• 計畫中文名稱	川芎之活性生物鹼 Tetramethylpyrazine 併用 Aspirin 對預防缺血性腦梗塞之研究		
• 計畫英文名稱	Study the Effect of Tetramethylpyrazine Combined with Aspirin on Ischemic Cerebral Infarction		
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• 計畫編號	CCMP94-RD-031	• 研究方式	委託研究
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• 執行機構	台北醫學大學醫學研究所		
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• 研究領域	基礎醫學類, 藥學		
• 研究人員	許準榕		
• 中文關鍵字	抗血小板；缺血性中風；aspirin；tetramethylpyrazine		
• 英文關鍵字	antiplatelet；ischemic stroke；aspirin；tetramethylpyrazine		
• 中文摘要	目前，抗血小板藥物已被建議使用在預防臨床上各類血管的病變，例如心肌梗塞、中風和心血管疾病。 在臨床上，目前已有數類抗血小板藥物應用在預防繼發性缺血性中風的產生，包含了 aspirin、ADP receptor anagonist (ticlopidine 和 clopidogrel)以及 glycoprotein IIb/IIIa antagonist，aspirin 的作用機轉爲不可逆的抑制 cyclooxygenase 而減少了 thromboxane A2 的生合成及抑制血小板的凝集，在這幾類藥物中，由於 aspirin 在預防繼發性缺血性中風的臨床試驗多、證據多、經濟效應好且具有不錯的療效，有 23%減少中風發生的危險率及 18%減少中風、心肌梗塞及血管死亡發生的危險率，所以 aspirin 亦是目前用來預防繼發性缺血性中風的首選藥物，同時爲了要提高預防繼發性缺血性中風的效果，已有臨床試驗(ESPS II study)併用兩種不同作用機轉的抗血小板藥物長效型的 dipyridamole 及 aspirin 來做測試，發現的確能提高至 37%減少中風發生的危險率，且在副作用的產生與單獨使用 aspirin 並無意義增加，同時亦有另一組臨床試驗(MATCH study)正在評估 clopidogrel 併用 aspirin 來預防中風的效果。 由於我們先前的計畫利用川芎之活性生物鹼 tetramethylpyrazine (TMPZ)來預防中風的動物模式中，我們發現 TMPZ (20 mg/kg)能有義意的減少腦梗塞面積約 60%的相對減少率($P < 0.01$)，其可能的作用機轉包含了 1. 抗血小板活性的作用：TMPZ 能夠促進 cGMP 的含量增加以及抑制 phospholipase C 的活性，2. 抗氧化的作用。 所以，本計畫的目的主要是併用 TMPZ 和 aspirin 來探討此兩種不同作用機轉的抗血小板藥物是否能更有效預防中風的形成，其研究方法爲利用大腦中動脈血管阻塞/再灌流模式動物實驗模式來造成缺血性腦中風，進而再評估此兩種藥物併用後之作用效果，其評估方法包括：腦梗塞區域之測定、行爲測試、脂質過氧化的測量、神經缺陷分級和抓力測試。		

• 英文摘要	Recently, a vast amount of randomized data supports the use of antiplatelet drugs to prevent serious vascular events (stroke, MI, and vascular death) in a wide range of patients at high vascular risk (eg, stroke survivors, MI survivors, claudicants). Several antiplatelet agents with different mechanisms of action are currently available for secondary prevention of ischemic stroke. They include aspirin, ADP receptor antagonist (ticlopidine and clopidogrel) and glycoprotein IIb/IIIa antagonist. Aspirin's mechanism of action is irreversible inhibition of cyclooxygenase, resulting in reduction of thromboxane A2 biosynthesis and attenuation of platelet aggregation. Of all antiplatelet agents, aspirin has more clinical trials, evidence and modest efficacy, and is inexpensive in secondary prevention of ischemic stroke. Aspirin leads to a modest reduction both in the risk of stroke (23%) and the combined end point of stroke, myocardial infection (MI), or vascular death (18%). Therefore, all data suggested that aspirin should be first-line antiplatelet therapy in the secondary prevention of stroke. Combining 2 antiplatelet agents with different mechanisms of action has been demonstrated to provide a substantial increase in efficacy in the ESPS II study. In this trial, the relative risk reduction for secondary stroke prevention was 37% with use of a combination of extended-release dipyridamole and aspirin. Importantly, the risk of major bleeding attributable to the combination therapy was no greater than that seen with aspirin alone. Another trial (MATCH study) is going to estimate the effect of clopidogrel combined with aspirin on secondary prevention of ischemic stroke. In the previous proposal, we found that tetramethylpyrazine (20 mg/kg) could significantly produce 60% reduction ($P<0.01$) of cerebral infarct size. The possible mechanisms of tetramethylpyrazine included 1) antiplatelet activity: increase of cGMP level and inhibition of phospholipase C activity, and 2) antioxidation. Therefore, we want to investigate whether tetramethylpyrazine combined with aspirin provide substantial increase in efficacy on cerebral ischemic infarction. We will use the model of middle cerebral artery (MCA) occlusion/reperfusion to study the effect of two drugs on infarct size, behavioral test, lipid peroxidation, neurological deficit and grip test after transient MCAO in rats.