

# Role of soluble and membrane-bound dipeptidyl peptidase-4 in diabetic nephropathy

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## Abstract

Diabetic nephropathy is one of the most frequent, devastating and costly complications of diabetes. The available therapeutic approaches are limited. Dipeptidyl peptidase type 4 (DPP-4) inhibitors represent a new class of glucose-lowering drugs that might also have reno-protective properties. DPP-4 exists in two forms: a plasma membrane-bound form and a soluble form, and can exert many biological actions mainly through its peptidase activity and interaction with extracellular matrix components. The kidneys have the highest DPP-4 expression level in mammals. DPP-4 expression and urinary activity are up-regulated in diabetic nephropathy, highlighting its role as a potential target to manage diabetic nephropathy. Preclinical animal studies and some clinical data suggest that DPP-4 inhibitors decrease the progression of diabetic nephropathy in a blood pressure- and glucose-independent manner. Many studies reported that these reno-protective effects could be due to increased half-life of DPP-4 substrates such as glucagon-like peptide-1 (GLP-1) and stromal derived factor-1 alpha (SDF-1a). However, the underlying mechanisms are far from being completely understood and clearly need further investigations.

## Key Words

- ▶ DPP-4
- ▶ diabetic nephropathy
- ▶ DPP-4 inhibitors
- ▶ GLP-1 and SDF-1a

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## Introduction

According to the global report on diabetes issued by the World Health Organization, the worldwide diabetes prevalence, the vast majority of these cases are attributed to type 2 diabetes, has increased to reach 8.5% of the population over 18 years of age in 2014. Type 2 diabetes is associated with many macrovascular and microvascular complications and known to be a major cause underlying kidney failure. Recently, new classes of drugs have been approved for the treatment of type 2 diabetes and extensive research is going on to investigate potential

beneficial effects, beside their glucose-lowering effects, on various diabetic complications such as diabetic nephropathy. These therapies include glucagon-like peptide 1 (GLP-1) agonists, dipeptidyl peptidase type 4 (DPP-4) inhibitors and sodium-glucose cotransporter (SGLT2) inhibitors (Ingelfinger & Rosen 2016). The aim of this review is to summarize the up-to-date literature on DPP-4 in the setting of diabetic nephropathy and to discuss DPP-4 as a potential target for the management of diabetic nephropathy.

## Discovery, molecular biology and renal expression of DPP-4

DPP-4 was first discovered by (Hopsu-Havu & Glenner 1966) as they identified it as a new enzyme in rat liver homogenate and rat kidney histological sections which is capable of hydrolysing glycyl-prolyl-B-naphthylamide, a synthesized chromogenic substrate. Later, further research revealed that the mouse thymocyte-activating molecule and CD26 antigen on T-lymphocyte are actually a plasma membrane-bound form of DPP-4 (Ulmer *et al.* 1990, Vivier *et al.* 1991). There are two forms of DPP-4, the plasma membrane-anchored form and the soluble form. The pleiotropic biological actions of DPP-4 are mainly attributed to its protease activity, degrading many substrates with different biological effects, interaction with extracellular matrix components, such as collagen and fibronectin, and acting as cell surface co-receptor affecting intracellular signal transduction. DPP-4 was increasingly brought into the spotlight after the approval of the DPP-4 inhibitors for treating type 2 diabetes (Mulvihill & Drucker 2014).

Regarding the enzymatic activity, DPP-4 is a specific serine peptidase which can cleave off N-terminal dipeptides provided that the penultimate amino acid is proline, hydroxyproline or alanine. Due to the high similarity between the parent peptide and the DPP-4-cleaved peptide, they differ usually only in two amino acids, very sensitive assays are required to differentiate between both forms. It is also challenging to compare the biological activity of the parent peptide versus the DPP-4-cleaved peptide which is not necessarily less active or inactive (Mulvihill & Drucker 2014).

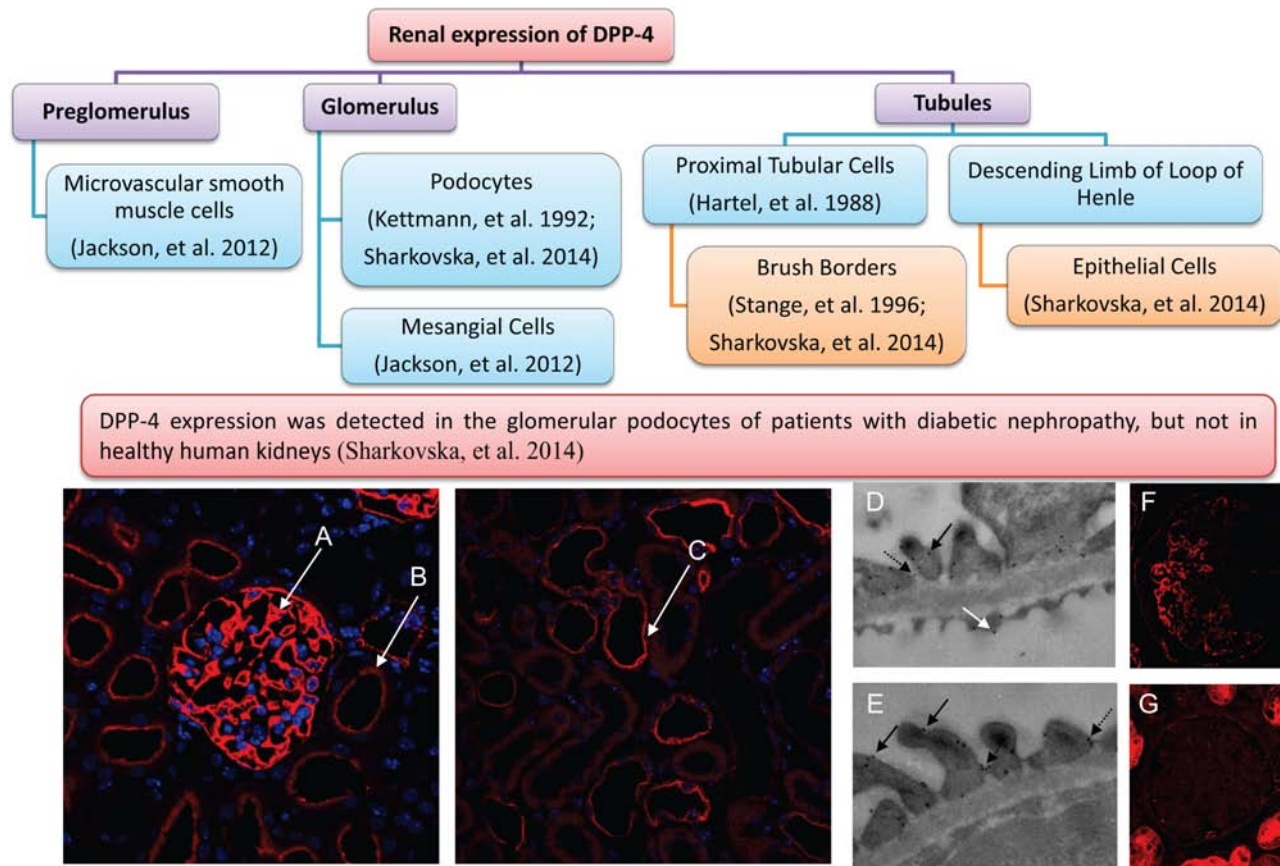
DPP-4 is expressed in many tissues including the kidney. Using quantitative real-time PCR and Western blot, DPP-4 mRNA and protein were detected in glomerular mesangial cells and preglomerular microvascular smooth muscle cells from spontaneously hypertensive and normotensive rats (Jackson *et al.* 2012). DPP-4 expression was also reported in glomerular podocytes and proximal tubules of the rat kidney (Hartel *et al.* 1988, Kettmann *et al.* 1992). Furthermore, DPP-4 expression was identified at the brush border membrane of human proximal tubular cells (Stange *et al.* 1996). Moreover, induction of diabetes, using streptozotocin plus high fat diet, up-regulated DPP-4 expression in the rat kidneys, primarily in renal tubular cells (Yang *et al.* 2007). In addition, our group described the expression of DPP-4 in glomerular podocytes and proximal tubules of the kidneys of normal and diabetic mice. Interestingly, immunofluorescence staining

detected the expression of DPP-4 in the glomerular podocytes of patients with diabetic nephropathy, but not in healthy human kidneys (Sharkovska *et al.* 2014). The renal expression of DPP-4 is summarized in Fig. 1. Interestingly, Wang and coworkers (Wang *et al.* 2014) found that rat kidney extracts showed the highest DPP-4 activity; however, plasma DPP-4 activity did not decrease after kidney transplantation from a DPP-4-deficient rat into a wild-type one indicating that the kidney is not the main source of soluble DPP-4 under normal healthy conditions. In addition, it was reported that urinary DPP-4 activity was significantly higher in type 2 diabetic patients with microalbuminuria, an early sign of diabetic nephropathy, compared to healthy individuals (Mitic *et al.* 2008). These observations highlight a potential role of DPP-4 in the development of diabetic nephropathy (von Websky *et al.* 2014).

## DPP-4 inhibition in animal models of diabetic nephropathy

DPP-4 inhibitors were tested in many animal models of chronic and acute kidney injury. In this section, we will focus on the studies investigating the renal effects of DPP-4 inhibitors in animal models of diabetic nephropathy. Sitagliptin, the first approved DPP-4 inhibitor, was tested in Zucker diabetic fatty (ZDF) rats as a model of type 2 diabetic nephropathy to investigate its effects on metabolic profile and kidney injury (Mega *et al.* 2011). Sitagliptin administration led to improved kidney function, decreased renal oxidative stress and abolished renal damage as illustrated by histological examination. The reno-protective effects of sitagliptin in this study could be at least partly attributed to its ability to ameliorate hyperglycaemia and serum triglycerides. Another study showed that vildagliptin could counteract kidney injury in terms of albuminuria, creatinine clearance and histological findings in streptozotocin (STZ)-induced diabetic rats (Liu *et al.* 2012). The authors suggested that the activation of GLP-1 receptor, modulation of cAMP, decreased oxidative stress and downregulation of TGFB1 might be involved in the reno-protective pathways of vildagliptin. Moreover, Kodera and coworkers (Kodera *et al.* 2014) reported that DPP-4 inhibition using PKF275-055 improved kidney parameters in STZ-induced diabetic rats through inhibition of inflammatory events as macrophage infiltration and suppression of nuclear factor- $\kappa$ B.

The reno-protective effects of DPP-4 inhibition in diabetic nephropathy could be a consequence of the antidiabetic actions of DPP-4 inhibitors. However,



**Figure 1**

DPP-4 expression in the kidney. DPP-4 (red) expression was detected in glomerular podocytes (A), the brush borders of the proximal tubular cells (B) and epithelia of descending limb of Henle’s loop (C) (immunofluorescence staining). DPP-4 (black dots) expression was detected (D and E) in the membrane of the podocyte foot process (black arrows), fenestrated endothelium (white arrows) and slit diaphragm (dotted arrow) (Immunogold electron microscopy). DPP-4 (red) expression was detected in glomerular podocytes of patients with diabetic nephropathy (F), but not in healthy human kidneys (G) (Immunofluorescence staining). The microscopic photos are reproduced, with permission, from Sharkovska Y, Reichetzeder C, Alter M, Tsuprykov O, Bachmann S, Secher T, Klein T & Hocher B, ‘Blood pressure and glucose independent renoprotective effects of dipeptidyl peptidase-4 inhibition in a mouse model of type-2 diabetic nephropathy’, *Journal of Hypertension*, volume 32, pages 2211–2223, <http://dx.doi.org/10.1097/HJH.0000000000000328>. Copyright 2014, Wolters Kluwer Health, Inc.

Sharkovska and coworkers (Sharkovska *et al.* 2014) found that in *db/db* mice, a model of type 2 diabetes, neither glucose metabolism nor blood pressure were affected by linagliptin treatment, despite that linagliptin was able to decrease the progression of diabetic kidney damage. These findings indicated that the renal beneficial actions of DPP-4 inhibition are independent on blood pressure and glucose metabolism. In addition, the DPP-4 inhibitor linagliptin reduced advanced glycation end products (AGEs) levels; the gene expression of their receptor (RAGE); 8-hydroxy-2'-deoxyguanosine, a marker of oxidative stress; and lymphocyte infiltration and intercellular adhesion molecule-1 (ICAM-1) mRNA levels, a proinflammatory peptide in the kidney of STZ-diabetic rats. Interestingly, these effects were not accompanied by improvement of hyperglycaemia (Nakashima *et al.* 2014). Furthermore,

DPP-4 deficiency led to similar findings in STZ-induced diabetic DPP-4 deficient rats, indicating that both DPP-4 inhibition and DPP-4 deficiency could be reno-protective by obstructing the AGE-RAGE axis (Matsui *et al.* 2015).

Also, DPP-4 inhibition using linagliptin led to decreased progression of diabetic nephropathy in STZ-induced diabetic CD-1 mice as demonstrated by measuring plasma cystatin C, urinary albumin-to-creatinine ratio (UACR) and histopathological examinations of the kidney. Linagliptin abolished endothelial levels of DPP-4 and integrin B1, a transmembrane receptor which bridges cell-cell and cell-extracellular matrix components interactions leading to decreased renal fibrosis through inhibition of TGFβ2-induced-endothelial-to-mesenchymal transition. These anti-fibrotic effects were mediated via microRNA 29 induction (Kanasaki *et al.* 2014, Shi *et al.* 2015).

Furthermore, gemigliptin normalized albuminuria, mesangial expansion, oxidative damage and podocyte apoptosis in the kidneys of *db/db* mice (Jung *et al.* 2015, Moon *et al.* 2016).

An interesting recent study revealed that linagliptin suppressed albuminuria in *Glp1r<sup>+/+</sup>* diabetic-prone Akita mice but not in *Glp1r<sup>-/-</sup>* diabetic-prone Akita mice, however, linagliptin was able to normalize the renal histopathology in both strains. These results showed that DPP-4 inhibition could have reno-protective effects through glucagon-like peptide-1 receptor (GLP-1R) and also through other substrates such as stromal derived factor-1 alpha (SDF-1a) independent of GLP-1R (Takashima *et al.* 2016).

The animal studies, which investigated DPP-4 inhibition in animal models of diabetic nephropathy, are summarized in Table 1 and the renal effects of DPP-4 inhibitors in diabetic nephropathy and the proposed underlying mechanisms

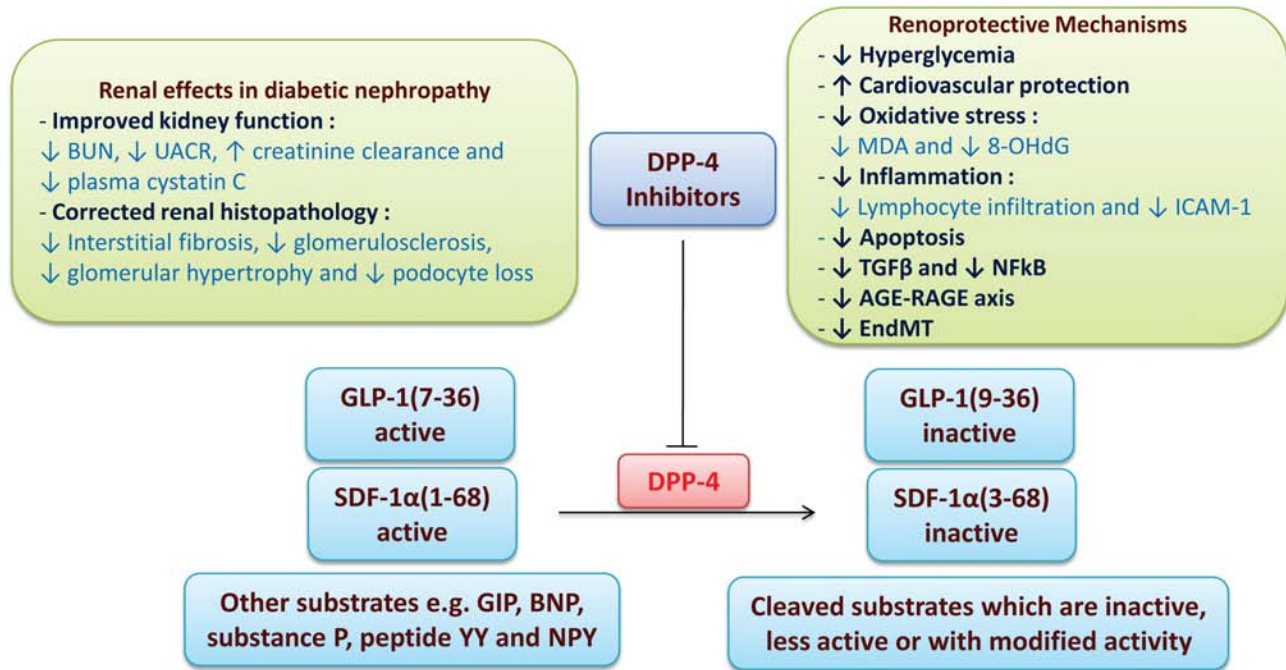
are outlined in Fig. 2. In conclusion, there are obviously different pathways involved in the reno-protective properties of DPP-4 inhibitors. This is most likely attributed to the fact that DPP-4 inhibition has a lot of potential peptide targets that might be involved in the pathogenesis of diabetic nephropathy. This is a fundamental difference from a pharmacological point of view to classical single target drugs such as angiotensin II receptor blockers (ARBs) which just block the angiotensin II receptor.

The finding that DPP-4 inhibitors have beneficial renal effects in animal models of diabetic nephropathy independent of blood pressure and plasma glucose encouraged stimulated research groups, including ours, to study DPP-4 inhibitors in models of non-diabetic nephropathy. DPP-4 inhibitors were found to have renal beneficial effects in animal models of non-diabetic nephropathy such as 5/6 nephrectomy (Tsuprykov *et al.* 2016)

**Table 1** DPP-4 inhibitors in animal models of diabetic nephropathy.

Animal model	DPP-4 inhibitor	Renal outcomes of DPP-4 inhibition	Reference
Zucker diabetic fatty (ZDF) rats	Sitagliptin	<ul style="list-style-type: none"> <li>- Decreased blood urea nitrogen (BUN)</li> <li>- Decreased renal malondialdehyde (MDA)</li> <li>- Less glomerular and tubulointerstitial lesions</li> </ul>	Mega <i>et al.</i> (2011)
Streptozotocin-induced diabetic rats	Vildagliptin	<ul style="list-style-type: none"> <li>- Decreased proteinuria, albuminuria and urinary albumin-to-creatinine ratio (UACR)</li> <li>- Improved creatinine clearance</li> <li>- Inhibited interstitial expansion, glomerulosclerosis and the thickening of the glomerular basement membrane</li> </ul>	Liu <i>et al.</i> (2012)
Streptozotocin-induced diabetic eNOS knockout mice	Linagliptin	<ul style="list-style-type: none"> <li>- Reduced glomerulosclerosis</li> <li>- Lower renal oxidative stress</li> <li>- Reduced albuminuria (only in combination with telmisartan)</li> </ul>	Alter <i>et al.</i> (2012)
Streptozotocin-induced diabetic rats	PKF275-055	<ul style="list-style-type: none"> <li>- Decreased urinary albumin excretion</li> <li>- Prevented mesangial matrix expansion</li> <li>- Inhibited macrophage infiltration</li> </ul>	Kodera <i>et al.</i> (2014)
Diabetic <i>db/db</i> mice	Linagliptin	<ul style="list-style-type: none"> <li>- Reduced albuminuria</li> <li>- Reduced interstitial fibrosis, glomerulosclerosis and podocyte injury</li> </ul>	Sharkovska <i>et al.</i> (2014)
Streptozotocin-induced diabetic rats	Linagliptin	<ul style="list-style-type: none"> <li>- Reduced albuminuria</li> <li>- Reduced lymphocyte infiltration into the glomeruli</li> </ul>	Nakashima <i>et al.</i> (2014)
Streptozotocin-induced diabetic DPP-4 deficient rats	Genetic DPP-4 deficiency	<ul style="list-style-type: none"> <li>- Decreased glomerular area</li> <li>- Decreased urinary excretion of albumin</li> </ul>	Matsui <i>et al.</i> (2015)
Streptozotocin-induced diabetic CD-1 mice	Linagliptin	<ul style="list-style-type: none"> <li>- Reduced plasma cystatin C levels and UACR</li> <li>- Ameliorated kidney fibrosis, glomerular size and mesangial area</li> </ul>	Kanasaki <i>et al.</i> (2014), Shi <i>et al.</i> (2015)
Diabetic <i>db/db</i> mice	Gemigliptin	<ul style="list-style-type: none"> <li>- Suppressed albuminuria</li> <li>- Decreased mesangial expansion</li> <li>- Suppressed podocyte apoptosis</li> <li>- Reduced oxidative damage</li> </ul>	Jung <i>et al.</i> (2015), Moon <i>et al.</i> (2016)
<i>Glp1r<sup>+/+</sup></i> and <i>Glp1r<sup>-/-</sup></i> diabetic-prone Akita mice	Linagliptin	<ul style="list-style-type: none"> <li>- Suppressed albuminuria (only in <i>Glp1r<sup>+/+</sup></i> diabetic-prone Akita mice)</li> <li>- Suppressed glomerulosclerosis, periglomerular fibrosis, podocyte loss, and renal oxidative stress</li> </ul>	Takashima <i>et al.</i> (2016)





**Figure 2**

DPP-4, its substrates and DPP-4 inhibitors in diabetic nephropathy. BUN, blood urea nitrogen; UACR, urinary albumin to creatinine ratio; MDA, malondialdehyde; 8-OHdG, 8-hydroxy-2'-deoxyguanosine; ICAM-1, intercellular adhesion molecule-1; TGFβ, transforming growth factor beta; NFκB, nuclear factor kappa B; AGE, advanced glycation endproducts; RAGE, receptor of AGE; EndMT, endothelial-to-mesenchymal transition; GLP-1, glucagon like peptide-1; SDF-1a, stromal derived factor-1 alpha; GIP, glucose dependent insulinotropic polypeptide; BNP, brain natriuretic peptide; NPY, neuropeptide Y.

2-kidney-1-clip hypertension (Chaykovska *et al.* 2013), tacrolimus-induced kidney injury (Lim *et al.* 2015), rat Thy-1 glomerulonephritis model (Higashijima *et al.* 2015) and unilateral ureteral obstruction (Min *et al.* 2014).

### Clinical data on DPP-4 inhibitors in diabetic nephropathy

There are few clinical studies which investigated the renal effects of DPP-4 inhibitors in diabetic nephropathy. A pooled analysis of four clinical studies reported that linagliptin on top of inhibitors of the renin-angiotensin-aldosterone system abolished UACR in type 2 diabetic subjects with prevalent albuminuria after 24 weeks of treatment and this effect was independent of the changes of HbA1c and systolic blood pressure (Groop *et al.* 2013). Another clinical study (Hattori 2011) revealed that 6 months of sitagliptin treatment lowered systolic and diastolic blood pressure, blood glucose, C-reactive protein, soluble vascular cell adhesion molecule 1 and UACR in patients with type 2 diabetes. In agreement with these findings, Sakata and coworkers (Sakata *et al.* 2013) demonstrated that fasting blood glucose, HbA1c, circulating soluble form of RAGE and UACR were

decreased after treatment with alogliptin for twelve weeks in Japanese patients with type 2 diabetes. In addition, type 2 diabetic patients, treated with saxagliptin and followed for a median of 2.1 years, were significantly more likely than patients treated with placebo, to have a lower UACR (Scirica *et al.* 2013). Moreover, Fujita and coworkers (Fujita *et al.* 2014b) performed a cross-over study to investigate the effects of sitagliptin and alogliptin in twelve patients, with diabetic nephropathy, taking ARBs. The treatment regimen consists of three periods; sitagliptin for 4 weeks, alogliptin for 4 weeks and again sitagliptin for 4 weeks. The switch from sitagliptin to alogliptin, a stronger DPP-4 inhibitor, was associated with declined UACR and oxidative stress and elevated urinary cAMP and plasma SDF-1a.

In a recent clinical study, Goldshtein and coworkers (Goldshtein *et al.* 2016) compared the change in UACR in type 2 diabetic patients with albuminuria receiving sitagliptin to those receiving sulphonylurea as add-on to metformin monotherapy. Both sitagliptin and sulphonylurea decreased albuminuria as an add-on therapy to metformin, however, sitagliptin resulted in greater reductions in albuminuria independent of glycemic control compared to sulphonylurea.

Interestingly, a randomized, double-blind and placebo-controlled clinical study (MARLINA-T2D TM) (Groop *et al.* 2015) to evaluate the glycemic and renal efficacy of linagliptin treatment for 24 weeks in patients with diabetic nephropathy on top of current treatment with angiotensin-converting-enzyme inhibitor (ACE-I) or ARBs was recently completed. No hemodynamic changes were induced after adding linagliptin to stable ACE-I or ARBs treatment regimens. Furthermore, linagliptin was shown to improve glycemic control without affecting UACR significantly (Cooper *et al.* 2016, Groop *et al.* 2016). This study was most likely too short to demonstrate a decrease in the slope of glomerular filtration rate (GFR). The potential beneficial renal effects of linagliptin are currently challenged in an ongoing long-term clinical trial (CARMELINA).

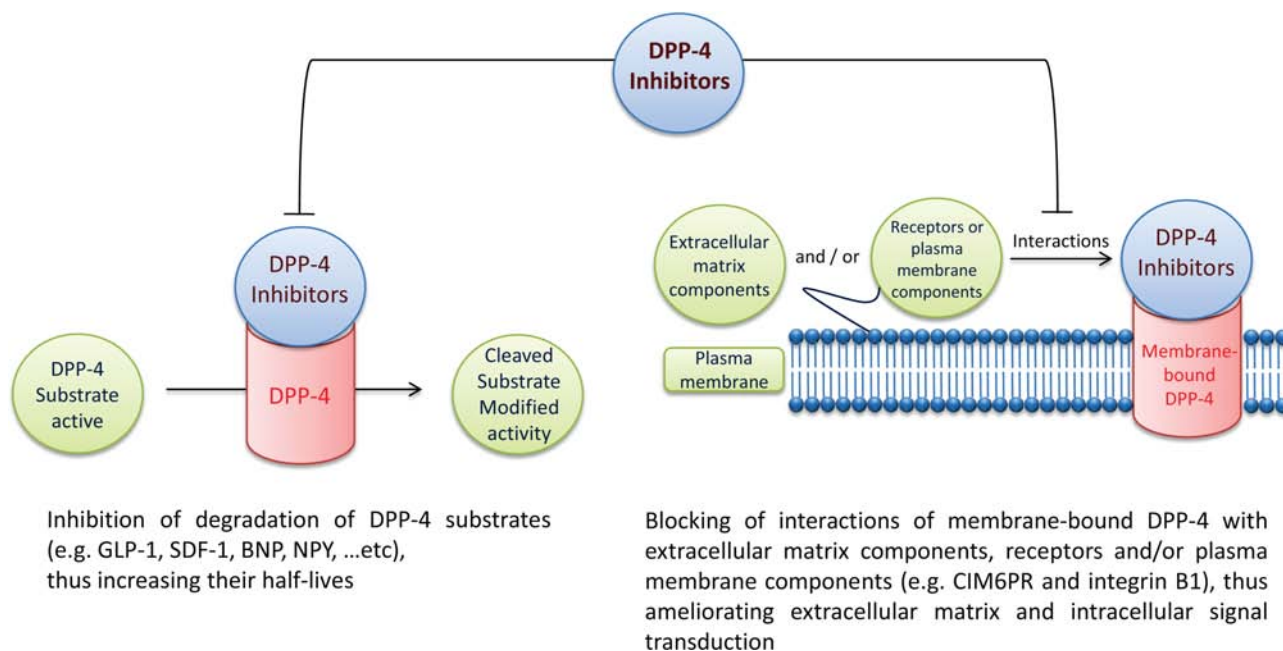
### Membrane-bound DPP-4

The two main pathways through which DPP-4 inhibition can ameliorate diabetic nephropathy are increased half-life of DPP-4 substrates, which have many biological actions, and inhibition of membrane-bound form of DPP-4 in the kidney, which could interact with extracellular matrix components and regulate intracellular signal transduction (Fig. 3). Panchapakesan and Pollock (2014), and Zeisberg and Zeisberg (2015) suggested a mechanism for the antifibrotic activity of linagliptin in the kidney. The membrane-bound

DPP-4 interacts minimally with the cation-independent mannose 6-phosphate receptor (CIM6PR) and integrin B1 in normoglycemic conditions, but these interactions increase in hyperglycemic conditions leading to the activation of TGFβ pathway and fibrosis. Linagliptin can block these interactions by binding and inhibiting the membrane-bound DPP-4. More research is needed to define the renoprotective mechanisms of DPP-4 inhibitors and this would help to discover novel pathways and targets through which diabetic nephropathy could be managed.

### Distinction between soluble and membrane-bound DPP-4

The only structural difference between the soluble and membrane-bound DPP-4 is that the soluble form lacks the cytoplasmic, transmembrane and flexible domains, whereas the two forms share all the other domains including the catalytic site (Mulvihill & Drucker 2014). Therefore, theoretically, any DPP-4 inhibitor can inhibit both soluble and membrane-bound DPP-4. Another important consideration is the volume of distribution of different DPP-4 inhibitors. We can hypothesize that DPP-4 inhibitors with greater volume of distribution, with a higher tissue-to-blood ratio, such as linagliptin could inhibit the membrane-bound DPP-4 more than the DPP-4 inhibitors with lower volume of distribution such as sitagliptin. In line with this



**Figure 3**

Pathways of the biological actions of DPP-4 inhibitors. GLP-1, glucagon like peptide-1; SDF-1α, stromal derived factor-1 alpha; BNP, brain natriuretic peptide; NPY, natriuretic peptide Y; CIM6PR, cation-independent mannose 6-phosphate receptor.

hypothesis, renal DPP-4 activity was significantly inhibited by linagliptin, while neither sitagliptin nor vildagliptin could elicit similar effect in a head-to-head comparison of the three compounds in a rat model of renal ischaemia-reperfusion injury (Reichetzeder *et al.* 2017). In this regard, more studies are needed to investigate the pharmacological differences between soluble and membrane-bound DPP-4 deeply and compare the available DPP-4 inhibitors regarding their ability to inhibit different forms of DPP-4 in the setting of diabetic nephropathy.

### DPP-4 substrates in diabetic nephropathy

DPP-4 can cleave many substrates with many biological actions. In this section, we will review GLP-1 and SDF-1 $\alpha$ , the most studied substrates of DPP-4 with potential roles in diabetic nephropathy.

#### GLP-1

GLP-1 is an incretin which is secreted from intestinal L-cells in response to oral glucose load and can stimulate insulin secretion from pancreatic B cells and inhibit glucagon release. GLP-1 is secreted in active form, GLP-1 (7–36), and rapidly degraded by DPP-4 into GLP-1 (9–36), rendering the active GLP-1 a very short half-life. Thus, two pharmacological approaches appeared to get use of the antihyperglycemic effects of GLP-1, first GLP-1 analogues such as exenatide and liraglutide which can resist degradation by DPP-4, and second DPP-4 inhibitors, the gliptins family, which can block the DPP-4-induced breakdown of GLP-1 (7–36) and other substrates. Both classes of drugs include approved drugs for the treatment of type 2 diabetes (von Websky *et al.* 2014). GLP-1R is expressed in the kidney in many species but the present literature on its exact localization needs more investigation due to doubts about the specificity and sensitivity of the available GLP-1R antibodies (Pyke & Knudsen 2013). In a study by Schlatter *et al.* (2007), GLP-1R was reported to be expressed in porcine renal proximal tubules at mRNA and protein levels. Moreover, GLP-1R expression was predominately detected in proximal tubular cells after staining of human and pig renal cortex. Using real-time RT-PCR in rat kidneys, (Crajoinas *et al.* 2011) revealed that GLP-1 receptor-mRNA expression was only detected in the glomerulus and proximal convoluted tubule. An interesting study revealed that *Glp1r* mRNA was localized only in glomerular capillary walls and renal blood vessels and not in tubules using *in situ* hybridization and these findings were confirmed by PCR (Fujita *et al.* 2014a).

The effects of GLP-1 in diabetic nephropathy have been investigated in many studies using degradation-resistant GLP-1R agonists. It was shown that exendin-4, a GLP-1 analogue, prevented glomerular endothelial dysfunction in the kidneys of STZ-diabetic mice by inhibiting the signalling pathway of angiotensin II and these renal protective effects were counteracted by protein kinase C- $\beta$  (PKC $\beta$ ) activation and reduced expression of GLP-1R using GLP-1R small interfering RNA in the glomerular endothelial cells (Mima *et al.* 2012). Exendin-4 treatment was also reported to delay the progression of diabetic nephropathy in *db/db* mice as indicated by decreased urinary albumin excretion and improved renal histopathology. These effects were accompanied by downregulation of TGF $\beta$ 1 expression, decreased collagen type IV accumulation, suppressed inflammation, reduced apoptosis and lower oxidative stress (Park *et al.* 2007). In alignment with these findings, many other studies also revealed renal beneficial effects of GLP-1 analogues in animal models of diabetic nephropathy suggesting many mechanisms behind these effects such as cAMP-protein kinase A pathway activation, inhibition of renal NAD(P)H oxidases (Hendarto *et al.* 2012, Fujita *et al.* 2014a), downregulation of AGE-induced protein arginine methyltransferase-1 expression (Ojima *et al.* 2013), decreased ICAM-1 production, reduced release of proinflammatory cytokines from macrophages (Kodera *et al.* 2011) and up-regulation of ATP-binding cassette transporter A1 (ABCA1) in glomerular endothelial cells, which promoted cholesterol efflux from cells and blocked inflammatory responses (Yin *et al.* 2016). Moreover, the natriuretic and diuretic effects of GLP-1 analogues and DPP-4 inhibitors through interaction with Na<sup>+</sup>/H<sup>+</sup> exchanger isoform 3 could play a role regarding their reno-protective effects. Interestingly, Rieg and coworkers (Rieg *et al.* 2012) reported that the natriuretic effect of exendin-4, but not alogliptin, was absent in *Glp1r*<sup>-/-</sup> mice, indicating that the natriuretic effect due to DPP-4 inhibition was not only mediated by GLP-1R activation. Moreover, exendin-4 showed antifibrotic effects in human mesangial cells cultured in a high glucose medium through attenuated expression of TGF $\beta$ 1 and connective tissue growth factor (CTGF) and activation of adenylate cyclase (Li *et al.* 2012).

In addition, literature provides some clinical data regarding renal effects of GLP-1 analogues. In a small study including twenty-three type 2 diabetic patients with diabetic nephropathy, treatment with liraglutide for twelve months on top of rennin-angiotensin system blockers led to a significant reduction in HbA1c, proteinuria and counteracted the progression of diabetic



nephropathy as indicated by decreasing the rate of decline in eGFR (Imamura *et al.* 2013). Also, another small placebo-controlled randomized trial reported that liraglutide was able to show renal beneficial effects in terms of reduction of urinary albumin excretion in type 2 diabetic patients with albuminuria (von Scholten *et al.* 2016). Moreover, eGFR was not affected but UACR was decreased by dulaglutide treatment in 6005 type 2 diabetic patients (Tuttle *et al.* 2016). Recently, the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) clinical trial was completed. It was revealed that the incidence of nephropathy events in type 2 diabetic patients was lower in the liraglutide group vs the placebo group; however the authors were uncertain whether this result relates to the direct renal effects of liraglutide, highlighting the need for more controlled clinical trials investigating the renal effects of GLP-1 analogues (Marso *et al.* 2016).

### SDF-1a

SDF-1, also known as CXCL12, is a chemokine which is widely expressed in many organs. SDF-1 has six isoforms which are formed by mRNA splicing. SDF-1a is the predominant isoform and cleaved and inactivated by DPP-4. It can exert many biological actions through two chemokine receptors, CXCR4 and CXCR7. SDF-1 is known to be involved in tissue repair by enhancing the migration of endothelial progenitor cells to sites of acute injury such as ischaemia (Mulvihill & Drucker 2014). It was reported that podocytes of *db/db* mice produced SDF-1a, which augmented proteinuria and glomerulosclerosis, while using the SDF-1 specific inhibitor NOX-A12 corrected glomerulosclerosis, enhanced the number of podocytes, maintained the peritubular vasculature and delayed the onset of albuminuria (Sayyed *et al.* 2009). In contrast, decreased endothelial SDF-1a was accompanied by proteinuria, enhanced oxidative stress, podocyte foot process effacement and increased glomerular size in Zucker obese rats. These findings were counteracted with linagliptin treatment (Nistala *et al.* 2014). Moreover, (Takashima *et al.* 2016) used *Glp1r<sup>-/-</sup>* diabetic-prone Akita mice to show that linagliptin enhanced renal SDF-1 expression leading to improved renal outcomes, independent of GLP-1R signalling, which were counteracted using AMD3100, a selective SDF-1 receptor blocker. Thus the available data on SDF-1 in the setting of diabetic nephropathy remain controversial and need more investigation.

### Other substrates

DPP-4 substrates include many other substrates such as glucose-dependent insulinotropic polypeptide (GIP), brain natriuretic peptide (BNP), substance P, peptide YY and neuropeptide Y (NPY). The available literature on the renal effects of these substrates in the setting of diabetic nephropathy is still limited partially due to a lack of sensitive assays which can differentiate between cleaved and uncleaved substrates.

In summary, DPP-4 is related to pathological kidney conditions including diabetic nephropathy. DPP-4 inhibition could be a promising approach for management of diabetic nephropathy. Given the pleiotropic actions of DPP-4, due to its wide range of substrates with different biological activities, the mechanisms by which DPP-4 inhibition could attenuate kidney injury are not well defined so far. More studies are required to clarify the reno-protective mechanisms of DPP-4 inhibition and more clinical trials are needed to validate this approach.

### Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review. BH has received research grants from Boehringer Ingelheim, the manufacturer of linagliptin.

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