砷暴露地區居民 HO-1 基因啓動子和 eNOS G894T 基因多形性與頸動脈粥狀硬化之相關研究

An association between carotid atherosclerosis and genetic plymorphisms of HO-1 gene promoter, eNOS G894T among residents in an arsenic-endemic area

中文摘要

動脈粥狀硬化已知爲一發炎性疾病，且是導致腦血管病變、心臟血管疾病、高血壓性疾病與糖尿病的主要次臨床症狀，而砷與這些疾病的相關性已被證實。過去研究指出原血紅素氧化酵素一型(heme oxygenase-1, HO-1)，與體內抗氧化壓力和抗發炎有關，其啓動子基因多形性影響著 HO-1 的活性，亦指出內皮型一氧化氮合成酵素(endothelial nitric oxide synthase, eNOS)的活性影響血管內皮功能，因此，本研究目的爲探討砷暴露地區居民 HO-1 基因啓動子和 eNOS G894T 基因多形性與頸動脈粥狀硬化之獨立及交互作用。本研究以民國八十六年於蘭陽盆地礁溪、壯圍、冬山及五結鄉四鄉中的十八個村所進行之四十歲以上居民健康檢查且接受過頸動脈杜卜勒(duplex ultrasonography)超音波檢查的民眾作爲研究母群，選取病例組 259 人和對照組 266 人，總研究樣本數爲 525 人。利用結構式問卷及標準化訪視流程收集研究對象之基本人口學資料並測量其生化值。並於民國八十年及八十六年起兩次家庭追蹤訪視收集井水，計算飲水砷濃度和累積砷暴露量。將萃取出來之 DNA 利用聚合酵素連鎖反應(polymerase chain reaction, PCR)、限制酵素作限制酵素片段長度多形性(restriction fragment length polymorphism, RFLP)和短陣序列分析(short tandem repeat polymorphism, STRP)來進行 HO-1 基因啓動子和 eNOS G894T 基因多形性之分析，將 HO-1 基因啓動子$(GT)n<27$ 定義爲 S 型對偶基，$(GT)n\geqq 27$ 爲 L 型對偶基，基因型分爲 SS、SL 和 LL 三種。結果顯示，在調整年齡和性別後，SL 型和 LL 型會增加罹患頸動脈粥狀硬化的危險對性，但未達統計顯著水準，而 eNOS G894T 變異者，則未發現其與罹患頸動脈粥狀硬化的相關。飲用含砷井水超過 50 μg/L 者且帶有 LL 及 SL 基因型者，其危險對比值分別爲 1.4 和 1.3 均未達到統計顯著水準，但飲用含砷井水低於 50 μg/L 且帶有 LL 及 SL 基因型者，其危險對比值分別爲 5.3 和 2.9。進一步合併飲水濃度資料進行交互作用分析時，飲水砷濃度>50 μg/L，基因型爲 SL 和 LL 者，相較於飲水砷濃度≦50 μg 且基因型爲 SS 者，罹患頸動脈粥狀硬化之危險對比值分別爲 4.1 及 4.5 均達統計顯著水準。在多變項分析結果顯示，當調整年齡、性別、總膽固醇及三酸甘油脂作用後，飲用含砷井水大於 50 μg/L 且具有 LL 及 SL 基因型者其危險對比值分別爲 4.4 及 4.2 均達統計顯著水準。由此顯示，在飲水砷濃度>50 μg 的環境暴露下，無法看到 HO-1 基因型對頸動脈粥狀硬化的影響，顯示當砷暴露高於某一程度時，其對疾病的影響大於基因作用。

英文摘要

Carotid atherosclerosis is known as an inflammatory disease and a subclinical syndrome of cerebrovascular, cardiovascular and peripheral vascular disease. The association between arsenic and vascular disease has been proved by many epidemiological studies. Heme oxygenase-1 (HO-1) seems to be a novel protective factor with potent anti-inflammatory and antioxidant effects. Many studies have been carried out to determine the relevance between DNA variants in the eNOS gene and vascular diseases. The aim of the study is to investigate the association between carotid atherosclerosis and genetic polymorphisms of HO-1 gene promoter, eNOS G894T among residents in Lanyan Basin which was a newly confirmed arsenic-endemic area. Residents age≧40 years old were recruited as study population. Among them, a total of 525 study subjects inculing 259 carted atherosclerosis cases and 266 controls were recruited. Each one was examined his/her carotid atherosclerosis by Duplex ultrasonography. Genetic polymorphisms of HO-1 gene promoter, eNOS G894T were detected by PCR, STRP and RFLP. Logistic regression analysis was used to estimate multivariate-adjusted odds ratios and 95% confidence intervals for various risk factors of carotid atherosclerosis. For studying subjects who drank well water with arsenic concentration higher than 50 μg/L, and also with HO-1 genotype of [S(GT)n<27] [L(GT)n≧27] and LL have age-sex-adjusted OR of 4.1 and 4.5, respectively, compared with referent group who drank well water with arsenic concentration lower and equal to 50μg/L, and also with SS genotype of HO-1. In addition, after adjustment for age, sex, total choletro, triglyceride, significant increase odds ratios of 4.4 and 4.2 mere observed among study subjects who drank well water contained arsenic level greater than 50μg/L and also with LL and SL genotype of HO-1, respectively. No significant association between G894T polymorphism in exon 7 of the eNOS gene and carotid atherosclerosis was found. These findings might imply that arsenic exposure played more important role on carotid atherosclerosis risk than genetic effects.