抗胃腸黏膜損傷生藥之研究

Studies on the Protective Effect of Herbal Medicine on Gastro-duodenal Mucosal Lesion

中文摘要

在西醫臨床上使用之藥物，諸如 atropine、ephedrine、morphine、aspirin 等許多來源均取自藥用之天然物，雖然有機化學之進步，可供合成方式來製造藥物，但是天然物（生藥）仍屬未來養生新藥開發之重要寶藏。邇來歐美先進國家對於天然資源之藥物開發與研究，莫不視爲重要計劃工作之一，因此本研究依動機，擬就消化性潰瘍來探討民間傳頌記載之常用中草藥材，期以發掘具有防治或療養效果之天然物，予以系統化分析與評估，尋出數種富含生物活性之成分，加以擴展應用，庶幾有裨益本國國民之衛生保健。首先，研究探討並評估比較高良薑、白朮、枳實、厚朴及白芍等多種生藥對抗大鼠消化道黏膜損傷之治療效果，藥材之水抽取液經由壓力式誘發胃黏膜損傷法、Shay 氏誘發胃黏膜損傷法、aspirin 誘發胃黏膜損傷法和 cysteamine 及 mepirizole 誘發十二指腸黏膜損傷法等急性黏膜病變試驗以及醋酸誘發胃黏膜損傷法、燒烙誘發胃黏膜損傷法等慢性黏膜病變試驗模式，以評定各種生藥材對於胃腸粘膜病變的保護效能。結果顯示白朮、白芍、枳殼、高良薑和厚朴等五種藥材具有良好的抗急性胃黏膜損傷以及零星不一的抗慢性胃黏膜損傷的效果，但不具對抗十二指腸黏膜損傷之作用，其抑制黏膜病變作用應爲細胞保護（cytoprotective）作用（如增加粘液分泌或其他增強胃粘膜屏障）而非抗胃酸分泌作用。

其次，華倫(Warren)和馬歇爾(Marshall)二位醫師於 1983 年成功地從人類胃竇部組織切片培養出幽門螺旋桿菌(Helicobacter pylori)，認爲它可能是造成胃潰瘍與十二指腸潰瘍的重要決定因子，消化性潰瘍的治療因而起了革命性的變化；因此，許多的消化系醫學界學者埋頭研究如何根除幽門螺旋桿菌，而它的治療方法更是不斷更新。在我傳統醫藥典籍裡，更多記載治療消化性潰瘍及抑菌之生藥材，諸如白芷、白朮、枳殼、黃連、厚朴、薄荷、白芍、紫蘇、黃柏、大黃、黃芩、高良薑等生藥，其在台灣地區的醫療市場均爲常用天然植物衍生藥品，今試以 in vitro 方式探討這些中草藥對於幽門螺旋桿菌的抑制效果，期求根除幽門桿菌的生藥有效成分。在探討 12 種生藥對幽門螺旋桿菌生長及尿素酵素活性之抑制狀況，有報告認爲極性溶媒萃取質僅對尿素酵素有輕度抑制作用，但非極性溶媒萃取質則強烈抑制幽門桿菌之生長，因此可以說：對於有關幽門螺旋桿菌的菌落成長，難以運用生藥之粗萃取質來抑制尿素酵素的活性，所以我們又從實驗證實對幽門桿菌生長抑制有效果之生藥裡，選擇了四種目前認爲含量居多的主成分：厚朴酚、小蘗鹼、桂皮酸、沒食子酸等純化合物，繼以偵測對三種 HP 幽門桿菌的抑制作用，比較結果顯示厚朴酚與小蘗鹼表現較佳，但仍不足與 ampicillin 比擬，而厚朴酚的最小抑制濃度爲 10~20 μg/ml。

由於胃本身的作用複雜而難以確定，諸如 histamine H2, gastrin 和 muscarine 受容器等對胃壁細胞的影響相互關係著，若某一方受阻斷劑（blockade）作用，另方面也將受到影響。爲了要確定其間某一藥物的作用機序，我們擬用離體器官實驗標本以選擇性受容器作用藥（receptor agonists）觀察彼此之拮抗情形，以判斷其作用機轉。而在厚朴的臨床應用中有很多與壓力反

應主要因素有關的用法，諸如用於治療胸腹膨滿、消化不良，或由精神壓力造成的消化器官異常等症狀，如今經過動物實驗證明厚朴等生藥對實驗性胃潰瘍的抑制效果良好，爲了進一步了解其主要成分在消化道的作用，即取得厚朴酚（magnolol）運用大鼠離體器官探討其對胃部平滑肌的影響與機制。最後得知厚朴酚可以直接作用於胃底平滑肌，對 acetylcholine、serotonin 與 histamine 產生三種類似的劑量依賴性之抑制作用，表示厚朴酚並不單獨作用在某一受容器上而抑制胃腸道之蠕動，厚朴酚對大鼠胃底平滑肌不僅作用顯著，劑量反應(dose-response)曲線右移，且能抑制最大反應，表現爲競爭性拮抗作用；這一現象的可能原因之一是厚朴酚促使 P-物質(substance-P)釋放，後者轉而刺激平滑肌，再從活化的受容器分離，使受容器暫時處於失去活性狀態，而不能再接受作用藥的作用，本實驗中厚朴酚於神經激胺對胃離體標本有先興奮後抑制作用、以及組織胺的快速耐受性現象等支持此一觀點。另外就是細胞外鈣離子(Ca^{2+})匯流至細胞內，使其濃度上昇而引發內臟平滑肌的收縮作用，欲使平滑肌回復鬆弛狀態就必須將鈣離子移走，calcium pump 即負起將鈣離子從平滑肌纖維內喞出到細胞外液或發展中的肌漿膜，胃體運動(gastric motility)亦可藉由 calcium fluxes 造成平滑肌細胞興奮與收縮耦合(excitation-contraction coupling)反應，厚朴酚既然可以直接作用於乙醯膽鹼(acetylcholine)和神經激胺(serotonin)等致效劑而抑制胃底平滑肌，即暗示厚朴酚有拮抗細胞外液 Ca^{2+} 內流之作用，甚至阻止開放離子通道、抑制細胞膜去極化(depolarizing)和動作電位在細胞內擴散，是故依此作用特性可推測厚朴酚對胃腸消化道蠕動之抑制機轉應爲鈣離子拮抗劑(calcium antagonist)或鈣離子通道阻斷劑(calcium channel blocker)。

英文摘要

Peptic ulcers are the common gastrointestinal diseases. The general medical treatment of peptic ulcers can be divided into two groups：inhibition of acid secretion and enhancement of the protective activity of the gastric mucosa. Since 1984, Helicobacter pylori has been causally related to the majority of cases of both duodenal and gastric ulcers, but the magnitude of this association in the United States has recently been called into question. H. pylori is a common infection, and most infected individuals do not develop ulcers and the pathogenic mechanisms distinguishing the subsets at risk for ulcers have not been defined. No optimal, simple antibiotic regimen for all H. pylori-infected ulcer patients has yet emerged. Simultaneous conventional ulcer therapy is therefore recommended to facilitate symptom relief and healing. For refractory ulcers, only maximal acid inhibition offers effective therapy. Several herbal drugs and folk medicines are listed in the Chinese Pharmacopoeia and are recommended in traditional Chinese medicine as digestive or stomachic agents. These vegetable drugs include Rhizoma Atractylodis (Atractylodes macrocephala), Radix Paeoniae (Paeonia lactiflora), Fructus Aurantii (Citrus aurantium), Rhizoma Alpiniae (Alpinia officinarum) and Cortex Magnoliae (Magnolia officinalis), etc.
The first studies aim to investigate the effects of Chinese herbal drugs (Atractylodes macrocephala Koidz, Paeonia lactiflora Pall., Citrus aurantium L., Alpinia officinarum

Hance and Magnolia officinalis Rehd. et Wils.) available in Taiwan on experimental gastric ulcers. Crude water extracts were tested against five experimental acute ulcers (stress ulcers, Shay's ulcers, aspirin-induced gastric ulcers, mepirizole-induced duodenal lesions and cysteamine-induced duodenal lesions) and two experimental chronic ulcers (acetic acid-induced and thermocautery ulcers) in rats. The results showed that Atractylodes macrocephala possessed significant protective effects against acute and chronic experimental ulcers in male Wistar rats. Alpinia officinarum and the other extracts also displayed statistically significant activities. These Chinese herbal drugs therefore possess antisecretory and anti-ulcer activities. In summary, the five Chinese herbal extracts demonstrated very good anti-ulcer activities against acute gastric ulcers but only sporadic activities against chronic gastric ulcers, and little or no effects in the intestinal ulcer models. The inhibition of ulcers by these agents may be attributed to cytoprotective (e.g., increase in mucus secretion or other actions that may bolster the gastric mucosal barrier) but not dependent on acid inhibition.

Helicobacter pylori (HP) is a microaerophilic gram-negative bacterium, and is now recognized as a major etiologic agent of chronic gastritis. HP urease is considered to play the critical role in the pathogenesis of gastritis and peptic ulcer. Both the eradication of these bacteria and the inhibition of HP urease for the treatment of patients with gastroduodenal disease. Thus, the water extracts of the Chinese herbs were studied to determine their inhibitory effects against urease activity and growth of HP in vitro. The results revealed that Cortex Magnoliae (Magnolia officinalis Rehder et Wilson), Rhizoma Coptidis (Coptis chinensis Franchet) and Rhizoma Rhei (Rheum palmatum L.) potently inhibited the growth of HP. However, these herbal drugs showed no inhibitory effect on HP urease except Herba Menthae (Mentha arvensis L.). Among the constituents from these medicines, the inhibitory effects of magnolol and berberine on the growth of HP were most efficient, followed by cinnamic acid and gallic acid. Minimum inhibitory concentrations (MICs) of magnolol were 10-20 μg/ml.

Magnolol was separated and purified from the rhizome of Magnolia officinalis, which had been demonstrated in pharmacological experiments using rats that they had protective effects on various experimental gastric ulcer. In this communication, we assess the isometric tension effects of magnolol on the contractile responsiveness of the isolated rat stomach fundus strip preparations. The results showed that magnolol significantly inhibited the contraction induced by cholinergic, histaminergic and serotonergic agonists. From the reports, we know that adenosine lacks an effect on the contractile cholinoceptors on smooth muscles of stomachs and the Ca^{2+} movements induced by ACh and by 5-HT are different and that difference in Ca^{2+} movements may cause the difference in contractile responses to the two agonists. It is suggested that magnolol is somehow related to a calcium channel blocker.