



行政院國家科學委員會專題研究計畫成果報告

計畫編號：NSC88-2314B-038-108

執行期限：87年8月1日至88年7月31日

主持人：陳盛煊 執行機構及單位名稱：臺北醫學院醫學系

一、中文摘要

本研究探討興奮性胺基酸(excitatory amino acids)及其受體亞型對於壓力性胃潰瘍的保護作用及 cAMP 濃度變化之影響。於腹腔注射投藥 30 分鐘後，將小白鼠放入恆溫箱 ($4\pm 1^{\circ}\text{C}$) 並限制其行動，觀察不同的壓力時間導致胃潰瘍的程度與 cAMP 之間的關係。結果得知，潰瘍程度和 cAMP 濃度成正比。當投與 L 型麩胺酸 (2, 4 和 8 mg/kg, i.p.) 30 分鐘後，以壓力 ($4\pm 1^{\circ}\text{C}$, 2 小時) 引起胃潰瘍，其呈現劑量-依存性地 (dose-dependent) 抑制胃潰瘍發生。而 NMDA (N-methyl-D-aspartic acid) (0.2, 1 和 2 mg/kg), QA (quisqualic acid) (2 and 5 mg/kg) 和 KA (kainic acid) (1, 2 and 5 mg/kg) 同樣呈現劑量-依存性地抑制潰瘍的產生。

並探討 NO 和 NMDA 在此保護作用中所扮演的角色。以 L-NNA, L-arginine 及 NMDA 對於壓力性潰瘍的保護作用和 cAMP 變化。以推測 NO 和 NMDA 在此保護作用中所扮演的角色。當投與 NMDA 1 mg/kg 時，對降低潰瘍面積產生可達 70% 的預防效果；此潰瘍減少時鼠胃中 cAMP 有下降之現象。且在 L-NNA (NO synthase inhibitor) 10 mg/kg 時可拮抗 NMDA 對壓力性潰瘍的保護作用。

上述結果顯示，L 型麩胺酸在壓力性潰瘍上可能參與胃黏膜障 (mucosal barrier) 之生理調節。其機制可能是由於降低 cAMP 的生成。而 NMDA 可促使內生性 NO 的釋放，且降低 cAMP 來參與胃黏膜障 (mucosal barrier) 之生理調節。

關鍵詞: cold-restraint stress, cAMP, 一氧化氮, 興奮性胺基酸,

Abstract

Excitatory amino acids and its subtypes including N-methyl-D-aspartate (NMDA), kainic acid (KA) and quisqualic acid (QA), which functions to protect mucosal damage and reduce cyclic AMP concentration were also investigated

in stress-induced gastric lesions. L-Glu and its subtypes were administered before cold-restraint stress ($4\pm 1^{\circ}\text{C}$, 2 hrs). The cAMP concentration of cold restraint-induced mucosal lesion was significantly different from the normal stomach. The present study was conducted to evaluate the effect of these drugs on the development of cold and restraint-induced gastric ulcers. Two hours of restraint at $4\pm 1^{\circ}\text{C}$ resulted in the production of gastric lesions in all mice. The cAMP concentration of cold restraint-induced was inhibited by L-Glu and its subtypes. L-Glu at 2, 4 and 8 mg/kg i.p. injection 30 min before stress significantly and dose dependently prevented gastric lesions. NMDA at 0.2, 1 and 2 mg/kg, QA at 2 and 5 mg/kg or KA at 1, 2 and 5 mg/kg administered 30 min before stress prevented gastric ulcer in dose dependently. On the other hand, whether NMDA protects gastric mucosa via NO by changing cAMP production were studied using cold-restraint stress (CRS)-induced gastric lesions in mice. NMDA at 1 mg/kg (i.p.) had about 70% prevention on the development of gastric ulcers. NMDA treatment and reduction of CRS-induced ulcer index by CRS was observed. NMDA significantly attenuated the increase in the cAMP and gastric lesions on the CRS stomach. L-NNA (NG-nitro-L arginine, a NO synthase inhibitor, i.p.) at 10 mg/kg potentiated the CRS induced gastric lesions.

All these results suggest that 1. L-Glu and its subtypes also may participate in a physiological modulation of the gastric mucosal barrier, 2. NMDA may participate in a physiological modulation of gastric mucosal barrier by releasing endogenous NO and attenuating the elevation of cAMP in the CRS stomach

Key Word: cold-restraint stress, cAMP/cGMP ratio, atropine, omeprazole, NO

二、緣由及目的

興奮性胺基酸(excitatory amino acids)在中樞神經系統中存在其受體,隨著各種選擇性的催動劑(agonist)及拮抗劑(antagonist)的發現,被區分為 NMDA (N-methyl-D-aspartic acid)、AMPA (-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid)、Kainate、L-AP4 (L-2-amino-4-phosphonobutanoic acid) 以及 metabotropic 等五大類¹。在興奮性胺基酸中,特別是 L 型麩胺酸 (L-Glutamic acid, L-Glu),目前被認為在哺乳類動物的中樞神經系統,作用於突觸(synapse)中為主要的興奮性神經傳遞物質^{2,3}。根據最近的研究報告指出,L 型麩胺酸之催動性神經,不僅存在於中樞神經系統,同時也存在於末梢自主神經系統^{4,5}而其經由 NMDA 受體作用於膽素激導性神經(cholinergic neuron)來控制腸的運動,亦已被証明^{4,5,6}。興奮性胺基酸的作用機轉有二:(1)直接打開離子通道來活化 ionotropic 受體。(2)興奮性胺基酸與 metabotropic 受體結合後,活化 G protein dependent phospholipase C,導致細胞內 inositol polyphosphates 以及 diacylglycerols 的增加^{7,8}。

根據本研究室發表的實驗結果顯示,興奮性胺基酸中 L 型麩胺酸(L-Glutamic acid)及天門冬酸(L-Aspartic acid)在大白鼠離體胃可以有效地減少胃酸分泌^{9,11}。而且証實了胃中存在 glutamatergic neurons 及 L-aspartic containing neurons。因此,本研究探討興奮性胺基酸對於壓力引起胃潰瘍的預防效果。

造成胃黏膜損害的病理成因有很多。一般認為與胃酸分泌¹²、周邊的組織胺作用¹¹、交感神經和迷走神經的興奮¹⁴、活化 pituitary-adrenal axis 引起 corticosteroids 和 catecholamines 由腎上腺髓質(adrenal medulla)釋放¹⁵、降低胃黏膜血流¹⁶及抑制前列腺素(prostaglandin)的合成¹⁷等因素有關。早期研究報告証實經由低溫(cold)及限制行動(restraint)的老鼠,可以造成胃黏膜潰瘍的產生¹⁸。而且其潰瘍發生位置只出現在胃體(body)部位¹⁹。此類型的壓力引起胃損害(lesion)形成,可能的作用機轉有四:(1)增加胃酸分泌。(2)降低胃黏膜血流。(3)前列腺素(prostaglandin)合成的兩相(biphasic)反應;以大白鼠為實驗動物,當壓力時間在兩小時以內,PGE2 含量增加,但是沒有胃損害發生²⁰;壓力時間為四小時²¹或七小時²²後,則 PGE2 含量減少,並產生胃損害。(4)胃的運動(motility);當胃的收縮為低頻率

(frequency)、高幅度(amplitude)、長時間(duration)時,易造成胃黏膜血流暫時地阻礙而形成胃損害^{19,23,24}。我們在第二部份的研究,選擇 cold-restraint 的模式來模擬人類因為壓力所引起的潰瘍。在實驗中,腹腔注射 L 型麩胺酸及其受體亞型的三種興奮性胺基酸,N-methyl-D-aspartic acid (NMDA),quisqualic acid (QA)和 kainic acid (KA)。觀察胃損害(gastric lesions)的變化及胃中 cyclic adenosine monophosphate (cAMP)含量的影響。並探討其對於壓力引起胃損害的預防效果。

三、結果與討論

1 正常小白鼠對於壓力引起的胃潰瘍作用

(1) 壓力時間的變化與 cAMP 含量的關係

ICR 小白鼠胃部的 cAMP 含量隨著壓力時間的增加而增加。當壓力時間為 1.5 小時,其 cAMP 含量增加量最為顯著 ($p < 0.05$),而且潰瘍面積最大。故接下來的研究採用 1.5 小時作為壓力誘導的時間 (Fig. 1)。

(2) 潰瘍的評估

CR 小白鼠經過 cold-restraint ($4 \pm 1^\circ\text{C}$, 2 hr) 處理後,其胃黏膜與正常的 ICR 小白鼠對照組比較,胃黏膜有明顯的損害現象發生。經由實體顯微照相觀察並計算其潰瘍指數,統計得知其潰瘍數目為 44.02 ± 1.00 ,潰瘍長度為 5.33 ± 0.78 mm,潰瘍面積為 9.04 ± 0.92 mm² (Table 1)。

2 L 型麩胺酸及其受體亞型 (NMDA, QA and KA) 對於壓力所引起之胃潰瘍的影響

(1) 潰瘍的評估

ICR 小白鼠於 cold-restraint ($4 \pm 1^\circ\text{C}$, 1.5 hr) 處理 30 分鐘前,分別投與 L 型麩胺酸及其受體亞型:L-Glu, NMDA, QA or KA,對於壓力引起的胃潰瘍於實體顯微照相觀察,有明顯的預防效果 (Table. 2)。L 型麩胺酸分別投與劑量 2、4 和 8 mg/kg,對於胃黏膜損害呈現劑量依存性的抑制作用。其潰瘍數目、潰瘍長度及潰瘍面積,與未接受投藥的小白鼠胃部比較,呈現有意義地減少 ($p < 0.05$)。最有效劑量為 8 mg/kg,其預防百分比可達 74.79%,IC₅₀ 為 4.79 mg/kg (Table. 2)。NMDA 分別投與劑量 0.2、1 和 2 mg/kg,對於胃黏膜損害呈現劑量-依存性的抑制作用。其潰瘍數目、潰瘍長度及潰瘍面積,與未接受投藥的小白鼠胃部比較,呈現有意義地減少 ($p < 0.05$)。最有效劑量為 2 mg/kg,其預防百分比可達 82.55%,IC₅₀ 為 0.231 mg/kg (Table. 3)。

Quisqualic acid 分別投與劑量 2 和 5 mg/kg, 對於胃黏膜損害呈現劑量依存性的抑制作用。其潰瘍數目、潰瘍長度及潰瘍面積, 與未接受投藥的小白鼠胃部比較, 呈現有意義地減少 ($p < 0.05$)。最有效劑量為 5 mg/kg, 其預防百分比可達 79.15%, IC_{50} 為 2.525 mg/kg (Table. 4)。

Kainic acid 分別投與劑量 1, 2 和 5 mg/kg, 對於胃黏膜損害呈現劑量依存性的抑制作用。其潰瘍數目、潰瘍長度及潰瘍面積, 與未接受投藥的小白鼠胃部比較, 呈現有意義地減少 ($p < 0.05$)。最有效劑量為 5 mg/kg, 其預防百分比可達 95.11%, IC_{50} 為 0.204 mg/kg (Table. 5)。

3. Nitric oxide 對於興奮性胺基酸在壓力所引起之胃潰瘍的影響

當接受生理鹽水處理的 ICR 小白鼠經過 CRS ($4 \pm 1^\circ\text{C}$, 1.5 hr) 處理後, 經由實體顯微照相觀察胃黏膜損傷程度, 其潰瘍點數 (U. No.) 為 44.71 ± 9.53 , 潰瘍指數 (U. I.) 為 $9.06 \pm 0.97 \text{ mm}^2$ 。小白鼠在 CRS 處理 30 分鐘前, 分別 i.p. 投與 L-arginine 200, 300 mg/kg, 以實體顯微照相觀察壓力引起之胃黏膜損傷程度, 結果投與 300 mg/kg 時, 對於胃黏膜損害呈現有意義的抑制作用 ($P < 0.05$); i.p. 投與 L-NNA (NO synthase inhibitor) 10 mg/kg 會些微增加潰瘍的程度, 但在統計上並無意義 (Table 6)。小白鼠在 CRS 處理 30 分鐘前, 分別 i.p. 投與 NMDA 0.2、1 和 2 mg/kg, 以實體顯微照相觀察壓力引起之胃潰瘍, 結果發現呈劑量依存性 (dose-dependent) 的預防效果。其潰瘍點數 (U. No.)、潰瘍長度 (U. L.) 及潰瘍面積 (U. I.), 與僅接受生理鹽水 (0.9% NaCl) 處理的小白鼠比較, 呈現有意義地減少 ($P < 0.05$), 其 IC_{50} 約為 0.32 mg/kg。最有效的劑量為 2 mg/kg, 潰瘍指數可由僅接受生理食鹽水時的 $11.13 \pm 0.92 \text{ mm}^2$ 降為 $2.50 \pm 0.68 \text{ mm}^2$, 其預防率可達 77.54% (Table 7), 因此接下來探討 NO 是否受 NMDA 受體調控之實驗我們取 NMDA 2 mg/kg 做為實驗劑量。

L-arginine 分別 i.p. 注射劑量 200 mg/kg 和 300 mg/kg, 在投與 L-arginine 300 mg/kg 時, 對於胃黏膜損害呈現有意義的抑制作用 ($P < 0.05$); 單獨 i.p. 投與 L-NNA 10 mg/kg 會些微增加潰瘍的程度, 但在統計上並無意義。另外 i.p. 注射 NMDA 加 L-NNA 10 mg/kg 後, 可以拮抗由 NMDA 所造成抑制潰瘍形成

的作用, 潰瘍指數由投與 NMDA 2 mg/kg 時的 $2.50 \pm 0.68 \text{ mm}^2$ 增加至 $8.17 \pm 0.74 \text{ mm}^2$, 且其預防率也由 77.54% 降為 26.59% (Table 7)。

(2) cyclic AMP 濃度變化的影響

再分別投與四種興奮性胺基酸, L-型麩胺酸 (8 mg/kg)、NMDA (2 mg/kg)、quisqualic acid (5 mg/kg) 以及 kainic acid (5 mg/kg), 其對於壓力引起的 cAMP 增加量的變化, 也呈現有意義減少的現象 ($p < 0.05$)。其中以 kainic acid 抑制 cAMP 增加量的作用最大, 約抑制其增加量的 85.5%。而 L-型麩胺酸對於 cAMP 的增加量亦抑制達 76.4% (Fig. 2)。

15.70 ± 1.24 與 11.92 ± 0.45 ($p < 0.001$) (Fig. 4, Fig. 5, Fig. 6)。

隨著實驗動物的不同, 所採用的壓力引起潰瘍的時間亦不相同。以大白鼠為例, 在許多報告中的壓力時間多為 3 至 7 小時^{21,22,25}。本實驗以小白鼠為實驗動物, 依據 cAMP 含量及潰瘍產生的面積而選擇以 1.5 小時作為壓力引起潰瘍的時間。根據本研究結果, L-型麩胺酸及其受體亞型的三種興奮性胺基酸, NMDA、QA、KA 對於 cold-restraint 壓力引起潰瘍, 皆呈現劑量-依存性的抑制作用。此結果顯示, L-型麩胺酸抑制壓力所引起的潰瘍, 可能經由 NMDA、AMPA 或 Kainate 等三種不同的興奮性胺基酸受體。又 L-型麩胺酸並不會通過血腦障壁, 所以腹腔注射投藥並不會對中樞系統造成不良的影響; 例如, 痙攣 (convulsion)、發作 (seizure)。而 NMDA 及 kainic acid 的投藥劑量亦低於其引起痙攣或發作的有效劑量²⁶⁻²⁸。另一方面, 投與此四種興奮性胺基酸藥物, 對於壓力引起的 cAMP 增加量亦呈現有意義地減少。早期報告證明 L-型麩胺酸活化 NMDA 受體而引起腸的收縮是經由 cAMP 依存性路徑 (dependent pathway) 引起乙酰膽鹼釋放⁹。由此推測, cAMP 作為第二傳訊物質與壓力性潰瘍有直接的關係。

因此, L-型麩胺酸及其受體亞型和一氧化氮等在壓力引起潰瘍實驗中, 可能是藉由細胞內 cAMP 的含量變化而抑制胃潰瘍的發生的效果。L-型麩胺酸及其三種受體亞型 (NMDA, QA, KA) 和一氧化氮和一氧化氮對於壓力所引起的胃潰瘍亦有劑量-依存性的抑制作用, 其可能藉著胃內第二傳訊物質 (cAMP) 的減少等作用機轉來參與胃黏膜之保護作用。

圖表:

Table 1: The duration of CRS on ulcer number (U.No.), ulcer length (U.L.) and ulcer index (U.I.) of gastric lesions in mice. Vehicle (0.9% NaCl) were given i.p. 30 min before CRS.

Treatment	n	Mucosal lesions			Preventive index (%)
		U.No.	U.L. (mm)	U.I. (mm ²)	
Time CRS (hr)					
Vehicle -	15	0/15	0	0	0
0.5 +	6	0/6	2.00 ± 0.58	1.67 ± 0.53	1.17 ± 0.44
1 +	6	0/6	3.00 ± 0.71	2.00 ± 0.58	4.17 ± 0.83
1.5 +	12	0/12	44.02 ± 1.00	5.33 ± 0.78	9.04 ± 0.92
2 +	4	2/6	30.83 ± 1.28	4.83 ± 0.90	8.57 ± 1.30

CRS, Cold-Restraint Stress.
Each entry represents mean values ± S.E.M.

Table 2: Effects of L-glutamic acid (i.p.) on stress-induced gastric lesion in mice.

Treatment	n	Mucosal lesions			Preventive index (%)
		U.No.	U.L. (mm)	U.I. (mm ²)	
i.p. Dose CRS (mg/kg)					
Vehicle -	15	0	0	0	0
Vehicle -	13	10.08 ± 0.15	5.31 ± 0.11	11.46 ± 0.18	
L-glutamic acid 2 +	11	9.45 ± 0.14	2.82 ± 0.09*	9.91 ± 0.21	13.54
L-glutamic acid 4 +	10	6.70 ± 0.20*	2.20 ± 0.11*	4.80 ± 0.32*	58.12
L-glutamic acid 8 +	10	5.00 ± 0.11*	1.60 ± 0.08*	2.89 ± 0.14*	74.79

CRS, Cold Restraint System.
Each value represents mean ± S.E.
* : Significantly different from control. (P < 0.05)

Table 3: Effects of NMDA (i.p.) on stress-induced gastric lesion in mice

Treatment	n	Mucosal lesions			Preventive index (%)
		U.No.	U.L. (mm)	U.I. (mm ²)	
i.p. Dose CRS (mg/kg)					
Vehicle -	15	0	0	0	0
Vehicle -	13	10.08 ± 0.15	5.31 ± 0.11	11.46 ± 0.18	
NMDA 0.2 +	9	6.56 ± 0.18*	1.78 ± 0.07*	6.06 ± 0.23*	47.16
NMDA 1 +	9	5.89 ± 0.16*	1.89 ± 0.09*	3.56 ± 0.25*	68.94
NMDA 2 +	9	4.11 ± 0.15*	1.22 ± 0.08*	2.00 ± 0.18*	82.55

CRS, Cold Restraint System.
Each value represents mean ± S.E.
* : Significantly different from control (P < 0.05)

Table 4: Effects of Quisqualic acid (i.p.) on stress-induced gastric lesion in mice.

Treatment	n	Mucosal lesions			Preventive ratio (%)
		U.No.	U.L. (mm)	U.I. (mm ²)	
i.p. Dose CRS (mg/kg)					
Vehicle -	15	0	0	0	0
Vehicle -	13	10.08 ± 0.15	5.31 ± 0.11	11.46 ± 0.18	
Quisqualic acid 2 +	9	7.22 ± 0.17*	2.61 ± 0.10	6.44 ± 0.20*	43.81
Quisqualic acid 5 +	9	5.78 ± 0.21*	1.44 ± 0.11	2.39 ± 0.13*	79.15

CRS, Cold Restraint System.
Each value represents mean ± S.E.
* : Significantly different from control. (P < 0.05)

Table 5: Effects of Kainic acid (i.p.) on stress-induced gastric lesion in mice

Treatment	n	Mucosal lesions			Preventive index (%)
		U.No.	U.L. (mm)	U.I. (mm ²)	
i.p. Dose CRS (mg/kg)					
Vehicle -	13	10.08 ± 0.15	5.31 ± 0.11	11.46 ± 0.18	
Kainic acid 1 +	9	7.00 ± 0.22	2.22 ± 0.11*	4.78 ± 0.28*	58.30
Kainic acid 2 +	9	5.78 ± 0.11*	2.00 ± 0.12*	3.94 ± 0.23	65.63
Kainic acid 5 +	9	3.11 ± 0.10*	0.58 ± 0.04*	0.56 ± 0.05*	95.11

CRS, Cold Restraint System.
Each value represents mean ± S.E.
* : Significantly different from control. (p < 0.05)

Table 6: Effects of N^G-nitro-L-arginine (L-NNA), L-arginine (L-Arg) or vehicle (0.9% NaCl) on ulcer number (U.No.) and ulcer index (U.I.) of gastric lesions in CRS mice. The drug and/or vehicle were given i.p. 30 minutes before CRS.

Treatment	n	Mucosal lesions		preventive ratio (%)
		U.No.	U.I. (mm ²)	
(i.p.) Dose CRS (mg/kg)				
Vehicle -	15	0	0	0
Vehicle -	7	44.71 ± 9.53	9.06 ± 0.97	
L-NNA 10 +	7	4.83 ± 0.60*	12.00 ± 0.57	-32.45
L-Arg 200 +	7	3.01 ± 0.54*	10.40 ± 0.16	-14.79
L-Arg 300 +	7	3.62 ± 0.51*	2.40 ± 0.74*	73.51

CRS, cold-restraint stress.
Each entry represents mean values ± S.E.M.
Significant difference at P < 0.05 : "a" from vehicle (CRS) group.

Table 7: Effects of N-Methyl-D-Aspartate (NMDA), N^G-nitro-L-arginine (L-NNA), L-arginine (L-Arg) or vehicle (0.9% NaCl) on ulcer number (U.No.), ulcer length (U.L.) and ulcer index (U.I.) of gastric lesions in CRS mice. The drug and/or vehicle were given i.p. 30 min before CRS.

Treatment	n	Mucosal lesions			Preventive ratio (%)
		U.No.	U.L. (mm)	U.I. (mm ²)	
(i.p.) Dose CRS (mg/kg)					
Vehicle -	15	0	0	0	0
Vehicle -	12	11.02 ± 1.00	5.33 ± 0.78	11.13 ± 0.92	
L-NNA 10 +	6	10.17 ± 0.70	4.83 ± 0.60	12.00 ± 0.57	-7.82
NMDA 2 +	6	3.08 ± 0.43*	1.43 ± 0.52*	2.50 ± 0.68*	77.54
NMDA+L-NNA 2 +	6	9.33 ± 1.48*	5.00 ± 1.33*	8.17 ± 1.28*	26.59
L-Arg 200 +	5	3.01 ± 0.54*	3.50 ± 0.48*	10.4 ± 0.16*	6.56
L-Arg 300 +	5	3.62 ± 0.51*	0.80 ± 0.58*	2.40 ± 0.74*	78.44

CRS, Cold-Restraint Stress.
Each entry represents mean values ± S.E.M.
Significant difference at P < 0.05 : "a" from vehicle (CRS) group ; "b" from NMDA group.

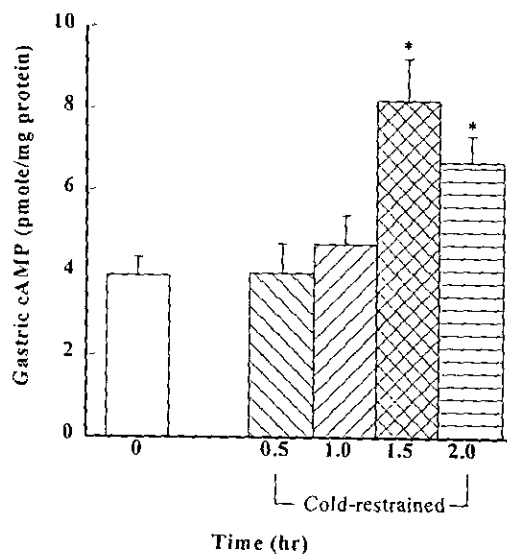


Fig. 1 The relationship between the duration of stress and the level of cAMP ratio in the stomach. Each column represents mean S.E.M. (n=5-6). Statistically significant difference at * $P < 0.05$ from 0 hr (no CRS) group.

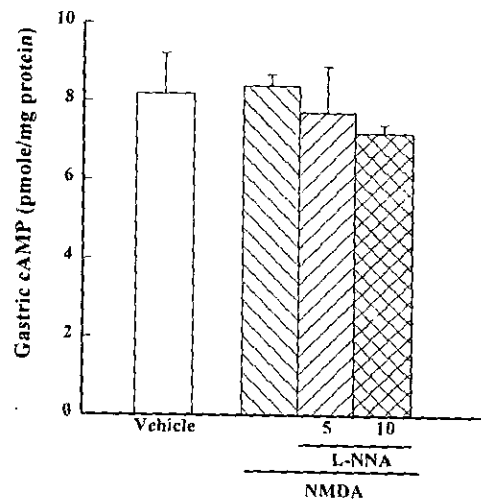


Fig. 3 Changes of cAMP in the mice stomach treated with Vehicle (0.9% NaCl) or L-NNA without and with addition NMDA. NMDA (2 mg), L-NNA (5 mg/kg) were given i.p. 30 min before CRS. Each column represents mean S.E.M. (n=5-6).

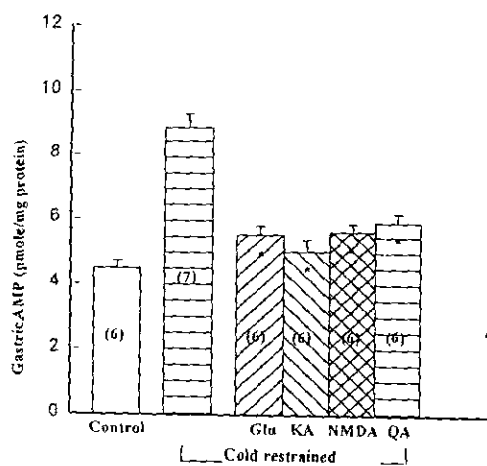


Fig.2 Effects of L-Glu, KA, NMDA or QA on cold-restraint stress and cAMP amounts in the stomach. (n=6-7). Each column represents mean $\pm$ SEM. (* $p < 0.05$, compared with untreatment group.)

四、計畫成果自評

本計畫之目的有三:

本計畫是二年一貫之研究

a. 壓力引起胃潰瘍之胃內之分子機轉

(cAMP 和 cGMP, IP₃ cAMP/cGMP 變化的關係)。

b. 壓力引起胃潰瘍和各種受體對於胃黏膜之防禦機轉的研究。

c. 壓力引起潰瘍和興奮性胺基酸及 NO 間的關係之研究。

綜合以上之研究結果, 壓力引起胃潰瘍的作用機轉將被了解。興奮性胺基酸及其受體亞型酸對於壓力引起胃潰瘍之癒合的作用及胃內之信號傳訊的變化, 可提供胃潰瘍的治療上更多的資料。以為將來研究壓力引起胃潰瘍的治療上之指標。

五、參考文獻

1. Watkins JC, Krosgaard LP and Honore T: Structure-activity relationships in the development of excitatory amino acid receptor agonists and competitive antagonist. *TIPS*, 11:25-33, 1990.
2. Curtis DR and Johnson GAR: Amino acid transmitters in the mammalian central nervous system. *Ergebn Physiol.*, 69:94-188, 1974.
3. Monaghan DT, Bridges RJ and Cotman CW: The excitatory amino acid receptors: Their classes, pharmacology, and distinct properties in the function of the central nervous system. *Annu Rev Pharmacol Toxicol*, 29:365-402, 1989.
4. Moroni F and Lizzi S: The presence of N-methyl-D-aspartate - type receptors for glutamic acid in the guinea pig myenteric plexus. *Neurosci. Lett.*, 68:57-62, 1986.
5. Luzzi S, Zilletti S and Moroni F: Agonists, antagonists and modulators of excitatory amino acid receptors in the guinea-pig myenteric plexus. *Br. J. Pharmacol.*, 95:1271-1277, 1988.
6. Shannon HE and Sawyer BD: Glutamate receptors of the N-methyl-D-aspartate subtype in the myenteric plexus of the guinea pig ileum. *J. Pharmacol. and Exp. Ther.*, 25: 518-523, 1989.
7. Sugiyama H, Ito I and Watanabe M: Glutamate receptor subtypes may be classified into two major categories: A study on xenopus oocytes injected with rat brain mRNA. *Neuron*, 3:129-132, 1989.
8. Mayer ML and Miller RJ: Excitatory amino acid receptors, second messengers and regulation of intracellular Ca⁺⁺ in mammalian neurons. *TIPS*, 11:254-260, 1990.
9. Tsai LH, Tsai W and Wu JY: Effect of L-glutamic acid on acid secretion and immunohistochemical localization of glutamatergic neurons in the rat stomach. *J. Neurosci. Res.*, 38:188-195, 1994.
10. Tsai L. H., Huang L. R., Chen S.-H., Liu H.-J., and Chou L.-S, 1999 Effects of L-Glutamic Acid on Acid Secretion and Mucosal Blood Flow in the Rat Stomach. 42 (3):181-187.
11. Tsai LH, Lee Y-J, Wu, J-Y, 1999 Effect of excitatory amino acid neurotransmitters on acid secretion in the rat stomach. *J. of Biomedical Science*, 6: 36-44.
12. Alphin RS, Vokac VA, Gregory RL and Tawes JW: Role of intragastric pressure, pH, and pepsin in gastric ulceration in the rat. *Gastroenterology*, 73: 495-500, 1977.
13. Hyden LJ, Thomas G and West GB: Inhibitors of gastric lesions in the rat. *J. Pharm. Pharmac.*, 30: 244-246, 1978.
14. Djahanguiri B, Sadeghi DJ, Pousti A and Firouzabadi A: Effect of a single dose of phentolamine, MJ 1999 and isoproterenol on histamine-induced gastric ulcer in guinea pigs. *Eur. J. Pharmacol.* 2: 315-316, 1968.
15. Takagi K and Okabe S: The effects of drugs on the production and recovery processes of the stress ulcer. *Jap. J. Pharmac.*, 18:9-18, 1968.
16. Hase T and Moss J: Microvascular changes of gastric mucosa in the development of stress ulcer in rats. *Gastroenterology*, 65: 224-234, 1973.
17. Whittle BJR: Temporal relationship between cyclooxygenase inhibition, as measured by prostacyclin biosynthesis, and the gastrointestinal damage induced by indomethacin in the rat. *Gastroenterology*, 80:94-98, 1981.
18. Nagy L, Fiegler M, Mozsik GY, Nemeth M, Ruzsa CS and Javor T: Some metabolic and biochemical alterations during the

- development of stress ulcers in rats forced to swim. *Int. J. Tiss. Reac.*, 4:363-371, 1983.
19. Hanson HM and Brodie DA: Use of the restraint rat technique for study of the antiulcer effect of drugs. *J. Appl. Physiol.*, 15(2): 291-294, 1960.
 20. Garrick T, Buack S and Bass P : Gastric motility is a major factor in cold restraint-induced lesion formation in rats. *Am. Physiol. Soci.*, 250:G191-G199, 1986.
 21. Basso N, Materia A, Forlini A : Prostaglandin generation in the gastric mucosa of rats with stress ulcer. *Surgery*, 94:104-108, 1983.
 22. Arakawa T, Kobagashi K and Nakamura H: Effect of water immersion stress on prostaglandin E2 in rat gastric mucosa. *Gastroenterol Jpn*, 16:236-241, 1981.
 23. Watanabe W: Some pharmacological factors involved in the formation and prevention of stress ulcer in rats. *Chem. Pharm. Bull*, 14:101-107, 1966.
 24. Mersereau WA, Hinchey EJ: The role of hypothermia-induced gastric hypercontractility in the genesis of the restraint ulcer. *Can. J. Surg*, 24:622-625, 1981.
 25. Beattie DE: Effect of drugs on rats exposed to cold-restraint stress. *J. Pharm. Pharmac*, 29:748-751, 1977.
 26. Dag KJE, Lubitz V and Jacobson KA: Effects of N⁶-cyclopentyl adenosine and 8-cyclopentyl-1,3- dipropylxanthine on N-methyl-D-aspartate induced seizures in mice. *Eur. J. Pharmacol.*, 249:265-270, 1993.
 27. Lehmann J, Schneider J, Tsai C, Pastor G and Wood PL: CPP, a selective N-methyl-D-aspartate (NMDA)-type receptor antagonist: Characterization in vitro and in vivo. *J. Pharmacol. Exp. Ther.*, 240:737-746, 1987.
 28. Meldrum and Chapman: Anticonvulsant action of 2-amino-7-phosphonoheptanoic acid against chemically- induced convulsion. *Excitatory amino acids and Anticonvulsant drug action*, 634, 1982.
 29. Takeuchi K, Ueshima K, Ohuchi T and Okabe S: The role of capsaicin-sensitive sensory neurons in healing of HCl-induced gastric mucosal lesions in rats. *Gastroenterology*, 106:1524-1532, 1994.
 30. Hagel J, Renner H, Rupp H and Domschke W: Gastric cytoprotection by actacids and papaverine in rats. *Hepato-gastroenterol*, 29:271-274, 1982.
 31. Hollander D, Tarnawski A and Gergely H: Protective effect of sucralfate against alcohol-induced gastric mucosal injury in the rat. *Gastroenterology*, 88:366-374, 1985.
 32. Leung FW, Guth PH, Scremin OU and Kauffman GL: Regional gastric mucosal blood flow measurements by hydrogen gas clearance in the anesthetized rat and rabbit. *Gastroenterology*, 87:28-36, 1984.