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Vildagliptin
A Viewpoint by Alan J. Garber

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Notwithstanding the appearance in the last decade of four additional classes of new oral antidiabetic agents and a panoply of analogues of human insulin, it appears that glycaemic control in patients with type 2 diabetes mellitus is no better and perhaps worse now than a decade ago. Part of the reason for this failure to adequately control diabetes is the progressive nature of the disease requiring ever more therapies in amounts and numbers to maintain glucose control once it is attained.

A new class of oral antidiabetic agents will soon receive approval in the US. These agents – dipeptidyl peptidase-4 (DPP-4) inhibitors – selectively inhibit a ubiquitous protease (DPP-4) that degrades a number of circulating polypeptides, including the incretins glucagon-like peptide (GLP)-1 and glucose-dependent insulinotropic polypeptide (GIP). These molecules have powerful agonistic properties with respect to meal-stimulated insulin and glucagon secretion; in the case of GLP-1, there is a blunting of its secretion as carbohydrate tolerance declines. In contrast, GIP stimulation of insulin secretion is lost in type 2 diabetic patients. The GLP deficiency of type 2 diabetes may be replaced by injectable derivatives of GLP-1, or alternatively the very short half-life of the incretin may be augmented by inhibiting its breakdown.

Vildagliptin, a novel and specific inhibitor of DPP-4, increases GLP-1-mediated incretin effects on insulin and glucagon secretion, thereby lowering postprandial and fasting glucose and glycosylated haemoglobin by significant amounts. These effects have been seen with vildagliptin as monotherapy and in combination with a variety of other oral antidiabetic agents, including metformin as well as sulfonylureas, thiazolidinediones and insulin itself. The glycaemic-lowering potential of the drug is intermediate in power between that of nateglinide and sulfonylureas. Unlike sulfonylureas, however, there appears to be no significant potential for hypoglycaemia since the regulation and coupling of glucose levels to insulin secretion is preserved. Of perhaps even greater importance is the lack of weight gain in patients taking vildagliptin monotherapy and the blunting of weight gain in those taking vildagliptin in combination with other agents.

Of a more theoretical interest are the observations in animals that DPP-4 inhibitors increase β-cell mass. They may, therefore, overcome and arrest the progressive decline of β-cell function and mass that is the hallmark of type 2 diabetes. If these observations can be reproduced in humans, DPP-4 inhibitors such as vildagliptin may provide a major advance for patients with type 2 diabetes – an epidemic disease which is exploding all around us. ▲