Joint meeting of Coronary Revascularization (JCR2017) in Busan, Korea

Increased Dipeptidyl Peptidase-4 Accelerates Diet-Related Vascular Aging and Atherosclerosis in ApoE-Deficient Mice under Chronic Stress

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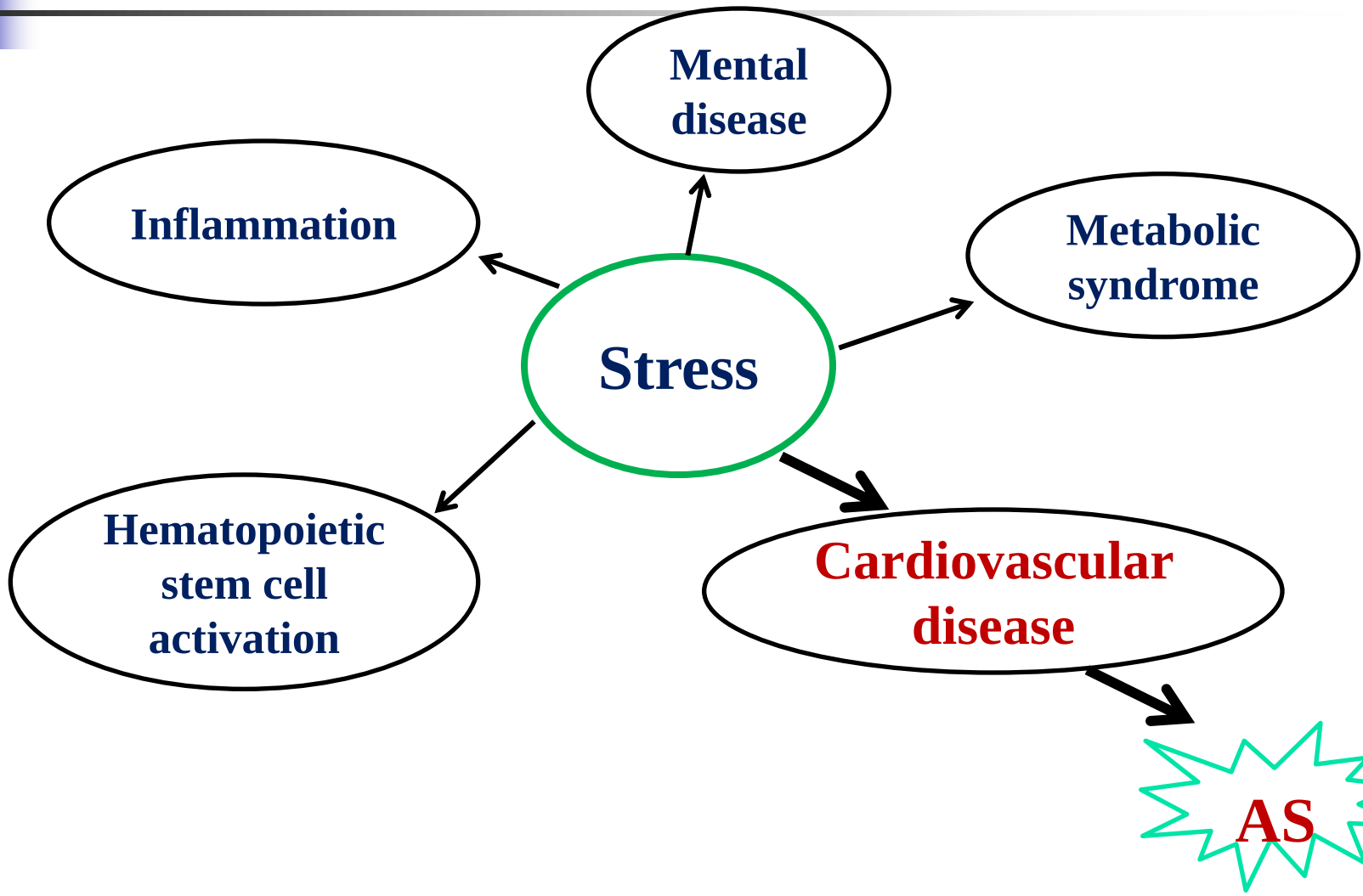
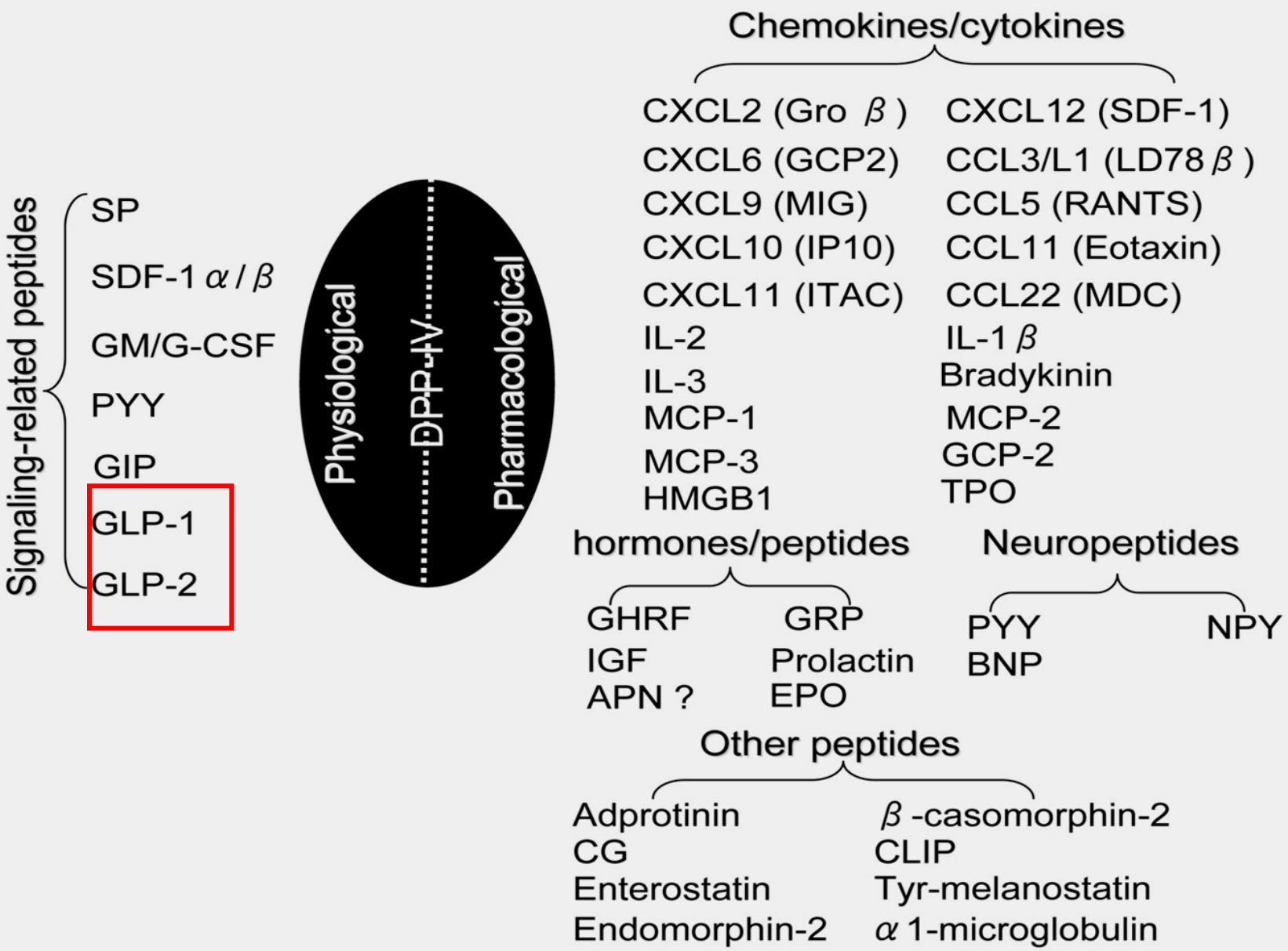
Stress and Disease



DPP-4 and its inhibitors

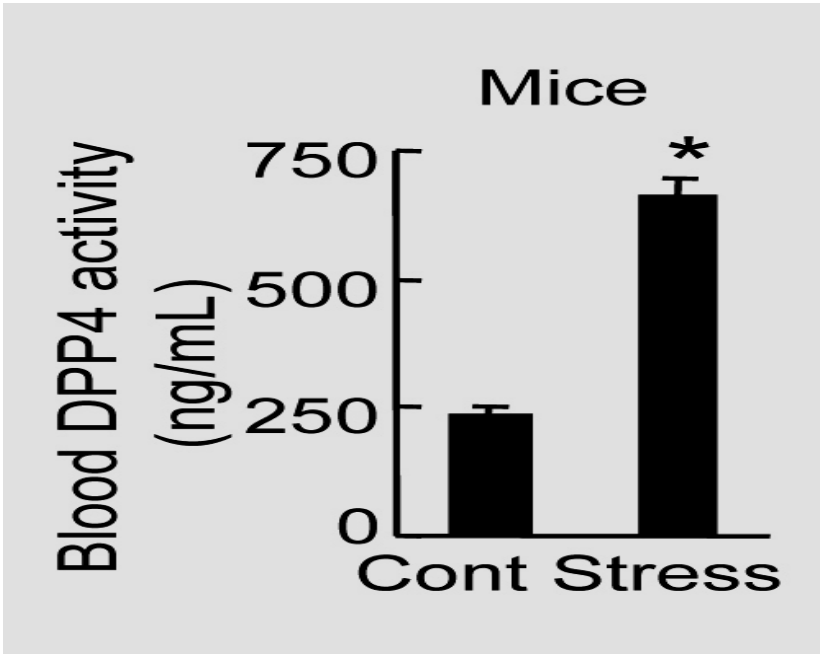
- DPP-4 is a complex enzyme that acts as a membrane-anchored cell surface exopeptidase that truncates a large number of peptides (e.g., hormones, cytokines, and growth factors). DPP-4 has gained considerable interest as a therapeutic target, and a variety of DPP-4 inhibitors that prolong the insulinotropic effects of glucagon-like peptide-1 (GLP-1) are widely used in clinical settings as antidiabetic drugs.

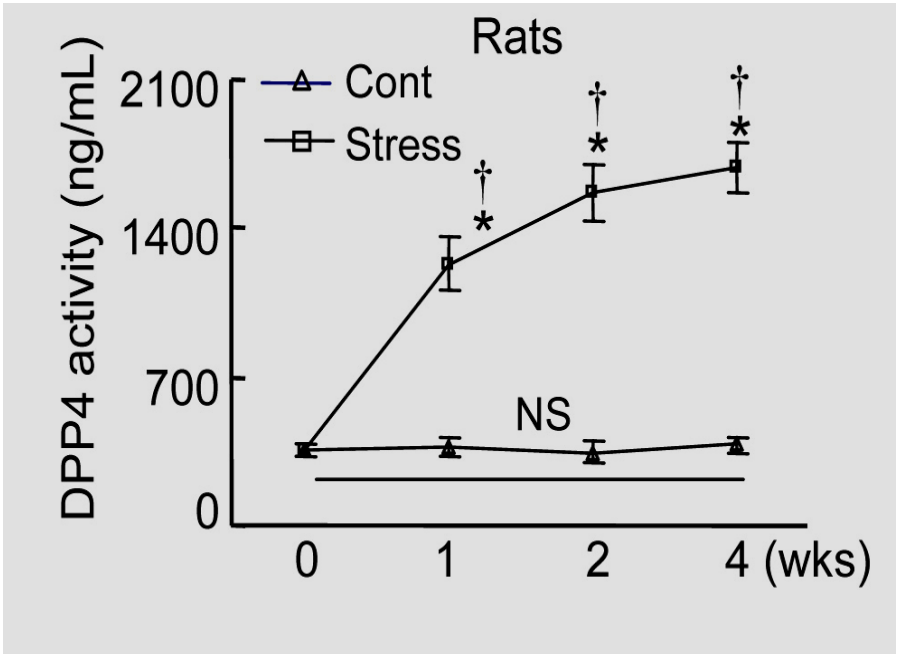
DPP-4 and it's substrates



Lei and Cheng. Circ J 2017;81:770-6

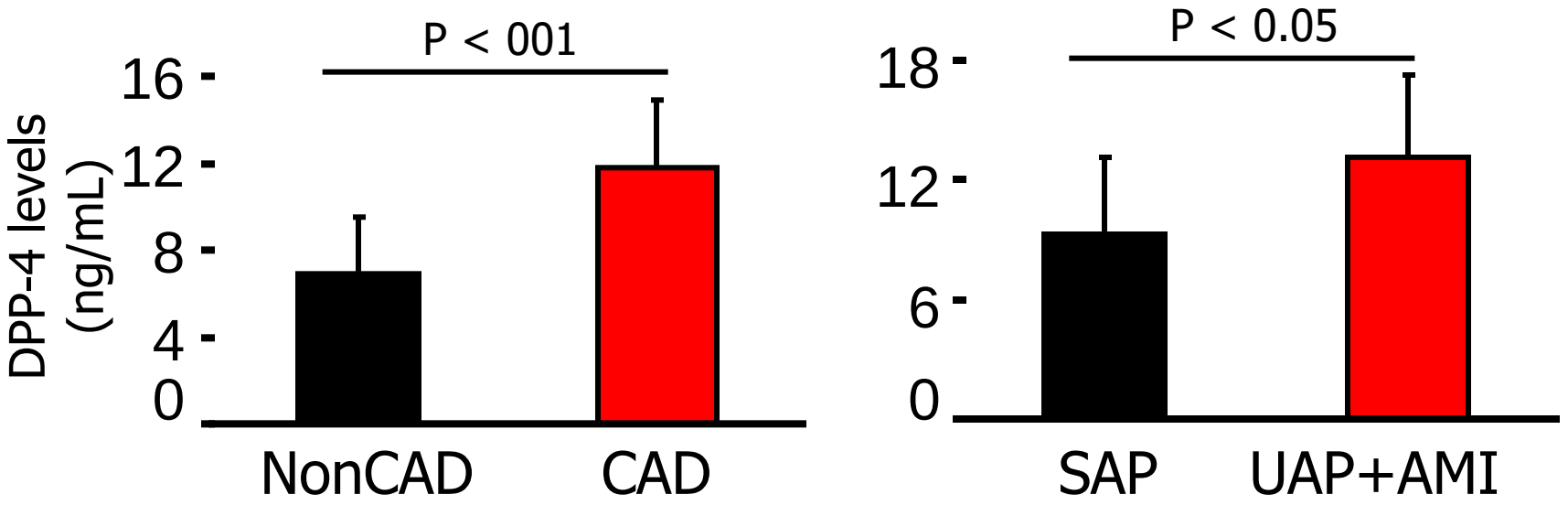
Chronic psychological stress increased blood DPP-4 levels in a time dependent manner





Zhu, Lei and Cheng. JAHA 2017;6:e006439

CAD and ACS patients had increased levels of plasma DPP-4



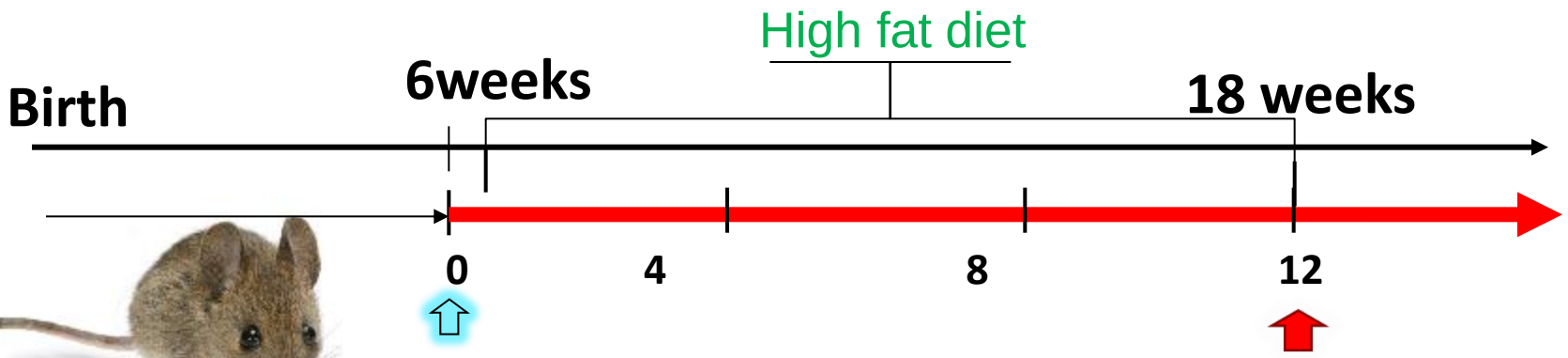
Zhu and Lei. PLOS ONE 2017;16:e160372

Objective

- The aim of our study was to investigate the effects of DPP-4 inhibitor on vascular aging and atherosclerotic plaque growth and the related mechanisms with special focusing on **APN-PPAR α** signaling activation in ApoE-/- mice under chronic psychological stress.

APN: adiopoectin; **PPAR-α:** Peroxisome Proliferator-Activated Receptor;

Protocol (1)



Group 1: HFD (Control)
Group 2: HFD + Stress (HD-S)

Sampling

¶ Blood
¶ Aortas

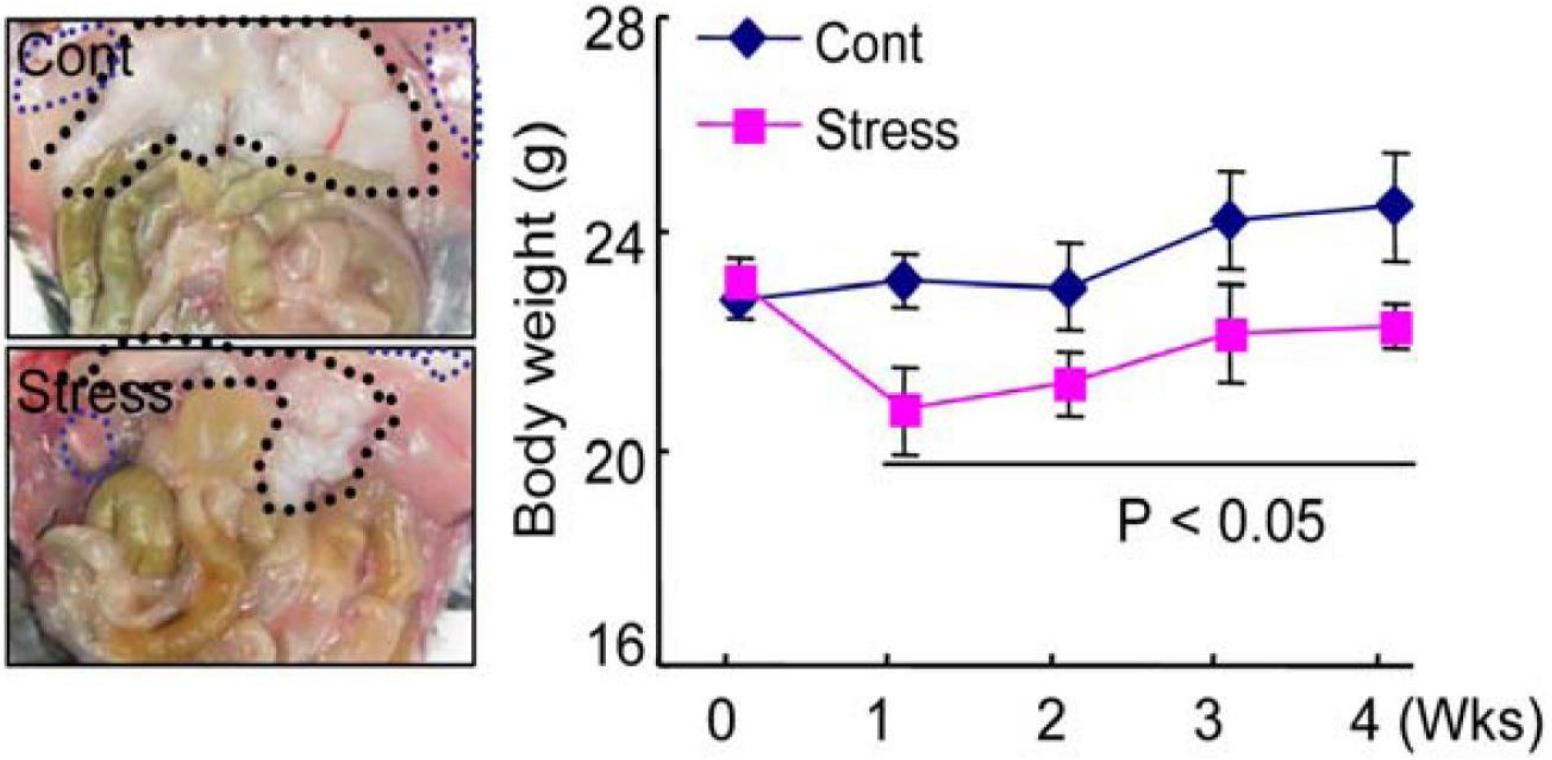
6-week-old male ApoE$^{-/-}$ mice
(KOR/StmSlc background)

Effects of stress on plasma lipid profile and DPP4, leptin, GLP-1, and APN levels

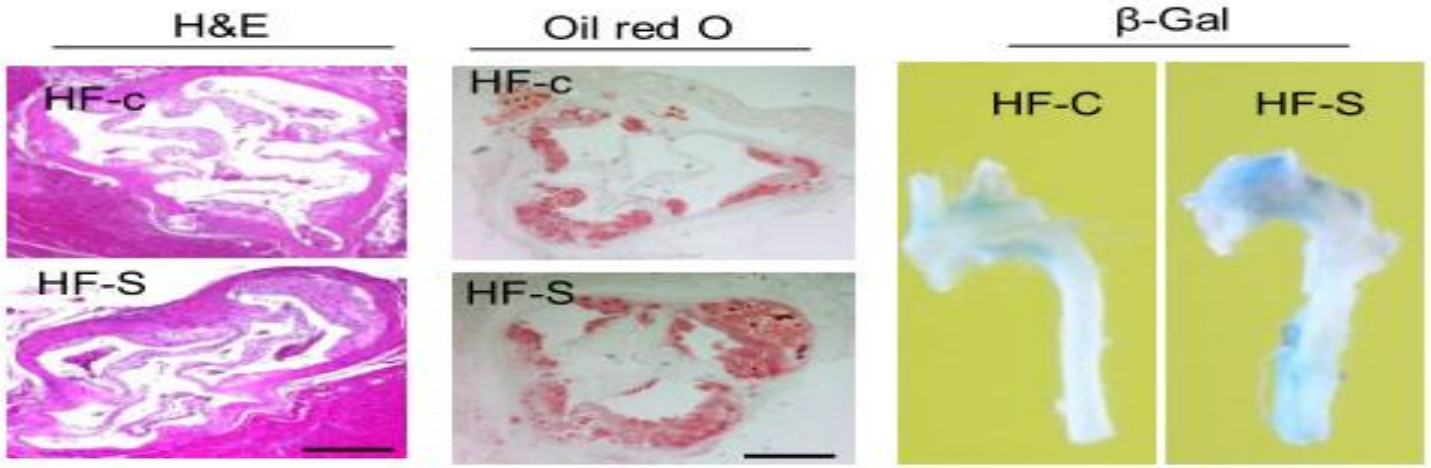
Parameter	Non-stress	Stress
T-ch (mg/dL)	575.2 ± 14.3	562.5 ± 15.8
HDL-C (mg/dL)	23.1 ± 2.2	23.0 ± 2.3
Triglyceride (mg/dL)	135.1 ± 4.8	73.5 ± 4.0**
NEFA (μEQ/L)	194 ± 12	106 ± 12**
BUN (mg/dL)	3.9 ± 0.3	4.2 ± 0.3
Creatinine (mg/dL)	0.5 ± 0.0	0.8 ± 0.0
Glucose (mg/dL)	39.3 ± 2.6	36.1 ± 2.9
DPP4 (ng/ L)	**305 ± 28**	**823 ± 34****
Leptin (pg/ml)	**402 ± 45**	**177 ± 25****
GLP-1 (pM)	**15.9 ± 1.1**	**9.2 ± 0.8****
APN (ng/mL)	**7577 ± 382**	**5619 ± 598***

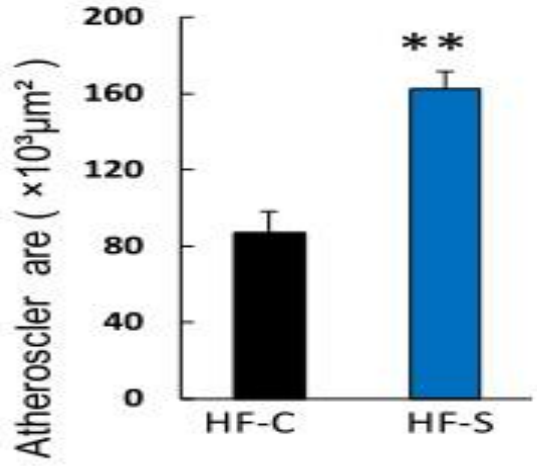
T-ch: total cholesterol; HDL-C: high-density lipoprotein cholesterol; NEFA: nonesterified fatty acid; BUN: blood urine nitrogen; DPP4: dipeptidyl peptidase-4; GLP-1, glucagon like protein-1; APN, adiponectin. Data are mean ± SEM. * $P< 0.05$, ** $P< 0.01$ by ANOVA and Tukey's *post hoc* tests.

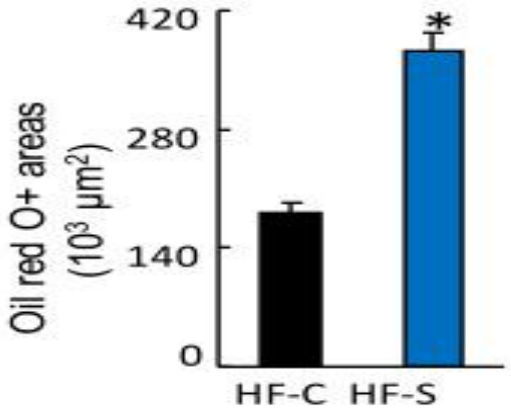
Stress reduced subcutaneous/inguinal adipose and body weight (BW)

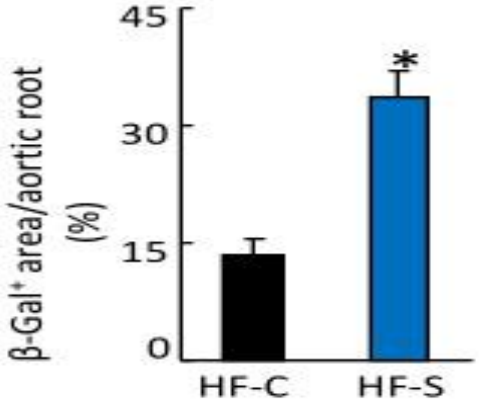


Stress accelerated vascular senescence and plaque lipid accumulation and growth

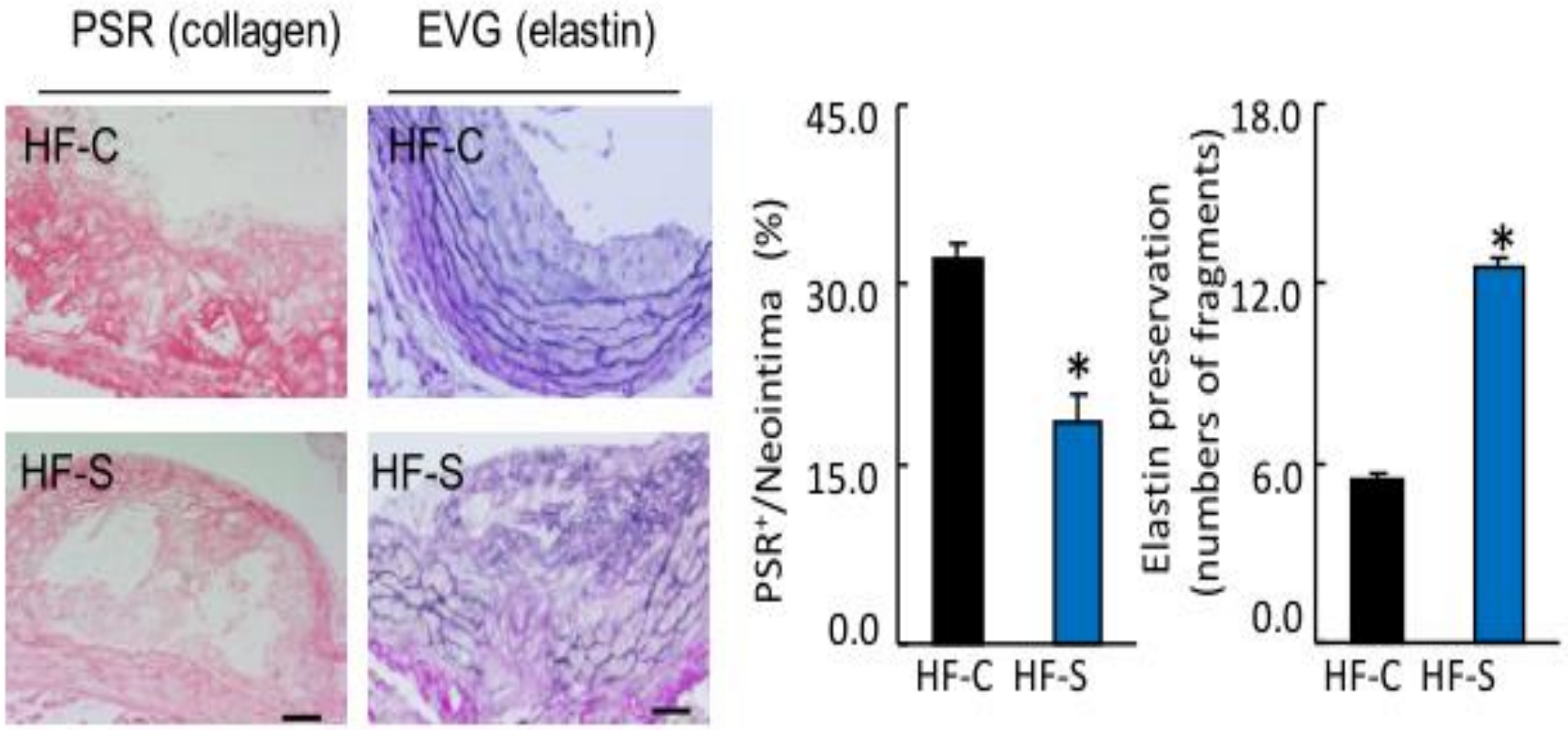




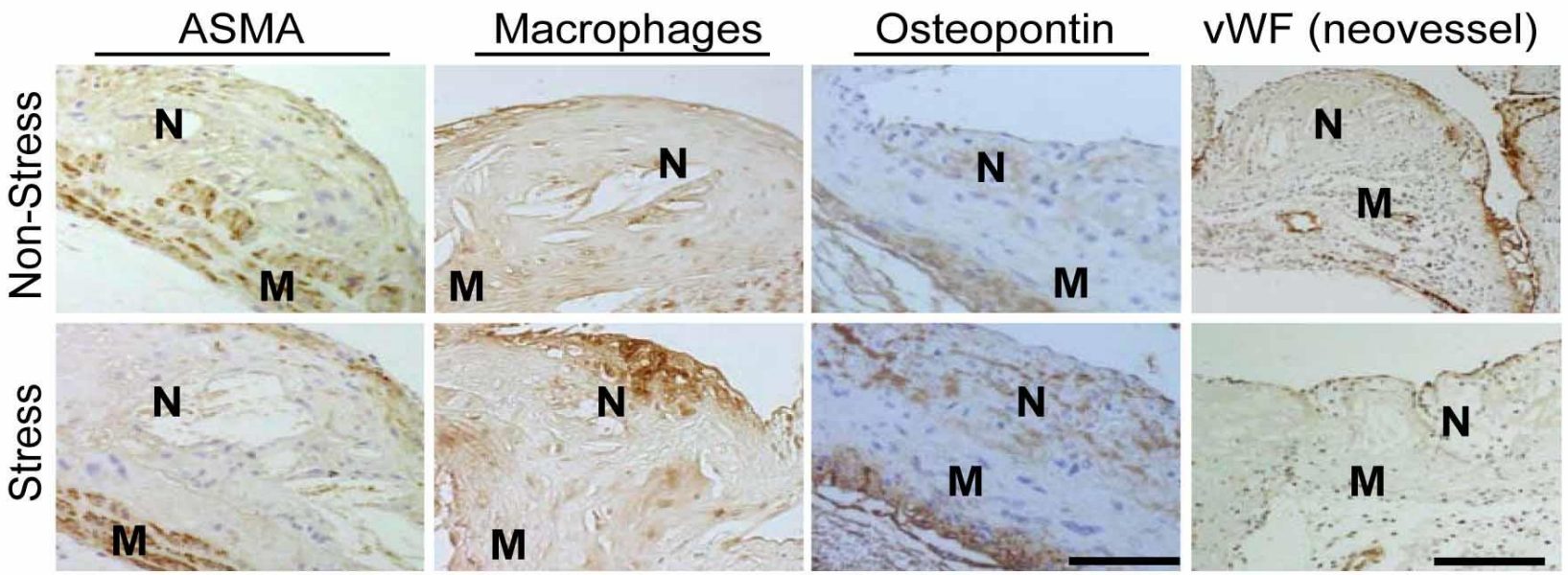


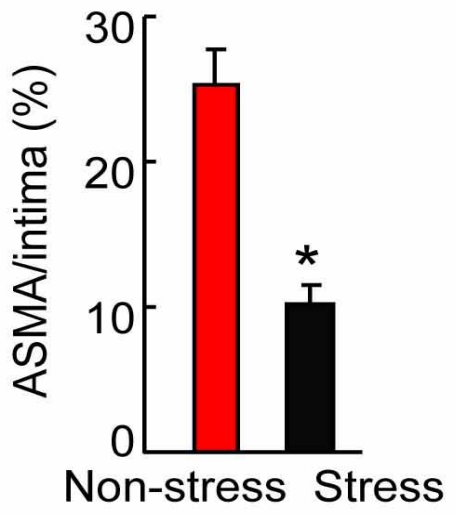


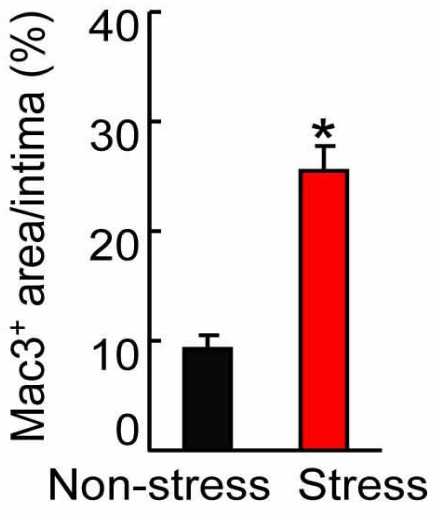
Stress reduced plaque collagen volume and promoted elastin degradation

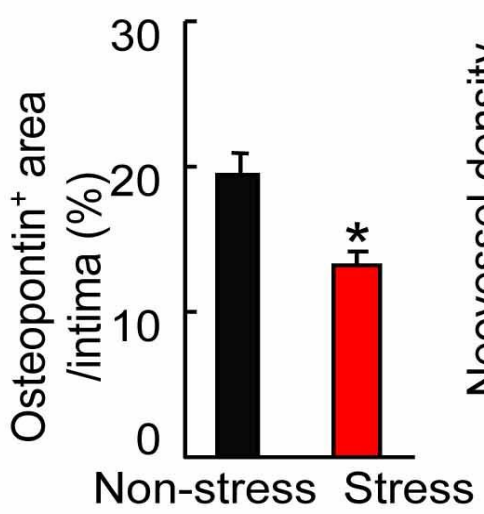


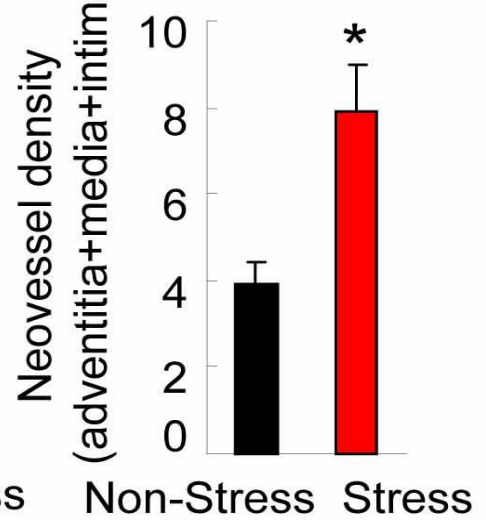
Stress enhanced mac infiltration, inflammatory chemokine expression and neovessel formation



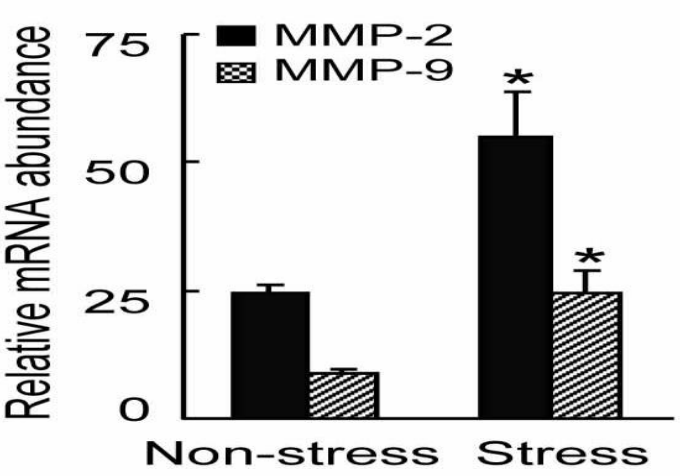


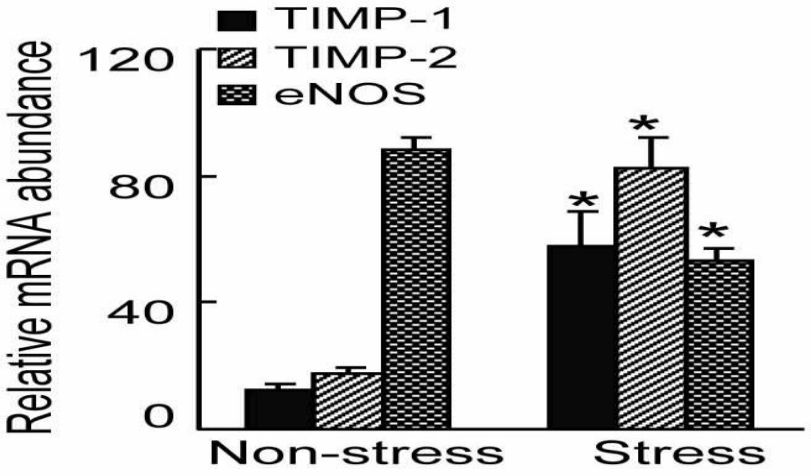


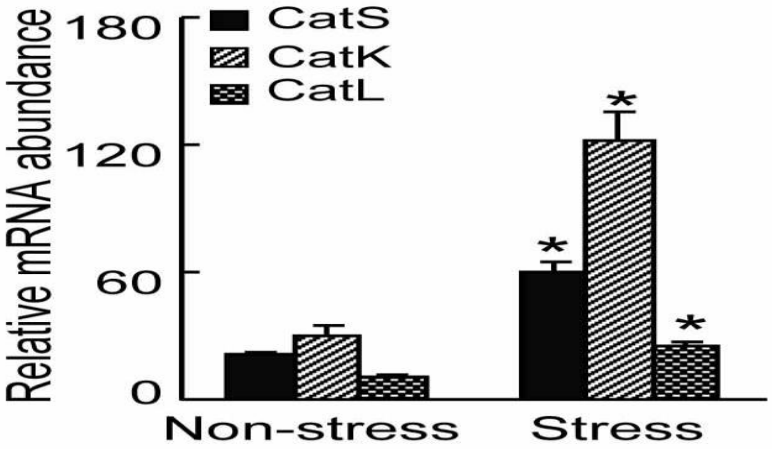


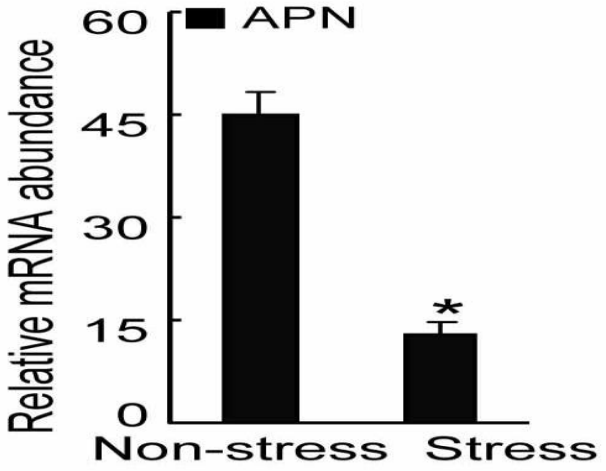


Stressed aortas had increased levels of MMP-2/-9, TIMP1/2, CatS/K/Land APN and decreased eNOs genes

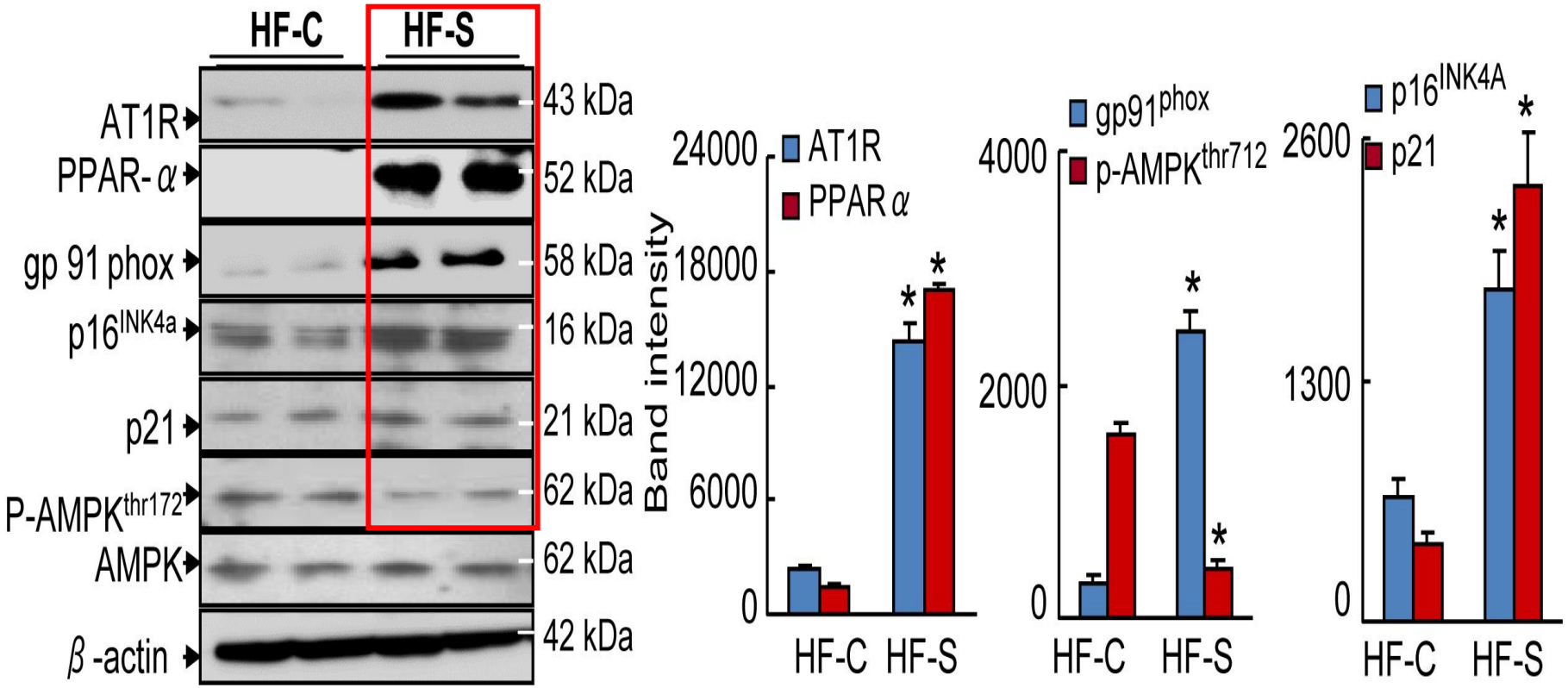




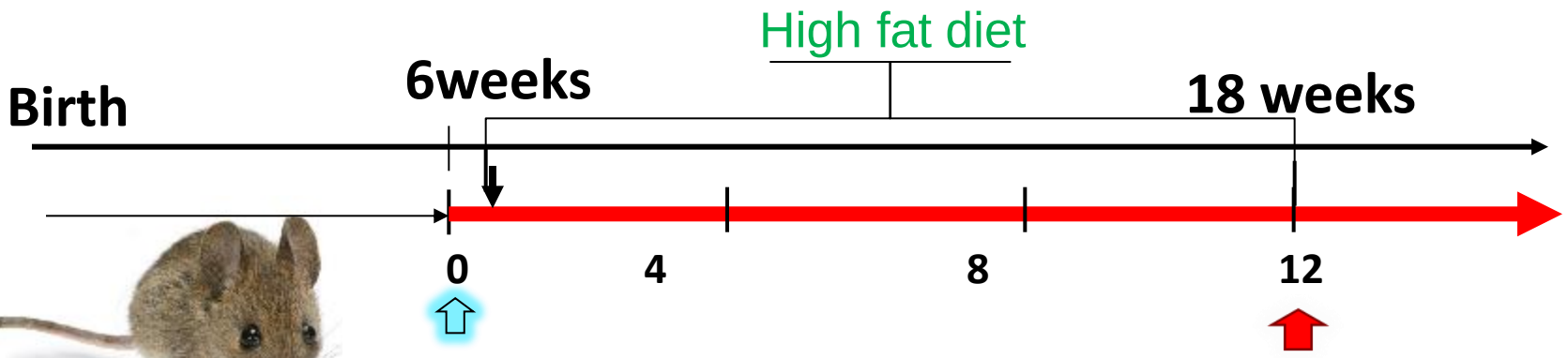




Stress increased levels of AT1R and gp91phox and decreased levels PPAR-α, except p-AMPK proteins



Protocol (2)



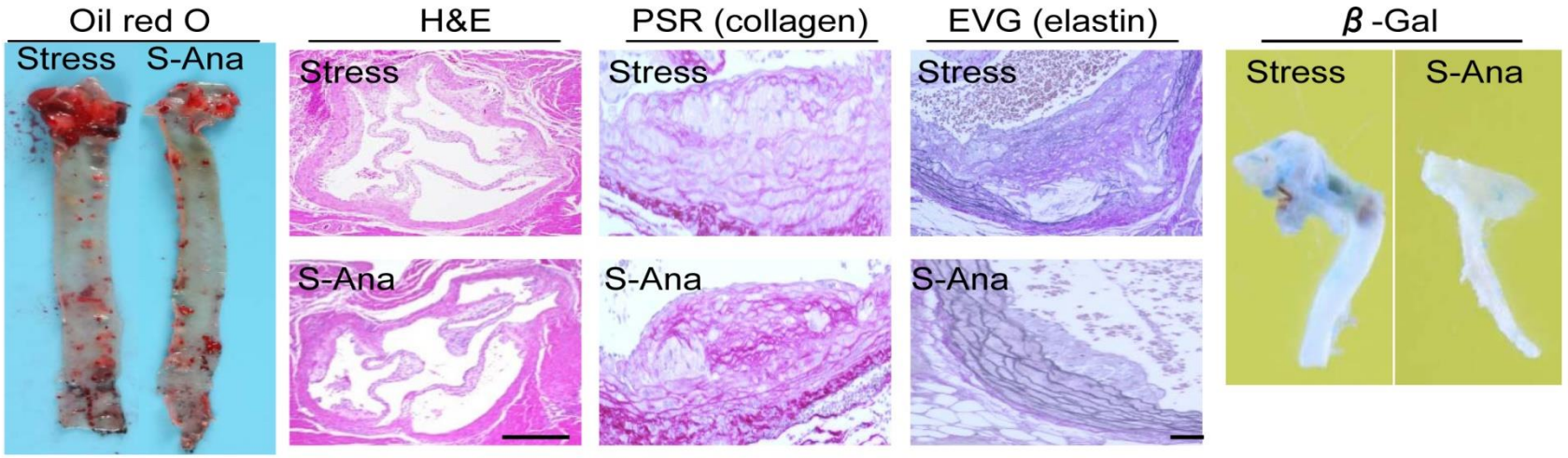
Group 1: HFD+Stress (Control)
Group 2: HFD+Stress+Anagliptin (S-Ana)

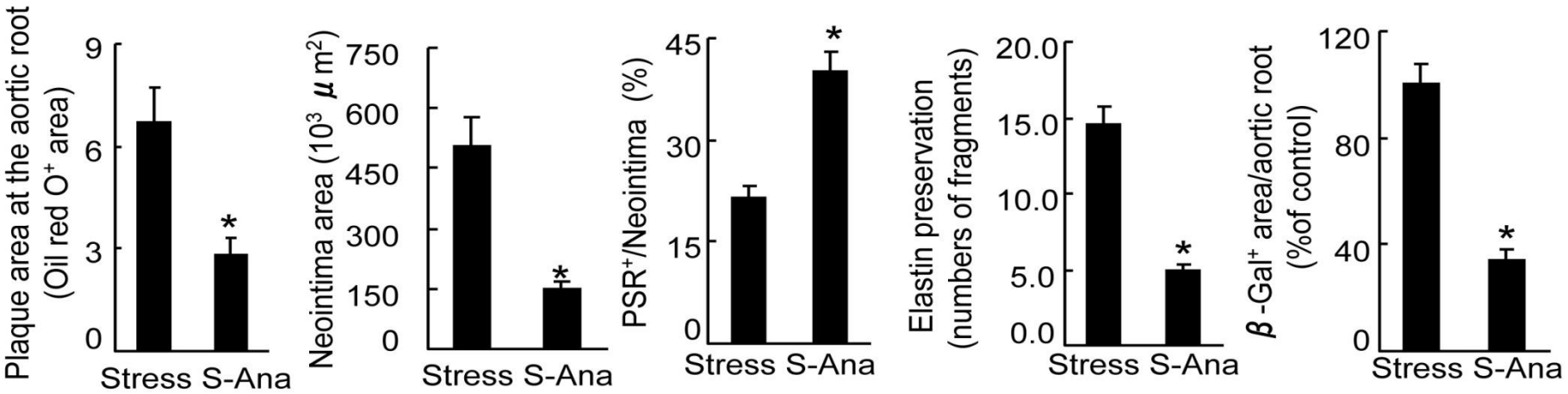
¶ Blood
¶ Aortas

DPP4 inhibition increased levels of APN and GLP-1 proteins

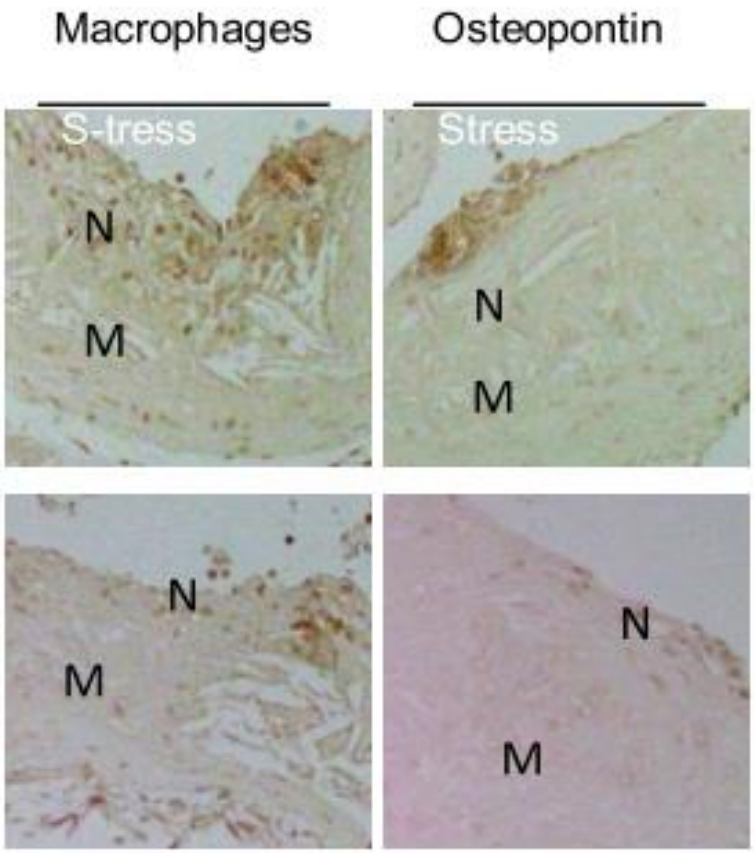
Parameter	Stress	S-Ana
Triglyceride (mg/dL)	21.1 ± 2.2	13.6 ± 3.1*
LDL (mg/dL)	47.6 ± 6.1	38.1 ± 12.5
HDL (mg/dL)	4.3 ± 0.2	5.0 ± 0.0
NEFA (μEQ/L)	152 ± 8	136 ± 13
BUN (mg/dL)	3.2 ± 0.4	4.1 ± 0.8
Creatinine (mg/dL)	0.5 ± 0.0	0.5 ± 0.0
DPP4 (ng/ L)	976 ± 4	477 ± 22**
Leptin (pg/ml)	214 ± 9	301 ± 25**
GLP-1 (pM)	11.3 ± 0.6	19.4 ± 0.8**
APN (ng/mL)	5574 ± 417	8492 ± 584**

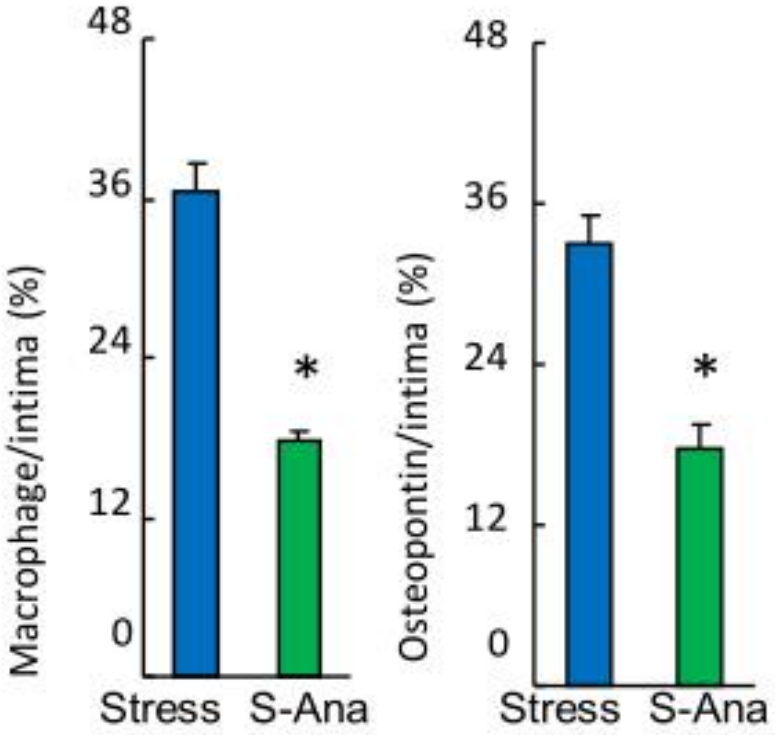
DPP4 inhibition mitigated vascular aging and plaque growth and collagen/elastin metabolism



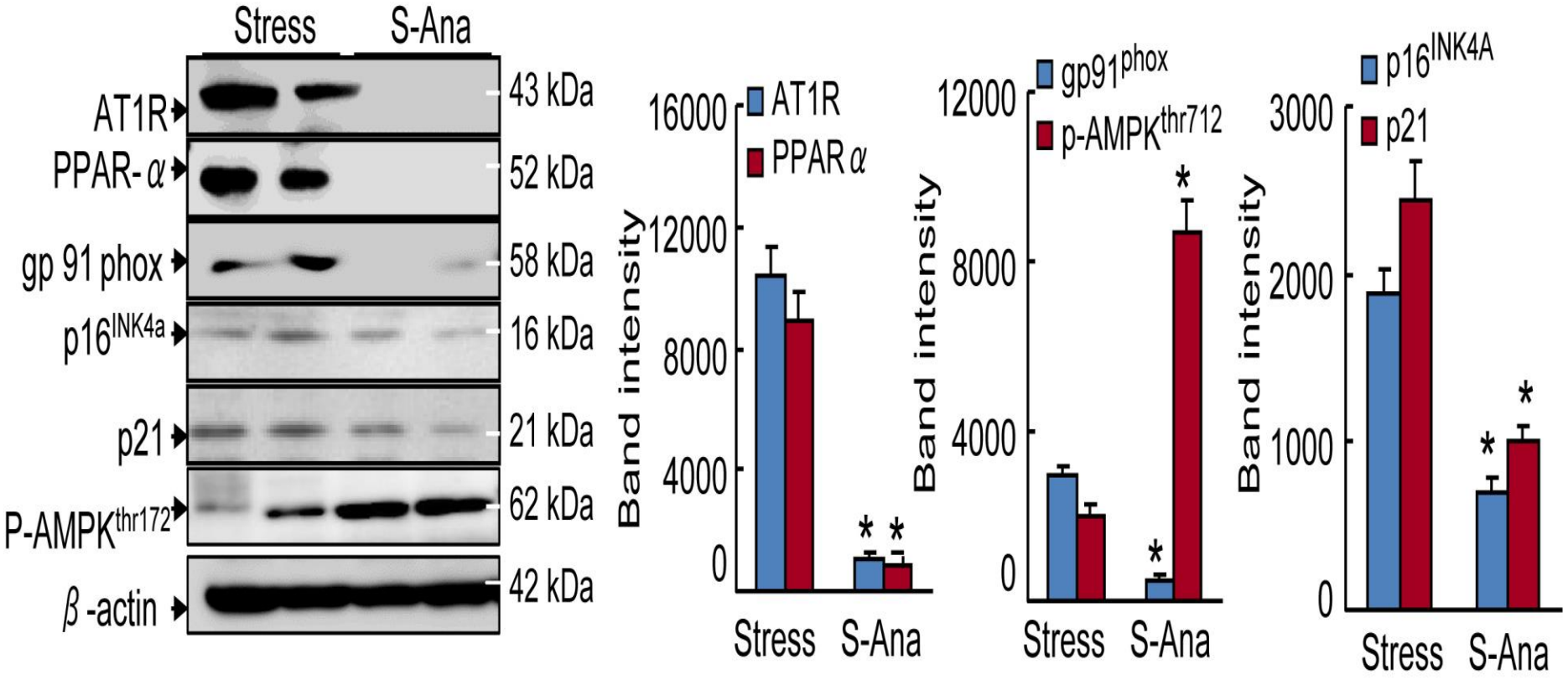


Anagliptin inhibited macrophage infiltration and inflammatory chemokine expression

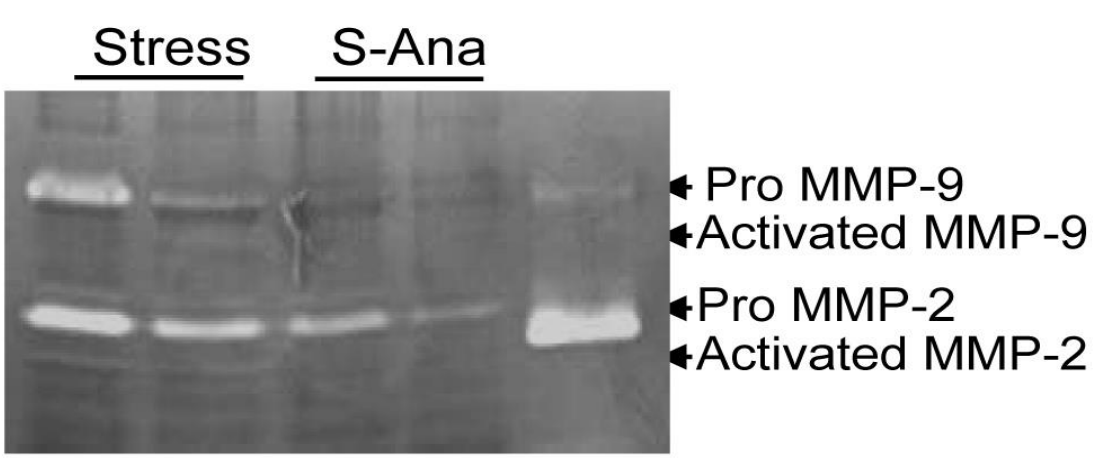


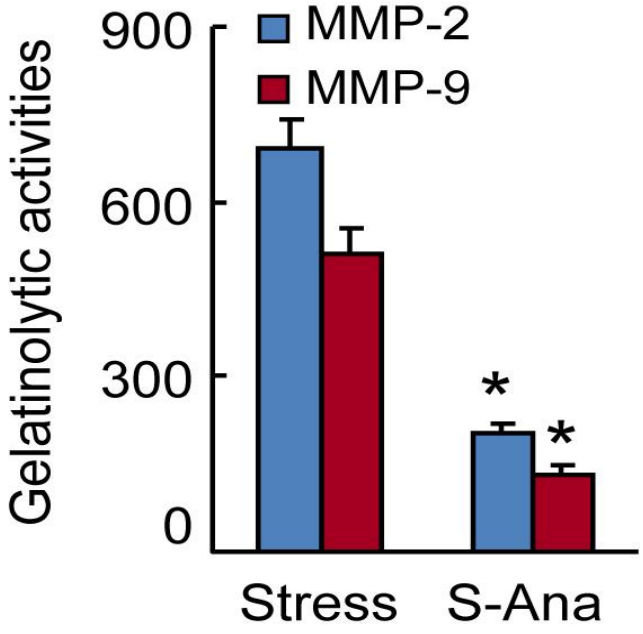


DPP4 inhibition mitigates the changes in AT1R, PPAR-α, p-AMPK , and gp91phox proteins

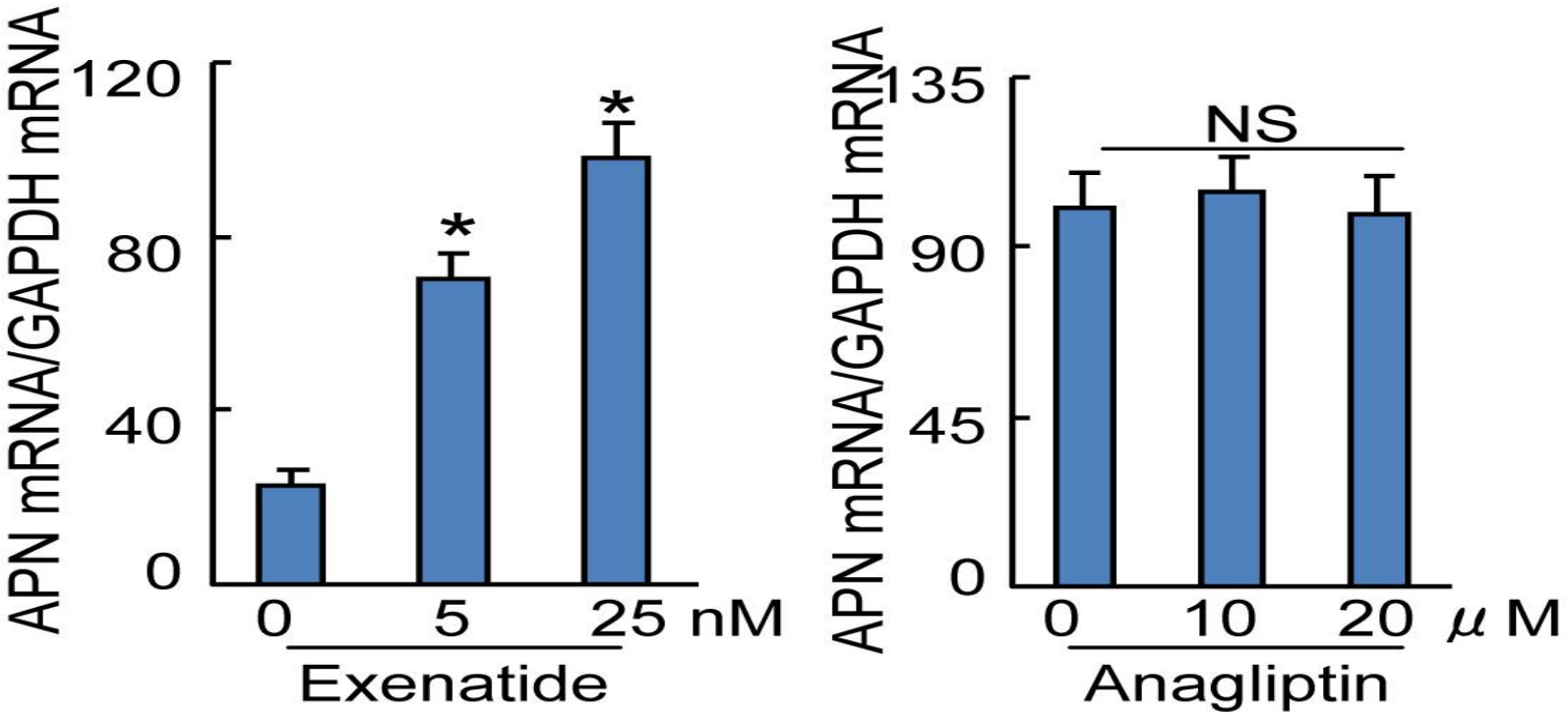


DPP4 inhibition reduced MMP-2/-9 activity

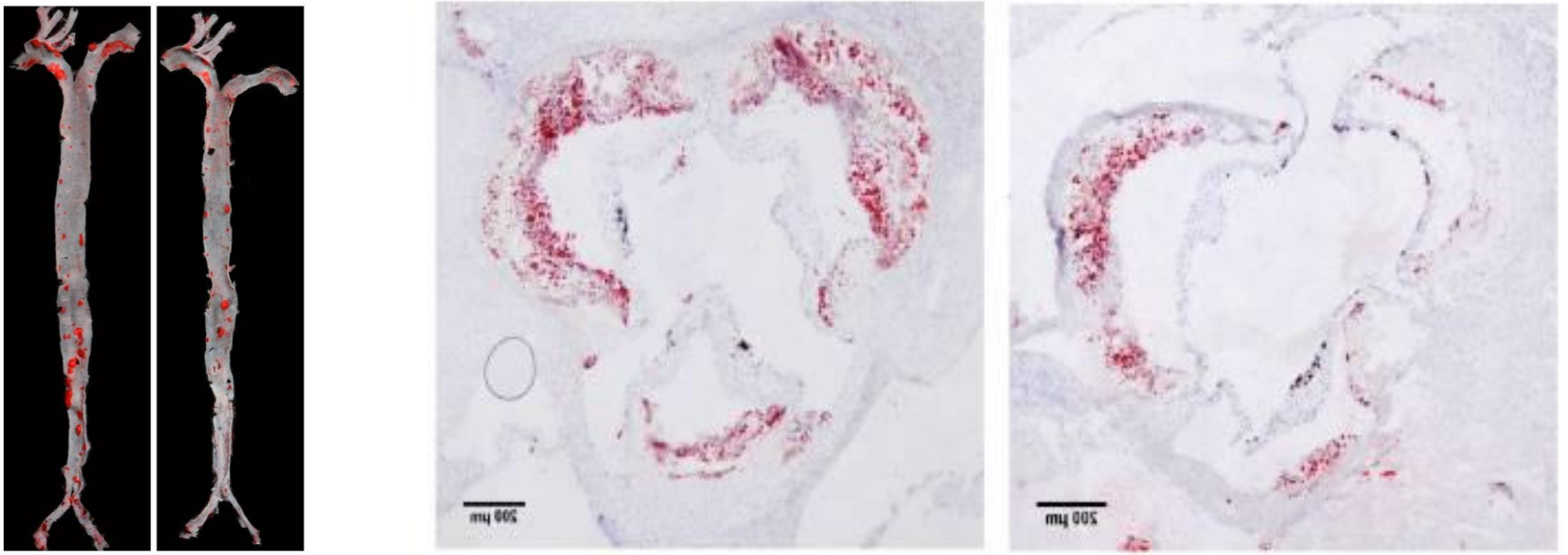




GLP-1 analogues exenatide stimulated APN expression in adipocytes in a dose-dependent manner, but not by anagliptin



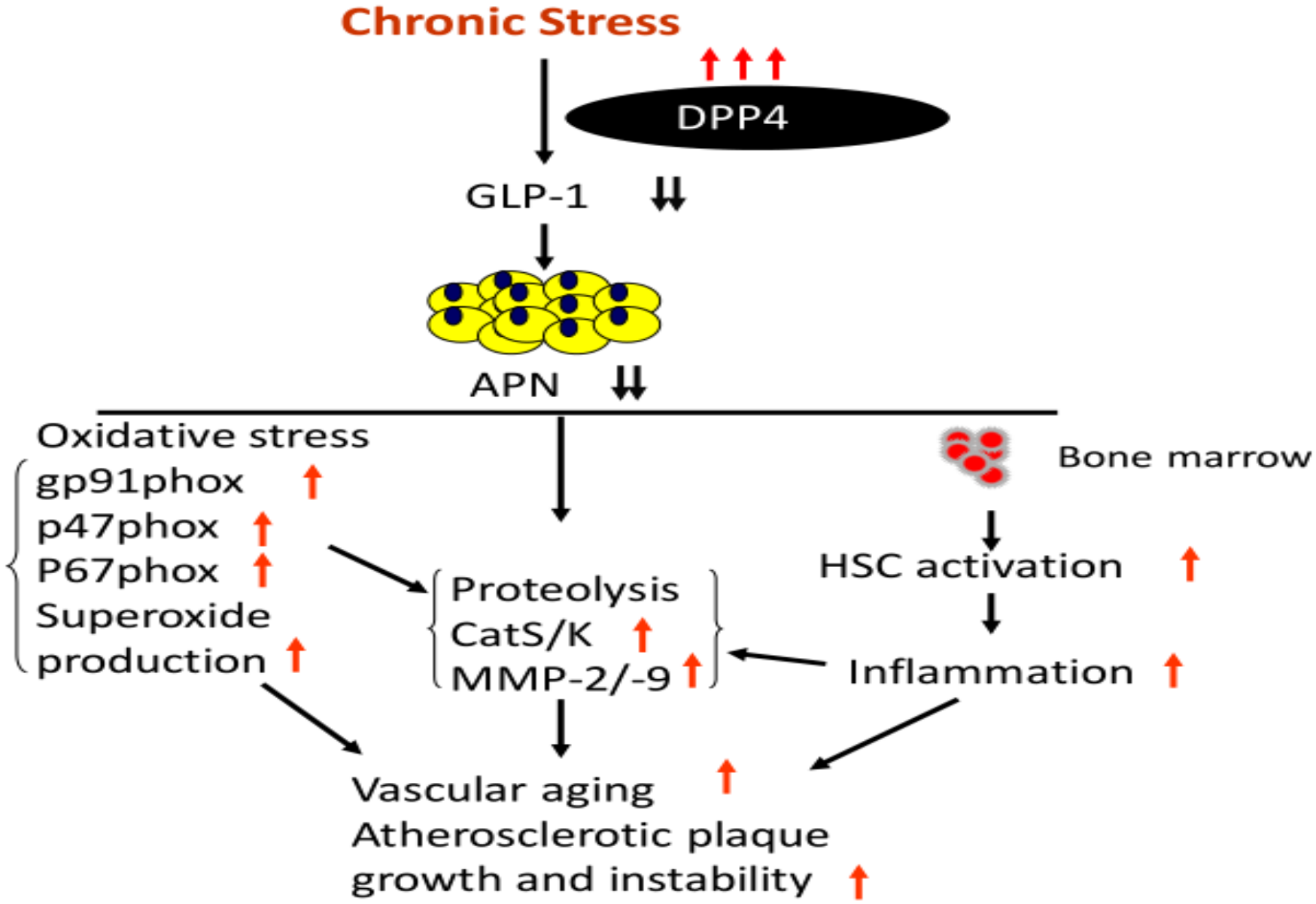
GLP-1 analogues exenatide improved atherosclerotic lesion formation



Oil red O staining

Yang and Lei et al. Atherosclerosis 2017;264:1-10

Proposed mechanisms



Conclusion

These results indicate that the DPP-4 inhibition-mediated benefits are likely attributable, at least in part, to attenuation the plaque inflammation, oxidative stress and proteolysis associated with GLP-1-mediated APN production in ApoE$^{-/-}$ mice under stress. Thus, DPP-4 will be a novel therapeutic target for the treatment of stress-related cardiovascular disease.

Thank You !

谢谢