Dipeptidyl Peptidase IV Inhibition Alters the Hemodynamic Response to Angiotensin-Converting Enzyme Inhibition in Humans With the Metabolic Syndrome

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I nhibitors of dipeptidyl peptidase IV (DPP-4; an ectoenzyme also called CD26) represent a novel, effective, and useful class of antidiabetic drugs for treatment of type 2 diabetes. Drugs in this class (eg, sitagliptin [Januvia], saxagliptin [Onglyza], and vildagliptin [Galvus]) afford significant and sustained reductions in hemoglobin A1c with a low risk of hypoglycemia and little effect on body weight.1 Because of this desirable pharmacological profile, and because of the emerging uncertainty regarding the safety of rosiglitazone2 and the inability of most antidiabetic agents to reduce macrovascular events,3 it is likely that DPP-4 inhibitors will be used extensively to manage the worldwide pandemic of type 2 diabetes. Indeed, sitagliptin is already the second leading branded oral antidiabetic agent in the United States.3 In the near future, tens of millions of patients will be taking DPP-4 inhibitors, many for the rest of their lives; thus, we should strive to fully understand the benefits and risks, both short-term and long-term, associated with DPP-4 inhibition. Because a high percentage of type 2 diabetics have the metabolic syndrome, the effects of DPP-4 inhibition in such patients are of particular importance. Moreover, because metabolic syndrome patients are nearly always subjected to multidrug regimens, clarifying the interactions of DPP-4 inhibitors with other medications prescribed for these patients (eg, antihypertensive drugs) is also a worthwhile investment.

Based on their biochemical mechanism, it is reasonable to anticipate that DPP-4 inhibitors, in addition to their beneficial effects, will likely express adverse actions and interactions with other drugs. DPP-4 metabolizes incretin hormones (eg, glucagon-like peptide-1 and glucose-dependent insulinotropic peptide), and consequently, DPP-4 inhibitors raise circulating levels of incretins and thereby exert antidiabetic actions by increasing insulin release, inhibiting glucagon secretion, and retarding gastric emptying.4 However, incretin hormones are not the only endogenous substrates for DPP-4. Indeed, there are ≥35 known peptide substrates for DPP-4;5,6 consequently, inhibition of DPP-4 no doubt modifies the levels of a broad array of biologically active peptides, and changes in levels of nonincretin peptide substrates (or products) of DPP-4 may entail adverse effects or drug–drug interactions.

Regarding potential drug–drug interactions, of particular importance are the interactions between DPP-4 inhibitors and angiotensin-converting enzyme (ACE) inhibitors. ACE inhibitors are prescribed widely for patients with type 2 diabetes (to control blood pressure, preserve renal function, treat heart failure, or prevent myocardial infarction, stroke, or death), therefore, a significant percentage of patients receiving DPP-4 inhibitors will be cotreated with an ACE inhibitor. Because both classes of drugs inhibit enzymes with multiple (and overlapping) substrates, interactions can and do occur. For example, DPP-4 inhibitors increase angioedema risk in patients treated with ACE inhibitors because ACE normally processes substance P (SP; a putative mediator of angioedema) to inactive fragments, yet, when ACE is inhibited, SP metabolism becomes strongly dependent on DPP-4 activity.7

In the current issue of Hypertension, Marney et al describe yet another interaction between DPP-4 inhibitors and ACE inhibitors.8 In this study, patients with the metabolic syndrome (as defined by the National Cholesterol Education Program criteria) received sitagliptin (100 mg per day) or placebo for 5 days in a randomized, cross-over design. On the fifth day of either sitagliptin or placebo, patients were administered 0, 5, or 10 mg of enalapril (only 1 dose of enalapril per patient), and mean arterial blood pressure (MAP) was measured repeatedly for 8 hours. Importantly, there was a statistically significant interaction between sitagliptin and enalapril on MAP. During the placebo arm of the study, not surprisingly, enalapril significantly and dose-dependently lowered MAP over the 8-hour observation period (2.7±2.1, −0.9±2.5, and −7.9±2.4 mm Hg in response to 0, 5, and 10 mg of enalapril, respectively; P<0.02 for dose effect of enalapril). In contrast, during the sitagliptin arm of the study, the effect of enalapril was altered (−2.3±2.0, −5.7±2.2, and −0.9±2.3 mm Hg in response to 0, 5, and 10 mg of enalapril, respectively; P=0.38 for dose effect of enalapril). Thus, in the absence of enalapril or in the presence of 5 mg of enalapril, sitagliptin mildly lowered MAP by ∼5 mm Hg [−2.3−2.7=−5; ie, the difference between the response to sitagliptin versus placebo in the absence of enalapril; −5.7−(−0.9)=−4.8; ie, the difference between the response to sitagliptin versus placebo in the presence of 5 mg of enalapril].

The interaction between sitagliptin and 10 mg of enalapril can be described from 2 alternative perspectives. One viewpoint is that sitagliptin blocks the antihypertensive response

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to 10 mg of enalapril. Another perspective is that in the presence of 10 mg of enalapril, sitagliptin actually increases MAP by 7 mm Hg \([-0.9 \text{ to } -7.9] = 7\); i.e., the difference between the response to sitagliptin versus the response to placebo in the presence of 10 mg of enalapril]. From both viewpoints, the net effect is that 100 mg of sitagliptin plus 10 mg enalapril yields little change in MAP. The results of this provocative study in patients with the metabolic syndrome are remarkably similar, both qualitatively and quantitatively, to findings previously reported by Jackson et al in spontaneously hypertensive rats. In this regard, Jackson et al demonstrate that in the absence of an ACE inhibitor, DPP-4 inhibition decreases MAP by 6 mm Hg; yet in the presence of a high dose of an ACE inhibitor, DPP-4 inhibition increases MAP by 12 mm Hg.

What might be the mechanism of the antihypertensive effects of DPP-4 inhibition in the absence of ACE inhibition or in the presence of a low dose of an ACE inhibitor? Given the large number of peptides metabolized by DPP-4, the answer to this question will likely be multifaceted. It is conceivable that the mild reduction in MAP induced by DPP-4 inhibition is mediated in part by attenuation of the metabolism of SP; however, additional studies are required to probe this hypothesis.

What about the mechanism of the pressor response to DPP-4 inhibition in the presence of a high dose of an ACE inhibitor? Because SP metabolism is particularly sluggish when both DPP-4 and ACE are simultaneously blocked and because SP in the brain may increase sympathetic outflow, Marney et al reasonably conclude that the mechanism of this drug–drug interaction may involve, in part, SP-induced increases in sympathetic tone. Consistent with this hypothesis, Marney et al observe that the sitagliptin-induced increase in MAP in the presence of 10 mg of enalapril is associated with evidence of sympathetic activation (e.g., increases in heart rate and plasma norepinephrine). Moreover, Jackson et al find that DPP-4 inhibition increases MAP in spontaneously hypertensive rats pretreated with an antihypertensive drug that does not block the sympathetic nervous system (e.g., captopril or hydralazine), yet DPP-4 inhibition does not increase MAP in spontaneously hypertensive rats pretreated with a ganglionic blocker (e.g., chlorisondamine). Thus, both studies are concordant in the conclusion that somehow DPP-4 inhibitors, in the presence of ACE inhibition, interact with the sympathetic nervous system to increase MAP in metabolic syndrome patients or spontaneously hypertensive rats.

However, the interaction between DPP-4 inhibitors and ACE inhibitors on blood pressure might involve more than just increases in sympathetic tone. Jackson et al also observe that inhibition of Y1 receptors with the selective Y1 receptor antagonist BIBP 3226 abolishes the pressor response to DPP-4 inhibition in ACE inhibitor–pretreated spontaneously hypertensive rats, suggesting a critical involvement of endogenous agonists of Y1 receptors. Neuropeptide Y1-36 (NPY1-36, a 36-aa peptide) is a cotransmitter in postganglionic sympathetic nerves that is released with norepinephrine and augments vasoconstrictor responses to norepinephrine via Y1 receptor activation. Importantly, by removing 2 amino acids from the N-terminus, DPP-4 converts NPY1-36 to NPY3-36, which is inactive at Y1 receptors. Therefore, as illustrated in the Figure, the combination of increased sympathetic tone (induced by simultaneous ACE and DPP-4 blockade in the central nervous system) accompanied by reduced metabolism of NPY1-36 to NPY3-36 could offset the antihypertensive effect of ACE inhibition (or said differently, could result in a pressor response to DPP-4 inhibition in the presence of a high dose of an ACE inhibitor).

How important is DPP-4 for the metabolism of NPY1-36? The answer is very, for 2 reasons: DPP-4 is likely the main enzyme that inactivates NPY1-36, and \( k_{cat}/K_m \) of DPP-4 for NPY1-36 is \( 7 \)-fold, 36-fold, and 73-fold greater for NPY1-36 compared with SP, glucagon-like peptide-1, and glucose-dependent insulinoergic peptide, respectively. Because \( k_{cat}/K_m \) is the most informative metric for comparing the effects of enzymes on low levels of endogenous substrates, DPP-4 could just as logically be named NPY-converting enzyme, and, in fact, DPP-4 inhibitors would likely increase relevant biophase levels of endogenous NPY1-36 more so than their intended therapeutic targets (i.e., incretins).

Will emerging studies uncover other effects of DPP-4 inhibitors that are mediated by inhibiting NPY-converting enzyme?
enzyme? In preliminary experiments, we observe that NPY1–36 and peptide YY1–36 (PYY1–36; an endogenous Y1 receptor agonist that is released from the gut and metabolized to PYY3–36 [which does not activate Y1 receptors] by DPP-4), stimulate the proliferation of and collagen production by pregglomerular microvascular smooth muscle cells and glomerular mesangial cells; and these effects are augmented by sitagliptin and blocked by BIBP 3226 (unpublished work in progress). This may be important because such effects in the long term are probably not desirable and could accelerate diabetic nephropathy. Indeed, Kirino et al report that in DPP-4–deficient rats (F344/DuCrCrlj rats; a strain of rats with a mutation in the DPP-4 gene that results in deficient DPP-4 activity), creatinine clearance 42 days after induction of diabetes (with streptozotocin) is 50% lower in DPP-4–deficient versus wild-type rats.

Perspective

The study by Marney et al has limitations; for example, the study involved only a small number of patients, did not examine the long-term interaction of DPP-4 inhibition plus high-dose ACE inhibition on arterial blood pressure, and did not define the limits of generalizability of the findings. It is entirely possible that in the long term, the interaction between these 2 classes of drugs on MAP disappears or that only a vanishingly small fraction of patients will experience this interaction in the long term. The DPP-4 inhibitors are a welcome and badly needed new class of antidiabetic drugs that provide clinicians with another important therapeutic tool to attenuate the ravages of type 2 diabetes. Nonetheless, given that only a small rise in MAP puts patients (particularly those with the metabolic syndrome) at increased risk of stroke, myocardial infarction, heart failure, and chronic kidney disease, we would be wise to better define the risks of DPP-4 inhibitors and their interactions with antihypertensive drugs. Hopefully, the study by Marney et al will encourage this endeavor.

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None.

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