三亞麻油酸抑制心肌細胞肥厚相關機轉之探討

The mechanisms of inhibitory effect of trilinolein on cardiomyocyte hypertrophy

中文摘要

心臟肥厚 (cardiac hypertrophy) 是心血管疾病的重要表徵。在臨床上心臟肥厚會導致心臟功能衰竭、心律不整、甚至猝死。許多研究證實心臟肥厚與氧自由基的生成有關。三亞麻油酸 (trilinolein) 是一種存在於植物的“不飽和脂肪酸”。在傳統中藥“川七”的根部富含此種脂肪酸，而“川七”在中國用來治療心血管疾病已有數百年歷史。國內經由陳保羅教授，鄭瑞棠教授及洪傳岳教授多年的研究已證實三亞麻油酸具有抗氧化作用，可保護心血管細胞遭受缺氧時的傷害。然而對三亞麻油酸在心血管細胞內的分子生物學作用機轉卻不清楚。本研究目的即探討三亞麻油酸是否會經由其抗氧化之作用來抑制心肌細胞肥厚之發生？如果有此抑制作用，其細胞內相關之訊息傳遞及分子機轉為何？我們以大白鼠心室之組織作心肌細胞 (cardiomyocyte) 的培養。以血管張力素-II (Angiotensin-II) 或正腎上腺素 (Norepinephrine) 刺激心肌細胞，發現心肌細胞的活性氧自由基族群 (reactive oxygen species；ROS) 會呈劑量相關性的有意義增加。而如先以三亞麻油酸處理的心肌細胞，血管張力素-II 或正腎上腺素所刺激 ROS 的生成會被抑制。同樣，血管張力素-II 或正腎上腺素所增加的心肌細胞蛋白質合成作用及肥厚相關基因 β-myosin heavy chain (β-MyHC) 的基因表現也會被三亞麻油酸所抑制。在訊息傳遞機轉方面，我們檢測 mitogen-activated protein kinases (MAPKs) 的磷酸化，發現三亞麻油酸可有意義地抑制血管張力素-II 或正腎上腺素所導致的 MAPKs 磷酸化現象。而血管張力素-II 所增加的轉錄因子 nuclear factor-kappa B 或 activator protein-1 的活性，也會被三亞麻油酸所抑制。而以上三亞麻油酸所產生的心肌細胞肥厚相關機轉的抑制作用，如以其它的抗氧化劑如 N-acetyl-cysteine (NAC) 亦可有相同的抑制作用，表示三亞麻油酸對心肌細胞肥厚的抑制與其抗氧化能力有關。

英文摘要

Cardiac hypertrophy is a major clinical feature of many cardiovascular diseases. Cardiac hypertrophy can cause heart dysfunction, cardiac arrhythmia, and even sudden death. Trilinolein, an unsaturated triacylglyceride, is found in the root of Sanchi (Panax notoginseng), which has been used as a traditional herbal medicine for treating cardiovascular disorder among Chinese for hundreds of years. Previous studies have demonstrated that trilinolein possessed antioxidative ability, which protected cardiovascular cells against hypoxic injury. However, the intracellular

molecular mechanisms of these protective effects of trilinolein on cardiovascular system are still unclear now. The aims of this research were attempt to investigate whether trilinolein could inhibit cardiac hypertrophy via its ability of antioxidation? And if trilinolein could inhibit cardiac hypertrophy, we want to identify the underlying signal transduction pathways and intracellular molecular mechanisms. Cultured neonatal rat cardiomyocytes were stimulated with norepinephrine or angiotensin II. We found that reactive oxygen species were significantly increased in a dose-dependent manner by norepinephrine and angiotensin II. Pretreatment with trilinolein significantly attenuated the norepinephrine- or angiotensin II-induced reactive oxygen species generation in cardiomyocytes. Protein synthesis (by assay of [3H]-leucine incorporation) and hypertrophy related gene expression (by measurement of the beta-myosin heavy chain promoter activity) were examined. Trilinolein significantly inhibited norepinephrine- or angiotensin II-increased protein synthesis, and beta-myosin heavy chain promoter activity. Other antioxidant, N-acetylcysteine (NAC), also significantly inhibited norepinephrine- or angiotensin II-increased protein synthesis, and beta-myosin heavy chain promoter activity. Furthermore, both trilinolein and N-acetylcysteine decreased norepinephrine- or angiotensin II-activated mitogen-activated protein kinases phosphorylation. And trilinolein and NAC also significant inhibited angiotensin II-stimulated transcriptional factors activities (activator protein-1-, or nuclear factor-kappa B- luciferase reporter binding activities). These data indicate that trilinolein inhibits norepinephrine- or angiotensin II-induced cardiomyocyte hypertrophy via its ability of attenuation of reactive oxygen species generation.