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LETTER

Discovery of dipeptidyl-peptidase IV—a 40 year journey from bench to patient

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Abbreviations
DPP-IV dipeptidyl-peptidase IV
GLP-1 glucagon-like peptide 1

To the Editor: In June 1966 V. K. Hopsu-Havu and G. G. Glenner identified a new enzyme in the course of histochemical studies in the rat kidney [1]. They went on to purify it from rat liver [2] and dog kidney [3]. It was also detected in many other tissues [4]. They used Gly-Pro-Na (glycyl-prolyl-naphthylamide) as a substrate, from which the enzyme released Gly-Pro. In other words this was a new dipeptidyl-peptidase, which later came to be known as dipeptidyl-peptidase IV (DPP-IV). Based on the Gly-Pro specificity, Hopsu-Havu and his collaborators speculated that it could be involved in collagen metabolism.

It was a further 10 years before an English–American research group purified and characterised the same enzyme, still not knowing its function. This group, soon joined by R. Mentlein, a German postdoctoral worker, studied substance P, which has the N-terminal Arg-Pro-Lys-Pro sequence. Their first paper described the effect of the enzyme on substance P. A decade later Mentlein and coworkers found that other hormones with the Xaa-Ala sequence were also hydrolysed. Two incretins came into this group: glucagon-like peptide 1 (GLP-1) and gastric inhibitory polypeptide [5]. Although the group did not know it at the time, this was the second important step towards a new class of therapeutic compounds.

The concept that gastrointestinal hormones influence pancreatic secretion is more than 100 years old. Moore et al. studied the extracts of duodenal mucosa on glycosuria in newly diagnosed diabetic patients in 1906 [6], but their data were inconsistent, perhaps because the extract was given orally. The incretin hypothesis was confirmed in the 1960s [7], when several investigators demonstrated that an oral glucose challenge induced a greater insulin response than the same amount given intravenously. A further 20 years passed before several groups identified GLP-1, particularly the truncated peptide (7–36), as the key player in the incretin effect in man. This heralded the ‘beginning of a new diabetes therapy based on the incretin concepts’ [7].

GLP-1 is characterised by a short half-life in blood (2–3 min), because of fast hydrolysis by DPP-IV. Several studies were published on DPP-IV inhibition and specific inhibitors of the enzyme in the 1980s, but it was some time before the interaction between DPP-IV inhibition, the incretin effect and glucose metabolism was appreciated. This came in 1998 when J. J. Holst and C. F. Deacon published a review [8] in which they proposed DPP-IV inhibition as a possible novel therapeutic agent for type 2 diabetes. This stimulated considerable interest in the development of a DPP-IV inhibitor for clinical use. The first two compounds in this class are now on the market, and others are in the pipeline.

So it was that an original observation by the Finnish scientist Hopsu-Havu and his coworker G. G. Glenner led to the development of a novel therapeutic class 40 years

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later. The story demonstrates how long it can take to develop a new drug, and confirms the importance of basic, discovery research. It may also stimulate readers to be alert to the physiological effects of interactions of different mechanisms and their potential therapeutic implications.

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