在體外模式下利用週期性機械力探討心肌細胞內加壓素基因表現及其分子調控之機轉

中文摘要

加壓素是一種血管收縮促進因子，可能參與高血壓和冠狀動脈硬化症的形成。目前研究顯示，在體外實驗模式下，加壓素可作爲心肌細胞肥大的指標基因，並可能與心血管疾病上扮演特定連結。在臨床上已有證據顯示，加壓素在心血管疾病上可視爲一種獨立潛在危險因子，在心肌細胞肥大及鬱血性心衰竭時，血漿中的加壓素含量會顯著增加。也有一些相關的研究指出在心血管系統中，ROS 也可能刺激加壓素的增加，進而誘發心肌細胞肥大和心肌纖維化，以致可以加速心血管疾病的病程變化，但目前對其分子調節機轉並不清楚。機械力過度負荷是造成心臟疾病原因之一，利用直接的機械展延來研究加壓素在心肌細胞的表現尚未被探討過，而且我們認爲加壓素在機械展延下之表現可能與 ROS 的調節作用有關。因此本篇研究的目的:在體外模式下利用週期性機械力探討心肌細胞內加壓素基因表現及其分子調控之機轉。本研究是將心肌細胞接種於一矽膠彈性膜上，再配合機械展延儀器，於每分鐘 60 次循環下達到 20% 或 10% 的展延程度。結果發現週期性機械力明顯地會使加壓素蛋白質與其訊息核糖核酸分子表現上升也會透過 STAT1 使的去氧糖核酸-蛋白質轉錄因子的結合活性能力上升。當加入相關抑制劑 (PD98059, NAC, ERK siRNA, urotensin II siRNA) 後則又會使的加壓素蛋白質和去氧核糖核酸-蛋白質轉錄因子的結合活性表現下降。最後得到的結論則是:心肌細胞在週期性機械力作用後會經由 ERK 和 STAT1 訊息傳遞路徑影響加壓素上升最後誘發導致心肌纖維化等等的相關心血管疾病。

英文摘要

Urotensin II is a potent vasoconstrictive peptide and involves in hypertension and atherosclerosis. A recent study identified that cardiomyocytes are able to express urotensin II receptor and receive the direct hypertroplic signal from urotensin II. Clinical evidence implicated that urotensin II as a potential independent risk factor for coronary heart disease which increased plasma urotensin II levels are correlated with cardiac hypertrophy and congestive heart failure. Thus, it suggested that urotensin II may play an important role in biological link of cardiovascular pathophysiologies. Several other studies have also indicated that ROS is also able to stimulate the generation of urotensin II in cardiovascular system and leading to cardiac hypertrophy. While urotensin II has been shown increase the degree of cardiovascular diseases but its molecular regulation mechanism remains unclear. Mechanical force overload is both cause and consequences of most heart diseases. How cyclical mechanical stretch affects the regulation of urotensin II in cardiacmyocytes has not been previously characterized. We sought to investigate the cellular and molecular mechanisms of regulation of urotensin II by cyclic stretch in cadiacmyocytes. In the present study, cadiacmyocytes grown on a flexible membrane base were stretched by vacuum to 20% of maximum elongation, at 60 cycles/min. Cyclic stretch significantly increased urotensin II protein and mRNA expression after stretch. Cyclic stretch also significantly increased DNA-protein binding activity of STAT1. Addition of PD98059, NAC, ERK siRNA, urotensin II siRNA 30 minutes before stretch inhibited the induction of urotensin II protein and abolished the DNA-protein binding activity induced by cyclic stretch. In conclusion, cyclic mechanical stretch enhances urotensin II expression in cultured cadiacmyocytes. The stretch-induced urotensin II is mediated by angiotensin II and ROS, at least in part, through ERK and STAT1 pathway.