NMDA 或/和 甘胺酸在鼠胃生理角色之研究

Physiological Roles of NM1-D-A(NMDA) or/ and Glycine on The Stomach

中文摘要

本研究探討 NMDA(N-methyl-D-aspartate)或/和 甘胺酸(glycine)對於大白鼠離體鼠胃酸分泌及其在小白鼠壓力性胃潰瘍上的影響。

在大白鼠離體鼠胃上灌流甘胺酸 10^{-6}M 到 10^{-2}M 可刺激胃酸分泌，且在 10^{-3}M 可達自發性胃酸分泌的 1.6 倍，及最大刺激效果。此種刺激胃酸分泌的作用可被 strychnine, atropine, tetrodotoxin , bicuculline 及 proglumide 所抑制，但無法被 cimetidine 所抑制。然而，單獨灌流 NMDA10^{-4}M 和 10^{-5}M 時，對于自發性胃酸分泌並無影響，但可降低由 oxotremorine 誘導的胃酸分泌，且此作用可因肝安酸 10^{-6}M 的加入而加強其抑制效果，但此加強作用無法被 strychnine 所拮抗。另一部份探討 NMDA 對壓力性潰瘍的保護作用及 cAMP/cGMP 比率(cAMP/cGMP ratio)變化，以推測 NO 和氨基酸在此保護作用中所扮演的角色。結果顯示不同壓力時間導致胃潰瘍的程度與 cAMP/cGMP 比率成正比。當腹腔投與 NMDA0.2mg/kg-2 mg/kg，對降低潰瘍面積產生可達 70%的預防效果；此潰瘍減少時屬胃執中 cAMP/cGMP 比率有下降之現象。若同時投與 NMDA 與甘胺酸可增強對壓力性潰瘍的保護，且在 L-NNA(NO synthase inhibitor)10mg/kg 時可拮抗 NMDA 對壓力的作用。

由上述結果中發現，肝氨酸刺激胃酸分泌的作用可能主要經由膽素激導神經(cholinergic neuron)上的對 strychnine 敏感的甘胺酸受體(strychnine-sensitive glycine sites)來調節胃酸的分泌。另一方面，NMDA 可降低油 oxotremorine 所誘導的胃酸分泌，且甘胺酸可經由對 strychnine 不敏感的甘胺酸受體(strychnine-insensitive glycine sites)來調節 NMDA 受體(NMDA receptor)的活性。此外，NMDA 在壓力性潰瘍上可能參與胃黏膜障(mucosal barrier)之生理調節。其機制可能是由於處促使內生性 NO 的釋放，且降低 cAMP/cGMP 比率；而本研究中之甘胺酸可能是參與調節 NMDA 受體活性的內生性物質(endogenous ligand)。

英文摘要

The effect of NMDA(N-methyl-D-aspartate)or/and glycine on acid secretion from the isolated rat stomach and cold-restraint stress (CRS)-induced gastric mucosal lesions in mice were investigated herein.

NMDA or/and glycine on acid secretion were studied using the everted preparation of rat stomach. Glycine at 10^{-6}M to 10^{-2} M induced acid secretion, and the maximal

secretion was obtained at 10^{-3} M, that is approximately 1.6-fold of the spontaneous secretion. Stimulation of acid secretion by glycine at 10^{-3}M was inhibited by strychnine, atropine, bicuculline and proglumide, but not by cimetidine. NMDA at 10^{-4}M and 10^{-5}M alone had no effect on acid secretion, but reduced the oxotremorine-stimulated acid secretion . These response of NMDA were potentiated by glycine 10^{-6}M in the perfusing medium. The potentiation of NMDA responses by glycine was not prevented by strychnine at 10^{-6}M.

On the other hand, whether NMDA protects gastric mucosa via NO, enhanced by glycine, and by altering cAMP/cGMP ratio were studied using cold-restraint stress()CRS-induced gastric lesions in mice. Gastric lesions induced by CRS caused an increase of cAMP/cGMP ratio were studied using cold-restraint stress(CRS)-induced gastric lesions in mice. Gastric lesions induced by CRS caused an increase of cAMP/cGMP ratio in the stomach. NMDA administered intraperitoneally (i.p.) to mice at 0.2 mg/kg-2 mg/kg showed a protective effect on gastric lesions induced by CRS. NMDA at 1 mg/kg (i.p.) had about 70％ prevention on the development of gastric ulcers. A high correlation ()$r=0.779, p<0.001$) of NMDA treatment and reduction of CRS-induced ulcer index by CRS was observed. NMDA significantly attenuated the increase in the cAMP/cGMP ratio and gastric lesions on the CRS stomach. Glycine (0.2mg/kg – 0.5 mg/kg) dose-dependently enhanced the protective effect of NMDA on mucosal layer in the CRS stomach.L-NNA (N^G-nitro-L-arginine, a NO synthase inhibitor,i.p.)at 10 mg/kg potentiated the CRS-induced gastric lesions.

These results suggest that 1.)glycine induces acid secretion via strychnine-sensitive glycine sites, probably located mainly in the cholinergic neurons; 2)NMDA reduces the oxotremorine-stimulated acid secretion, and the response is potentiated by glycine via strychnine insensitive glycine sites to modulate NMDA sensitivity; 3.)NMDA or/and glycine may be involved in the modulation of gastric acid secretion; 4.) NMDA receptors may participate in a physiological modulation of gastric mucosal barrier by relesing endogenous NO and attenuating the elevation of cAMP/cGMP ratio in the CRS stomach; 5.)glycine may also be an endogenous ligand capable of modulating NMDA sensitivity.

Key Word : NMDA, glycine, isolated stomach,
acid secretion, cold-restraint stress, NO.