NEW HYPOTHESES IN CLINICAL MEDICINE

Do Dipeptidyl Peptidase-4 Inhibitors Cause Heart Failure Events by Promoting Adrenergically-Mediated Cardiotoxicity? Clues from Laboratory Models and Clinical Trials

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Running title: Mechanisms of Cardiotoxicity of DPP4 Inhibitors

Subject Terms:
Diabetes, Type 2
Heart Failure

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ABSTRACT

Rationale: Dipeptidyl peptidase-4 (DPP-4) inhibitors have increased the risk of heart failure events in both randomized clinical trials and observational studies, but the mechanisms that underlie their deleterious effect remain to be elucidated. Previous work has implicated a role of these drugs to promote cardiac fibrosis.

Objective: This paper postulates that DPP-4 inhibitors increase the risk of heart failure events by activating the sympathetic nervous system to stimulate cardiomyocyte cell death, and it crystallizes the findings from both experimental studies and clinical trials that support the hypothesis.

Methods and Results: Inhibition of DPP-4 not only potentiates the actions of glucagon-like peptide-1 (which can increase myocardial cyclic AMP), but it also potentiates the actions of stromal cell-derived factor-1 (SDF-1), neuropeptide Y and substance P to activate the sympathetic nervous system and stimulate beta-adrenergic receptors to cause cardiomyocyte apoptosis, presumably through a Ca++/calmodulin-dependent protein kinase II pathway. An action of SDF-1 to interfere with cyclic AMP and protein kinase A signaling may account for the absence of a clinically overt positive chronotropic effect. This conceptual framework is supported by the apparent ability of beta-blocking drugs to attenuate the increased risk of DPP-4 inhibitors in a large-scale clinical trial.

***Conclusion*:** Sympathetic activation may explain the increased risk of heart failure produced by DPP-4 inhibitors. The proposed mechanism has major implications for clinical care, since in the treatment of patients with type 2 diabetes, DPP-4 inhibitors are widely prescribed, but beta-blockers are underutilized because of fears that they might mask hypoglycemia.

Keywords:
Dipeptidyl peptidase-4 inhibitors; heart failure; diabetic cardiomyopathy; sympathetic nervous system; adrenergic stimulation; Stromal cell-derived factor-1; neuropeptides/leptin/neuropeptide Y; growth substances.

Nonstandard Abbreviations and Acronyms:

DPP-4	Dipeptidyl peptidase-4 inhibitors

Evidence That DPP-4 Inhibitors Increase the Risk of Heart Failure.

Dipeptidyl peptidase-4 inhibitors are popular choices for the management of type 2 diabetes, because of their tolerability and their ability to reliably lower blood glucose with oral administration. However, the use of DPP-4 inhibitors can lead to worsening heart failure in patients with established cardiovascular disease or metabolic abnormalities.[1]

The US Food and Drug Administration has issued a warning about an increased risk of serious heart failure events for both saxagliptin and alogliptin.[2] In the SAVOR-TIMI53 trial, patients treated with saxagliptin experienced an increased risk of hospitalization for heart failure.[3] In the EXAMINE trial, patients without a prior history of heart failure were hospitalized for heart failure more frequently when treated with alogliptin, as compared with placebo.[4] Additionally, in the VIVIDD trial of patients with both diabetes and left ventricular systolic dysfunction, vildagliptin lead to adverse effects on cardiac remodeling and a higher risk of cardiovascular hospitalization and death.[5] A pooled analysis suggested increased adverse heart failure events with linagliptin.[6]

A large-scale trial with omarigliptin did not note an increased risk of heart failure, but risk estimates were unreliable because of the small number of events.[1,7] Although a large-scale trial with sitagliptin did not report an increased risk of heart failure hospitalizations, the estimates of risk may have been influenced by a high prevalence of metformin use and a low and declining use of insulin as background treatments.[1] Worsening heart failure with all DPP-4 inhibitors has been reported in several meta-analyses and observational studies.[8-10] Furthermore, adverse heart failure events have been disproportionately reported among users of DPP-4 inhibitors in clinical practice;[11] clinical deterioration may be particularly apparent following the initiation of treatment.[12] The weight of evidence is consistent with a class effect of these drugs.[1]

Mechanisms by Which DPP-4 Inhibitors Could Lead to Heart Failure.

Certain antihyperglycemic drugs lead to worsening heart failure because they promote sodium retention. However, DPP-4 inhibitors block sodium reabsorption in the renal tubules, and thus, their effects of the kidney cannot explain the increased the risk of heart failure.[13]

Effects of DPP-4 Inhibitors on the Heart: Could DPP-4 inhibitors lead to heart failure by exerting a deleterious effect on the heart? In experimental models, DPP-4 inhibition has been accompanied by increases in myocardial cyclic AMP, which is related to potentiation of endogenous glucagon-like peptide-1 (GLP-1).[14,15] Although sustained increases in cyclic AMP may exacerbate the clinical course of heart failure,[16] the increase produced by GLP-1 receptor signaling might be confined to intracellular microdomains that are not linked to pathways that cause deleterious effects on cardiomyocytes.[17-20] Such compartmentation may help to explain why DPP-4 inhibitors do not increase in heart rate, unlike long-acting GLP-1 analogs.[21]

However, GLP-1 is not the only substrate for DPP-4, and many of the actions of DPP-4 inhibitors are due to their potentiation of other endogenous peptides that have important effects on the cardiovascular system. Specifically, DPP-4 acts to degrade stromal cell-derived factor-1 (SDF-1), a stem-cell chemokine that acts via CXCR4 and CXCR7 receptors.[22] In addition, by acting as a converting enzyme, DPP-4 modulates the cardiovascular responses to neuropeptide Y (NPY), thereby shifting its activities away from the NPY-Y1 receptor.[23] Finally, DPP-4 can degrade substance P, a tachykinin neuropeptide that signals through the NK1 receptor.[24] Therefore, DPP-4 inhibition potentiates the actions of endogenous SDF-1, NPY and substance P, which can adversely affect both cardiac structure and function. Circulating levels of these peptides are characteristically increased in patients with heart failure.[25-27]

Could potentiation of SDF-1, NPY and substance P underlie the effect of DPP-4 inhibitors to increase the risk of heart failure? Heart failure in patients with diabetes can present with a preserved ejection fraction or a reduced ejection fraction.[28] Patients with impaired systolic function primarily have a disorder that is characterized by cardiomyocyte loss and stretch, whereas those with values for ejection fraction in the normal range typically have evidence of a systemic inflammatory state that leads to cardiac fibrosis and decreased ventricular distensibility.[28] Could the actions of DPP-4 inhibitors increase the likelihood of both phenotypes of heart failure that are seen in type 2 diabetes?

Effects of DPP-4 Inhibitors on Cardiac Inflammation and Fibrosis: Diabetes is characterized by increased epicardial fat,[29] and inflammation of adipose tissue can be exacerbated by both GLP-1 and CXCR4 receptor signaling.[30-32] An inflammatory state in epicardial adipose tissue can be readily transmitted to the underlying myocardium.[33] Such a mechanism may explain why potentiation of SDF-1 leads to myocardial fibrosis[34] and why cardiac fibrosis is enhanced by DPP-4 inhibition but prevented by CXCR4 antagonism.[35,36] Interestingly, potentiation of the actions of substance P and NPY by DPP-4 inhibition can also promote profibrotic pathways in the myocardium.[23,37]

However, the effects of DPP-4 inhibitors in patients with a known diagnosis of heart failure with a preserved ejection fraction have not been formally investigated, and conceivably, an effect of fibrosis to exacerbate the clinical course of these patients might require prolonged periods of therapy. Yet, in both randomized clinical trials and observational studies, the increased risk of heart failure events with DPP-4 inhibitors was seen early following initiation of treatment.[10,19] Furthermore, the adverse effects on cardiac remodeling seen with vildagliptin were observed in patients with heart failure and a reduced ejection fraction.[12] This disorder is characterized primarily by an loss of cardiomyocytes rather than inflammation and fibrosis in the myocardium.[28]

Effects of DPP-4 Inhibitors on Cardiomyocyte Viability and Death: The sympathetic nervous system contributes importantly to the progression of heart failure in patients who have impaired systolic function, accounting for the benefits of long-term beta-blockade in these individuals. Interestingly, in experimental heart failure, potentiation of the effects of endogenous SDF-1 acts on the central nervous system to cause a striking increase in sympathetic outflow.[38,39] Both NPY and substance P (which are coreleased with norepinephrine from nerve terminals) can further increase sympathetic nerve activity, particularly in the periphery.[24,40,41] As a result of these potentiating effects, DPP-4 inhibition predictably leads to an increase the outflow of impulses to peripheral sympathetic nerves and the release of norepinephrine in both experimental and clinical studies, particularly in patients with diabetes, especially when they are receiving drugs that block the renin-angiotensin system.[42-45]

What are the consequences of the sympathetic overactivity produced by DPP-4 inhibition? Agonism of beta-adrenergic receptors can aggravate heart failure though two potential mechanisms.[46] On the one hand, beta-receptor stimulation can lead to increases in cyclic AMP, signaling through protein kinase A and cardiotoxicity.[47,48] However, this response appears to be attenuated by SDF-1, possibly because the chemokine acts (through a G_i protein-coupled mechanism) to inhibit the cyclic AMP response to beta-receptor stimulation.[49,50] Interference with cyclic AMP signaling may explain the action of DPP-4 inhibition to attenuate adrenergically-mediated hypertrophy and arrhythmias and may contribute to the lack of a positive chronotropic response to DPP-4 inhibitors in clinical trials.[51,52] On the other hand, beta-receptor stimulation also leads to increased signaling through Ca++/calmodulin-dependent protein kinase II (CaMKII), which may be the primary mechanism by which sympathetic overactivity causes calcium overload, cardiomyocyte apoptosis and adverse cardiac remodeling.[46,53-55] Interestingly, this effect on CaMKII does *not* appear to be attenuated by SDF-1; in fact, potentiation of SDF-1 and other peptides by DPP-4 inhibitors is likely to increase the activity of CaMKII because of an increased sympathetic nerve traffic.[38-41] This may explain why experimental suppression of SDF-1 and CXCR7 acts to attenuate the response to beta-adrenergic receptor stimulation and ameliorate adverse cardiac remodeling following

myocardial infarction;[56,57] additionally, high levels of SDF-1 may act directly to cause apoptosis in the myocardium.[58] These deleterious actions could be further augmented by an effect of DPP-4 inhibitors to potentiate NPY and substance P. Stimulation of the NPY-Y1 receptor leads to detrimental effects on the structure and function of cardiomyocytes,[59] and potentiation of substance P can also accelerate cardiomyocyte apoptosis.[60]

Interaction of DPP-4 Inhibitors and Beta-Blockers in the SAVOR-TIMI53 Trial: The possibility that DPP-4 inhibitors can contribute to the evolution of heart failure by sympathetic activation is supported by the findings in a large-scale clinical trial. In SAVOR-TIMI53, an increased risk of hospitalizations for heart failure was observed in patients who were treated with saxagliptin, but the magnitude of this effect was meaningfully attenuated in patients who were concomitantly treated with beta-blockers.[10] Saxagliptin increased the risk of heart failure by 81% in the 6330 patients not receiving beta-blockers (hazard ratio 1.81 [1.21, 2.76]), but by only 18% in the 10,162 patients who were treated with beta-blockers (hazard ratio 1.18 [0.97, 1.43]). The latter effect was not significant despite a greater degree of statistical power; the interaction P value for the influence of beta-blockers on the risk of saxagliptin was 0.06.

Summary and Conclusions.

The use of DPP-4 inhibitors in type 2 diabetes is accompanied by an increased risk of heart failure, which appears to be a class effect of these drugs, although the magnitude of risk may be influenced by concurrent therapy.[8] Many mechanisms could contribute to this deleterious effect, including activation of the sympathetic nervous system to stimulate beta-receptor signaling and cause cardiomyocyte cell death. Inhibition of DPP-4 potentiates the actions of SDF-1, neuropeptide Y and substance P to increase sympathetic nerve traffic and (through beta-receptor stimulation) could cause cardiomyocyte injury and loss (through a CaMKII mechanism). This framework could explain why beta-blockers appeared to have attenuated the risk of heart failure with DPP-4 inhibition in a large-scale trial. The proposed hypothesis warrants further study, and if confirmed, the postulated mechanisms have important implications for patient care. In patients with type 2 diabetes, DPP-4 inhibitors are popular, but beta-blockers are underutilized because of fears of masking hypoglycemia.

DISCLOSURES

Dr. Packer has recently consulted for Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Cardiorentis, Celyad, Daiichi Sankyo, Gilead, NovoNordisk, Novartis, Relypsa, Sanofi, Takeda and ZS Pharma.

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FIGURE LEGENDS

Figure 1. Potential Mechanisms By Which Dipeptidyl Peptidase-4 (DPP-4) Inhibitors Can Promote Adrenergically-Mediated Adverse Effects on the Myocardium.

NOVELTY AND SIGNIFICANCE

What Is Known?

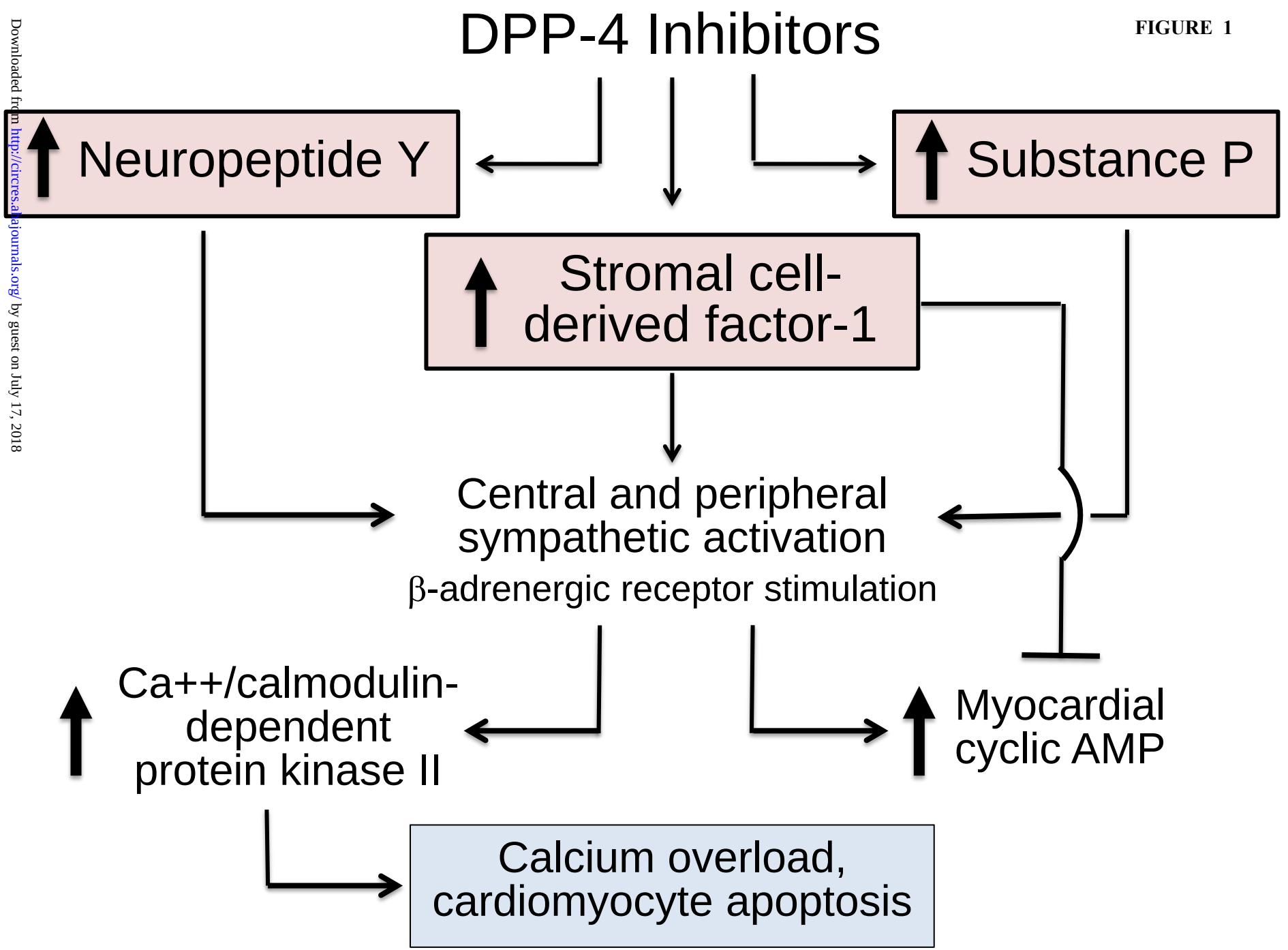
- Dipeptidyl peptidase-4 inhibitors are commonly prescribed for the treatment of patients with type 2 diabetes.
- The major concern with the use of these drugs has been their effect to increase the risk of serious heart failure events.
- Previous studies have suggested that this deleterious effect could result from an action of these drugs to promote cardiac fibrosis.

What New Information Does This Article Contribute?

- Dipeptidyl peptidase-4 inhibitors augment the effects of many endogenous peptides that are capable of stimulating the sympathetic nervous system.
- The use of these drugs has been shown to cause stimulation of the sympathetic nervous system, which can cause deleterious effects on the structure and function of the heart muscle.

The use of Dipeptidyl peptidase-4 inhibitors has been shown to incrase the risk of heart failure events in both randomized clinical trials and observational studies. The importance of this deleterious action is highlighted by the fact that the risk of worsening heart failure events with dipeptidyl peptidase-4 inhibitors is diminished when the effects of the sympathetic nervous system are blocked by the use of beta-adrenergic receptor blocking drugs. This information is important because dipeptidyl peptidase-4 inhibitors (but not beta-blockers) are widely used in patients with type 2 diabetes.

FIGURE 1



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