中文題目:在心肌梗塞大鼠內皮接受體抑制交感神經再生係經由PI3K/Akt訊息傳遞

英文題目: Inhibition of Endothelin Receptors on Sympathetic Innervation via a PI3K/Akt-dependent Pathway in Post-infarcted Rats

作　　者: 張倉惟[1], 楊晨佳[1], 李聰明[1,2]

服務單位: 安南醫院心臟內科[1], 中國醫藥大學醫學系[2]

前言:Although endothelin (ET)-1 has been shown to upregulate nerve growth factor (NGF) expression after myocardial infarction, the molecular mechanisms are largely unknown. We investigated whether selective ET receptor blockers attenuate cardiac sympathetic reinnervation through restoring phosphatidylinositol 3-kinase (PI3K)/Akt/glycogen synthase kinase (GSK)-3β activity.

材料及方法: Twenty-four hours after coronary ligation, male Wistar rats were randomized to either vehicle, ABT-627 (an ET_A receptor antagonist), or A-192621 (an ET_B receptor antagonist) for 4 weeks.

結果和結論:Sympathetic hyperinnervation after infarction was confirmed by myocardial norepinephrine measurement and immunofluorescent analysis. This was paralleled by a significant upregulation of NGF protein and mRNA in the vehicle-treated rats, which reduced after administering ABT-627, not A-192621. Arrhythmic scores during programmed stimulation in the vehicle-treated rats were significantly higher than those treated with ABT-627. In an *in vivo* study NGF was significantly decreased through activation of PI3K/Akt signaling pathway in the presence of ABT-627, which was also confirmed by the *ex vivo* study showing the increased NGF levels by the use of PI3K inhibitors (wortmannin and LY294002). Furthermore, lithium chloride, an inhibitor of GSK-3β, decreased NGF levels, suggesting the involvement of GSK-3β as a downstream molecule of PI3K/Akt pathways. These data demonstrate that the ET_A receptor antagonism is a critical mediator to attenuate sympathetic hyperinnervation probably through the restoration of PI3K/Akt/GSK-3β signaling. Inhibition of GSK-3β-mediated pathways is novel regulators of sympathetic innervation and potential pharmacological targets for arrhythmias.

Keywords: Arrhythmias; Glycogen synthase kinase-3; Myocardial infarction; Nerve growth factor.