中文題目:抑制 Dipeptidyl Peptidase-4 (DPP-4)之作用藉由 PKA 相關路徑來降低心肌梗塞後心律不整

英文題目: Dipeptidyl Peptidase-4 Inhibition Attenuates Arrhythmias via a PKA-dependent Pathway in Infarcted Hearts

作　　者: 陳韋廷[1], 李聰明[1], 張念中[2]

服務單位: 安南醫院心臟內科[1] 臺北醫學大學附設醫院心臟內科[2]

Background: The effect of dipeptidyl peptidase-4 (DPP-4) inhibitors on arrhythmias remained unknown. The aim of this study was to investigate whether sitagliptin attenuates arrhythmias through inhibiting *nerve growth factor (NGF)* expression, focusing on cAMP downstream signaling such as protein kinase A (PKA) and exchange protein directly activated by cAMP (Epac).

Methods and Results: Male Wistar rats were randomized to either vehicle or sitagliptin for 4 weeks starting 24 hours after ligating coronary artery. Post-infarction was associated with increased oxidative stress. Measurement of myocardial norepinephrine levels revealed a significant elevation in vehicle-treated rats compared with sham. Compared with vehicle, infarcted rats treated with sitagliptin significantly increased cAMP levels, and decreased DPP-4 activity, oxidative stress, NGF levels and immunofluorescence-stained sympathetic hyperinnervation. Arrhythmic scores were significantly lower in the sitagliptin-treated infarcted rats than in vehicle. *Ex vivo* studies showed that sitagliptin increased phosphorylated cAMP response element binding protein (CREB), which can be reversed by H-89 (a PKA inhibitor), not brefeldin A (an Epac inhibitor). *Heme oxygenase-1* (*HO-1*) expression was increased by a PKA agonist but not by an Epac agonist. *HO-1* expression was attenuated in KG-501 (a CREB inhibitor)-treated infarcted rats in the presence of a PKA agonist.

Conclusions: Sitagliptin protects ventricular arrhythmias by attenuating NGF-induced sympathetic innervation via upregulation of *HO-1* expression in a cAMP/PKA/CREB-dependent antioxidant pathway in the non-diabetic infarcted rats.