidney. A long-acting release formulation of exenatide was also developed by coupling the peptide to microspheres, which slows drug release; this formulation can be administered once a week instead of twice daily.

"GLP1RAs can also reduce the risk of atherosclerotic cardiovascular disease … and kidney outcomes"

Early clinical trials showed that both DPP4 inhibitors and GLP1RAs were well tolerated and that, compared with placebo, they could reduce HbA_{1c} in patients with T2D being treated with metformin. Subsequent studies have indicated that GLP1RAs are more effective than DPP4 inhibitors in lowering HbA_{1c}. In general, short-acting GLP1RAs strongly inhibit gastric emptying and delay glucose absorption, but this effect is not sustained as GLP1R activity levels decline after drug administration. By contrast, human GLP1-based drugs maintain GLP1R activation over longer periods of time, and have been shown to lower HbA_{1c} and fasting plasma glucose levels to a greater extent than exendin-4-based drugs, with the exception of once-weekly exenatide, which is also a long-acting drug.

A systematic review and comparison analysis published in 2016 concluded that GLP1RAs are generally well tolerated and, although they can potentiate hypoglycaemia, the risk of this adverse event is reduced compared with that associated with other glucose-lowering agents such as short-acting insulin. Gastrointestinal symptoms are also common, although they are often transient; long-acting compounds seem to have the lowest risk of nausea, diarrhoea and vomiting.

Data collected in several clinical trials indicate that, compared with placebo, GLP1RAs can also reduce the risk of atherosclerotic cardiovascular disease (including cardiovascular and all-cause mortality) and kidney outcomes in patients with T2D. However, the benefits of incretin drugs extend beyond the treatment of T2D. Obesity, for example, can reduce the release of GLP1 and blunt its glycaemic control, although the underlying mechanisms remain unclear. In patients with obesity, a combination of GLP1RAs and lifestyle therapy improves weight loss compared with placebo.

GLP1RAs also have therapeutic benefits in other conditions associated with obesity and insulin resistance. In patients with nonalcoholic steatohepatitis, GLP1RAs improved weight loss and the liver phenotype, potentially through metabolic and anti-inflammatory effects.

The demonstrated ability of GLP1RAs to lower HbA_{1c} and fasting plasma levels of glucose confirms that they are promising anti-hyperglycaemic agents, and their additional metabolic effects suggest that their benefits might extend well beyond the treatment of patients with T2D.

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Milestone study

Htike, Z. Z. et al. Efficacy and safety of glucagon-like peptide-1 receptor agonists in type 2 diabetes: a systematic review and mixed-treatment comparison analysis. *Diabetes Obes. Metab.* **19**, 524–536 (2017)

Further reading

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