양산부산대학교병원

Microvascular complications and incretin-based therapy

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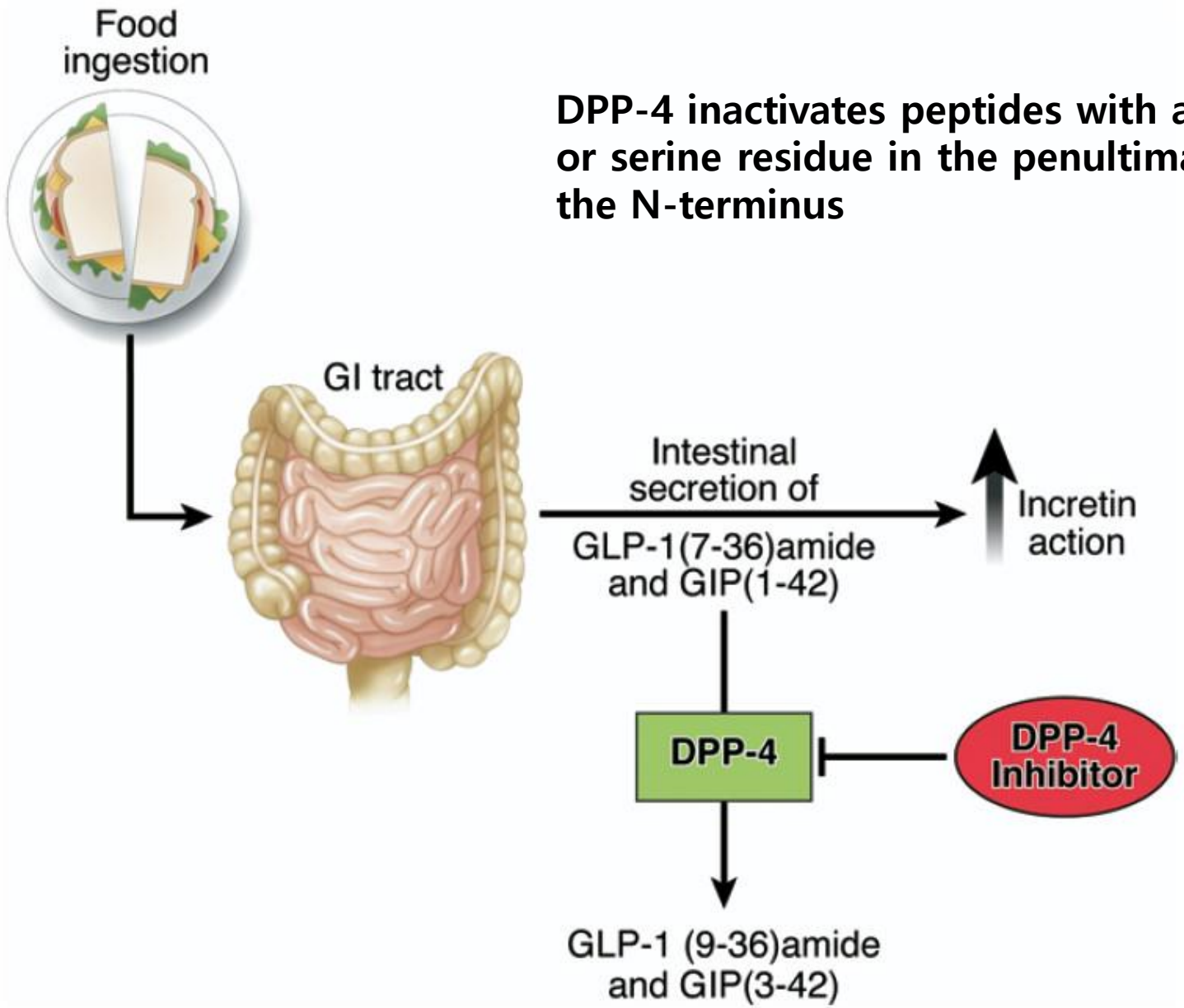
내분비내과 강양호

본 발표와 관련된 이해관계

없 음

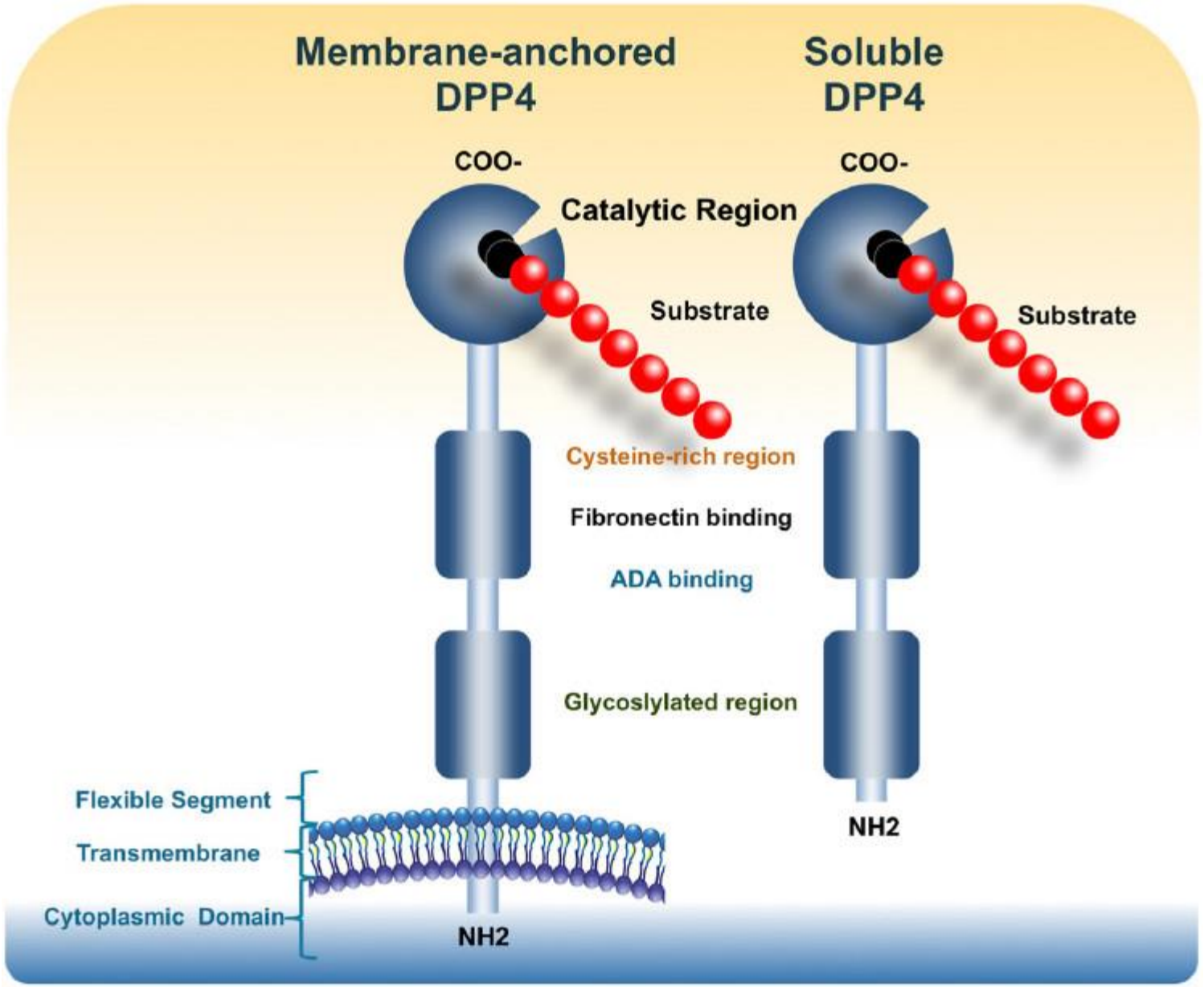
Dipeptidyl peptidase-4 (DPP4) inhibitor



DPP-4 inactivates peptides with an alanine, proline, or serine residue in the penultimate position from the N-terminus

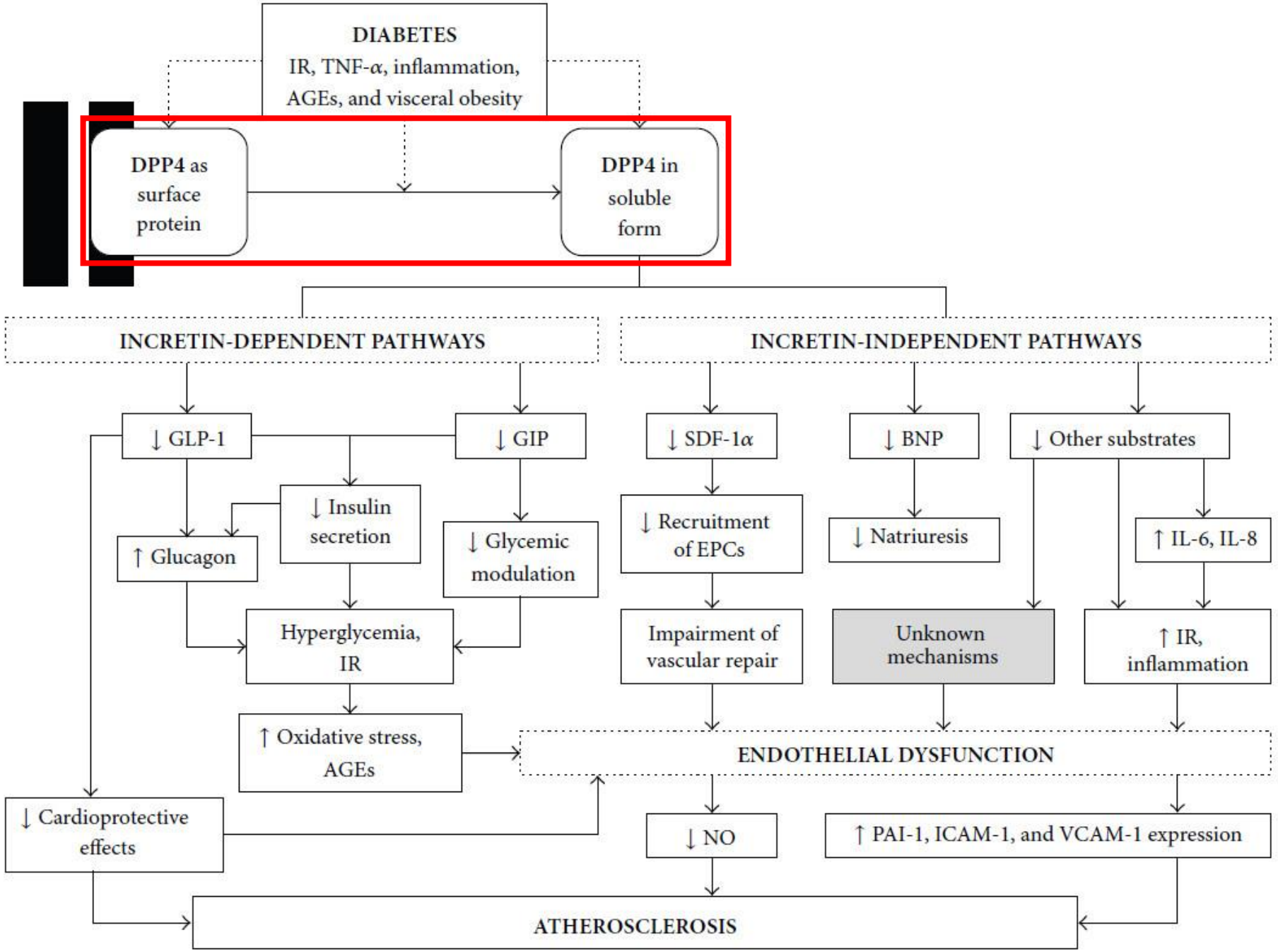
Baggio, L. L. and D. J. Drucker (2007). "Biology of incretins: GLP-1 and GIP." Gastroenterology 132(6): 2131-2157.

Membrane-bound DPP4 and soluable DPP4



DPP-4 also circulates as a soluble form in the plasma, which lacks the cytoplasmic and transmembrane domain with preserved catalytic activity

Mulvihill, E. E. and D. J. Drucker (2014). "Pharmacology, physiology, and mechanisms of action of dipeptidyl peptidase-4 inhibitors." Endocr Rev 35(6): 992-1019.



Silva Junior, W. S., et al. (2015). "Dipeptidyl Peptidase 4: A New Link between Diabetes Mellitus and Atherosclerosis?" Biomed Res Int 2015: 816164.

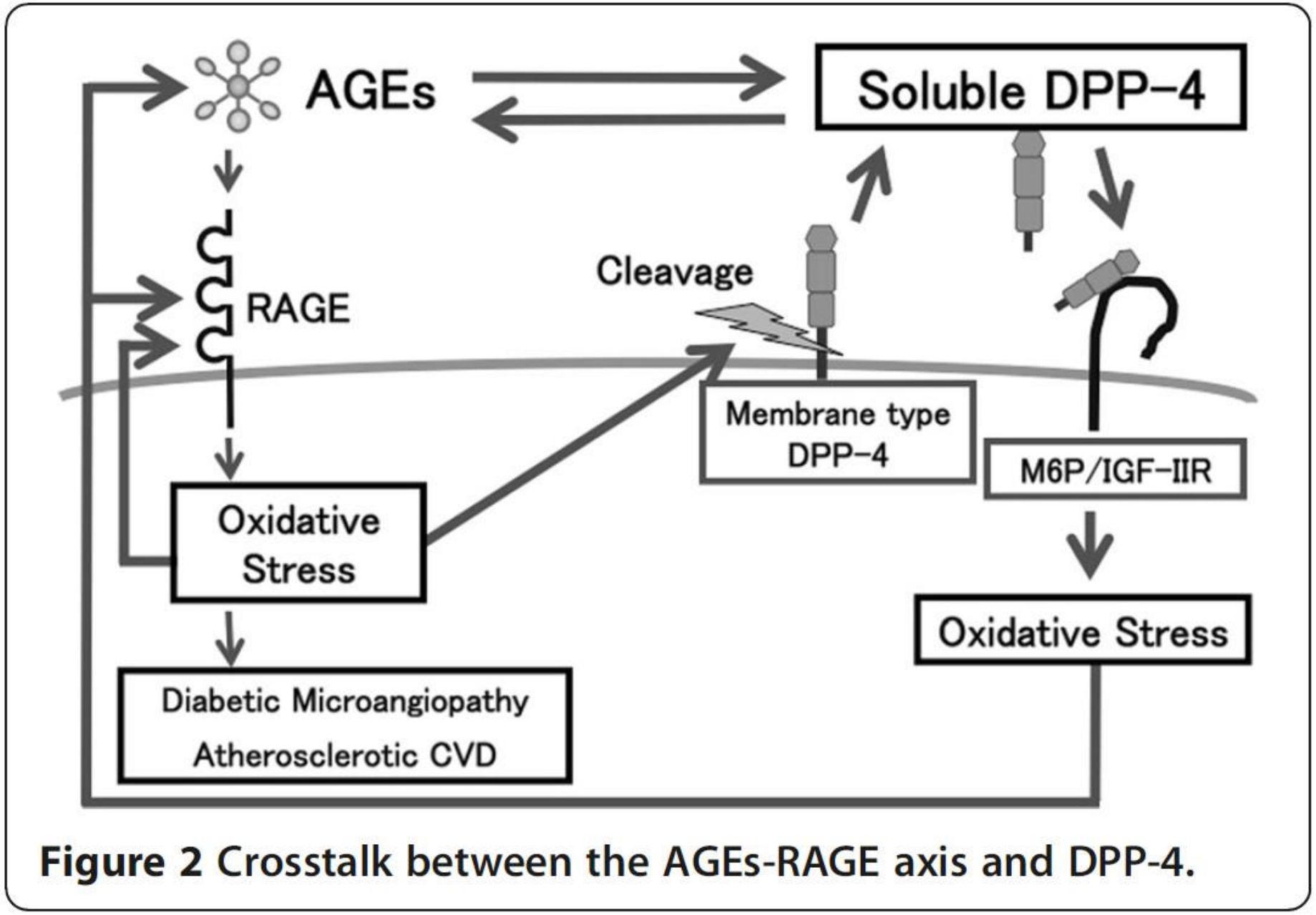
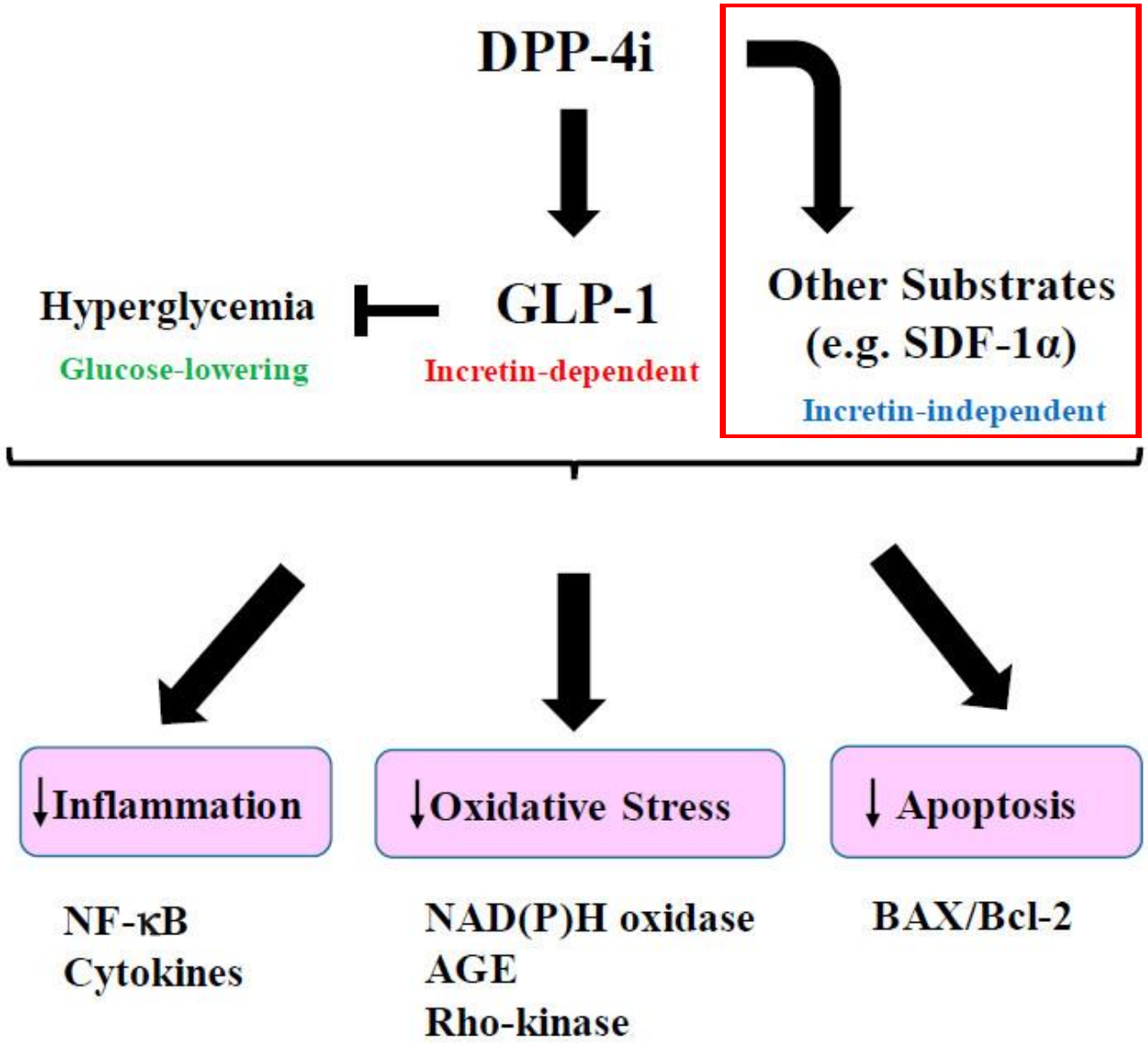


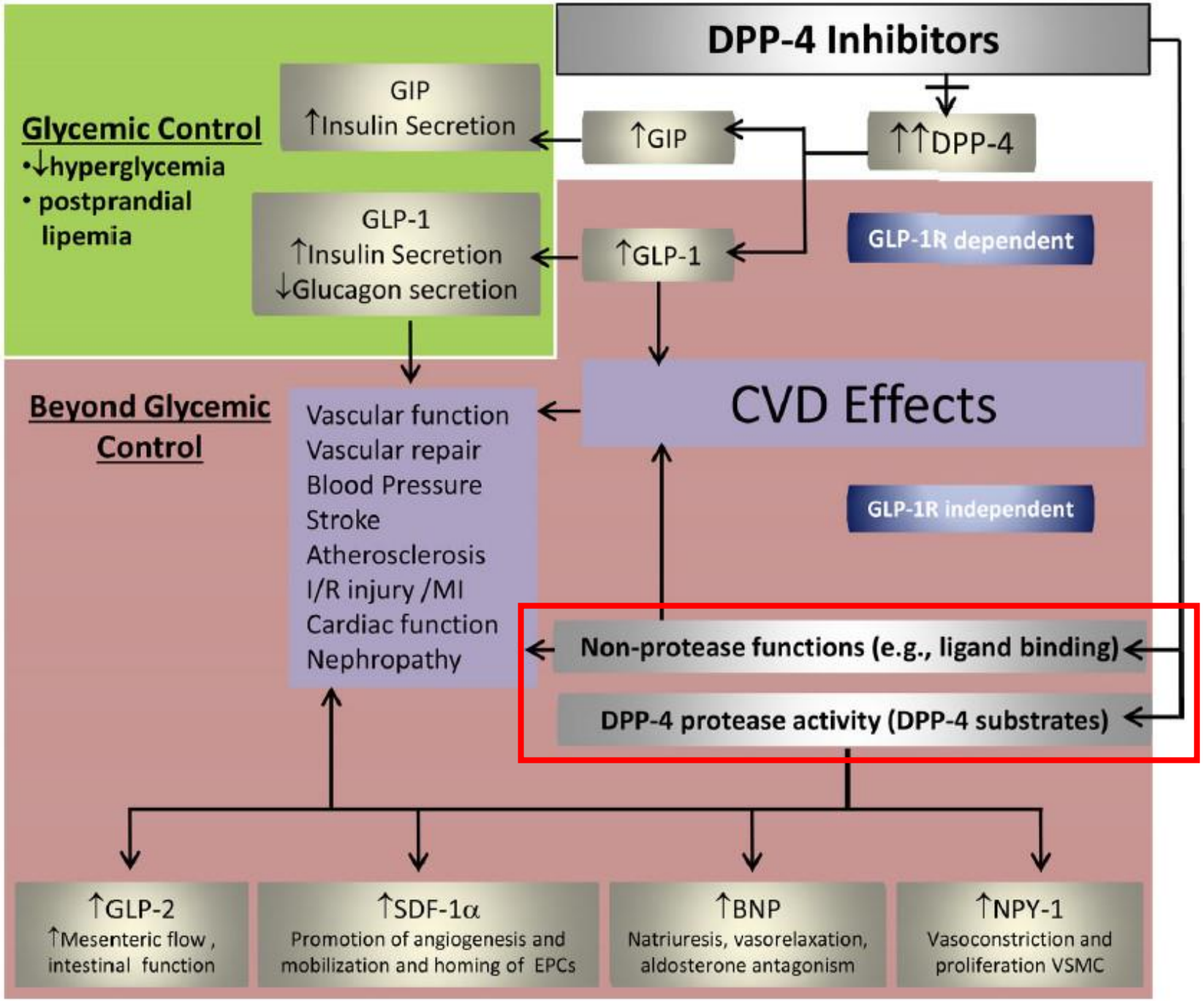
Figure 2 Crosstalk between the AGEs-RAGE axis and DPP-4.

Yamagishi, S., et al. (2015). "Crosstalk between AGEs-receptor RAGE axis and DPP4-incretin system in diabetic vascular complications." Cardiovasc Diabetol 14: 2.

Dipeptidyl peptidase-4 (DPP4) inhibitor



Kawanami, D., et al. (2016). "Incretin-Based Therapies for Diabetic Complications: Basic Mechanisms and Clinical Evidence." Int J Mol Sci 17(8).



DPP-4i will have multiple effects beyond glycemic control…

Aroor, A. R., et al. (2014). "Pleiotropic effects of the dipeptidylpeptidase-4 inhibitors on the cardiovascular system." Am J Physiol Heart Circ Physiol 307(4): H477-492.

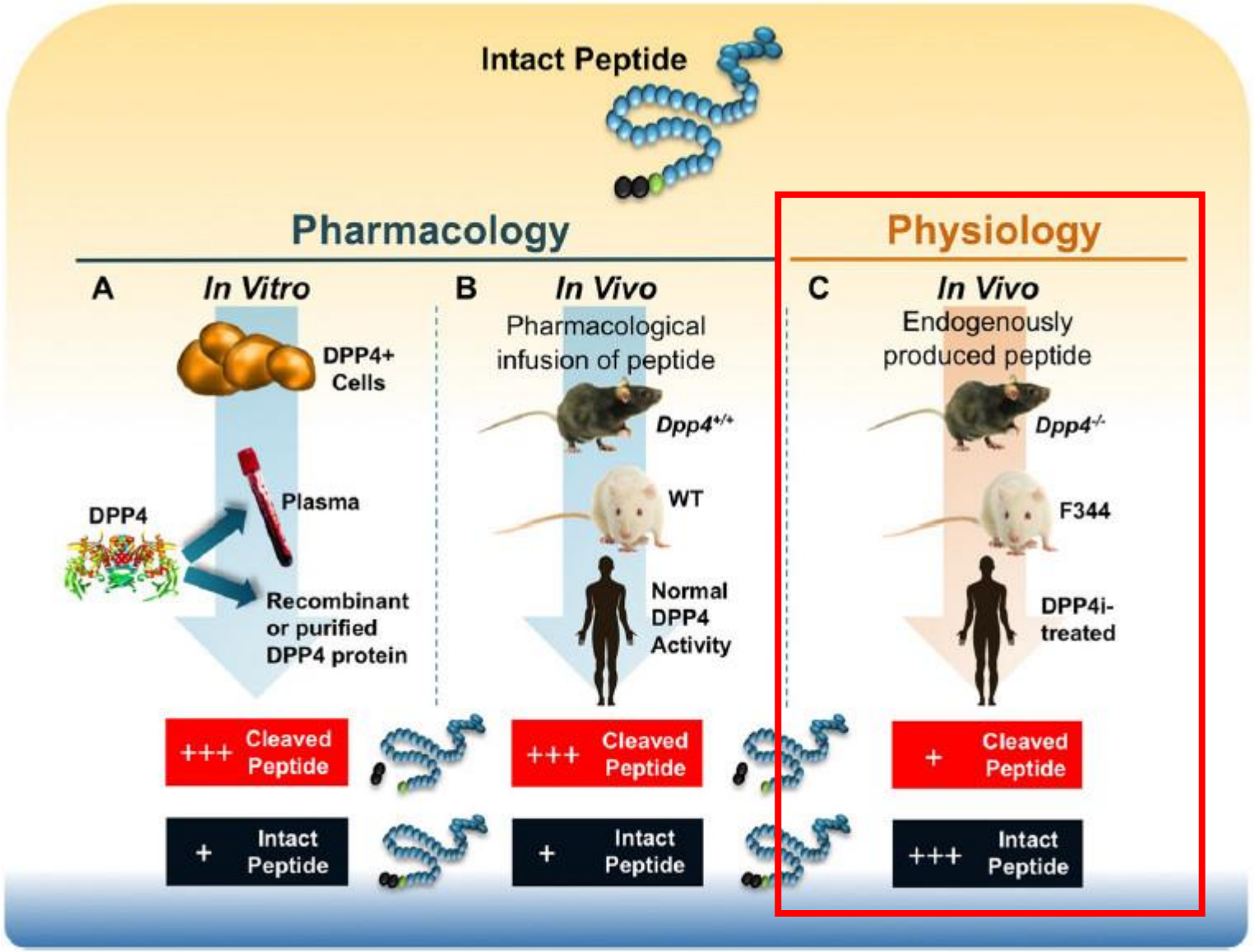
Possible enzymatic substrates of DPP-4

Regulatory peptides	Brain natriuretic peptide, GIP, gastrin-releasing peptide (GRP), GLP1, GLP2, GRH, pituitary adenylate-cyclase-activating polypeptide (PACAP)-(1–38), vasoactive intestinal peptide (VIP)
Chemokines	Eotaxin (CCL11), IP10 (CXCL10), I-TAC (CXCL11), macrophage-derived chemokine (MDC, CCL22), monokine induced by gamma-interferon (CXCL9), RANTES (CCL5), stromal cell-derived factor-1 (CXCL12), monocyte chemotactic protein-2, granulocyte chemotactic protein-2
Neuropeptides	NPY(1–36), substance P, PYY(1–36), bradykinin, endomorphin-2
Others	Granulocyte macrophage-colony stimulating factor (GM-CSF) G-CSF, erythropoietin, Interleukin-3, fibroblast growth factor-2, thrombopoietin

IP, interferon-γ-inducible protein; I-TAC, Interferon-inducible T cell a chemoattractant; RANTES, regulated on activation normal T cell expressed and secreted.

Kim, N. H., et al. (2014). "The nonglycemic actions of dipeptidyl peptidase-4 inhibitors." Biomed Res Int 2014: 368703.

Pharmacological DPP4 Substrates <<< Physiological DPP4 Substrate…

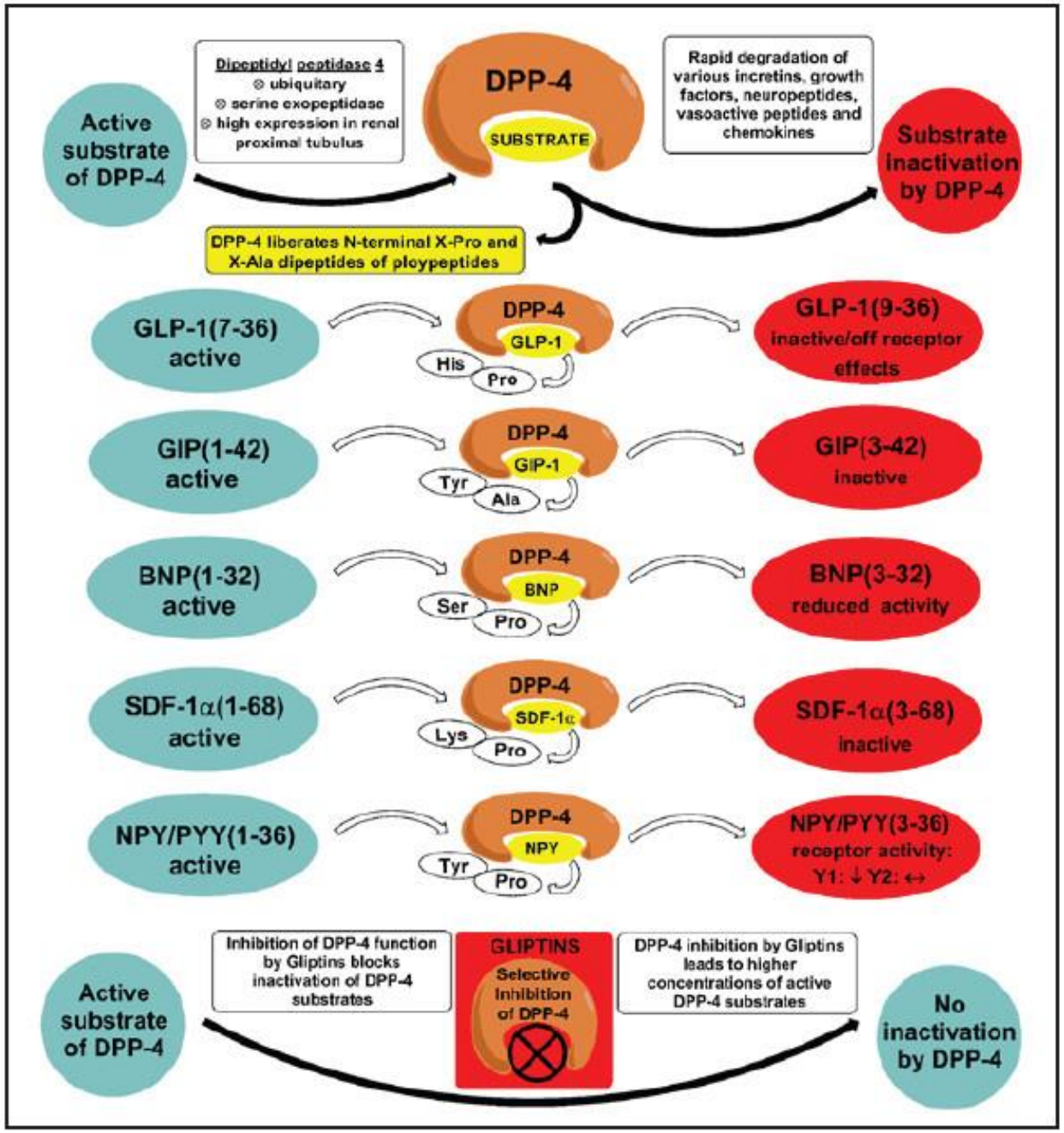


Physiological Substrates	N-Terminal Sequence
GIP	**YA**EGTF. . .
GLP-1	**HA**EGTF. . .
GLP-2	**HA**DGSF. . .
PYY	**YP**IKPE. . .
SDF-1	**KP**VSLS. . .
SP	**RP**KPQQFFGLM. . .

Experimental paradigms for identification of DPP4 substrates

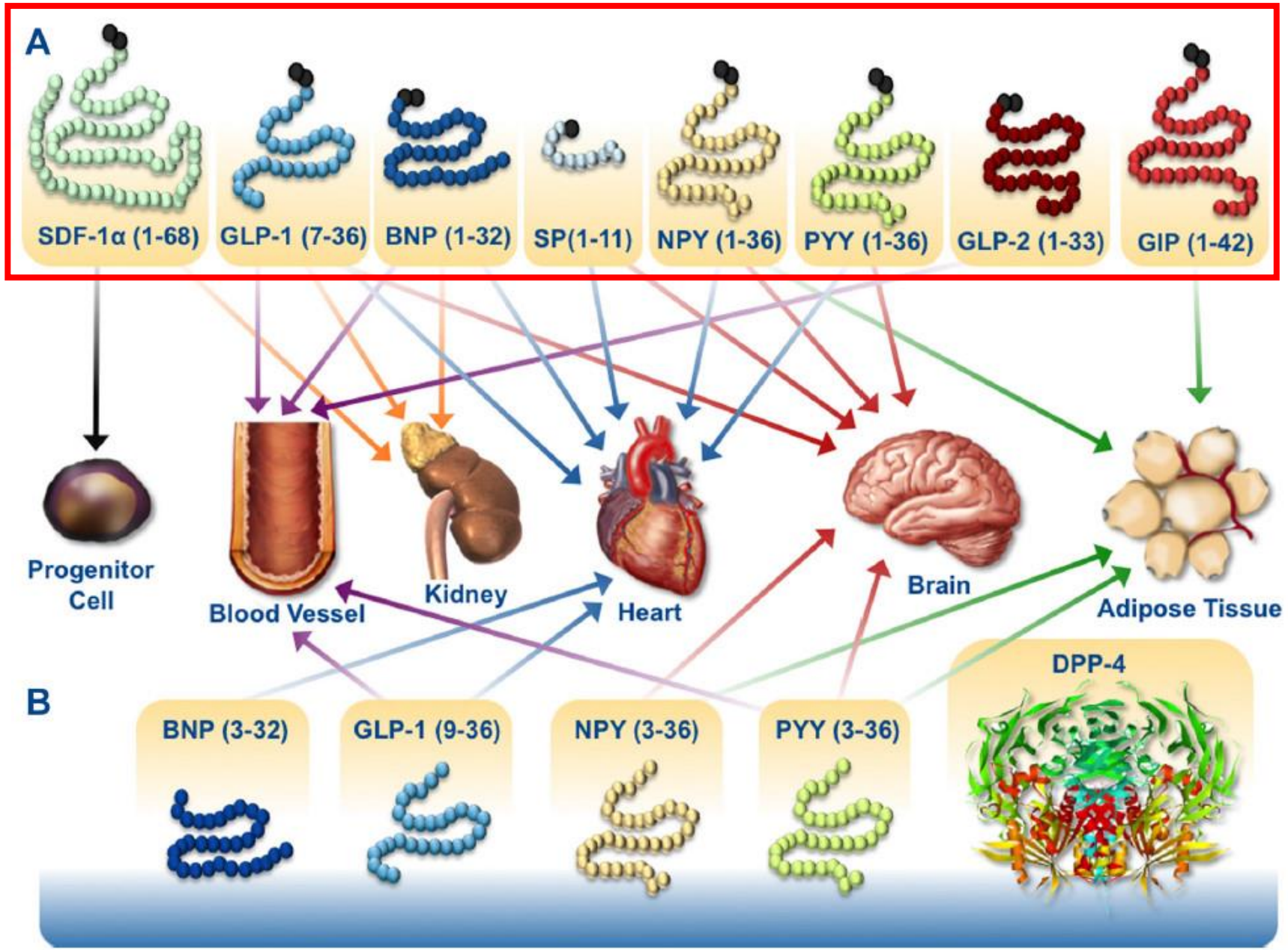
Mulvihill, E. E. and D. J. Drucker (2014). "Pharmacology, physiology, and mechanisms of action of dipeptidyl peptidase-4 inhibitors." Endocr Rev 35(6): 992-1019.

Fig. 1. Substrates of DDP-4 with potential cardio-renal effects. DPP-4, type 4 dipeptidyl peptidase; GLP-1, type 1 glucagon like peptide; GIP, gastric inhibitory polypeptide; BNP, brain natriuretic peptide; SDF-1, type 1 stromal derived factor; NPY, neuropeptide; PYY, peptide YY; His, histidine; Pro, proline; Tyr, tyrosine; Ala, alanine; Ser, serine.



Hocher, B., et al. (2012). "Renal and cardiac effects of DPP4 inhibitors--from preclinical development to clinical research." Kidney Blood Press Res 36(1): 65-84.

DPP-4 Substrates that directly or indirectly regulate cardiovascular function

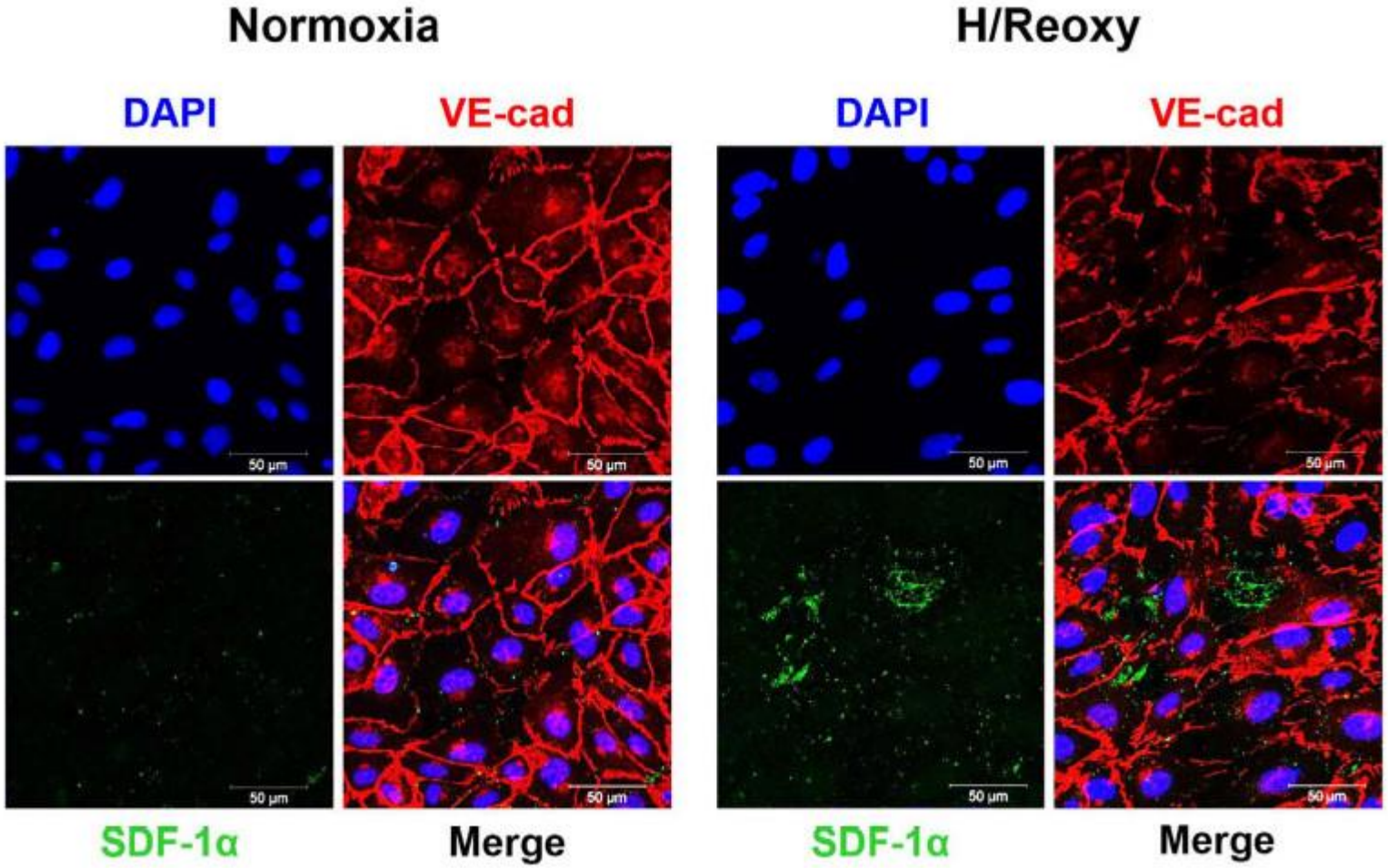


Ussher, J. R. and D. J. Drucker (2012). "Cardiovascular biology of the incretin system." Endocr Rev 33(2): 187-215.

Stromal cell derived factor-1α (SDF-1α)

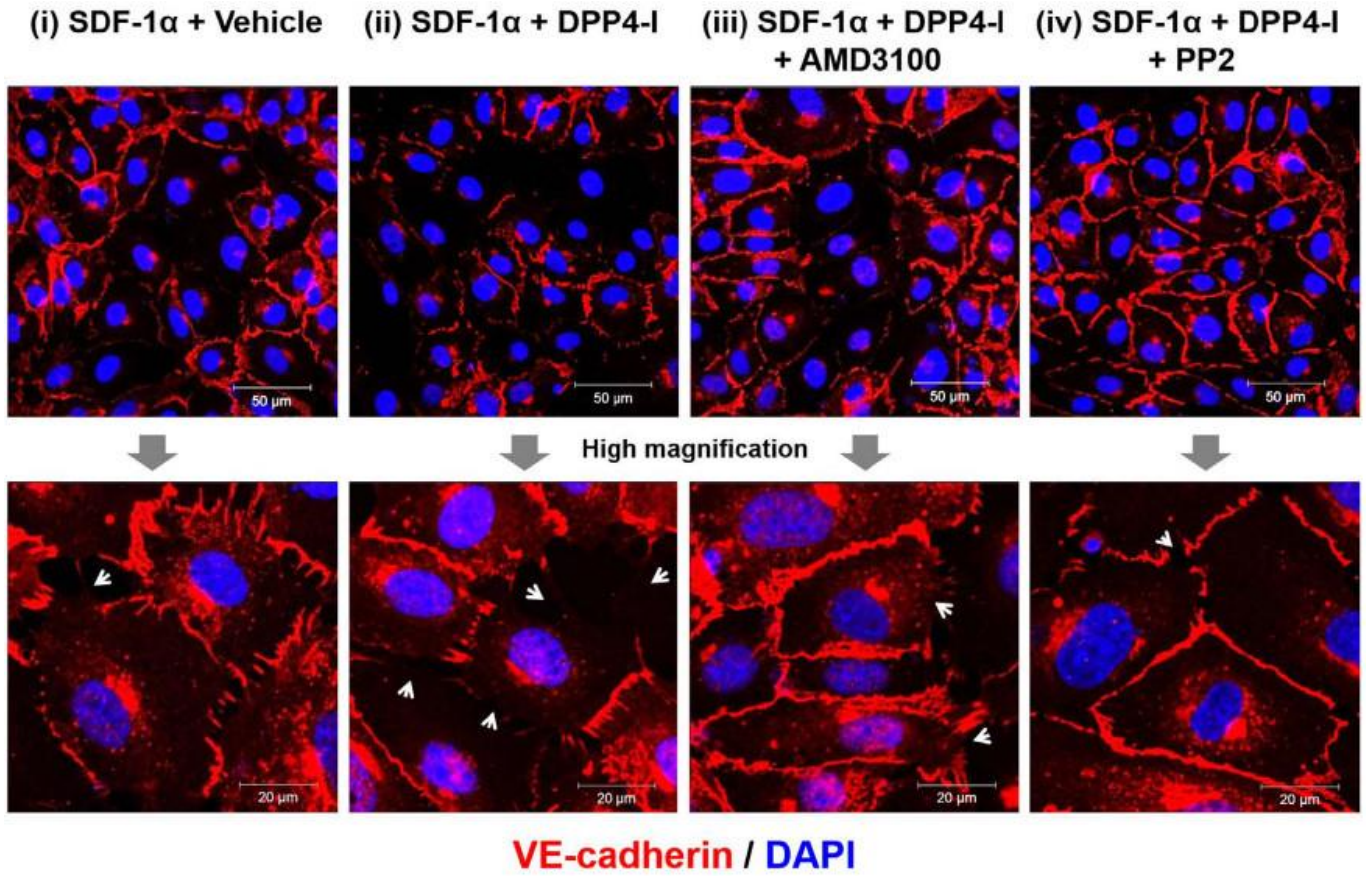
- a chemokine that attracts stem cell such as hematopoietic stem cells (HSCs) and endothelial progenitor cells (EPCs)
- SDF-1α is increased in damaged tissue and promotes tissue repair and angiogenesis
- the inhibition of DPP4 stabilizes biologically active SDF-1α

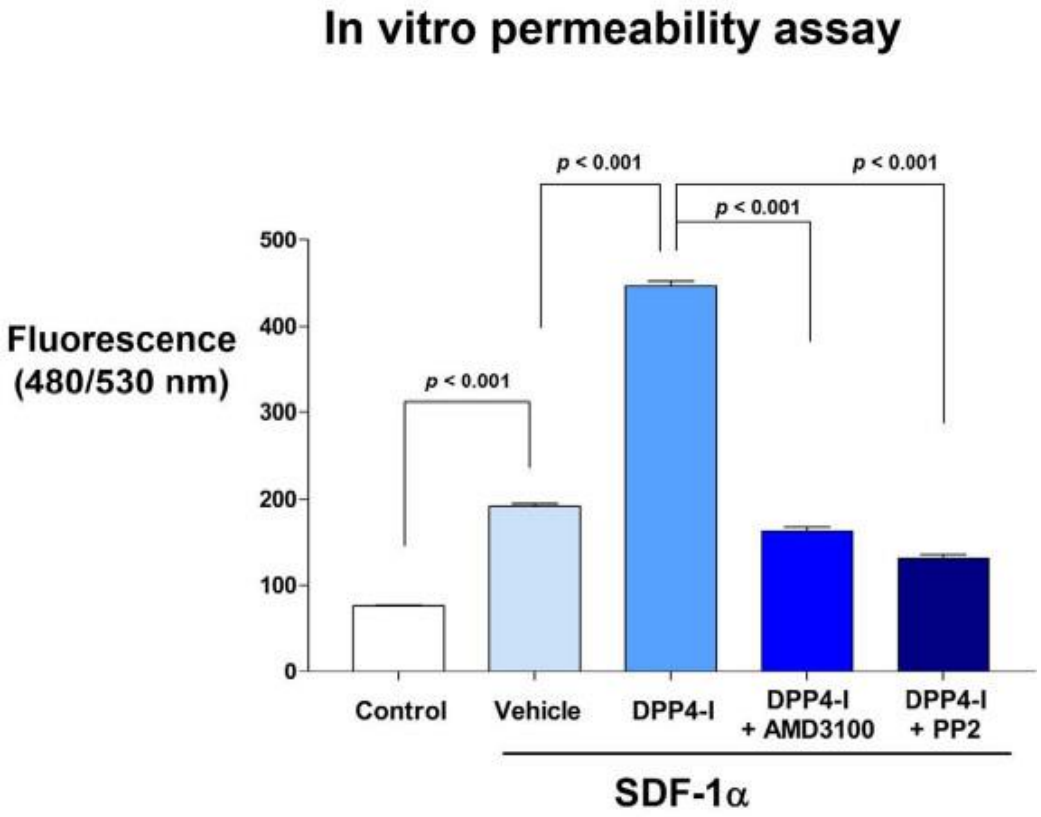
The SDF-1α/CXCR4/Src/VE-cadherin signaling pathway…



Lee, C. S., et al. (2016). "Dipeptidyl Peptidase-4 Inhibitor Increases Vascular Leakage in Retina through VE-cadherin Phosphorylation." Sci Rep 6: 29393.

The SDF-1α/CXCR4/Src/VE-cadherin signaling pathway…

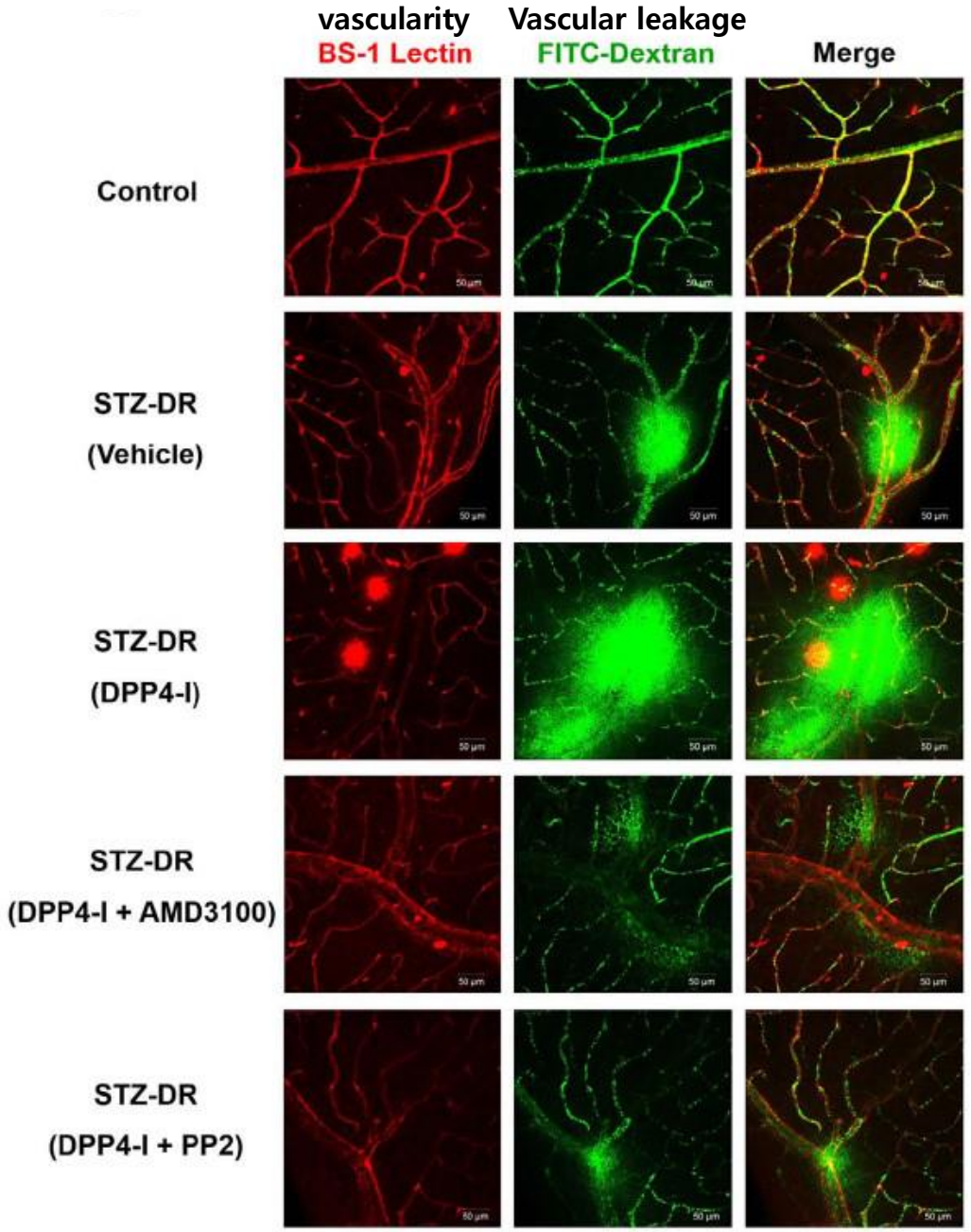




AMD3100: CXCR4-blocker

PP2: Src-inhibitor

Lee, C. S., et al. (2016). "Dipeptidyl Peptidase-4 Inhibitor Increases Vascular Leakage in Retina through VE-cadherin Phosphorylation." Sci Rep 6: 29393.



DPP4-inhibitors might aggravate diabetic retinopathy???

by increasing vascular permeability through the SDF-1α /CXCR4 axis, followed by Src activation and phosphorylation of VE-cadherin

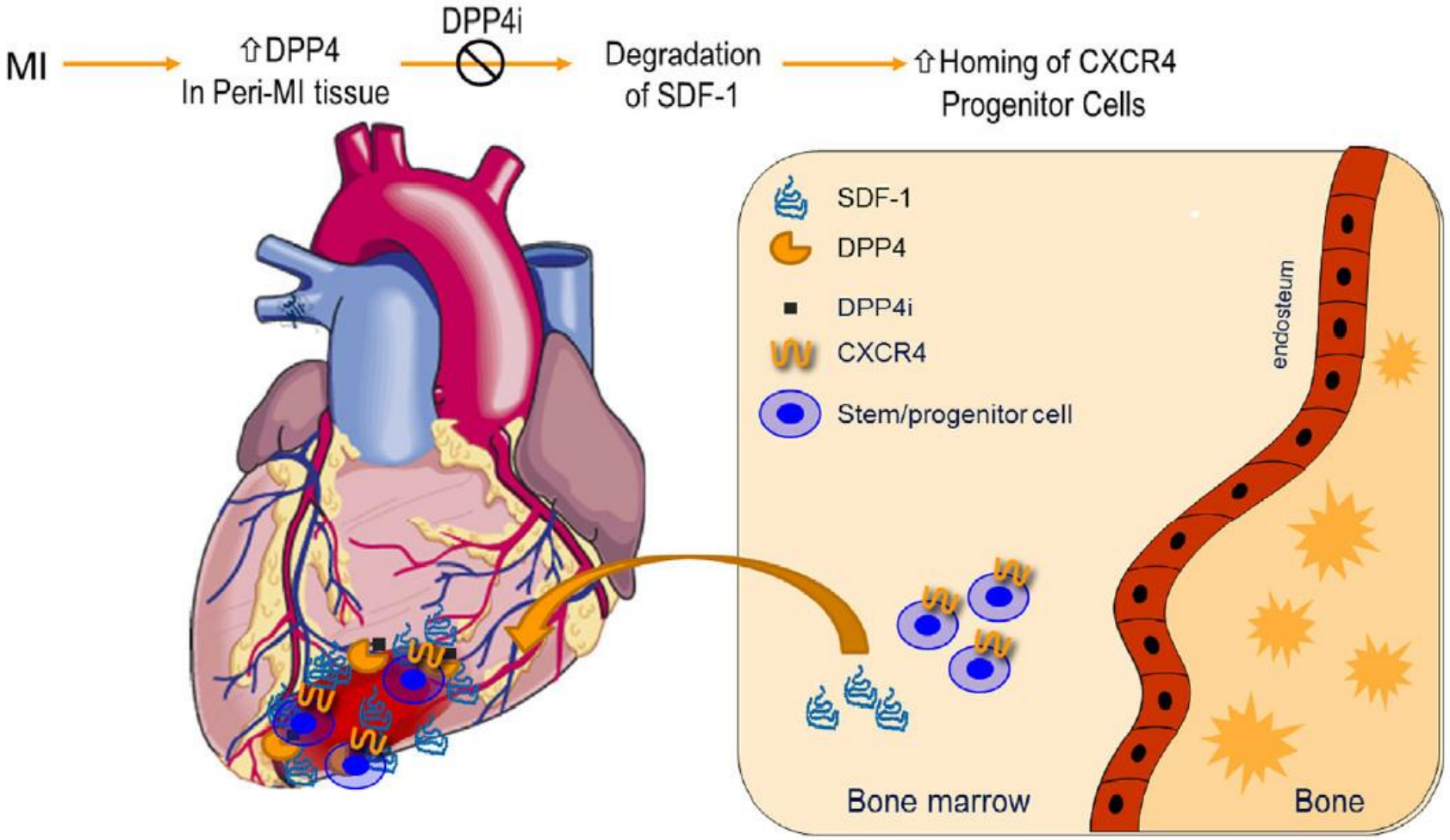
AMD3100: CXCR4-blocker

PP2: Src-inhibitor

Lee, C. S., et al. (2016). "Dipeptidyl Peptidase-4 Inhibitor Increases Vascular Leakage in Retina through VE-cadherin Phosphorylation." Sci Rep 6: 29393.

Possible benefit roles of SDF-1α

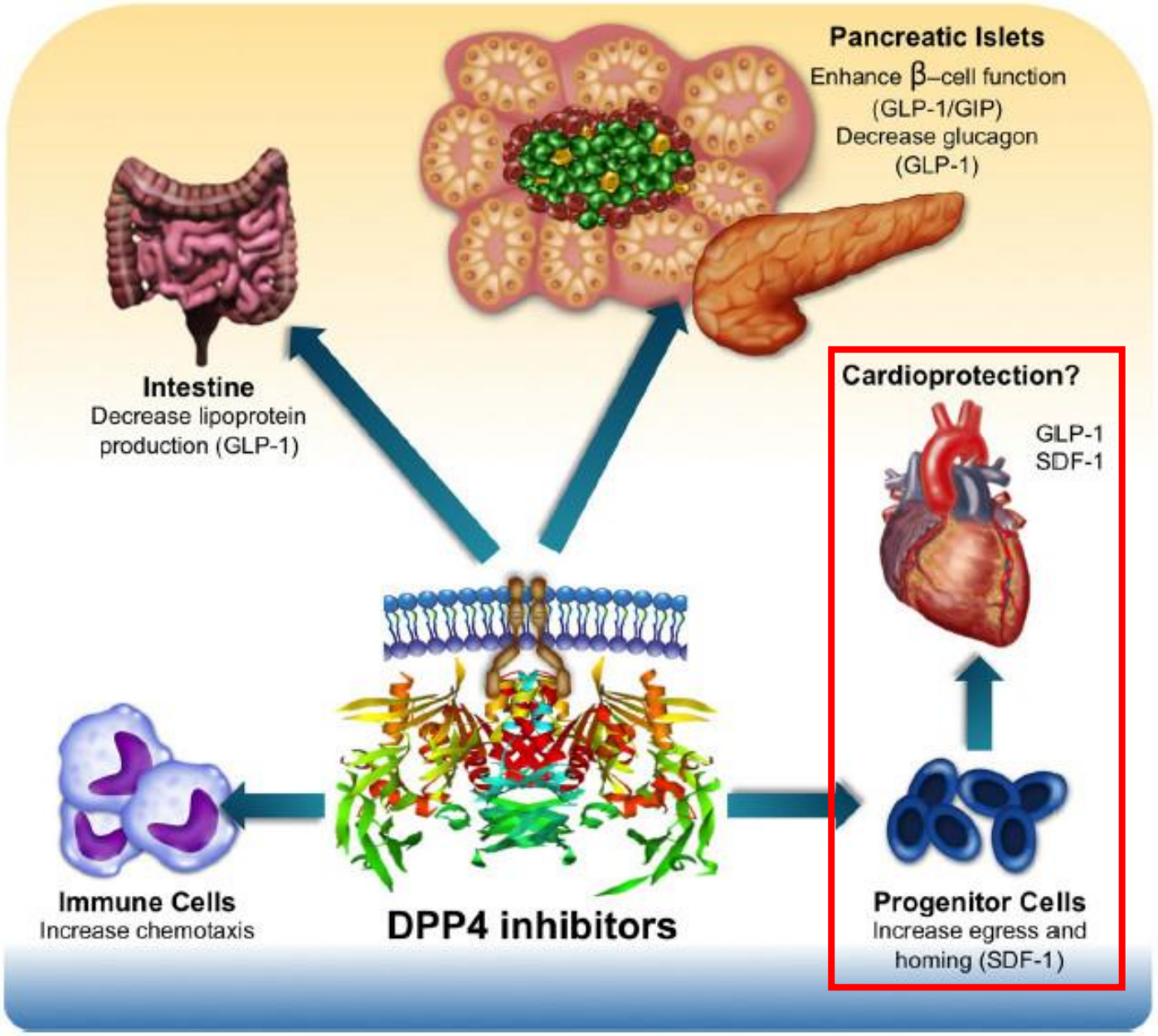
DPP4 inhibitors preserves SDF-1, which results in an enhanced homing of CXCR4+ progenitor cells from bone marrow to infarcted tissues



CXCR4, chemokine (C–X–C motif) receptor 4; DPP4i, DPP4 inhibitor; MI, myocardial infarction; SDF-1, stromal-derived factor-1.

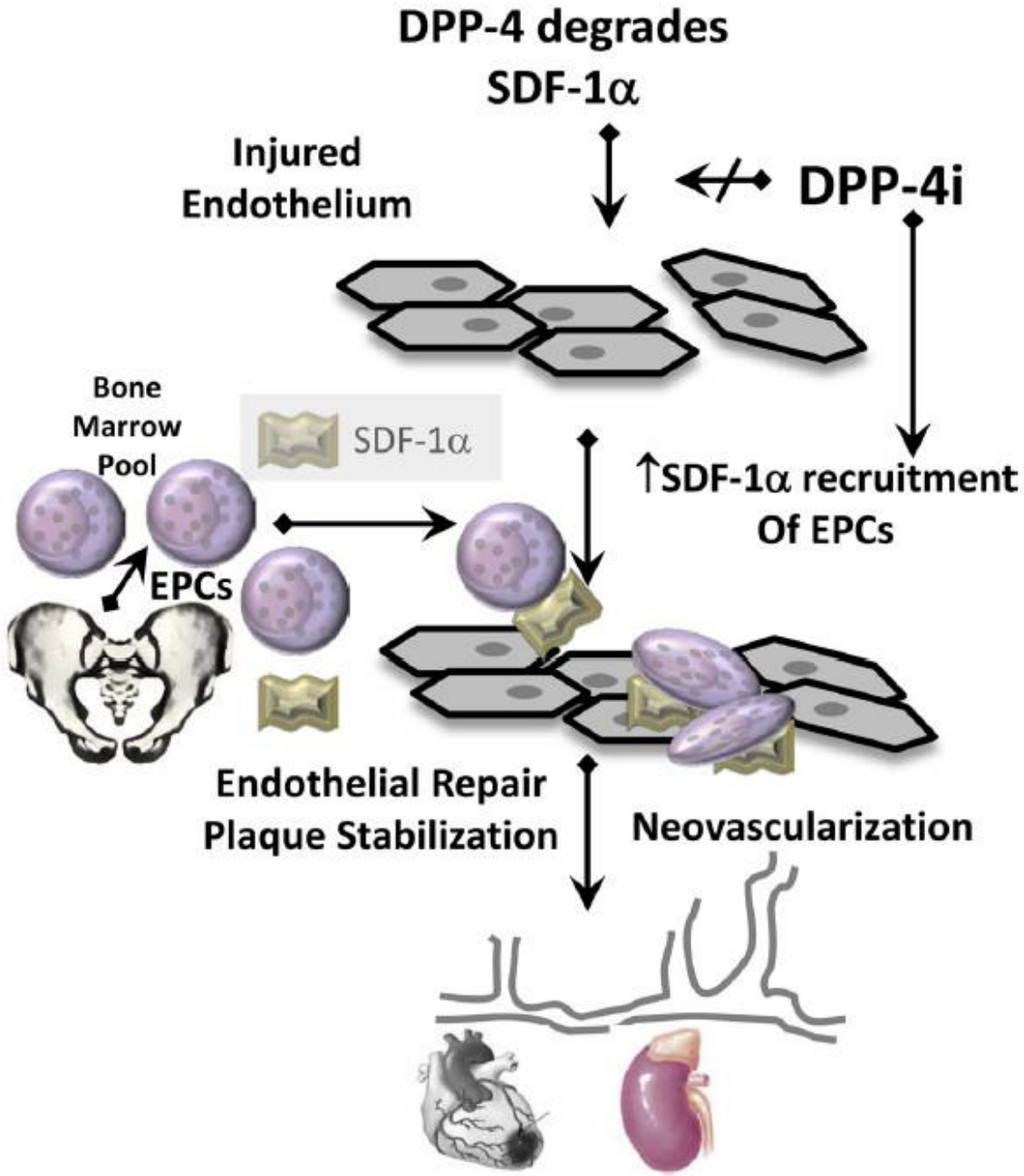
Zhong, J. and S. Rajagopalan (2015). "Dipeptidyl Peptidase-4 Regulation of SDF-1/CXCR4 Axis: Implications for Cardiovascular Disease." Front Immunol 6: 477.

Endocrine pathways altered during DPP4 inhibition



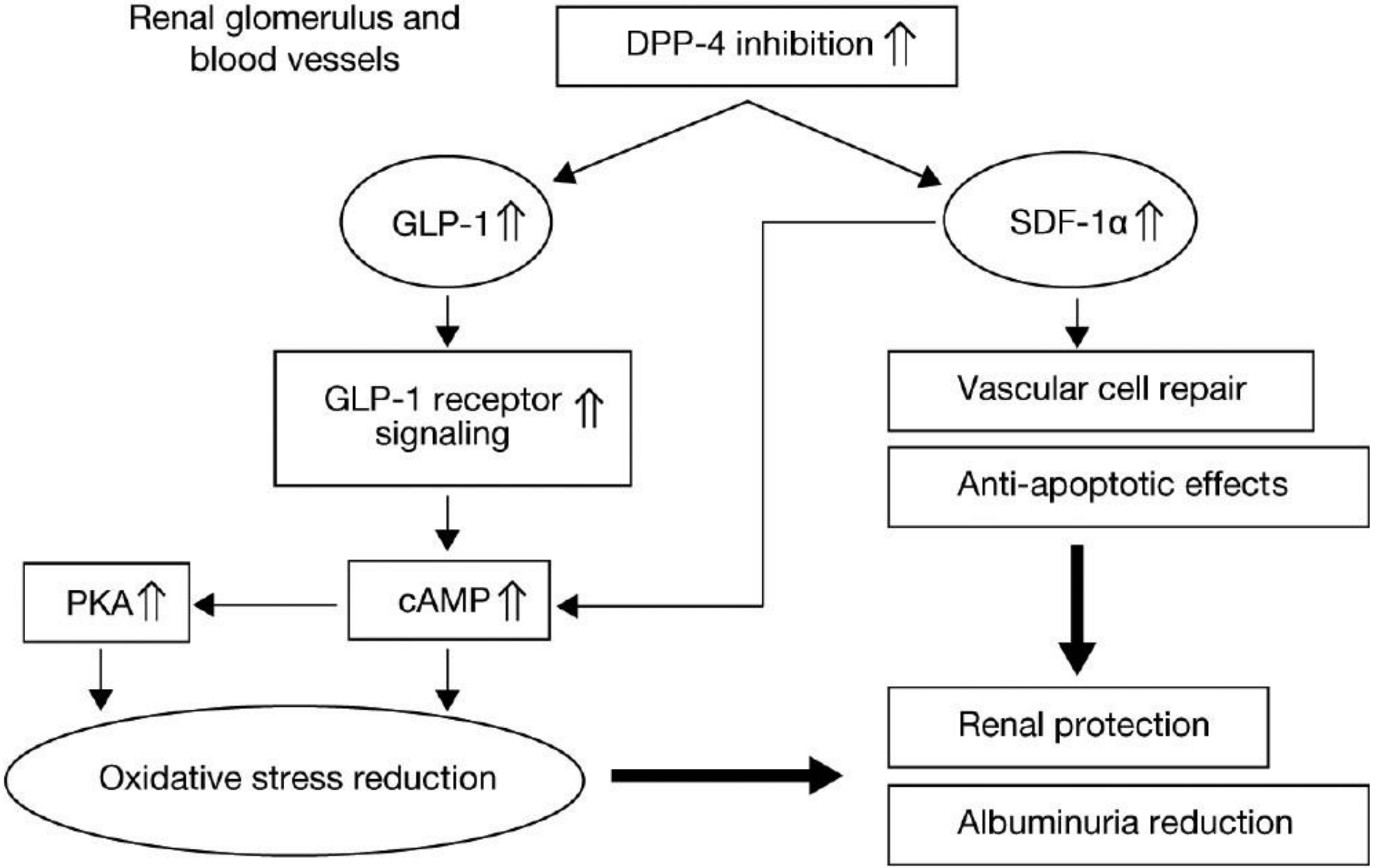
Mulvihill, E. E. and D. J. Drucker (2014). "Pharmacology, physiology, and mechanisms of action of dipeptidyl peptidase-4 inhibitors." Endocr Rev 35(6): 992-1019.

Possible benefit roles of SDF-1α



Aroor, A. R., et al. (2014). "Pleiotropic effects of the dipeptidylpeptidase-4 inhibitors on the cardiovascular system." Am J Physiol Heart Circ Physiol 307(4): H477-492.

Possible benefit roles of SDF-1α



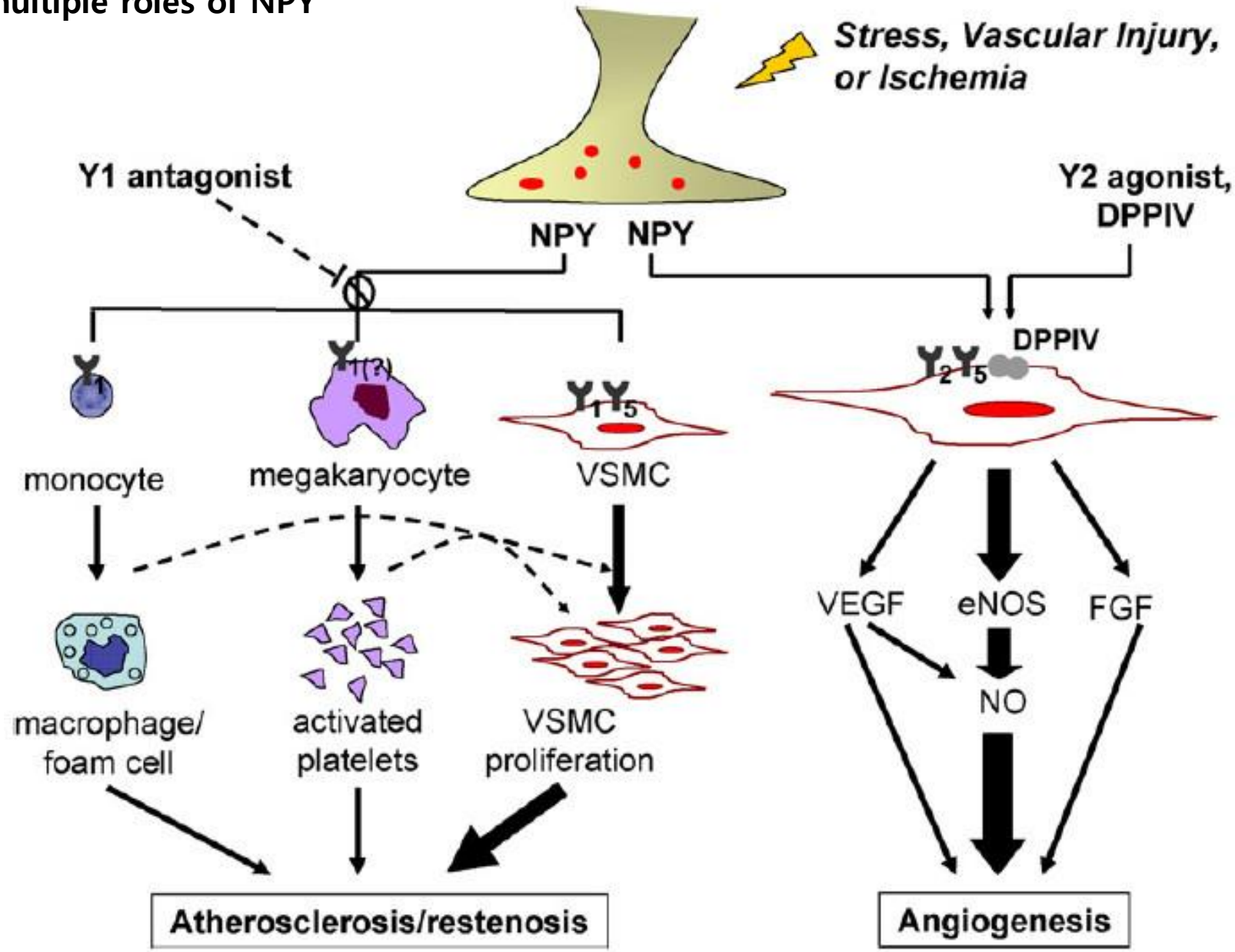
Fujita, H., et al. (2014). "DPP-4i with alogliptin on top of ARB ameliorates albuminuria via up-regulation of SDF-1α in T2D with incipient nephropathy." Endocr J 61(2): 159-166.

Neuropeptide Y (NPY)

- a ubiquitous hormone that has both central and peripheral effects that work to maintain homeostasis
- actions are mediated by its receptors, Y1–Y6
- Pro-atherogenic actions of NPY and stress
- NPY and angiogenesis

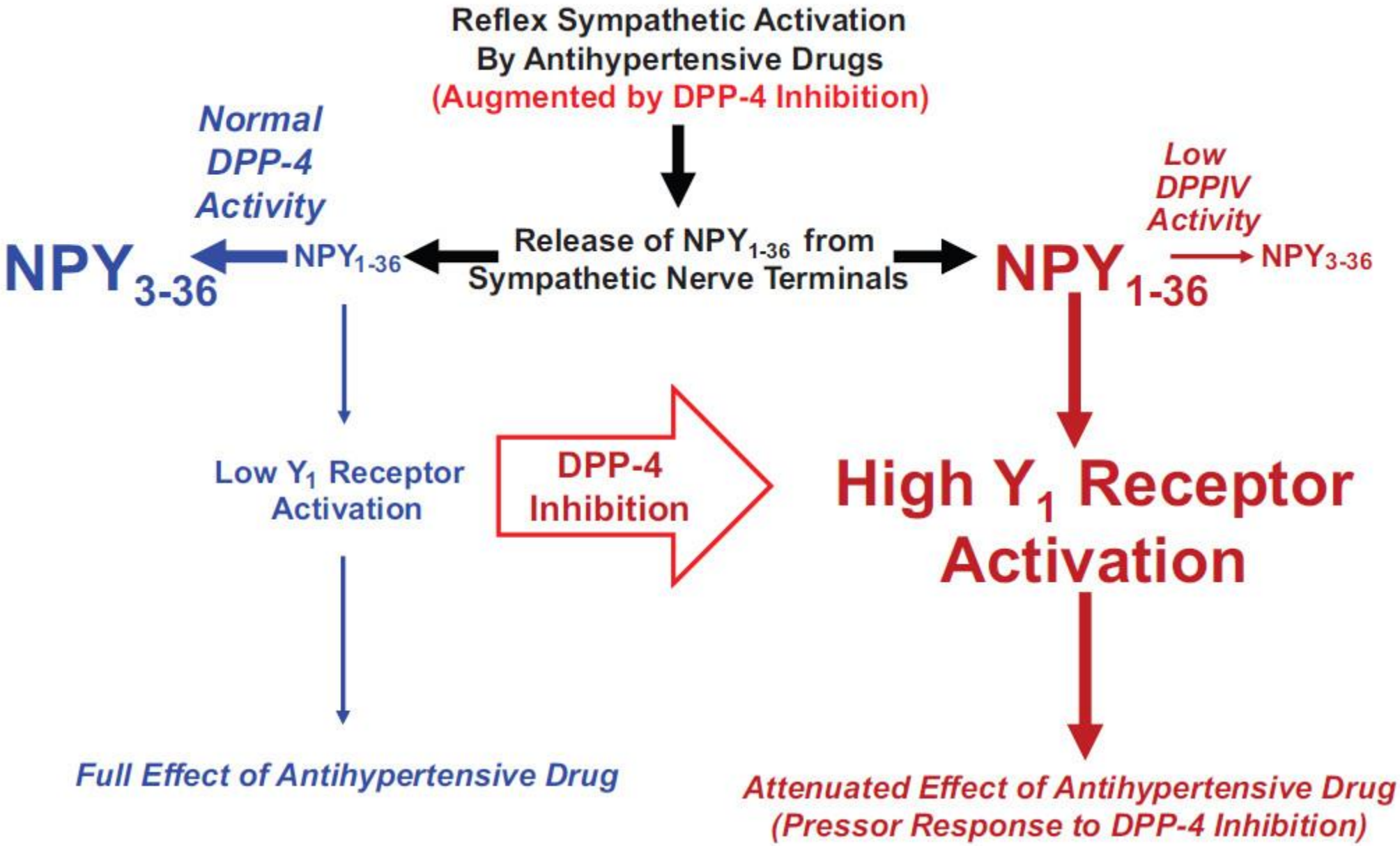
Kuo, L. E., et al. (2007). "Stress, NPY and vascular remodeling: Implications for stress-related diseases." Peptides 28(2): 435-440.

The multiple roles of NPY



DPP4-I might sustain NPY(1-36) capacity to increase the hypertensive response to AT-II…

Kuo, L. E., et al. (2007). "Stress, NPY and vascular remodeling: Implications for stress-related diseases." Peptides 28(2): 435-440.



Jackson, E. K. (2010). "DPP4 inhibition alters the hemodynamic response to ACE inhibition in humans with the metabolic syndrome." Hypertension 56(4): 581-583.

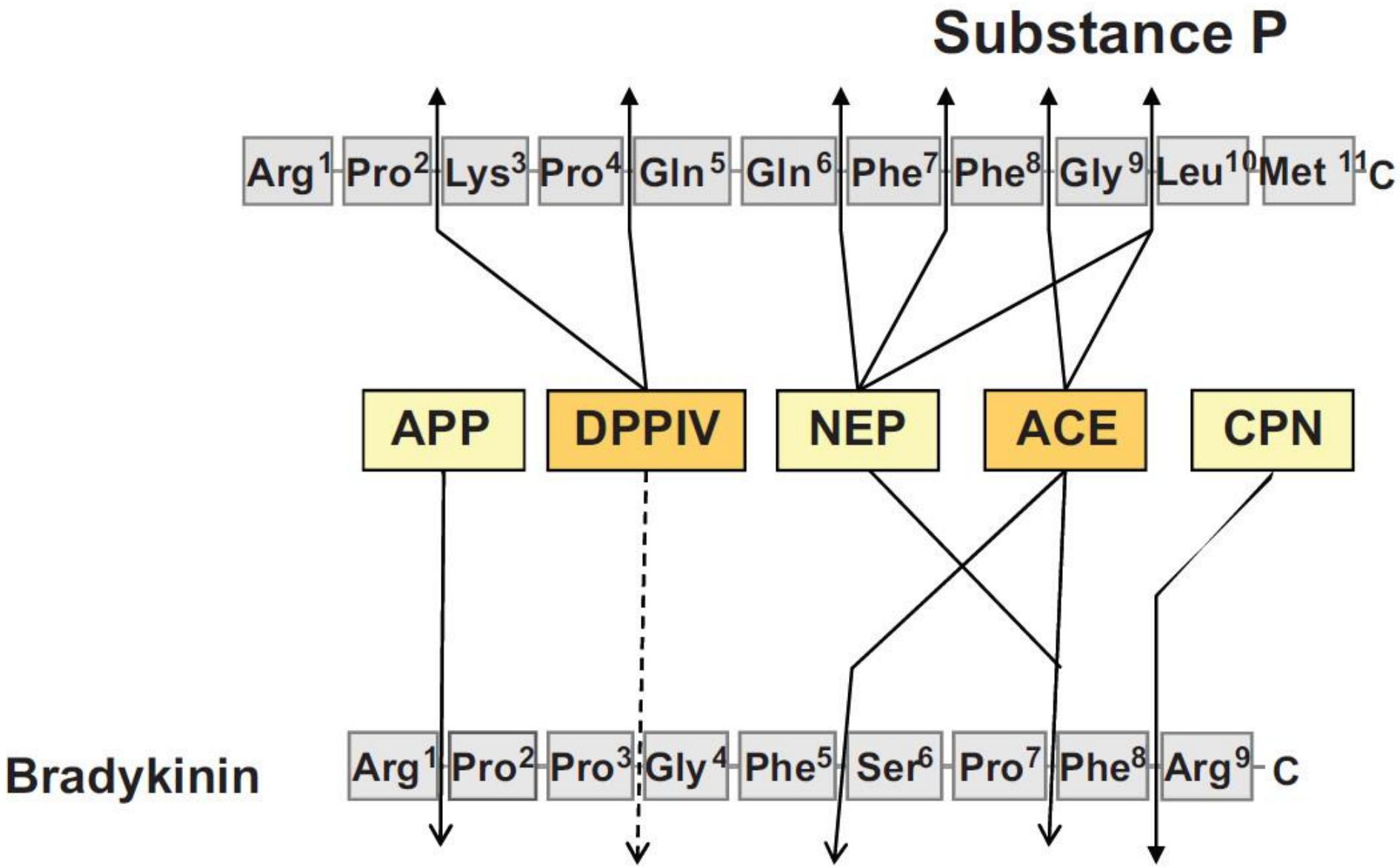
B-type natriuretic peptide (BMP)

- plays a critical role in regulating body fluid homeostasis, has vasodilator effects, and is a marker of HF
- i.v. BNP(3-32) infusion resulted in less natriuresis, diuresis, and vasodilation compared to i.v. infusion of BNP (1-32) in animal models
- may be another DPP-4 substrate that can play an important role in blood pressure regulation

Vanderheyden, M., et al. (2009). "Dipeptidyl-peptidase IV and B-type natriuretic peptide. From bench to bedside." Clin Chem Lab Med 47(3): 248-252.

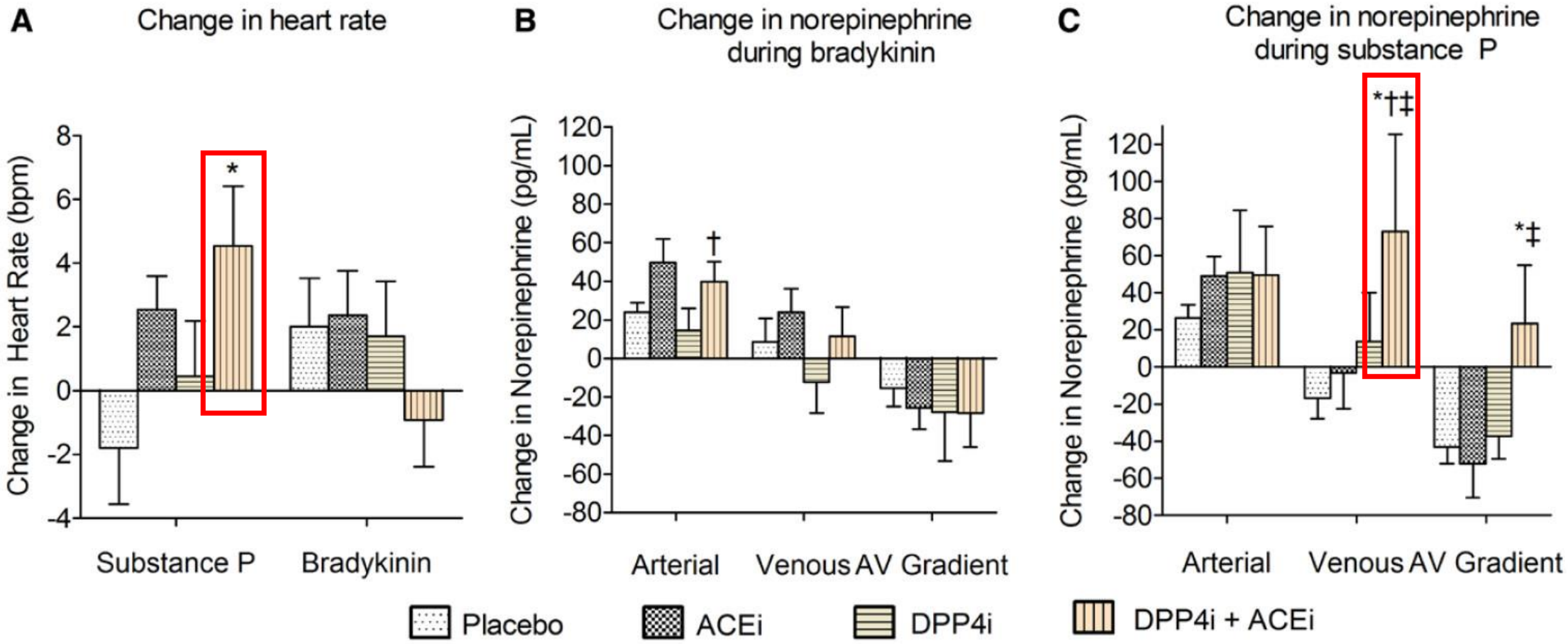
Substance P

- acts as a vasodilator
- can increase sympathetic outflow
- is able to increase sympathetic activity during combined inhibition of angiotensin-converting enzyme (ACE) and DPP4



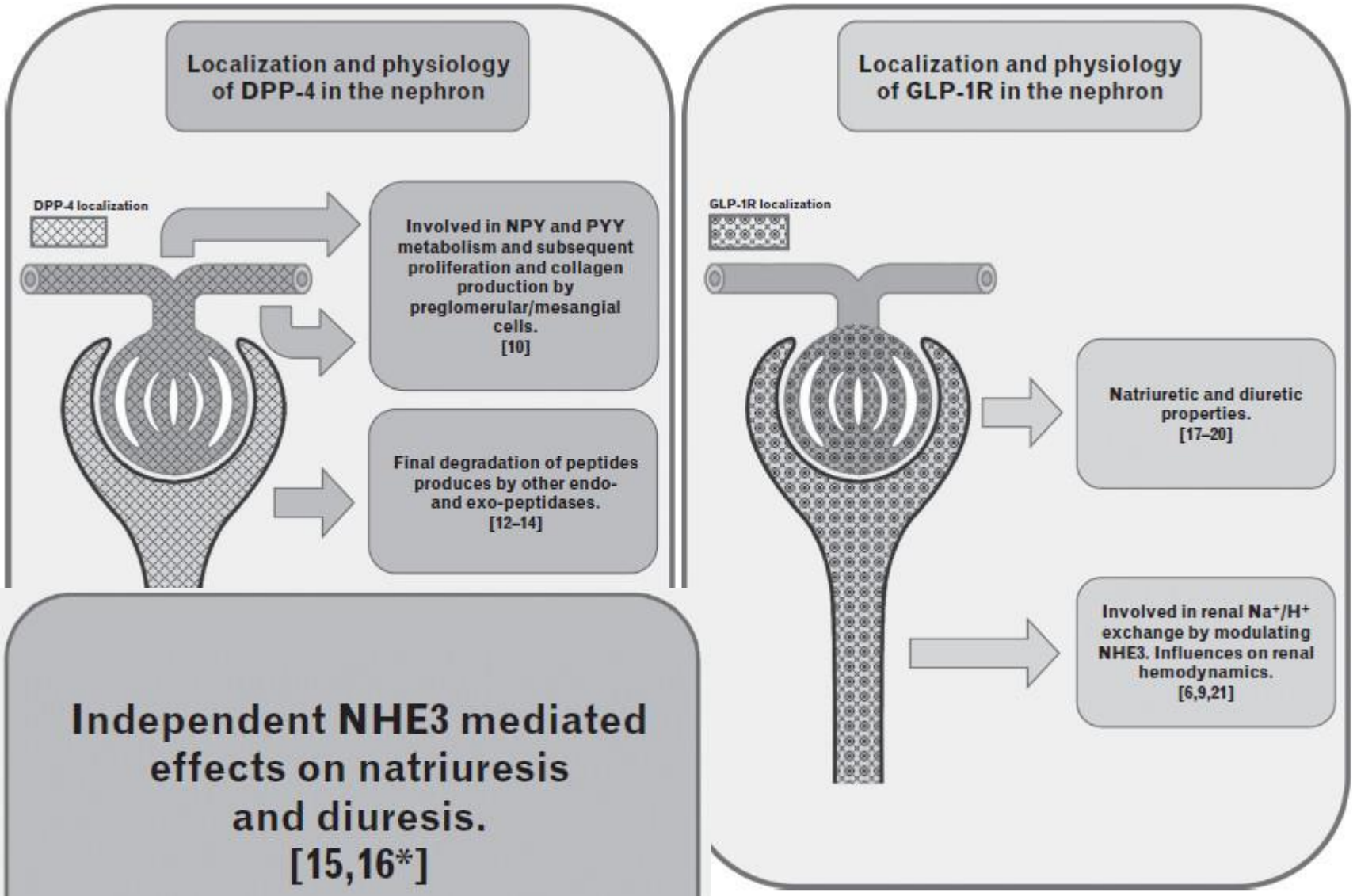
Brown, N. J., et al. (2009). "Dipeptidyl peptidase-IV inhibitor use associated with increased risk of ACE inhibitor-associated angioedema." Hypertension 54(3): 516-523.

Substance P increased HR and vascular release of norepinephrine during combined ACE and DPP4 inhibition



Devin, J. K., et al. (2014). "Substance P increases sympathetic activity during combined ACE and DPP4 inhibition." Hypertension 63(5): 951-957.

The effects of DPP4-I on Blood Pressure ?



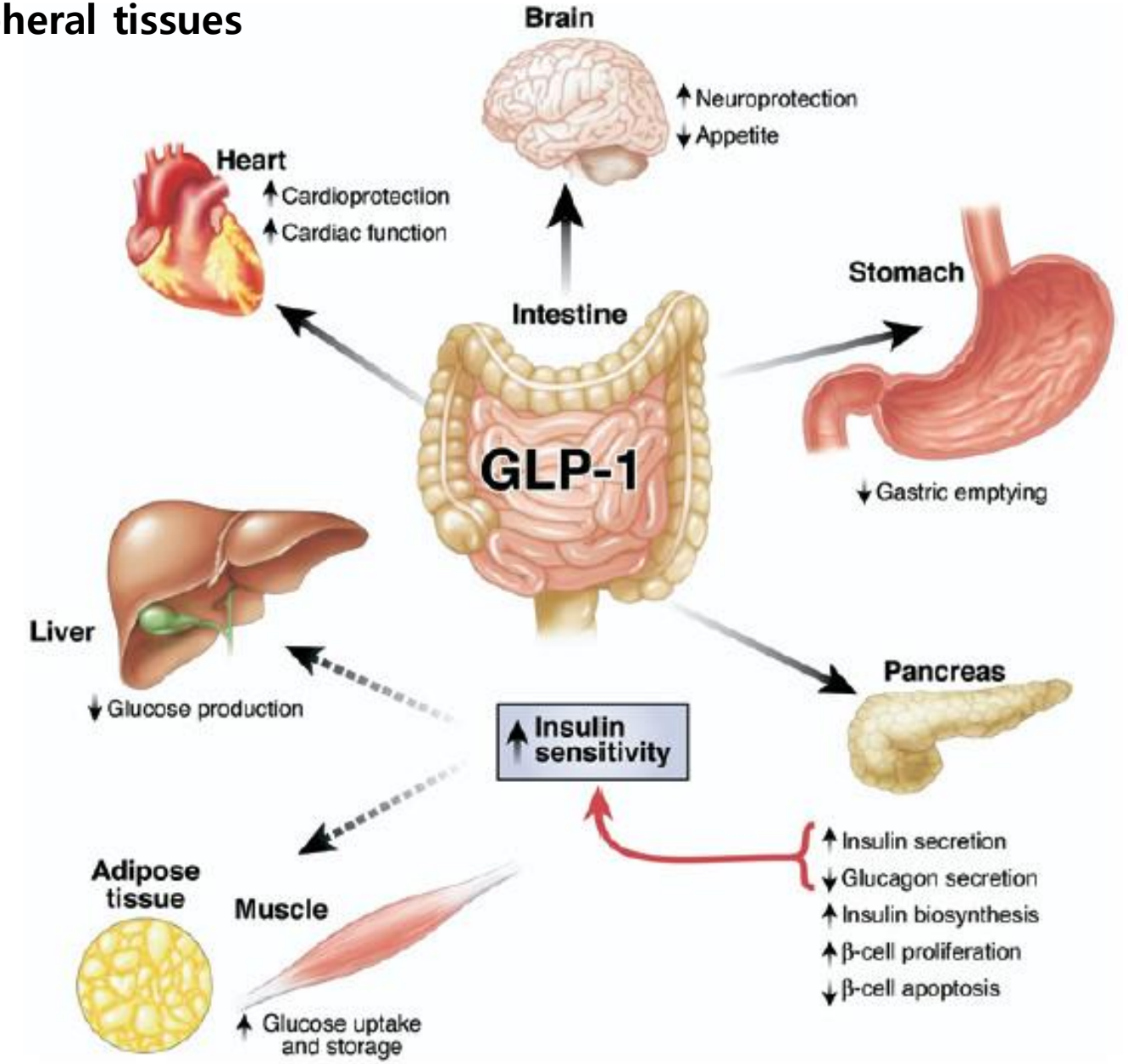
DPP-4 forms a complex with Na^+/H^+ exchanger 3 at the level of the brush membrane

DPP4 inhibition may interfere with Na^+resorption mechanism, significantly increasing natriuresis, thereby reducing blood pressure levels

Avogaro, A. and G. P. Fadini (2014). "The effects of dipeptidyl peptidase-4 inhibition on microvascular diabetes complications." Diabetes Care 37(10): 2884-2894.

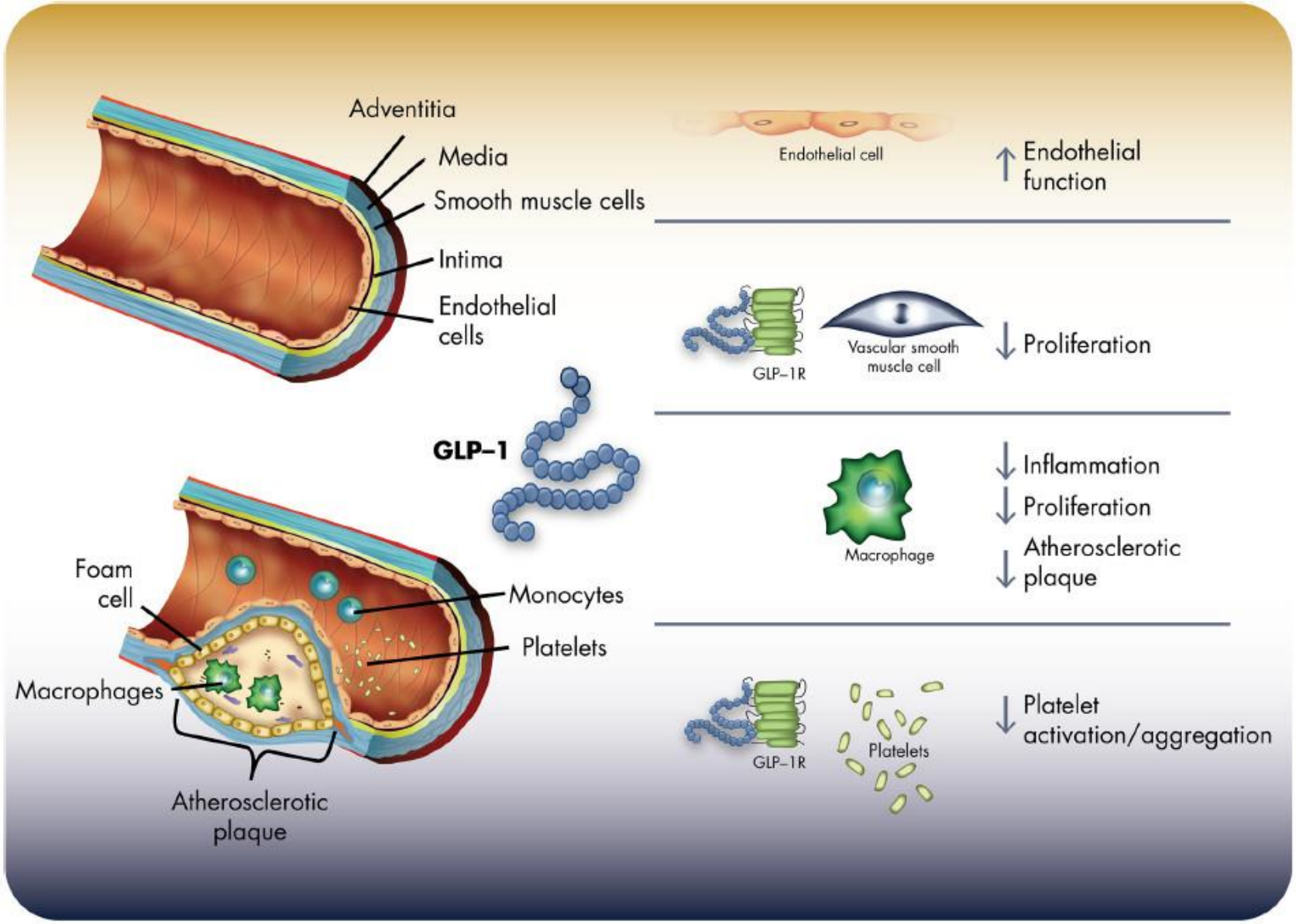
von Websky, K., et al. (2014). "Physiology and pathophysiology of incretins in the kidney." Curr Opin Nephrol Hypertens 23(1): 54-60.

GLP-1 actions in peripheral tissues

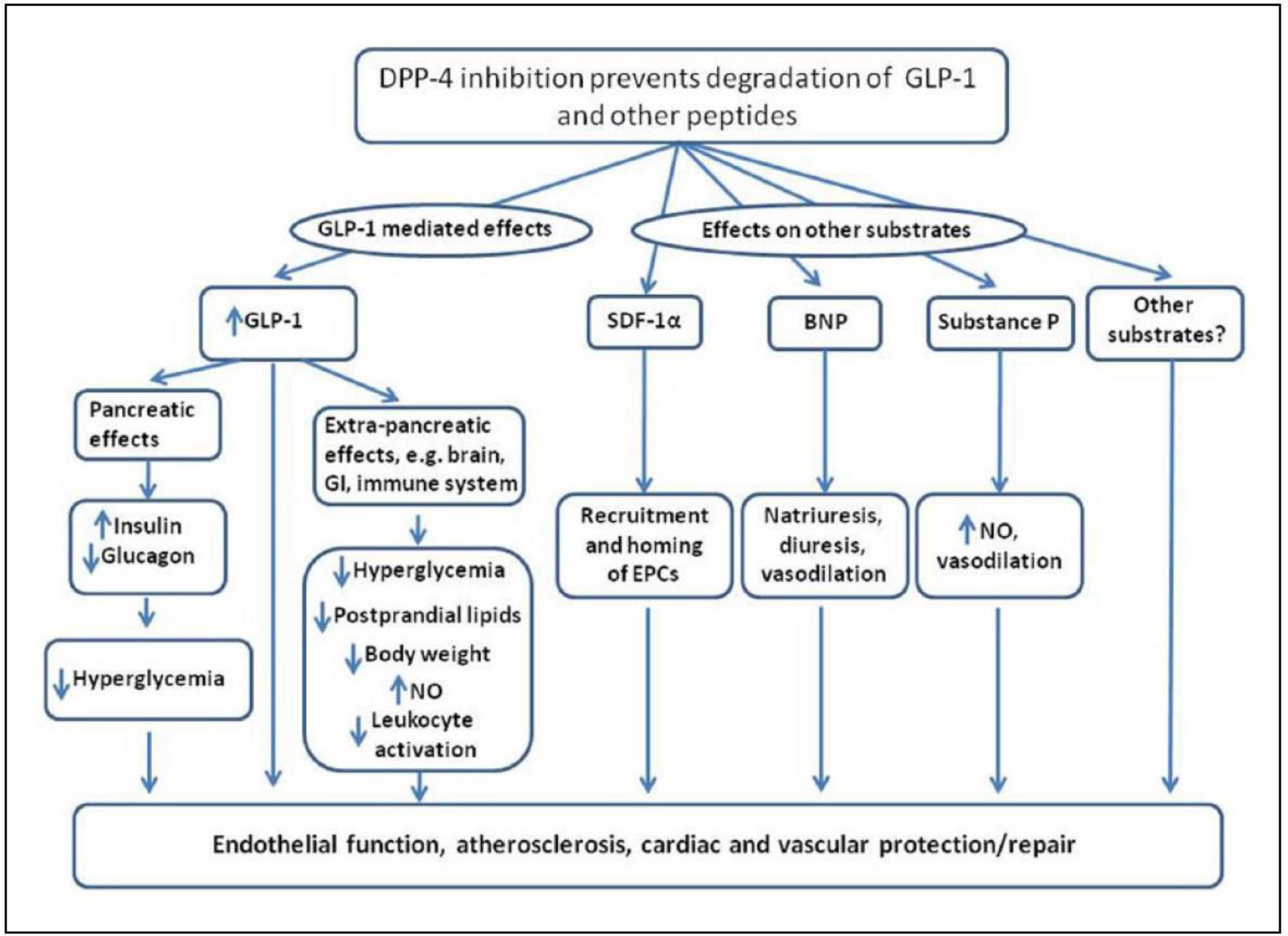


Baggio, L. L. and D. J. Drucker (2007). "Biology of incretins: GLP-1 and GIP." Gastroenterology 132(6): 2131-2157.

The vascular biology of GLP-1 action

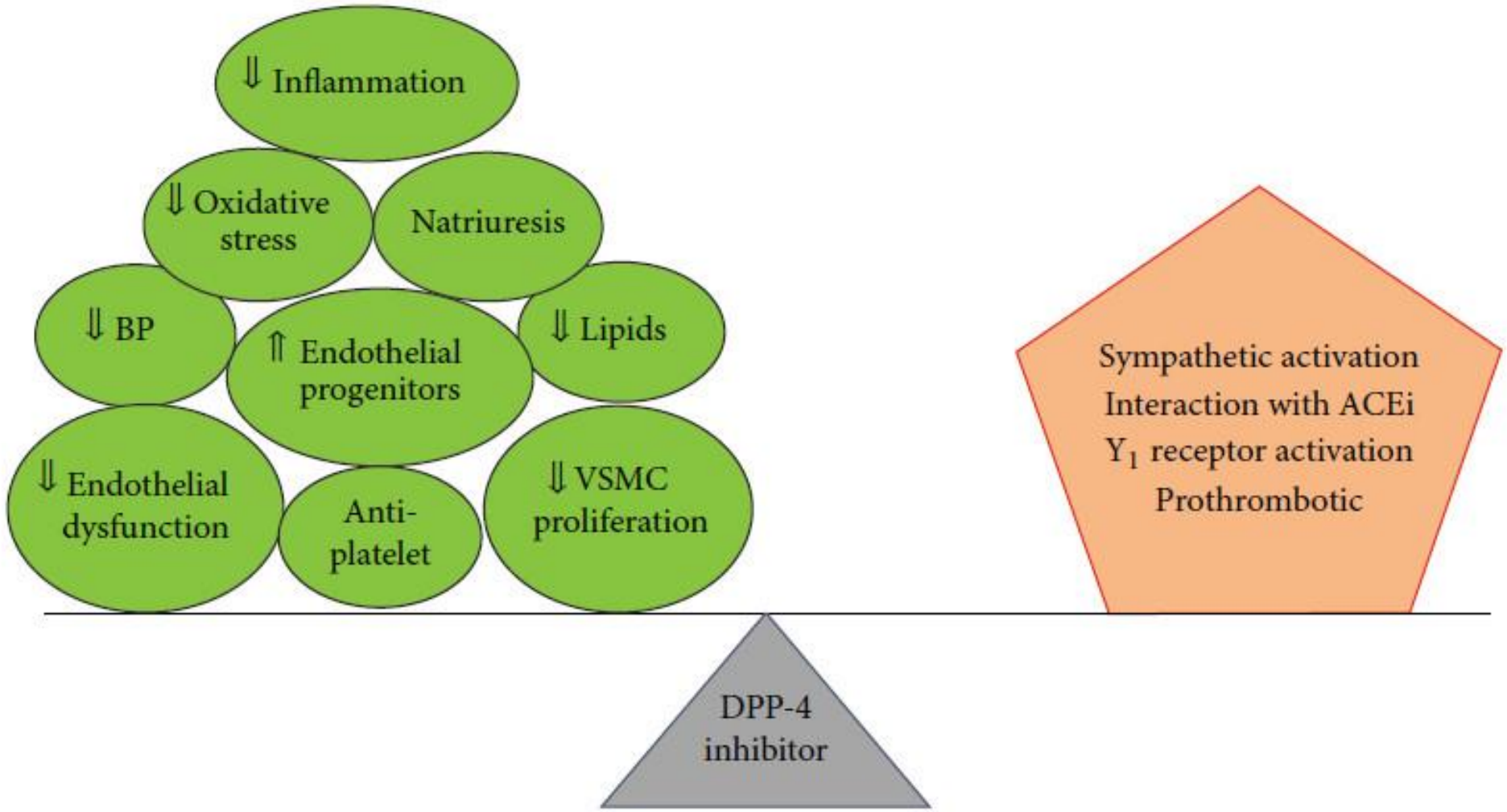


Pujadas, G. and D. J. Drucker (2016). "Vascular Biology of Glucagon Receptor Superfamily Peptides: Mechanistic and Clinical Relevance." Endocr Rev 37(6): 554-583.



Koska, J., et al. (2015). "Cardiovascular effects of dpp4 inhibitors in patients with type 2 diabetes." Diab Vasc Dis Res 12(3): 154-163.

Nonglycemic actions ofDPP-4 inhibitor in relation with pathophysiology of CV disease



Kim, N. H., et al. (2014). "The nonglycemic actions of dipeptidyl peptidase-4 inhibitors." Biomed Res Int 2014: 368703.

Summary of the effects of DPP4-I on Diabetic Nephropathy

Experimental	
Model	Effects
Sitagliptin in Zucker diabetic fatty rats	↓ Tubulointerstitial and glomerular lesions
	↓ Apoptosis
Linagliptin in STZ diabetic rats	↓ AGE and RAGE, ↓ Oxidative stress
	↓ Albuminuria, ↓ Glomerulosclerosis
Vildagliptin in STZ diabetic rats	↑ GFR, ↓ Albuminuria,
	↓ Glomerulosclerosis, ↓ Interstitial fibrosis

Clinical	
Drug and patients	End point
Sitagliptin in 36 T2D	↓ hs-CRP, ICAM-1, ↓ Albuminuria
Vildagliptin in 47 T2D	↓ Albuminuria
Linagliptin vs. placebo in 217 T2D	↓ Albuminuria
Saxagliptin vs. placebo in >16,000 T2D	↓ Microalbuminuria

Avogaro, A. and G. P. Fadini (2014). "The effects of dipeptidyl peptidase-4 inhibition on microvascular diabetes complications." Diabetes Care 37(10): 2884-2894.

Summary of the effects of DPP4-I on Diabetic Retinopathy

Experimental	
Model	Effects
Sitagliptin in Zucker diabetic fatty rats	↓ Nitrosative stress, inflammation, apoptosis
	↓ Blood-retinal barrier changes, ↑ EPCs
Sitagliptin in STZ diabetic rats	↓ Permeability, ↓ Blood-retinal barrier changes
	↓ Inflammation, apoptosis
Vildagliptin in OLETF T2D rats	↓ VEGF, ICAM-1, PAI-1, and PEGF

Clinical	
Drug and patients	End point
Saxagliptin vs. placebo in 50 T2D without retinopathy	↓ Blood flow, ↑ Vasodilation

Avogaro, A. and G. P. Fadini (2014). "The effects of dipeptidyl peptidase-4 inhibition on microvascular diabetes complications." Diabetes Care 37(10): 2884-2894.

Summary of the effects of DPP4-I on Diabetic Neuropathy

Experimental	
Model	Effects
Vildagliptin in STZ diabetic rats	↓ Nerve fiber loss
PKF275-055 in STZ diabetic rats	↑ Na^+/K^+-ATPase activity,
	↑ Nerve conduction velocity
	↑ Mechanical and thermal sensitivity
Sitagliptin in nicotinamide/STZ T2D rats	↑ Strength and paw function, ↓ Nerve cell loss

Clinical
No data available so far

Avogaro, A. and G. P. Fadini (2014). "The effects of dipeptidyl peptidase-4 inhibition on microvascular diabetes complications." Diabetes Care 37(10): 2884-2894.

Effects of exenatide on measures of diabetic neuropathy in subjects with type 2 diabetes: results from an 18-month proof-of-concept open-label randomized study

- 46 T2D with mild-moderate DPN
- randomized to a twice daily exenatide group (n = 22) or daily insulin glargine (n = 24)
- After 18 months of follow-up, **no significant differences were observed** in the prevalence of confirmed clinical neuropathy, intra-epidermal nerve fiber density, and nerve conductions studies.
- There were **no significant changes** in the measures of CAN

Jaiswal, M., et al. (2015). "Effects of exenatide on measures of diabetic neuropathy in subjects with T2D: results from an 18-month proof-of-concept open-label randomized study." J Diabetes Complications 29(8): 1287-1294.

Summary of the effects of DPP4-I on Foot ulcers

Experimental	
Model	Effects
Linagliptin in ob/ob T2D mice	↑ Epithelialization, ↑ Myofibroblasts
	↓ Inflammation

Clinical	
Drug and patients	End point
Vildagliptin vs. placebo in 106 diabetic patients with ulcers	↑ Granulation tissue, ↑ Capillary density
	↑ HIF-1a and VEGF, ↓ Nitrotyrosines
	↓ Proteasome activity

Avogaro, A. and G. P. Fadini (2014). "The effects of dipeptidyl peptidase-4 inhibition on microvascular diabetes complications." Diabetes Care 37(10): 2884-2894.

Clinical trials that investigated the effects of incretin-based therapies on the cardiovascular outcome in patients with T2D

Trial	Drug/Doses	Patients	Primary Composite Outcome	Result (Risk of Cardiovascular Events)
SAVOR-TIMI53 [57] (2.1 years)	Saxagliptin 2.5 mg or 5 mg/day (on the basis of estimated glomerular filtration rate (eGFR) at baseline)	T2D patients who had a history of, or were at risk for, cardiovascular events (n = 16,492)	Cardiovascular death, myocardial infarction, or ischemic stroke	⟷ (no change)
EXAMINE [67] (1.5 years)	Alogliptin 6.25 mg or 12.5 mg or 25 mg (same as above)	T2D patients with either an acute myocardial infarction or unstable angina requiring hospitalization within the previous 15 to 90 days (n = 5380)	Cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke	⟷
TECOS [68] (3.0 years)	Sitagliptin 50 mg or 100 mg/day (same as above)	T2D patients who had a history of major coronary artery disease, ischemic cerebrovascular disease, or atherosclerotic peripheral arterial disease (n = 14,671)	Cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina	⟷
ELIXA [69] (2.1 years)	Lixisenatide 20 μg/day	T2D patients who had had a myocardial infarction or who had been hospitalized for unstable angina within the previous 180 days (n = 6068)	Cardiovascular death, myocardial infarction, stroke, or hospitalization for unstable angina	⟷
LEADER [62] (3.8 years)	Liraglutide 1.8 mg/day	T2D patients ⩾50 years of age with at least one cardiovascular coexisting condition or ⩾60 years of age with at least one cardiovascular risk factor (n = 9340)	Cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke	↓ (decrease)

Kawanami, D., et al. (2016). "Incretin-Based Therapies for Diabetic Complications: Basic Mechanisms and Clinical Evidence." Int J Mol Sci 17(8).

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

Outcome	Liraglutide (N = 4668)	Placebo (N = 4672)	Hazard Ratio (95% CI)	P Value
	no. of patients (%)	*no. of patients (%)*		
Microvascular event	355 (7.6)	416 (8.9)	0.84 (0.73–0.97)	0.02
Retinopathy	106 (2.3)	92 (2.0)	1.15 (0.87–1.52)	0.33
Nephropathy	268 (5.7)	337 (7.2)	0.78 (0.67–0.92)	0.003

Marso, S. P., et al. (2016). "Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes." N Engl J Med.

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

Outcome	Semaglutide (N=1648)	Placebo (N=1649)	Hazard Ratio (95% CI)*	P Value
	no. (%)	*no. (%)*		
Primary composite outcome†	108 (6.6)	146 (8.9)	0.74 (0.58–0.95)	<0.001 for noninferiority; 0.02 for superiority
Retinopathy complications§	50 (3.0)	29 (1.8)	1.76 (1.11–2.78)	0.02
New or worsening nephropathy¶	62 (3.8)	100 (6.1)	0.64 (0.46–0.88)	0.005

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transient worsening of diabetic retinopathy with glucose control ?

Marso, S. P., et al. (2016). "Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes." N Engl J Med 375(19): 1834-1844.

Brief report

The impact of improved glycaemic control with GLP-1 receptor agonist therapy on diabetic retinopathy

ABSTRACT

Rapid improvement in glycaemic control with GLP-1 receptor agonist (RA) therapy has been reported to be associated with significant progression of diabetic retinopathy. This deterioration is transient, and continuing GLP-1 RA treatment is associated with reversal of this phenomenon. Pre-existent maculopathy, higher grade of retinopathy and longer duration of diabetes may be risk factors for persistent deterioration.

Varadhan, L., et al. (2014). "The impact of improved glycaemic control with GLP-1RA therapy on diabetic retinopathy." Diabetes Res Clin Pract 103(3): e37-39.

Recent Reports

Effect of Linagliptin on Vascular Function: A Randomized, Placebo-controlled Study

Patients and Intervention: Forty participants with type 2 diabetes were included in a 12-wk treatment of either linagliptin 5mg/d or placebo.

Main Outcome Measures: Micro- and macrovascular functions were assessed using laser Doppler coupled with iontophoresis and with brachial flow-mediated dilation, respectively. Mitochondrial function was assessed by phosphorus-31 metabolites changes in the calf muscle measured by magnetic resonance spectroscopy. Circulating endothelial progenitor cells, as well as inflammatory cytokines, growth factors, and biomarkers of endothelial function were also quantified.

Results: Linagliptin was associated with an increase in axon reflex-dependent vasodilation, a marker of neurovascular function ($P = .05$). A trend indicating increased endothelium-dependent microvascular reactivity was observed ($P = .07$). These were associated with decreases in concentrations of IFNγ ($P < .05$), IL-6 ($P = .03$), IL-12 ($P < .03$), and MIP-1 ($P < .04$) following linagliptin treatment when compared with placebo.

Conclusions: This study demonstrates that linagliptin tends to improve endothelial and neurovascular microvascular function and is associated with decreased markers of inflammation in patients with type 2 diabetes. There was no significant effect of linagliptin on mitochondrial function, macrovascular function, or endothelial progenitor cells. (***J Clin Endocrinol Metab*** **101: 4205–4213, 2016)**

Recent Reports

PROTECTIVE EFFECTS OF DIPEPTIDYL PEPTIDASE-4 INHIBITORS ON PROGRESSION OF DIABETIC RETINOPATHY IN PATIENTS WITH TYPE 2 DIABETES

Purpose: To investigate the effects of dipeptidyl peptidase-4 (DPP4) inhibitors on the progression of diabetic retinopathy (DR) in patients with Type 2 diabetes based on the DR severity scale.

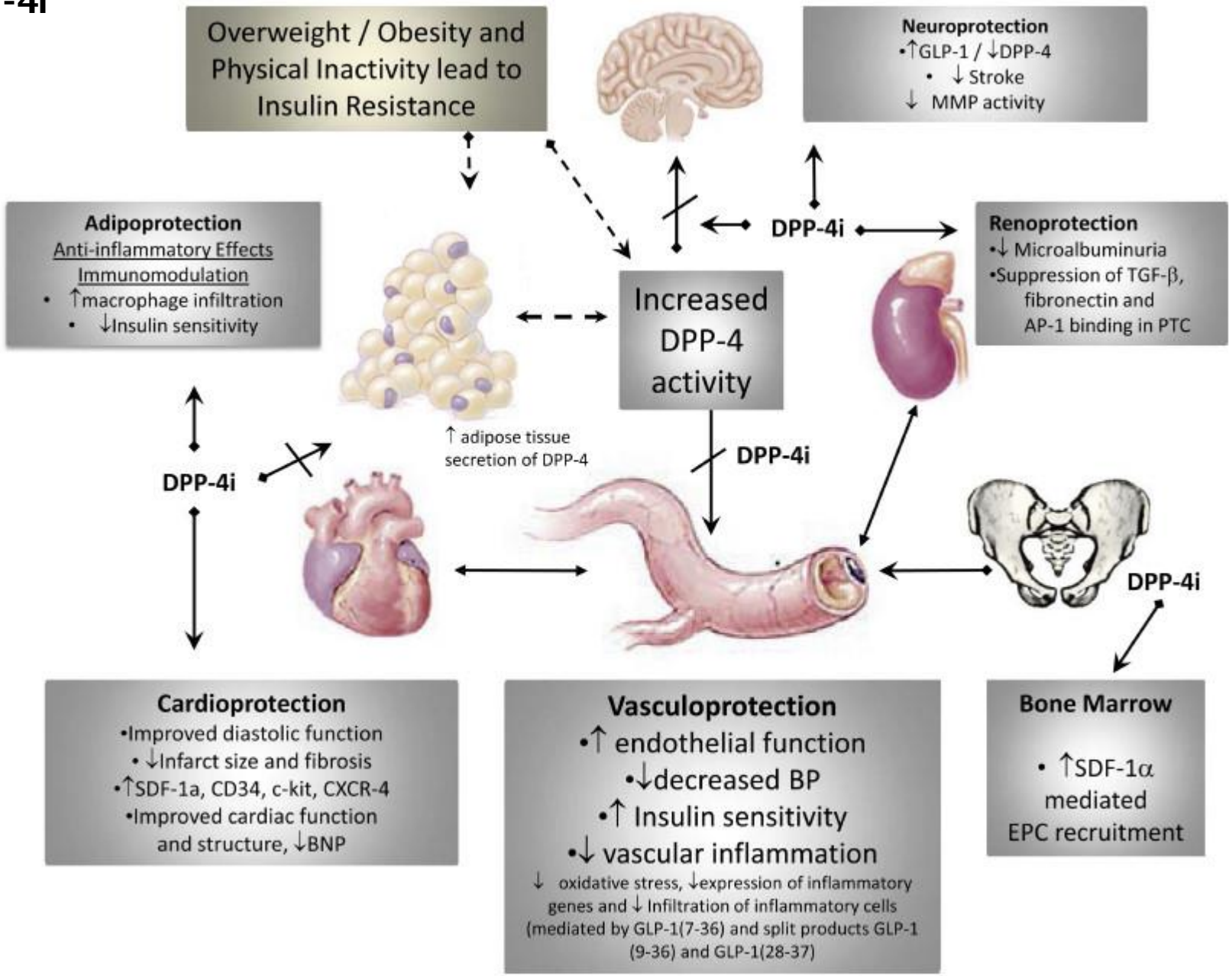
Methods: The medical records of 82 patients with Type 2 diabetes enrolled from 2005 to 2015 were retrospectively reviewed. Fundus photographs were graded using Early Treatment Diabetic Retinopathy Study methods. The associations between baseline risk factors and progression of DR were investigated.

Results: Seven of 28 patients treated with DPP4 inhibitors and 26 of 54 treated with other hypoglycemic agents showed progression of retinopathy, defined as one or more steps on the Early Treatment Diabetic Retinopathy Study scale ($P = 0.043$). Only treatment with DPP4 inhibitors significantly reduced the progression of DR in patients after propensity score matching ($P = 0.009$). Treatment with DPP4 inhibitors was associated with a lower risk of DR progression ($P = 0.011$).

Conclusion: Treatment with DPP4 inhibitors was the independent protective factor against the progression of DR, aside from improving glycemic control. This is the first study to show the benefits of DPP4 inhibitors in reducing DR progression, and provides encouraging preliminary data for further evaluation of DPP4 inhibitors in the progression of DR in a randomized, double-blind, placebo-controlled trial.

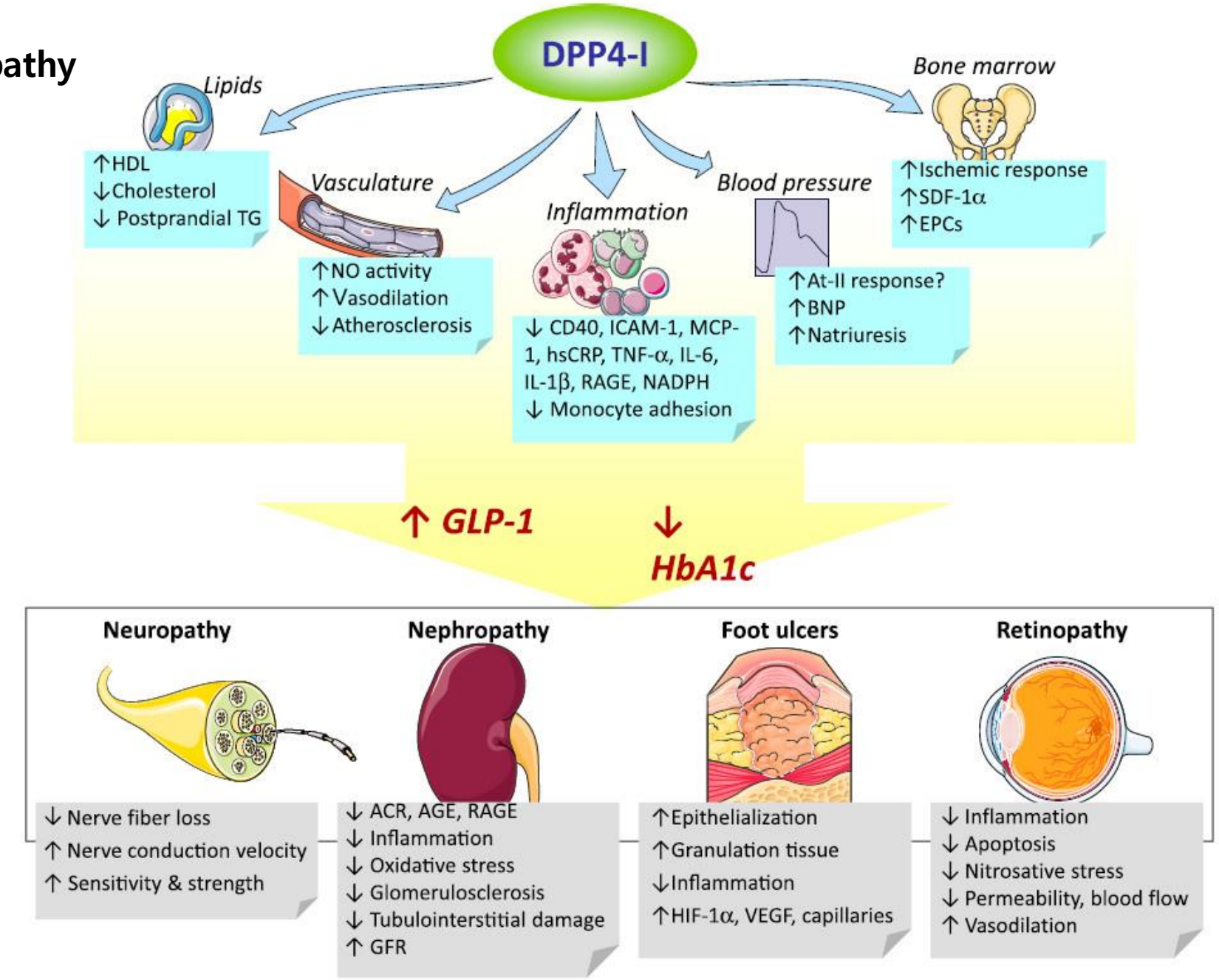
RETINA 36:2357–2363, 2016

Pleiotropic effects of DPP-4i



Aroor, A. R., et al. (2014). "Pleiotropic effects of the dipeptidylpeptidase-4 inhibitors on the cardiovascular system." Am J Physiol Heart Circ Physiol 307(4): H477-492.

the roles of DPP4i
on diabetic microangiopathy



Avogaro, A. and G. P. Fadini (2014). "The effects of dipeptidyl peptidase-4 inhibition on microvascular diabetes complications." Diabetes Care 37(10): 2884-2894.

경청해 주셔서 감사합니다.

해운대 청사포