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Review

Blood Pressure-Lowering Effects of Incretin-Based Diabetes Therapies

Julie A. Lovshin MD, PhD*, Bernard Zinman MD

Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Division of Endocrinology and Metabolism, University of Toronto, Toronto, Ontario, Canada

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ABSTRACT

Glucagon-like peptide-1 receptor (GLP-1) agonists and dipeptidyl-peptidase-4 (DPP-4) inhibitors are therapies that are used to treat hyperglycemia in patients with type 2 diabetes mellitus. Although both of these medication types primarily lower prandial and fasting blood glucose levels by enhanced GLP-1 receptor signalling, they have distinct mechanisms of action. Whereas DPP-4 inhibitors boost patient levels of endogenously produced GLP-1 (and glucose-dependent insulinotropic peptide) by preventing its metabolism by DPP-4 enzymatic activity, GLP-1 receptor agonists are either synthetic analogues of human GLP-1 or exendin-4 based molecules. They are tailored to resist hydrolysis by DPP-4 activity and to provide longer durability in the circulation compared with native GLP-1. Several roles for incretin-based diabetes therapies beyond the endocrine pancreas and their glycemic-lowering properties have now been described, including attenuation of cardiac myocyte injury and reduction in post−ischemic infarction size after cardiovascular insult. Favourable outcomes have also been observed on systolic blood pressure reduction, postprandial intestinal lipoprotein metabolism, endothelial cell function, modulation of innate immune-mediated inflammation and surrogate markers of renal function. As hypertension is an independent risk factor for premature death in patients with type 2 diabetes, potential favourable extrapancreatic actions, particularly within the heart, blood vessels and kidney, for this drug class are of considerable clinical interest. Herein, we highlight and provide critical appraisal of the clinical data supporting the antihypertensive effects of GLP-1 receptor agonists and DPP-4 inhibitors and link possible mechanisms of action to clinical outcomes reported for this drug class.

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RÉSUMÉ

Les agonistes des récepteurs du GLP-1 (*glucagon-like peptide—1*) et les inhibiteurs de la dipeptidyl-peptidase-4 (DPP-4) sont des traitements utilisés pour traiter l'hyperglycémie des patients souffrant du diabète sucré de type 2. Bien que ces deux types de médicaments abaissent principalement les glycémies prandiale et à jeun en améliorant la signalisation des récepteurs du GLP-1, leurs mécanismes d'action sont distincts. Tandis que les inhibiteurs de la DPP-4 stimulent les concentrations du GLP-1 endogène des patients (et du GIP [*glucose-dependent insulinotropic peptide*]) en empêchant son métabolisme par l'activité enzymatique de la DPP-4, les agonistes des récepteurs du GLP-1 sont soit des analogues synthétiques du GLP-1 humain ou des molécules de l'exendine-4. Ils sont en mesure de résister à l'hydrolyse par l'activité de la DPP-4 et d'avoir une plus longue durabilité dans la circulation comparativement au GLP-1 natif. Les nombreux rôles des traitements à base d'incrétine, outre le pancréas endocrine et leur propriétés hypoglycémiantes, ont maintenant été décrits, à savoir l'atténuation des lésions cardiomyocytaires et la réduction de la taille de l'infarctus postischémique après l'agression cardiovasculaire. Des résultats favorables ont également été observés sur la réduction de la pression artérielle systolique, le métabolisme postprandial des lipoprotéines élaborées par l'intestin, le fonctionnement des cellules endothéliales, la modulation de la réaction inflammatoire de l'immunité innée et les marqueurs de substitution de la fonction rénale. Comme l'hypertension est un facteur de risque indépendant de la mortalité prématurée des patients souffrant du diabète de type 2, les actions extrapancréatiques potentiels favorables, particulièrement sur le cœur, les vaisseaux sanguins et les reins,

* Address for correspondence: Julie A. Lovshin, MD, PhD, Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, 600 University Avenue, TCP5-1003 Mailbox 39 Toronto, Ontario M5G 1X5, Canada.
E-mail address: Lovshin@lunenfeld.ca

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de cette classe de médicaments présentent un intérêt clinique considérable. Dans cet article, nous soulignons et donnons une appréciation critique des données cliniques appuyant les effets antihypertenseurs des agonistes des récepteurs du GLP-1 et des inhibiteurs de la DPP-4, et nous faisons le lien entre les mécanismes d'action possibles et les résultats cliniques de cette classe de médicaments.

Introduction

Glucagon-like peptide-1 receptor (GLP-1) agonists and dipeptidyl-peptidase-4 (DPP-4) inhibitors are therapies that are used to treat hyperglycemia in patients with type 2 diabetes mellitus (1,2). Although both of these medication types primarily lower prandial and fasting blood glucose levels by enhanced GLP-1 receptor signalling, they have distinct mechanisms of action (1,2). Whereas DPP-4 inhibitors boost patient levels of endogenously produced GLP-1 (and glucose-dependent insulinotropic peptide [GIP]) by preventing its metabolism by DPP-4 enzymatic activity, GLP-1 receptor agonists are either synthetic analogues of human GLP-1 or exendin-4-based molecules. They are tailored to resist hydrolysis by DPP-4 activity and to provide longer durability in the circulation compared with native GLP-1 (1,2).

Several roles for incretin-based diabetes therapies beyond the endocrine pancreas and their glycemic-lowering properties have now been described, including attenuation of cardiac myocyte injury and reduction in post-ischemic infarction size after cardiovascular insult. Favourable outcomes have also been observed on systolic blood pressure reduction, postprandial intestinal lipoprotein metabolism, endothelial cell function, modulation of innate immune-mediated inflammation and on surrogate markers of renal function (3,4). As hypertension is an independent risk factor for premature death in patients with type 2 diabetes, potential favourable extrapancreatic actions, particularly within the heart, blood vessels and kidney, for this drug class are of considerable clinical interest. Herein, we highlight and provide critical appraisal of the clinical data supporting the antihypertensive effects of GLP-1 receptor agonists and DPP-4 inhibitors as well as link possible mechanisms of action to clinical outcomes reported for this drug class.

Biology of glucagon-like peptide-1

Two distinct groups of medications, the glucagon-like peptide-1 receptor (GLP-1R) agonists and the DPP-4 inhibitors, comprise the class of agents known as incretin-based diabetes therapies (Table 1) (5). These medications have overlapping mechanisms of action for glycemic reduction through either potentiation of endogenous GLP-1 levels or through direct activation of the GLP-1 receptor (a 7-transmembrane, g-protein coupled receptor) to promote insulin secretion, inhibit glucagon secretion, and delay gastric emptying (5). Glucagon-like peptide-1 is an endogenously produced hormone of the distal human gut, synthesized within specialized enteroendocrine cells embedded in the intestinal mucosa known as L cells (6). Although intestinal GLP-1 secretion is triggered by a diverse variety of factors (metformin, interleukin-6, bile acids, and so forth), the classical view is that GLP-1 is secreted in the gut in response to nutrient ingestion as part of the enteroinsular axis (7).

The half-life of GLP-1 in human plasma is very short owing to the proteolytic actions of DPP-4, and DPP-4 is the principle regulator of GLP-1 activity in humans (8). DPP-4 is also known as CD26 (cluster of differentiation 26) or adenosine deaminase complexing protein 2, and occurs in 2 principle forms: 1) as a membrane-bound glycoprotein in immune cell types, and 2) as a circulating serine exopeptidase that inactivates circulating polypeptides (9). In addition to GLP-1, DPP-4 regulates the activity of a number of substrates, including the insulinotropic factor GIP, GLP-2 (an intestinal growth factor), B-type natriuretic peptide (a ventricular-derived peptide secreted in response to cardiomyocyte stretch), stromal-derived growth factor-1-alpha (a homing factor for endothelial progenitor cells) and several other neuropeptides, growth factors and chemokines with varied functions (10). Although GLP-1 is considered the predominant incretin hormone responsible for blood glucose-lowering effects in humans, GIP is also an endogenous incretin hormone with insulinotropic properties whose bioactivity is regulated through DPP-4 (for this review, we will focus primarily on the effects of GLP-1). In the absence of small-molecule inhibitors of DPP-4 activity (DPP-4 inhibitors), the half-life of biologically active GLP-$1^{7\text{-}36\text{amide}}$ in humans is less than 2 minutes (11). GLP-1 concentrations are also regulated by renal excretion, and this has pharmacokinetic implications for administration of GLP-1R agonists in the setting of renal dysfunction (12).

GLP-1 is also synthesized from the proglucagon gene in the brain (hypothalamus, brainstem) where it potently activates central satiety centres that express the GLP-1R, regulating appetite and food intake in humans (13). Body weight losses in the range of 3 kg to 5 kg are typically observed following chronic GLP-1R agonist administration, whereas the currently available DPP-4 inhibitors are weight neutral irrespective of the dose administered. Of those studied, it has been reported that GLP-1R agonists cross the blood-brain barrier (14,15) and some have been associated with neuroprotective effects in the central nervous system in different preclinical models of neurodegeneration (16), and more recently, in improving clinical performance scales in the setting of Parkinson disease (17). In addition to neuroprotection, GLP-1R signalling in the central nervous system may

Table 1
Pharmacologic differences in incretin-based diabetes therapies

Incretin-based therapy	Dose	Administration
GLP-1R agonist		
Liraglutide[*,†,‡]	1.2–1.8 mg	SC, once daily
Exenatide[*,†,‡]	5–10 μg	SC, twice daily
Lixisenatide[†]	20 μg	SC, once daily
Exenatide extended release[†,‡]	2 mg	SC, once weekly
Albiglutide[†,‡]	30 mg	SC, once weekly
Dulaglutide	1.5 mg	SC, once weekly
Semaglutide	0.8–1.6 mg	SC, once weekly
DPP-4 inhibitor		
Sitagliptin[*,†,‡]	50–100 mg	Oral, once daily
Saxagliptin[*,†,‡]	2.5–5 mg	Oral, once daily
Alogliptin[*,†,‡]	25 mg	Oral, once daily
Linagliptin[*,†,‡]	5 mg	Oral, once daily
Vildagliptin[‡]	50 mg	Oral, once/twice daily

SC, subcutaneous.
The antidiabetes drug class known as incretin-based diabetes therapies consists of 2 distinct categories: 1) the GLP-1R agonists, which are administered once (or twice) daily subcutaneously for the shorter-acting agents or once weekly subcutaneously for the longer-acting agents, lower blood glucose levels through direct activation of the GLP-1 receptor; and 2) the DPP-4 inhibitors, which are administered once daily by mouth, primarily lower blood glucose levels through preventing the breakdown of the incretin hormones GLP-1 and GIP.

[*] Approved for use by Health Canada for the treatment of type 2 diabetes.
[†] Approved for use by the Food and Drug Administration for the treatment of type 2 diabetes.
[‡] Approved for use by European Medicines Agency for the treatment of type 2 diabetes.