Dipeptidyl Peptidase-IV Inhibition for the Treatment of Cardiovascular Disease — Recent Insights Focusing on Angiogenesis and Neovascularization —

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Dipeptidyl peptidase IV (DPP-IV) is a complex enzyme that acts as a membrane-anchored cell surface exopeptidase and transmits intracellular signals through a small intracellular tail. DPP-IV exists in human blood in a soluble form, and truncates a large number of peptide hormones, chemokines, cytokines, and growth factors in vitro and in vivo. DPP-IV has gained considerable interest as a therapeutic target, and a variety of DPP-IV inhibitors that prolong the insulinotropic effects of glucagon-like peptide-1 (GLP-1) are widely used in clinical settings as antidiabetic drugs. Indeed, DPP-IV is upregulated in proinflammatory states, including obesity and cardiovascular disease with and without diabetes mellitus. Consistent with this maladaptive role, DPP-IV inhibitors seem to exert a protective role in cardiovascular disease. In addition to their GLP-1-dependent vascular protective actions, DPP-IV inhibitors exhibit GLP-1-independent beneficial effects on angiogenesis/neovascularization via several signaling pathways (e.g., stromal cell-derived factor-1α/C-X-C chemokine receptor type-4, vascular endothelial growth factor-A/endothelial nitric oxide synthase, etc.). This review focuses on recent findings in this field, highlighting the role of DPP-IV in therapeutic angiogenesis/neovascularization in ischemic heart disease and peripheral artery disease.

Key Words: Angiogenesis; Dipeptidyl peptidase-IV; Endothelial cells; Endothelial progenitor cells; Stromal cell-derived factor-1

The discovery of incretin-based treatments represents a major therapeutic advance in the medical management of cardiometabolic disorders, and the development of dipeptidyl peptidase IV (DPP-IV) inhibitors as antidiabetic drugs was based on the concept that these agents would enhance systematic and tissue glucagon-like peptide-1 (GLP-1) levels, causing an improvement in the insulinotropic effects of blood sugar. It is well known that angiogenesis/neovascularization is very important for the management of ischemic heart disease (IHD) and peripheral arterial disease (PAD). In the past 5 years, the DPP-IV inhibitors (e.g., alogliptin, saxagliptin and sitagliptin) have proven their cardiovascular safety in terms of the major cardiac outcomes in type 2 diabetes mellitus (T2DM) patients at high cardiovascular risk. Clinical and laboratory evidence indicates that DPP-IV inhibitors help prevent ischemic cardiovascular injury by stimulating angiogenic action via an inhibition of the DPP-IV-mediated catalytic degradation of several active chemokines and cytokines and/or an improvement of vascular endothelial growth factor-A (VEGF-A)/endothelial nitric oxide synthase (eNOS)-dependent mechanisms. In this review we summarize the available information regarding the mechanistic contributions of DPP-IV inhibitors in vascular regeneration associated with IHD and PAD.

What Is DPP-IV?

DPP-IV Family and Their Functions

The human gene encoding DPP-IV has been reported to localize to chromosome 2 locus 2q24.2. DPP-IV is a member of a complex gene family, several members of which nonspecifically truncate many structure-related peptides (including cytokines, chemokines, neuropeptides, hormones, and growth factors). It is known that the DPP-IV protease family comprises fibroblast activation protein α, seprase, DPP-VI, DPP-VIII, DPP-IX, DPP-IVβ, quiescent cell proline dipeptidase, prostate-specific membrane antigen, thymus-specific serine protease, attractin, N-acetylated α-linked acidic dipeptidases I, II and L, and other DPP-IV activity and/or structural homologs.
In the initial years after its discovery, DPP-IV (also known as T-cell activation antigen CD26 or adenosine deaminase -binding protein 2) was considered to be a 766-amino acid serine exopeptidase belonging to the S9B protein family and to cleave 2 alanine or X-proline dipeptides from the N-terminus of polypeptides in the extracellular space. DPP-IV has been shown to be widely expressed on cell surface peptidase, which exerts a complex biology involving the cell membrane-related activation of intracellular signal transductions, cell-cell cross-talk, and proteolytic activity displayed by the membrane-anchored and soluble forms of the enzyme. In addition to its enzymatic activity, another important function of DPP-IV is interaction with a range of ligands. Over the past decade, emerging data have revealed unexpected roles for DPP-IV in intracellular signaling, cell apoptosis, oxidative stress production, immune activation and insulin resistance. Recently, Waumans and colleagues clearly demonstrated that among the DPP-IV family members, DPP-VIII and IX inhibition attenuated M1 macrophage activation in mice. Moreover, it was reported that DPP-VIII and IX inhibition induced pro-caspase-1-dependent monocyte and macrophage pyroptosis. These activities confer a broad range of molecular functions on the DPP family, with clinical implications for a potential pathological role in inflammatory and metabolic diseases. Recent preclinical findings have highlighted the role of DPP family members (especially DPP-IV) in ischemia-related angiogenesis.

DPP-IV Expression and Activity
DPP-IV, which is one of the most potent serine peptidases, is reported to show widespread expression in mammalian tissues. DPP-IV is expressed on endothelial cells (ECs), endothelial progenitor cells (EPC), some immune cells (e.g., natural killer cells, monocytes, lymphocytes, and dendritic cells) and inflammatory cells (i.e., macrophages) in pathological conditions. Because of its wide distribution, DPP-IV inhibition is a promising approach in various medical fields, such as inflammation regulation, hematopoiesis recovery, and immunomodulation, and of course in angiogenesis, as highlighted in this review. The role for membrane-bound DPP-IV relates to both its enzymatic and non-catalytic activities via bindings to contiguous protein on the plasma membrane or in the extracellular matrix. Iwaki-Egawa and colleagues reported that the N-terminal intracellular domain contributes to enzymatic activity, and it was later demonstrated by the Chung group that the transmembrane region is responsible for the main enzymatic activity. In addition to the transmembrane domain, DPP-IV presents as a soluble form (called soluble CD26) in the plasma to exhibit its enzymatic activity, which is the extracellular domain of the peptide considered to be cut down from the cell plasma membrane.

DPP-IV Substrates
DPP-IV exerts many physiological and pharmacological functions by regulating its extremely abundant substrates (Figure 1). It is established that inhibition of DPP-IV can promote insulin secretion and improve glucose tolerance in humans via the GLP-1-dependent pathway. It was also shown that DPP-IV inhibitors can improve glucose tolerance in Glp1r−/− mice, suggesting that DPP-IV has its own biological roles independent of GLP-1. In addition, DPP-IV truncates a large number of peptide hormones and chemokines in vitro, whereas comparatively few peptides have been characterized as endogenous physiological substrates for DPP-IV in vivo. It is known that there are putative N-terminal alanine or proline DPP-IV truncation sites in many cytokines, chemokines, hormones and growth factors (e.g., stromal cell-derived factor-1α (SDF-1α), colony-stimulating factor (CSF), granulocyte macrophage-CSF, granulocyte-CSF, erythropoietin, interleukin-3 (IL-3), IL-1α, IL-6, high-mobility group box 1 (HMGB1), thrombopoietin, leukemia inhibitory factor, and others) (Figure 1). This raises the possibility that DPP-IV can regulate neovascularization through the degradation and modification of these angiogenesis-related factors. Given the potential effects of DPP-IV on angiogenesis, DPP-IV inhibitors have recently been considered as a pharmacological target for ischemic diseases.

DPP-IV Function in Neovascularization:
Mechanisms of Action at the Molecular and Cellular Levels

Individual DPP family members may be involved in angio-
DPP-IV Inhibition Modulates Neovascularization via SDF-1/CXCR4 Axis-Dependent EPC Mobilization and Functions

EPCs have been shown to play an essential role in ischemia-induced neovascularization under pathological conditions. Accumulating clinical studies have been conducted to explore whether DPP-IV inhibitors, a GLP-1 agonist or an analog have a vascular beneficial effect in patients with severe cardiovascular disease via an EPC-mediated cellular mechanism. PAD patients with T2DM treated with DPP-IV inhibitors have increased numbers of circulating pro-angiogenic cells. Laboratory studies demonstrate that DPP-IV inhibition increases new blood vessel formation via an enhancement of bone-marrow (BM)-derived EPC-like circulating pro-angiogenic cells and by homing in to the vasculature of ischemic muscles and myocardium.

In addition, a recent animal study showed that the GLP-1 analog exendin-4 protected a critical ischemic hindlimb by promoting angiogenesis. Together with our clinical study showing that the GLP-1 receptor agonist exenatide protected against progenitor cell dysfunction in response to ischemia-reperfusion injury, these findings suggest that incretin-based medications can facilitate both vascular regeneration via the improvement of EPC mobilization and homing and their cellular functions in humans and animals.

DPP-IV has been shown to inactivate SDF-1 by cleavage at its NH2-terminus. SDF-1 (also known as CXCL12) is an 8-kDa peptide that is generally expressed in BM, heart (e.g., heartstromal cells, ECs, and cardiomyocytes), kidney, brain, spleen, liver, thymus and muscle. SDF-1 is one of the most important cytokines secreted from injured tissues; it attracts BM-derived EPCs and facilitates ischemic muscle and cardiac tissues’ angiogenesis. DPP-IV inhibition enhances angiogenic actions through SFK-mediated alleviation of vascular regeneration in response to ischemia.

The findings showed that SDF-1 activity was also sensitive to other exopeptidases such as MMP family members (e.g., MMP-2 and MMP-9), showing that the GLP-1 receptor agonist exenatide protected against progenitor cell dysfunction in response to ischemia-reperfusion injury. In 2002, Christopherson et al demonstrated that inhibition of DPP-IV-related SDF-1 degradation facilitated human cord blood CD34+ EPC proliferation and homing to ischemic tissues. Ten years later, Shigeta et al demonstrated in animal models of diabetes that DPP-IV modulated cardiac dysfunction in chronic heart failure by partially membrane-bound DPP-IV/SDF-1-dependent angiogenic actions. Moreover, several clinical studies also demonstrated that

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**Figure 2.** Proposed mechanisms of DPP-IV inhibition-mediated alleviation of vascular regeneration in response to ischemic stress. The following information and 2 proposed mechanisms are shown: (1) pharmacologic or genetic inhibition of DPP-IV can promote ischemia-induced neovascularization via SDF-1/CXCR4- and/or NPY/Y2R-Y5R-dependent mechanisms that are mediated by the protection of chemokine and neuropeptide inactivation and the improvement of EPC mobilization and homing and EC functions; (2) pharmacologic DPP-IV inhibition enhances angiogenic actions through SFK, endothelial nitric-oxide synthase; G-CSF, granulocyte colony-stimulating factor; GLP, glucagon-like peptide; SDF, stromal cell-derived factor; SFK, Src family kinase; Y2R, subtype of NPY receptor 2. Other abbreviations as in Figure 1.
DPP-IV inhibition ameliorated circulating pro-angiogenic cell numbers and angiogenesis via an SDF-dependent signal in ischemic PAD patients with T2DM.\(^5,24\) Collectively, these findings indicated that regulation of SDF-1 activity by inhibiting DPP-IV activity could present a common mechanism in the protection of cardiovascular tissues against ischemic stress.

Although most of the previous findings support the concept that DPP-IV inhibitors are extremely beneficial to angiogenesis (Table), differing viewpoints still exist. Clinical observations have shown that impaired neovascularization is probably attributable, at least in part, to inflammation-induced BM exhaustion and reduced progenitor cell mobilization associated with reductions in the levels of BM DPP4 and MMP-9 and changes in the SDF-1/CXCR4 interaction in patients with critical PAD.\(^41\) In addition, Sun and coworkers\(^42\) recently tested the function of DPP-IV in angiogenesis, using a DPP-IV\(^-/-\) rat model. They obtained the contrary findings that it was DPP-IV and not a DPP-IV inhibitor that played a positive role in maintaining vascular function and tissue perfusion. Under their experimental conditions, compared with age-matched DPP-IV\(^+/-\) rats, DPP-IV\(^-/-\) rats showed poor endothelial function, circulating EPC numbers and responses to granulocyte-CSF and angiogenic actions.\(^42\) Theirs was the first study using a DPP-IV deletion rat model to validate the role of DPP-IV in ischemia-induced angiogenesis. Based on these findings and those of their previous studies, Sun et al pointed out the lack of SDF-1a concentration gradients between the BM and circulation in DPP-IV\(^-/-\) rats after ischemic surgery, and they suggested this may be attributable to compensatory increases in other blood SDF-1 degradation

### Table. Studies Examining the Expected Effects of DPP-IV Inhibition on Cardiac Injury and Neovascularization in Human and Animal Models

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Subjects</th>
<th>Dose</th>
<th>Year</th>
<th>Targeted cells</th>
<th>Model/diseases</th>
<th>Major observations</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diprotin A (Ile-Pro-Ile)</td>
<td>Human</td>
<td>5 mmol/L</td>
<td>2002</td>
<td>CD34+ hemopoietic cells</td>
<td>Human cord blood</td>
<td>Inhibition of endogenous DPP-IV activity enhanced CD34+ hemopoietic cells’ response to SDF-1α</td>
<td>Christopherson et al(^3)</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>Mouse</td>
<td>5–20 mg/kg/day</td>
<td>2012</td>
<td>EPCs</td>
<td>CLI model</td>
<td>Sitagliptin increased SDF-1 level in a dose-dependent manner</td>
<td>Huang et al(^2)</td>
</tr>
<tr>
<td>PKF275–055 (DPP-IV inhibitor)</td>
<td>Mouse</td>
<td>39 mg/kg/day</td>
<td>2016</td>
<td>EPCs</td>
<td>Myocardial ischemia model</td>
<td>DPP-IV inhibitor enhanced SDF-mediated EPCs mobilization</td>
<td>Fiordaliso et al(^18)</td>
</tr>
<tr>
<td>Linagliptin (BI 1356) and BI 14361</td>
<td>Rat</td>
<td>Linagliptin: 3 mg/kg BI14361: 3 mg/kg</td>
<td>2013</td>
<td>Circulating PCs</td>
<td>MI/IR model</td>
<td>Inhibition of DPP-IV leads to the recruitment of CXCR-4+ circulating PCs via the reduced cleavage of SDF-1α</td>
<td>Hocher et al(^46)</td>
</tr>
<tr>
<td>Decreased expression of DPP-IV</td>
<td>Human</td>
<td>100 mg/day</td>
<td>2010</td>
<td>EPCs</td>
<td>T2DM</td>
<td>Sitagliptin increased the EPC number via upregulation of SDF-1α</td>
<td>Fadini et al(^4)</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>Human</td>
<td>2.5 mg renal dose-adjusted formulation</td>
<td>2014</td>
<td>PACs CD14+</td>
<td>T2DM</td>
<td>Saxagliptin reversed the dysfunction of PAs</td>
<td>Poncina et al(^8)</td>
</tr>
<tr>
<td>Protease-resistant (MMP2, DPP-IV SSDF-1 (S4V))</td>
<td>Rat</td>
<td>0.01–0.1 mg/kg</td>
<td>2011</td>
<td>EPCs</td>
<td>MI</td>
<td>SSDF-1 (S4V) likes an antagonist of DPP-IV increased the capillary density after MI</td>
<td>Kanki et al(^29)</td>
</tr>
<tr>
<td>Protease-resistant SSDF-1(S4V)</td>
<td>Mouse</td>
<td>11 μmol/L</td>
<td>2011</td>
<td>CD31+ cells</td>
<td>CLI model Matrigen plug assay</td>
<td>SSDF-1(S4V), which was resistant to the cleavage of DPP-IV, increased blood flow and the density of arterioles</td>
<td>Segers et al(^34)</td>
</tr>
<tr>
<td>DPP-IV(^-/-)</td>
<td>Mouse</td>
<td>2009</td>
<td>Circulating CXCR-4+ stem cells</td>
<td>MI</td>
<td>DPP-IV depletion promoted SDF-1α/CXCR4 homing axis</td>
<td>Zaruba et al(^27)</td>
<td></td>
</tr>
<tr>
<td>DPP-IV(^-/-)</td>
<td>Rat</td>
<td>2014</td>
<td>c-kit+ /Sca-1+ cells</td>
<td>MI/RI model</td>
<td>DPP-IV depletion increased level of SDF-1α/CXCR4</td>
<td>Chua et al(^43)</td>
<td></td>
</tr>
<tr>
<td>Vildagliptin</td>
<td>Human</td>
<td>50 mg b.i.d.</td>
<td>2012</td>
<td>CD31+ cells</td>
<td>Diabetic chronic ulcers</td>
<td>Vildagliptin increased the ulcer capillary density through GLP-1-mediated HIF-1α/VEGF signaling pathway</td>
<td>Marfella et al(^23)</td>
</tr>
<tr>
<td>Vildagliptin</td>
<td>Mouse</td>
<td>0.6 mg/mL/day</td>
<td>2014</td>
<td>ECs (CD31+)</td>
<td>CLI model</td>
<td>Vildagliptin modulated revascularization by 3 potential pathways</td>
<td>Ishii et al(^9)</td>
</tr>
</tbody>
</table>

CL1, critical limb ischemia; CXCR4, C-X-C family (SDF-1) receptor; DPP-IV, dipeptidyl peptidase; DPP-IV\(^-/-\), DPP-IV deficiency; EPCs, endothelial progenitor cell; GLP-1, glucagon-like protein-1; HIF-1α, hypoxia-inducible factor-1α; IPAD, ischemic peripheral arterial disease; MI, myocardial infarction; MI/IR, myocardial infarction/reperfusion injury; MMP-2, matrix metalloproteinase-1; PACs, pro-angiogenic cells; PCs, progenitor cells; SDF-1α, stromal cell-derived factor-1α; SSDF-1, protease-resistant stromal cell-derived factor-1; T2DM, type 2 diabetes mellitus; VEGF, vascular endothelial cell growth factor.
enzymes (e.g., DPP-8 and DPP-9) and decreases in the levels of BM niche-cleaving SDF-1 exopeptidases (MMP-2 and MMP-9) in DPP-IV−/− rats. On the other hand, Fadini et al. have shown that although DPP-IV genetic inhibition could restore ischemia-induced mobilization in diabetes, they clearly demonstrated that DPP-IV activity was required for G-CSF-induced mobilization. Furthermore, DPP-IV was differently expressed and had different activity according to the stem cell compartment (BM vs. peripheral blood vs. target tissue). Thus, the analysis of stem cell compartmentalization in humans and DPP-IV genetic animals led us to discover mechanisms of BM unresponsiveness in diabetes determined by tissue-specific DPP-IV dysregulation.

Clinical observations have shown that pharmacological DPP-IV activity inhibition facilitates angiogenic actions via an improvement in SDF-1α-mediated circulating proangiogenic cell functions in T2DM patients with PAD. The ability of pharmacological DPP-IV inhibition to increase blood SDF-1 levels is likely to contribute to the stimulation of revascularization under ischemic experimental conditions in mice. In addition, in rat and mouse acute myocardial ischemic injury models, experimental observations revealed that the prevention of SDF-1 degradation by DPP-IV inhibition led to an enhancement of C-X-C family (SDF-1) receptor (CXCR4) circulating progenitor cells.

DPP-IV Inhibition Promotes Angiogenesis Through the VEGF-A/eNOS) Signaling Pathway
In vitro and in vivo studies have demonstrated that pharmacologic inhibition of DPP-IV proteolytic activity promotes angiogenesis and facilitates EC migration, aortic EC-derived sprouting, and angiogenesis. Accumulating evidence shows that the upregulation of plasma GLP-1 levels are partially responsible for the beneficial actions of DPP-IV inhibition. Recent study demonstrated that the GLP-1 analog liraglutide exhibited angiogenic properties via the induction of vascular endothelial cell growth factor (VEGF) in islet transplantation. Thus, it has been speculated that DPP-IV may have one or more roles in the process of angiogenesis by mediating a GLP-1/VEGF pathway. It was reported that hypoxia-inducible factor-α (HIF-α) is expressed in response to the hypoxic gradient, and can affect the recruitment of EPCs by activating VEGF and inducible NOS. In diabetic patients with chronic foot ulcers, Marfella and colleagues report that DPP-IV inhibition raised the GLP-1 concentration, and then via a GLP-1-mediated HIF-1α/VEGF pathway as well as by a reduction in oxidative stress, DPP-IV inhibition exhibited beneficial effects on the angiogenesis process and wound healing of the ulcers. In a mouse model of critical ischemic hindlimb, Ishii et al. showed that vildagliptin can modulate the EC network formation by increasing GLP-1 levels, and that treatment with vildagliptin enhanced blood flow recovery and capillary density in the ischemic limbs of control mice. More importantly, vildagliptin also increased the incorporation of cultured human umbilical vein endothelial cells (HUVECs) into vascular-like structures without GLP-1.

Potential molecular mechanisms underlying the improvement of DPP-IV inhibition-mediated angiogenesis in response to ischemic stress are as follows: (a) pharmacological DPP-IV catalytic activity inhibition promotes ischemia-induced angiogenesis through an Scr kinase-dependent eNOS-Akt activation mechanism; (b) the vasculoprotective activities of DPP-IV inhibitors in vivo are related to both GLP-1-dependent effects and GLP-1-independent actions; and (c) the beneficial effects of GLP-1 on angiogenesis in vivo are mediated in part via the ability of vildagliptin to increase adiponectin (APN) secretion. Based on these findings, we propose that DPP-IV inhibition facilitates EC angiogenic events via VEGF/Src kinase-mediated eNOS-Akt signaling activation, an effect that may be mediated by both GLP-1-dependent and -independent mechanisms. Although the exact interaction between DPP-IV and HIF-1α/eNOS/VEGF is still unclear, this interaction may play a vital function in multiple aspects of the angiogenic process. The further investigations will be needed to explore this issue.

DPP-IV Inhibition May Stimulate Angiogenesis via an HMGB1-Dependent Erk1/2 Signaling Pathway
HMGB1 is one of the DPP-IV substrates, and it has a DPP-IV cleavage site. DPP-IV and its inhibitors can be expected to affect angiogenesis via modulation of HMGB1. One study demonstrated that HMGB1 promotes angiogenic activities by ERK1/2 phosphorylation in cultured HUVECs. When pretreated with DPP-IV, the phosphorylation of ERK was remarkably reduced, indicating that DPP-IV influences angiogenesis via the HMGB1/ERK1/2 signaling pathway. At present, the evidence suggesting that DPP-IV could impair HMGB1 angiogenic function is limited, but the relationship between them is established. Further clinical and basic research is necessary to test this idea.

DPP-IV/DPP-IV Inhibitors and Neuropeptide Y (NPY) in Angiogenesis
NPY colocalizes with DPP-IV, which cleaves Tyr(1)-Pro(2) from NPY(1–36) to form NPY(3–36), resulting in the formation of a non-Y1 receptor (Y1R, a subtype of NPY receptor) agonist, which remains to produce angiogenic actions. NPY has been reported to stimulate ECs’ proliferation and migration. It was shown that the expression of DPP-IV in the microvascular endothelium of atherosclerotic tissue may shift NPY’s affinity toward the angiogenic receptor (Y2R/Y5R) and therefore enhance angiogenesis and lesion vulnerability. This is the pathology of atherosclerosis, but at present there are no new reports about NPY and DPP-IV in ischemic disease.

Accumulating evidence indicates that NPY is essential for angiogenic activity. However, a 2001 in vitro study revealed that although DPP-IV expression was stimulated by endothelial wounding, DPP-IV blocking with monoclonal antibodies (E19 and E26) significantly inhibited HUVEC migration, compared with untreated cells, and blocked wound healing in response to NPY (1–36) but not NPY (3–36). These findings suggest a contrary explanation of the effects of DPP-IV inhibitors in the process of angiogenesis. A cancer biology study revealed that hypoxia acts a molecular switch, shifting NPY activity from Y1R/Y5R-dependent cell apoptosis and activating the Y2R/Y5R/DPP-IV/NPY(3–36) axis, which enhances Ewing sarcoma stem cell activities and facilitates angiogenesis. It thus seems that DPP-IV inhibitors may suppress angiogenesis through inhibition of NPY activities. What is the truth about the regulation of angiogenic phenomena by the interaction between DPP-IV and NPY? From the perspective of physiology and pathology in angiogenesis-related tumors and ischemic cardiovascular diseases, further clinical and basic studies are required to determine the exact roles in the interaction between DPP-IV and the NPY/YRs axis.
DPP-IV/DPP-IV Inhibitors and APN in Angiogenesis

Previous clinical studies reported that DPP-IV inhibitors led to a significant increase of the plasma APN concentrations in vivo. Ishii and colleagues confirmed that in an ischemic-induced revascularization model, DPP-IV inhibitors clearly augmented the expression of GLP-1 and APN and stimulated the cell network formation of ECs, whereas in APN-deficient mice, DPP-IV inhibitors only partially increased blood flow in the ischemic limb muscle. This indicates that the angiogenic ability of DPP-IV inhibitors may be partly via a GLP-1/APN-dependent mechanism.

Circulating DPP-IV as a Novel Biomarker for IHD and PAD

Circulating levels of DPP-IV catalytic activity have been reported to be increased in some basic and clinical studies of subjects with metabolic disorders. A recent single cross-sectional clinical study of Chinese patients with T2DM showed that increased plasma DPP-IV levels were associated with a high prevalence of subclinical atherosclerosis. A small prospective population study also reported that increased plasma DPP-IV activity was an independent predictor of IHD. Thus, increased DPP-IV levels might serve as a novel biomarker for ischemic cardiovascular disease, even without DM.

Conclusions

In addition to the DPP-IV inhibitor-mediated glucose-lowering effect, it is very important to establish the molecular biology underlying pharmacological DPP-IV catalytic activity inhibition-related negative and positive angiogenic actions, because promoted angiogenesis could be one of the mechanisms through which DPP-IV inhibitors exert their pleiotropic, direct cardiovascular protective effects under pathological ischemic conditions in humans and animals. DPP-IV/DPP-IV inhibitors interact with many angiogenesis-related factors and cells. In short, the existing evidence indicates that DPP-IV inhibitors have great significance and huge potential in the neovascularization process in ischemic cardiovascular disease. Increased plasma DPP-IV levels can serve as a novel biomarker of ischemic cardiovascular disease.

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Conflicts of Interest

None declared.