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DPP-4 Inhibition and the Known Unknown

Diabetes 2016;65:2124–2126 | DOI: 10.2337/dbi16-0023

COMMENTARY

Science sometimes moves very slowly. Observations in 1964 (1,2) that the insulin response to oral (and enteral) glucose is substantially greater than that to an isoglycemic intravenous glucose infusion (the incretin effect), followed by characterization of the two known incretin hormones, glucose-dependent insulinotropic polypeptide (GIP) (1973) and glucagon-like peptide 1 (GLP-1) (1985), have only recently led to the development of two classes of antidiabetes drugs, GLP-1 agonists and dipeptidyl peptidase 4 (DPP-4) inhibitors, now used widely in the management of type 2 diabetes. GIP and GLP-1 are predominantly released from the proximal and distal intestine, respectively, primarily in response to enteral nutrients, and stimulate insulin secretion in a glucose-dependent manner (3). Attenuation of the incretin effect is probably an early marker of β-cell dysfunction (4). In type 2 diabetes, the incretin effect is markedly reduced (5), partly because the insulinotropic effect of GIP is essentially lost, whereas pharmacological doses of GLP-1 still stimulate insulin secretion substantially (6). GLP-1 also suppresses glucagon and slows gastric emptying (3,7).

Following their release, GLP-1 and GIP are rapidly degraded by the ubiquitous enzyme, DPP-4. The concept that inhibition of DPP-4 may represent a therapy for type 2 diabetes was expressed in a seminal article by Deacon et al. (8) in 1995. DPP-4 inhibition markedly increases circulating intact (active) GLP-1 and GIP concentrations. In 2006, the first DPP-4 inhibitor, sitagliptin, was approved by the U.S. Food and Drug Administration, and some 11 different DPP-4 inhibitors are now available worldwide. Their efficacy in reducing HbA_{1c} is comparable to other oral hypoglycemic drugs, but the risk of adverse effects, particularly hypoglycemia (because insulin stimulation is glucose dependent) and weight gain, is much less (3). It has been assumed that the increase in active GLP-1 accounts for glucose lowering by DPP-4 inhibition in type 2 diabetes—an assumption now shown to be only partly correct.

The elegant study by Nauck et al. (9) reported in this issue of *Diabetes* provides important insights regarding the mechanisms underlying glucose lowering by DPP-4 inhibition that are consistent with, and complimentary to, outcomes reported by Aulinger et al. (10) (Fig.1). In the study by Nauck et al. (9), a total of 32 patients with type 2 diabetes managed by diet or metformin and 29 healthy control subjects received vildagliptin 100 mg or placebo for 10 days in a crossover design. Meal tests, with concurrent assessment of gastric emptying, were performed on days 9 and 10, with and without intravenous exendin [9-39], a GLP-1 receptor antagonist. The primary end point was a modified insulinogenic index, i.e., the ratio of the insulin secretory response relative to plasma glucose, for 4 h postprandially. In patients with type 2 diabetes, insulinogenic indices (based on insulin, C-peptide, or insulin secretory rates) were increased by vildagliptin and reduced by exendin [9-39], but, importantly, the difference between these conditions was only ∼50%. Hence, as concluded by Aulinger et al. (10) who evaluated the effects of sitagliptin, only about half of the insulinotropic effect of DPP-4 inhibition could be attributed to GLP-1. Exendin [9-39] also accelerated gastric emptying, whereas vildagliptin apparently had no effect. The original prespecified primary end point (glucagon) could, unfortunately, not be used because of cross-reactivity of exendin [9-39] in the immunoassay for glucagon. Although both Nauck et al. (9) and Aulinger et al. (10) evaluated the contribution of GLP-1 to the insulinotropic effect of DPP-4 inhibition, there were substantial differences in study design: *1*) different DPP-4 inhibitors were used, *2*) the duration of DPP-4 treatment differed from 2 to 9–10 days, *3*) the dose of exendin [9-39] used by Nauck et al. was lower, *4*) Nauck et al. studied a mixed meal rather than a 75-g glucose drink, and *5*) Nauck et al. included a control group without diabetes.

The studies performed by Aulinger et al. (10) and Nauck et al. (9) provide compelling evidence that GLP-1–dependent

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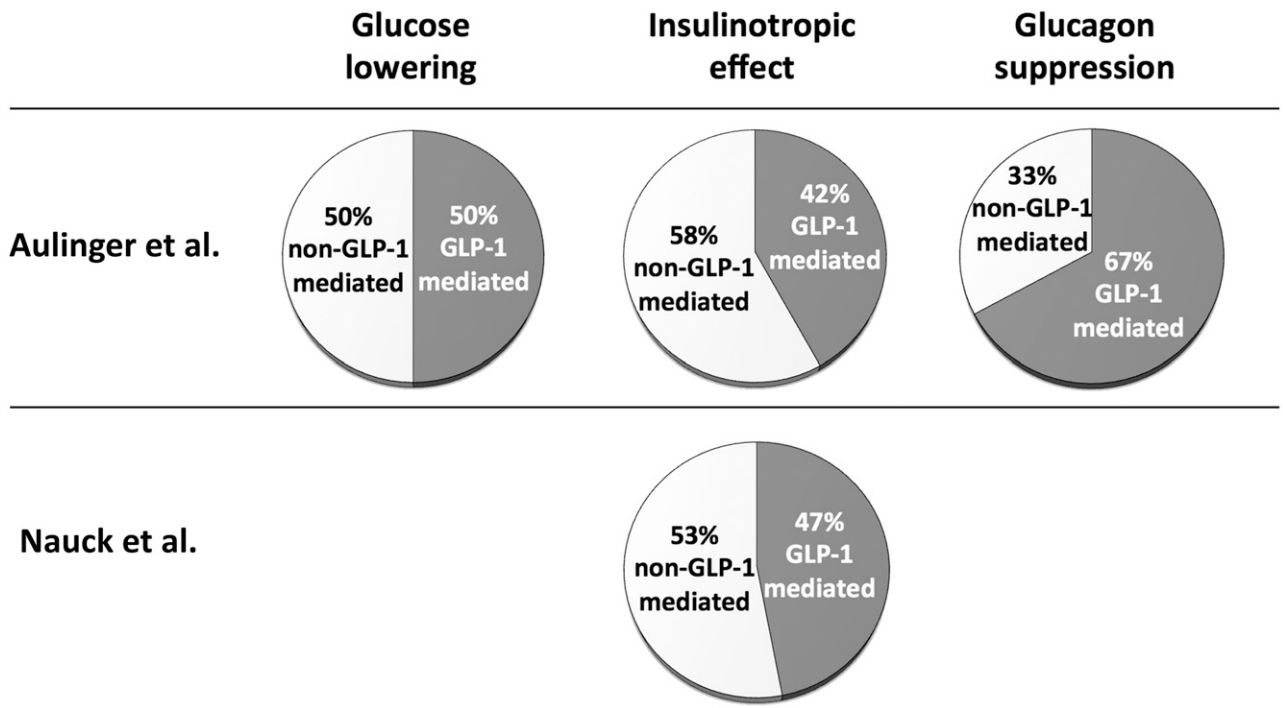

Figure 1—Relative contribution of GLP-1–mediated vs. non-GLP-1–mediated mechanisms by which DPP-4 inhibitors lower glycemia, stimulate insulin, and suppress glucagon in patients with type 2 diabetes, studied after oral glucose (Aulinger et al. [10], using sitagliptin) or a mixed meal (Nauck et al. [9], using vildagliptin). For the study by Aulinger et al., these proportions have been calculated from mean data for incremental areas under the curve for blood glucose (240 min), insulin-to-glucose ratio (240 min), and glucagon (60 min), using the method proposed by the authors for the glucose-lowering effect. For the study by Nauck et al., the proportions are derived from the area under the curve for the insulin secretion rate–to–glucose ratio (240 min) as shown in their Fig. 2.

and –independent mechanisms are both important in glucose lowering by DPP-4 inhibitors, the latter represents the "known unknown." A potential confounder is that exendin [9-39] administered intravenously may incompletely antagonize intestinal GLP-1 receptors. In mice, inhibition of intestinal DPP-4 reduces plasma glucose without affecting plasma DPP-4 activity, GLP-1, or GIP (11). DPP-4 inhibition affects the degradation of other hormones; Nauck et al. (9) refer to four possibilities: GIP, oxyntomodulin, pituitary adenylate cyclase–activating peptide, and stromal cell–derived factor-1α. A role for GIP would not be surprising; in mice, DPP-4 inhibition reduces glycemia with targeted deletion of either, but not both, incretin receptors (12). Moreover, the insulinotropic response to GIP can be partially restored in patients with type 2 diabetes after a period of improved glycemic control (13), including that induced by a DPP-4 inhibitor (14). However, we observed a lack of glucose lowering by sitagliptin in patients with relatively well-controlled type 2 diabetes when glucose was infused intraduodenally at a rate sufficient to stimulate substantial GIP, but minimal GLP-1, secretion (15). Unfortunately, a specific GIP receptor antagonist is not available for use in humans.

Along with insulin secretion and sensitivity, gastric emptying, which exhibits substantial interindividual variation, is a major determinant of postprandial glycemia (16). Studies using intraduodenal infusions of glucose indicate that GIP is the major contributor to the incretin effect in health when duodenal glucose delivery is $\leq$2 kcal/min and that GLP-1 assumes increasing importance at rates $\geq$3 kcal/min (17). In health and type 2 diabetes, the incretin effect is greater when glucose is delivered intraduodenally at 4 kcal/min compared with 2 kcal/min (18). Hence, the effect of DPP-4 inhibition on gastric emptying is of interest. Although Nauck et al. (9) found no effect measured by a breath test (9), there is probably a modest slowing (10,19), albeit much less than that induced by short-acting GLP-1 agonists (16). Gastric emptying is also a determinant of the glycemic response to DPP-4 inhibition (19,20), and strategies that slow gastric emptying and stimulate GLP-1 secretion, such as whey preloads (19), potentiate glucose lowering.

The studies of Nauck et al. (9) and Aulinger et al. (10) serve to remind the scientific community, including the pharma industry, that even for a specifically designed drug class such as DPP-4 inhibitors, mechanisms of action warrant careful scrutiny. In this way, "unknowns" can be resolved to provide therapeutic advances.

Duality of Interest. M.H. has participated in the advisory boards and/or symposia for Novo Nordisk, Sanofi, Novartis, Eli Lilly, Merck Sharp & Dohme, Boehringer Ingelheim, and AstraZeneca and has received honoraria for this activity. T.W. has received research funding from AstraZeneca. K.L.J. has received research

funding from Sanofi and drug supplies from Merck Sharp & Dohme. C.K.R. has received research funding from AstraZeneca, Merck Sharp & Dohme, Eli Lilly, and Novartis. No other potential conflicts of interest relevant to this article were reported.

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