• 計畫中文名稱	探討 Indene 相關結構衍生物抑制基質金屬蛋白酵素表現與血管放鬆之機轉並評估其對活體出血性腦中風動物之保護作用		
• 計畫英文名稱	Protective Mechanisms of Indene Related Derivatives on Anti-Matrix Metalloproteinase Expression and Vasorelaxation in Subarachnoid Hemorrhage Model in vivo		
• 系統編號	PC9706-0751	• 研究性質	基礎研究
• 計畫編號	NSC96-2320-B038-021-MY3	• 研究方式	學術補助
• 主管機關	行政院國家科學委員會	• 研究期間	9708 ~ 9807
• 執行機構	臺北醫學大學藥理學科		
• 年度	97 年	• 研究經費	1320 千元
• 研究領域	基礎醫學類		
• 研究人員	蕭哲志		
• 中文關鍵字	--		
• 英文關鍵字	--		
• 中文摘要	腦中風的病理機制非常複雜，因此至今腦中風的治療相當不易且多爲經驗支持性療法。目前有關腦中風導致神經元細胞死亡的機轉包括麩胺酸胺基酸之興奮性傷害、鈣離子的堆積、自由基與崩解性酵素的傷害。另一方面，自由基與發炎性成分也可造成腦部血管叢的傷害與功能失常，進而更降低血流之供應。現今有關出血性腦中風(主要爲蜘蛛腦膜下腔出血)的治療性藥物主要是降腦壓劑、抗氧化劑、神經穩定劑與抗發炎性藥物。基質金屬蛋白酵素(matrix metalloproteinases, MMPs)爲一種能夠分解細胞外基質與結締纖維的蛋白水解酵素，因而對於組織之結構重組、修補與破壞都扮演相當重要之角色。同時 MMPs 的含量與活性表現受到許多方式嚴密地調節控制。許多文獻指出，由蜘蛛腦膜下腔出血引發之廣泛性血腦障壁破壞與異常基質崩解作用有關，其主要原因源自相關細胞產生及釋放大量 MMPs 所致，諸如血管內皮細胞、嗜中性白血球/單核球或腦部巨噬細胞等。一般而言，發炎性細胞激素以及生長因子等，均會刺激細胞表現 MMPs 基因及其酵素蛋白之生合成。白血球(單核球/小神經膠細胞)目前被認爲在出血性腦傷害上扮演相當重要的角色。腦出血性中風所造成的腦水腫主要源自於升高的腦壓與血腦障壁的損害，而活化的白血球所釋出的活性氧屬與基質金屬蛋白酵素反應可導致相關腦組織之病變。因此在本實驗室的研究構想上，抗嗜中性白血球/單核球/小神經膠細胞與抗中風爲主要藥物評估與發展的方向。根據本實驗室初步之研究結果顯示 indene 類衍生物 benzydamine 具有濃度效應抑制腫瘤壞死因子所誘發 MMP-9 的活化與產生。另一方面此藥在初步血管實驗上發現具有鬆弛之效用。因此本實驗室將探討此藥物抑制發炎性介質表現及調節血管張力之機轉。本計畫主要探討四大主題，第一點釐清不同發炎介質所誘發 MMP-2/9、ADAM (a disintegrin and metalloproteinase)-17、TIMPs 及 TNF-α 之作用機轉路徑。第二點將探討 indene		

	類衍生物(如 benzydamine)在嗜中性白血球、單核球或神經膠細胞抑制上述發炎介質產生之分子機轉與比較。第三點利用主動脈及大腦基底動脈血管組織進行張力實驗以分析 indene 類衍生物(含 benzydamine)之血管作用機轉，尤其是 Rho-kinase 之影響性，再者評估此類成分對於白血球誘導血管內皮失常之緩解作用。最後利用多種蜘蛛腦膜下腔出血動物模式(含基因轉殖小鼠)評估各發炎介質產生差異與腦病變之程度，更進一步評估這些具生物活性 indene 類衍生物的抗腦血管痙.作用與神經血管保護治療作用。
• 英文摘要	The treatment of stroke is still elusive and largely empirical because its pathophysiology is complicated and not yet well understood. Several mechanisms of neuronal injury in stroke have been proposed including glutamate-induced excitotoxicity, calcium overload, free radicals, and degradative enzymes. The pharmacological treatment of subarachnoid hemorrhage (SAH) is included a program of anti-edema agents, antioxidants, neurostabilizers, and specific anti-inflammatory agents. Matrix metalloproteinases (MMPs) can catalyze and degrade extracellular neuronal ground substances and connecting fibers, which have their function to maintain neuronal tissue structure and function. Thus, MMPs play several important roles in tissue remodeling, repairing and destroys. The levels and activities of MMPs are strictly regulated and controlled in various ways. Much evidence has been indicated that neutrophil, monocyte and cerebral microglia synthesize and secrete several MMPs those participate in the disruption of blood-brain barrier in SAH. In general, inflammatory cytokines and several growth factors can stimulate MMPs gene expression. The releasing chemical mediators such as free oxyradicals and MMPs from phagocytes are directly involved in the pathogenesis and development of hemorrhagic injury by reducing neuronal viability and cerebral edema. Furthermore, reduction of microvascular blood flow has been occured as a consequence of post-subarachnoid vasospasm. Evidence to date indicates that activated phagocytes may play a significant role in the genesis of blood-brain barrier damage after CNS trauma by triggering the peroxidative damage within the vascular endothelium. In the preliminary studies, we had found benzydamine as an indene related derivative with anti-MMP-9 expression and vasorelaxant effects. The aims of this project will to investigate four major points, first, clarification of the signal transduction of different inflammatory mediators whose actions involvement through NF-κB, MAPKs, Akt or interacting pathways upon MMP-2/9, ADAM (a disintegrin and metalloproteinase)-17, TIMPs or TNF-α expression in the phagocytes. Secondly, We will investigate and compare the inhibitory mechanisms of bioactive indene related derivatives on inflammatory mediator expression of human neutrophils, monocytic THP-1 and microglial BV-2 cells. Thirdly, on the aspect of vascular relaxation, we will use the isolated rat aortic and cerebral basilar rings to investigate the vasodilatory mechanisms, especially the role of Rho-kinase, and its effect on phagocyte-induced endothelial dysfunction. Especially, anti-monocyte/microglial MMP expression and cerebral vasorelaxant actions are two mechanism targets of this research. Finally, some of these bioactive agents will be evaluated on their neurovascular protection and anti-vasospasm in the subarachnoid hemorrhage in vivo models.