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Review

Inhibitors of dipeptidyl peptidase-4 as therapeutic agents for individuals with type 2 diabetes: a 25-year journey

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Abstract

In the 25 years since the hypothesis was first described, therapeutic use of inhibitors of dipeptidyl peptidase-4 (DPP-4i) as a novel approach to the treatment of type 2 diabetes has become established widely, with several compounds now available to exemplify the class. Although the clinical profiles of members of the DPP-4i class have been reviewed extensively, the underlying pragmatic small molecular design and pharmaceutical properties of these agents have seldom been addressed in the context of establishment of the class as treatments for type 2 diabetes. Among the reasons contributing to the wide acceptance of DPP-4i as oral anti-hyperglycaemic therapy are: (i) the endocrine basis of their pharmacology; (ii) their chemical 'simplicity' and low molecular mass; (iii) their pharmacological selectivity for their target mechanism of action; (iv) the nature of physiologically relevant substrates for the enzyme; (v) their relative ease of formulation into tablets; (vi) their efficacy as glucose-lowering agents; (vii) their absorption, distribution, metabolism and elimination profiles; and (viii) their limited tolerability issues.

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Introduction

The hypothesis that inhibition of the enzyme dipeptidyl peptidase-4 (DPP-4) might constitute a novel, endocrine-based approach to the treatment of type 2 diabetes was first published in 1995 [1–3]. The mechanism of action described by Deacon *et al.* in 1995 [1] involved the specific, pharmacological inhibition of the physiological, enzymatic, breakdown of glucagon-like peptide 1 (GLP1) and glucose-dependent insulinotropic polypeptide (GIP), resulting in accumulation of the biologically active forms of both hormones. Proof that the hypothesis was relevant physiologically depended upon the availability of precise assay technology that could discriminate between intact and truncated versions of the two incretin hormones [1]. The availability of prototypical, although poorly selective, DPP-4 inhibitors (DPP-4i), such as valine pyrrolidide [4], enabled proof of concept to be established in animal models of type 2 diabetes [5]. The objective of the DPP-4i concept was to provide a drug that would possess anti-hyperglycaemic efficacy with the major advantage of having relative freedom from the risk of hypoglycaemia owing to the glucose-dependent insulinotropic effect of the incretin hormones [6].

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DPP-4i as a successful approach to treatment of type 2 diabetes

Since their launch as therapies (as early as 2006), DPP-4i have become widely used treatments for type 2 diabetes, not only as an adjunct to the use of metformin, but also as monotherapy in people intolerant to metformin, and in combination with other treatments for the disease. There have been many reviews focusing of the clinical properties of the various DPP-4i and the reader is directed to such articles elsewhere [7,8]. This review focuses instead on the endocrine and pharmacological origins of the DPP-4i concept and a discussion of the possible underlying reasons why DPP-4i have become a well-tolerated and effective therapeutic option for treatment of type 2 diabetes—based largely upon their underlying chemical simplicity. The reasons for this success are, arguably, multi-fold and are looked at in detail below.

Endocrine basis of drug design

DPP-4i possess anti-hyperglycaemic efficacy indirectly as a result of a reduction in the otherwise rapid degradation and

What's new?

- This is an intentionally brief review highlighting aspects of the design of dipeptidyl peptidase-4 (DPP-4) inhibitors that are often overlooked in more conventional reviews. It has been written primarily with the purpose of informing primary care healthcare professionals.
- The review focuses upon how the pharmacology and some properties of small molecules have facilitated the successful development of therapeutic agents.
- The review is timely because it is now 25 years since the hypothesis to treat type 2 diabetes with inhibitors of DPP-4 was first described in the literature.
- The chemical and pharmacological properties of DPP-4 inhibitor drugs that make them suitable for oral therapy of type 2 diabetes are discussed.
- Features distinguishing small molecules from biotechnological alternatives are reviewed briefly.

inactivation of the incretin hormones GLP1 and GIP. Increases in the intact and biologically active sequences of both peptides lead to insulin release and, in the case of GLP1, suppression of glucagon release in a glucose-dependent manner [6]. Two aspects of this endocrinological effect are noteworthy. First, the risk of hypoglycaemia is reduced because both incretin hormones only affect insulin and glucagon release appropriately, according to the prevailing glucose concentrations [6]. Second, incretin-based therapies are the only currently available therapies that address the α-cell defect of type 2 diabetes, wherein hepatic glucose production is elevated pathophysiologically [9]. A reduction in the risk of hypoglycaemia is a distinct advantage over the use of sulphonylureas [7]. Sulphonylureas cause insulin release via closure of ATP-sensitive potassium channels, a mechanism that is not fully dependent upon the extracellular glucose concentration [10]. Prior to the discovery of DPP-4i, the development of small molecule therapies based upon an endocrine starting point was, to a certain extent, pioneered during discovery of the angiotensin-I converting enzyme inhibitor, captopril [11]. Inhibition of the rapid breakdown of the inactive precursor peptide angiotensin I into the active product angiotensin II is now thought to be the principal mechanism of action of the angiotensin-I converting enzyme inhibitor. It was this knowledge of endogenous rapid cleavage of labile substrates that led to the thought that the stability of GLP1 and GIP in their intact, biologically active forms, could be markedly improved by preventing the primary route of degradation into largely inactive metabolites *in vivo* [1], analogous to a second known endocrine effect of angiotensin-I converting enzyme inhibition, i.e. inhibition of the breakdown of biologically active bradykinin.

Pragmatic molecular design

DPP-4i are low molecular mass organic molecules; often, but not always, structurally based upon a metabolically stabilized dipeptide 'skeleton' (e.g. saxagliptin, sitagliptin and vildagliptin) [12]. The straightforward physical chemical properties of members of the DPP-4i class make them relatively simple to formulate and are commensurate with desirable absorption, distribution, metabolism within, and elimination from, the body. The dipeptide structure of some inhibitors can be viewed as analogous to the labile site of its primary endogenous substrates – such as the N-terminal portion of GLP1. The result of the drug discovery process was the identification of purely selective inhibitors with affinity typically in the low nanomolar range [12]. Low molecular mass drugs (smaller than ~ 500 Da) also have the advantage of a generally lower rate of attrition during drug development [13,14]. Another advantage of small molecules, as opposed to peptide-based medicines, is that the chance of immunological reactions (e.g. immuno-neutralizing and other antibody formation) is considerably less. It may be pointed out that, as a drug-design principle in a more general sense, enzyme inhibitors are frequently successfully introduced and clinically used drugs; arguably aspirin, statins and angiotensin-I converting enzyme inhibitors being among the most commonly used and beneficial medicines currently available. Some pertinent attributes of small molecules are summarized in Table 1.

Table 1 How small molecules address a 'wish list' for an everyday therapy.

Attribute	
Low molecular weight	Helps to ensure high levels of oral absorption, as well as reproducible interdosing exposure and pharmacokinetic profiles without the use of absorption enhancers
Physical chemistry	Commensurate with desired absorption, distribution within the extracellular space, drug metabolism and drug elimination properties
Chemical structure	Minimizes any undue drug metabolism of the drug *in vivo*
Pharmacology	Selectivity for the pharmacological target vs non-specific, or off-target, activity
Pharmacy	Formulation as a tablet as either the individual component or a constituent part of a fixed-dose combination with commonly co-administered agents (e.g. metformin, SGLT2i)
Efficacy	Effective glucose lowering in comparison with alternative agents
Potency	Effective glucose lowering at reasonable dose levels

SGLT2i, sodium–glucose cotransporter-2 inhibitor.

Selectivity for the DPP-4 enzyme

During development of DPP-4i, counter-screening against other enzymes resulted in the development of highly selective DPP-4i molecules [15]. Achieving a high degree of selectivity for the target enzyme is considered an essential step during drug development, again to help ensure that off-target and/or non-specific activities do not occur [16]. Although any difference in the absolute degree of selectivity between some members of the DPP-4i class has not been attributed to any known clinical tolerability or safety issue to date, it is generally regarded as desirable to pharmacologically impact the intended target alone.

Physiologically relevant substrates for DPP-4

As mentioned above, DPP-4i increase the levels of not only intact and biologically active GLP1, but also GIP. The contribution of GIP to the glucose-lowering efficacy and lack of hypoglycaemic risk has been reviewed recently [17] and points to an important aspect of the mechanism of action of enzyme inhibitors in that more than one effector endocrine mediator may be relevant to their therapeutic effect(s). This further distinguishes DPP-4i from other approaches used to treat type 2 diabetes, i.e. multiple effector systems. Much interest has been shown in the development of dual GLP1 and GIP incretin agonists and it may be that DPP-4i could be regarded as pragmatic alternatives to such hybrid molecules, at least as far as the endocrine mechanism of action is concerned. It is important to note that only physiologically relevant substrates are affected by pharmacological enzyme inhibition. In the case of DPP-4i, very few substrates have been shown to be affected by the drugs from a physiological standpoint [18], and initial concerns that several endocrine systems would be affected by DPP-4i, leading to the possibility of multiple mechanism-led side effects, have been shown to be largely groundless.

Pharmaceutical considerations

Although biotechnology offers tremendous potential for the creation of novel medicines, conventional medicinal chemistry-based approaches to rational drug design continue to offer substantial advantages due to the inherent relative simplicity of the approach. Small molecules are often the easiest to optimize pharmacologically, and to formulate for use as therapeutic agents. As such, the available DPP-4i are designed to be fully compatible with the formulation of fixed-dose combinations with other commonly used agents such as metformin and sodium–glucose cotransporter 2 inhibitors (SGLT2i). Good oral availability makes systemic exposure to the drug reproducible and reliable, largely irrespective of the individual's dietary habits. Ensuring high levels of oral availability avoids reliance upon the addition of complex and sometimes inefficient absorption-enhancing co-factors, and removes the need for subcutaneous injection of often difficult to manage liquid-based formulations. Accordingly, the preferences of both physicians and individuals with type 2 diabetes for therapies that are administered orally are addressed.

Efficacy as glucose-lowering agents

The overall clinical profiles of the DPP-4i have been reviewed extensively elsewhere [15,19]. Briefly, the glucose-lowering efficacy of DPP-4i has been shown to be largely non-inferior to other commonly used oral anti-hyperglycaemic agents, such as metformin and sulphonylureas [15]. The glucose lowering effect of DPP-4i has also been shown to be largely additive to those of most other oral anti-hyperglycaemic agents, presumably because of complimentary mechanisms of action [15]. Moreover, the clinical utility of DPP-4i is underlined by the fact that they have proven to be effective blood glucose-lowering agents at every stage of type 2 diabetes treatment, from initial first-line application and to combination with basal insulin [15]. Added to their efficacy, clinical uptake of DPP-4i has also been facilitated because, as mentioned above, they may readily be co-formulated in fixed-dose combination tablets. For example, fixed-dose combination with metformin is used particularly frequently, and, moreover, has the supportive, mechanistic basis that metformin is a GLP1 secretagogue [20], thereby increasing the level of GLP1 that can be preserved in the intact form by a DPP-4i.

Drug absorption, distribution, metabolism and elimination

The pharmacokinetic–pharmacodynamic profiles of DPP-4i are commensurate with effective therapy—most of them being suitable for once-daily dosing. As a general principle, a drug can be eliminated unchanged predominantly via either the bile or urine, or can be metabolized systemically prior to elimination of its metabolites. These properties may negate any need to reduce dose levels, should one or other route of elimination be compromised, in order to keep systemic exposure to the drug within appropriate ranges. Several DPP-4i have been designed such that drug metabolism is either absent or limited, so formation of a family of chemical breakdown products following administration may be avoided (e.g. alogliptin, linagliptin and sitagliptin). This has the advantage that the number of 'foreign' molecular species circulating is minimized; exposure to only one chemical entity reducing any chance of molecule-specific tolerability issues, chemically based toxicities, etc. Furthermore, lack of drug metabolism limits the potential for drug–drug interactions with co-administered therapies.

Limited tolerability issues

Remembering that all drugs either have the potential to or are known to cause tolerability issues, and that physicians should always prioritize this aspect of therapy, it is noteworthy that DPP-4i are, in the main, mostly well tolerated

and easy to use. Long-term cardiovascular outcome trials are available with most DPP-4i (e.g. alogliptin, linagliptin, saxagliptin and sitagliptin) and these studies underline the relatively good tolerability of this class of agents [21]. Infrequently encountered or delayed-onset drug safety issues may always be an issue with any relatively recently introduced therapeutic agent and further vigilance over the longer term is therefore essential.

Conclusion

In the 25 years since the concept of DPP-4i was first proposed and more than 12 years since their introduction, DPP-4i have become established therapy for type 2 diabetes. The physical chemical properties of DPP-4i molecules are straightforward and, consequently, may help avoid the potential pitfalls in overly complicated and suboptimal dosing regimens of other agents as treatment choices for a chronic disease such as type 2 diabetes. As small molecules, they have been relatively easy to optimize for selectivity for the DPP-4 enzyme and may be readily formulated for oral administration both as single chemical entities and in combination with other commonly administered compounds such as metformin. This pragmatic approach to drug design has assisted their uptake and use clinically.

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Competing interests

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References

1 Deacon CF, Nauck MA, Toft-Nielsen M, Pridal L, Willms B, Host JJ. Both subcutaneously and intravenously administered glucagon-like peptide 1 are rapidly degraded from the NH_2-terminus in type 2-diabetic patients and in healthy subjects. *Diabetes* 1995; **44**: 1126–1131.
2 Carr RD. Drug development from the bench to the pharmacy: with special reference to dipeptidyl peptidase-4 inhibitor development. *Diabet Med* 2016; **33**: 718–722.
3 Holst JJ, Deacon CF. Inhibition of the activity of dipeptidyl-peptidase IV as a treatment for type 2 diabetes. *Diabetes* 1998; **47**: 1663–1667.
4 Schön E, Born I, Demuth HU, Faust J, Neubert K, Steinmetzer T *et al*. Dipeptidyl peptidase IV in the immune system. Effects of specific enzyme inhibitors on activity of dipeptidyl peptidase IV and proliferation of human lymphocytes. *Biol Chem Hoppe Seyler* 1991; **372**: 305–311.
5 Ahrén B, Holst JJ, Mårtensson H, Balkan B. Improved glucose tolerance and insulin secretion by inhibition of dipeptidyl peptidase IV in mice. *Eur J Pharmacol* 2000; **404**: 239–245.
6 Nauck MA, Kleine N, Ørskov C, Holst JJ, Willms B, Creutzfeldt W. Normalization of fasting hyperglycaemia by exogenous glucagon-like peptide 1 (7–36 amide) in type 2 (non-insulin-dependent) diabetic patients. *Diabetologia* 1993; **36**: 741–744.
7 Deacon CF, Lebovitz HE. Comparative review of dipeptidyl peptidase-4 inhibitors and sulphonylureas. *Diabetes Obes Metab* 2016; **18**: 333–347.
8 Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet* 2006; **368**: 1696–1705.
9 Petersen MC, Vatner DF, Shulman GI. Regulation of hepatic glucose metabolism in health and disease. *Nat Rev Endocrinol* 2017; **13**: 572–587.
10 Ashcroft FM, Gribble FM. ATP-sensitive K+ channels and insulin secretion: their role in health and disease. *Diabetologia* 1999; **42**: 903–919.
11 Antonaccio MJ. Development and pharmacology of angiotensin converting enzyme inhibitors. *J Pharmacol* 1983; **14**(Suppl 3): 29–45.
12 Berger JP, SinhaRoy R, Pocai A, Kelly TM, Scapin G, Gao YD *et al*. A comparative study of the binding properties, dipeptidyl peptidase-4 (DPP-4) inhibitory activity and glucose-lowering efficacy of the DPP-4 inhibitors alogliptin, linagliptin, saxagliptin, sitagliptin and vildagliptin in mice. *Endocrinol Diab Metab* 2018; **1**: e00002.
13 Lipinski CA. Lead- and drug-like compounds: the rule-of-five revolution. *Drug Discov Today Technol* 2004; **1**: 337–341.
14 Leeson PD, Springthorpe B. The influence of drug-like concepts on decision-making in medicinal chemistry. *Nat Rev Drug Discov* 2007; **6**: 881–890.
15 Deacon CF, Holst JJ. Dipeptidyl peptidase-4 inhibitors for the treatment of type 2 diabetes: comparison, efficacy and safety. *Expert Opin Pharmacother* 2013; **14**: 2047–2058.
16 Huggins DJ, Sherman W, Bruce Tidor T. Rational approaches to improving selectivity in drug design. *J Med Chem* 2012; **55**: 1424–1444.
17 Deacon CF. Metabolism of GIP and the contribution of GIP to the glucose-lowering properties of DPP-4 inhibitors. *Peptides* 2020; **125**: 170196.
18 Mulvihill EE, Drucker DJ. Pharmacology, physiology, and mechanisms of action of dipeptidyl peptidase-4 inhibitors. *Endocr Rev* 2014; **35**: 992–1019.
19 Gallwitz B. Clinical use of DPP-4 inhibitors. *Front Endocrinol (Lausanne)* 2019; **10**: 389.
20 McCreight LJ, Bailey CJ, Pearson ER. Metformin and the gastrointestinal tract. *Diabetologia* 2016; **59**: 426–435.
21 Scheen AJ. The safety of gliptins: updated data in 2018. *Expert Opin Drug Saf* 2018; **17**: 387–405.