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Effects of L-Glutamic Acid on Acid Secretion and Mucosal Blood Flow in the Rat Stomach

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Abstract

The effect of intravenous administration of L-glutamic acid (L-Glu) on gastric acid secretion and gastric mucosal blood flow (GMBF) in anesthetized rats were investigated. Infusion with synthetic L-Glu alone had no effect on spontaneous acid secretion. However, L-Glu reduced histamine- (2 mg/kg/hr) or oxotremorine- (1 μg/kg/hr) stimulated acid secretion, whereas L-Glu had no effect on acid secretion induced by pentagastrin (8 μg/kg/hr). Furthermore, this inhibitory effect of L-Glu on histamine- or oxotremorine- stimulated acid secretion was blocked by 6,7-dinitroquinoxaline-2,3-dione (DNQX), a non-NMDA receptor antagonist. The effect of L-Glu on gastric mucosal microcirculation in the anesthetized rats was evaluated by using Laser Doppler Flowmetry (LDF). The results showed that L-Glu did not significantly reduce both mucosal and serosal blood flow in stomach. No significant modulatory effect on histamine- or oxotremorine-stimulated increase in GMBF was noted after infusion with L-Glu. It is concluded that L-glutamic acid is capable of the modulating of gastric acid secretion via ionotropic non-NMDA receptors, but do not affect on GMBF. However, L-glutamic acid showed no effect on acid secretion by itself.

Key Words: L-glutamic acid, histamine, oxotremorine, non-NMDA Receptor, gastric acid secretion, gastric mucosal blood flow

Introduction

Excitatory amino acids (EAAs), particularly, L-glutamic acid (L-Glu) is generally accepted as the main transmitters mediating synaptic excitation in the mammalian CNS (1, 6-8, 17, 25). It is believed that EAAs exert their effects either by activating ionotropic receptors which lead directly to the opening of ion channels, e.g., Na^+, K^+, and Ca^{2+} channels, or by stimulating metabotropic receptors which activate phospholipase C in a G-protein-mediated fashion leading to increased intracellular levels of inositol polyphosphates, and diacyl glycerols (17, 21, 25, 34, 40). In addition to their function as a major excitatory neurotransmitter in the CNS, EAAs and their receptors have also been identified in the mammalian enteric nervous system and are believed to play important functions there (20, 26, 33). L-Glu has been shown to serve as neurotransmitters acting at the NMDA receptor to control the motility of intestine perhaps through their interaction with cholinergic neurons (20, 26, 33). On the other hand, L-Glu has been reported to reduce the oxotremorine-, histamine- or gastrin-stimulated gastric acid secretion in the isolated stomach via non-NMDA (AMPA/QA and KA) ionotropic glutamate receptors (41). Previous studies in this laboratory have shown evidence for the presence of glutamatergic neurons in the stomach (37).

Several investigations have demonstrated a consistent relationship between gastric acid secretion and gastric blood flow (2-4, 10, 12, 16, 22, 27). It is known that gastric secretagogues such as histamine

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and pentagastrin cause an increase in gastric mucosal blood flow (GMBF) simultaneously with an increase of acid secretion (11, 16, 17, 24, 39), but the mechanisms underlying such GMBF responses yet to be determined. In fact, Svanes et al (35) and Perry et al (30) showed a linear relationship between GMBF and acid secretion, which suggested that GMBF might be important in maintaining acid secretion through the supply of O_2 and substrates to parietal cells.

In this report, evidence is presented to show that in vivo administration of L-Glu to rats reduces the oxotremorine- or histamine-stimulated gastric acid secretion perhaps via non-NMDA glutamate receptors. In addition, the effect of intravenous administration of L-Glu on GMBF in anesthetized rats is also investigated.

Materials and Methods

Animals

Males Sprague-Dawley rats were housed in air-conditioned room with 12/12 hr light/dark cycles, fed with regular chows and allowed free access to drinking water. The rats weighing 250-300 g were fasted but were allowed to drink water for 24 hr before sacrificed for each experiment.

Measurement of Gastric Secretion

The rats were anesthetized with pentobarbital sodium (45 mg/kg, i.p.). A cannula (Y-shaped) was inserted into the trachea to facilitate of spontaneous breathing and occasional aspiration of secretions. A low-pressure transducer connected to one side of the cannula was used to monitor respiratory movements. The esophagus was carefully ligated and the trachea was cannulated at the cervical portion. The abdomen was opened by a small midline incision and a round-tip polyethylene cannula (3.5 cm in length and 0.4 cm in diameter) was inserted into the stomach via an incision in the duodenum. The cannula was held in place by two ligatures around the duodenum, one to the oral and the other to the anal directions of the incision and the abdominal incision was sutured. Drugs were infused via cannula inserted into the bilateral femoral veins. Body temperature, maintained at 37 ± 0.5 °C by a heating pad and a heating lamp, was monitored with a rectal thermometer. The animals received 1 ml of physiological saline every 1 hr through femoral vein to avoid dehydration during the observations. In addition, haematocrit values were also obtained before and after the experiment to check for adequate hydration of the animals.

The gastric lumen was perfused at a rate of 1 ml/min with saline solution, pH 7.0, at 37°C and the perfusate was automatically titrated in the reservoir with NaOH 0.01 N using a pH stat (Autotitrator VIT90, Radiometer Corp., Copenhagen, Denmark). The femoral vein was cannulated for administration of drugs. The amount of basal acid secretion was collected and determined after a 40-60 min equilibration period. The basal acid secretion during the 10-min period prior to the experiments was about 0-4 μEq/10 min. The responses to drug treatments in the stomach were expressed as the secretory ratio (R) which is defined as described elsewhere (38).

$$R = \frac{\text{Acid sec tetion evoked by drugs}}{\text{Average spontaneous acid sec retion}}$$

Measurement of Gastric Mucosal Blood Flow (GMBF)

Under anesthesia, the abdomen was opened through a midline incision, the gastrohepatic ligaments were cut, and the stomach was gently exteriorized. Since movements of the stomach and respiration during the experiment could change the probe position, the stomach was gently placed on a transparent four-legged table-like plastic slide and fixed with fine sutures to metal needles inserted at both sides of the stomach. Fixation by this method would eliminate motion artifacts. A small bore (8.5-mm od.) plastic cannula was then inserted through a small incision in the forestomach and tied in place to allow free access to the gastric lumen. Gastric blood flow (GBF) was recorded continuously with a Laser Doppler Flow (LDF) monitor (Model MBF3D, Moor Instruments Ltd, Devon) as described before (36). The principle of LDF for assessment of GBF has been described previously in detail (9, 13). A stainless steel laser optic probe (1.65-mm od.; Moor Instruments) was inserted into the gastric lumen via the plastic cannula and was allowed to rest gently on the gastric corpus mucus. Warm 37°C saline was poured continuously over the stomach to keep the tissues moist. The probe was placed just above and perpendicular to the mucosal or serosal surface, and its position fixed by a metal stand. Stable recordings could be obtained for a long period up to 1 hr after intravenous administration. Injection of 1-ml saline had no effect on the stability of the Laser Doppler signal. The readings were transferred on to floppy disks for subsequent analysis.

Experimental Protocol

The following studies were performed to investigate the mechanisms of GMBF responses induced by intravenous infusion of histamine or oxotremorine. Previous studies showed that

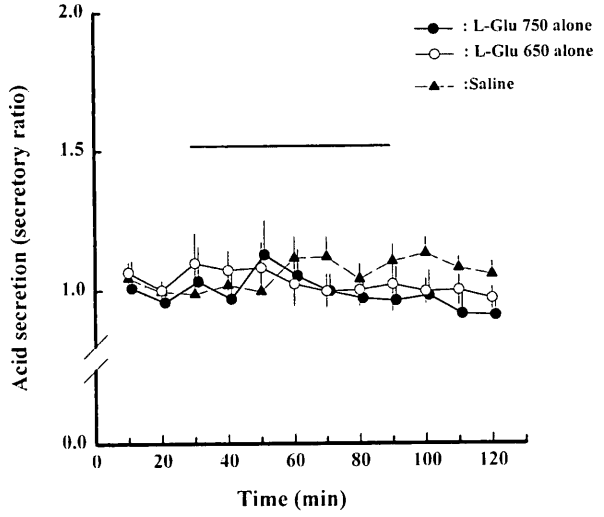

Fig. 1. Effects of L-glutamic acid on spontaneous acid secretion in perfused stomach of anesthetized rats. Acid secretion expressed as secretory ratio was plotted against the duration expressed in min. L-glutamic acid (750 μg/kg/hr) and L-glutamic acid (650 μg/kg/hr) was infused intravenously via the femoral vein. Data represent mean ± SEM of values determined for specimen collected every 10-min from 6 to 7 rats.

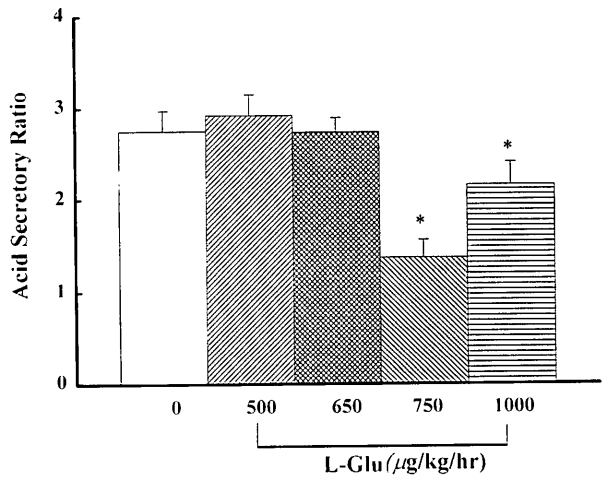

Fig. 2. Dose-dependent inhibition of histamine-stimulated acid secretion by infusion of L-glutamic acid in anesthetized rats. Acid secretion as secretory ratio was plotted against a 30-min period. Each dose of L-glutamic acid was added 30 min after the application of histamine (2 mg/kg/hr). Gastric acid secretions in the fraction collected during the 30-min period after L-Glu administration was determined. Data represent mean ± SEM (n=6). * Significant difference ($p<0.05$) from the response of group of rats treated with histamine alone.

intravenous infusion of histamine (2 mg/kg/ hr) or oxotremorine (1 μg/kg/ hr) increased both GMBF and acid secretion. These same doses of histamine and oxotremorine were used in the subsequent studies.

The effects of L-Glu (750 μg/kg/ hr) on GMBF responses to histamine and oxotremorine were examined. The animals were intravenously infused with saline for 10 min followed by subsequent infusion with histamine (2 mg/kg/hr) or oxotremorine (1 μg/kg/ hr) for another 30 min. L-Glu (750 μg/kg/ hr) was intravenously administered 20 min after the histamine or oxotremorine infusion. Control animals received saline as the vehicle via the same route.

Drugs

L-glutamic acid, oxotremorine, histamine dihydrochloride, pentagastrin, and pentobarbital sodium were purchased from Sigma Chemical Co. (St. Louis, MO). 6,7-dinitroquinoxaline-2,3-dione (DNQX) was obtained from RBI (Natick, MA). All other chemicals used were of reagent grade and obtained from regular commercial sources.

Statistical Analysis

Results were expressed as mean ± SEM for each study (n: sample number). Data were analyzed by Dunnett's test or Student's t-test and a P value of 0.05 or less was considered statistically significant.

Results

Effect of L-Glutamic Acid on Spontaneous Acid Secretion

In general, spontaneous acid secretion reached a steady state after equilibration for two hours. The average of spontaneous acid secretion after equilibration was 1.691 ± 0.992 μmol/10 min, which was taken as the control value. L-Glu alone at 650 μg/kg/hr or 750 μg/kg/hr had no significant effect on the spontaneous acid secretion (Fig. 1).

Effect of L-Glutamic Acid on Noncholinergic Agents-Induced Acid Secretion

Histamine and pentagastrin, two non-cholinergic agents, were employed to stimulate acid secretion in the rat stomach. Infusion of histamine at 2 mg/kg/hr stimulated acid secretion to an extent of about 2.7 times at 70 min interval (Figs. 2, 3A). L-Glu was found to block acid secretion induced by histamine. L-Glu (500 μg/kg/hr to 1 mg/kg/hr) showed a dose-dependent inhibition of histamine (2 mg/kg/hr)-induced increase in acid secretion (Fig. 2). L-Glu at 750 μg/kg/hr inhibited about 80% of histamine (2 mg/kg/hr)-induced acid secretion. The secretory ratio was reduced from about 2.748 to 1.364 at 80 min by 750 μg/kg/hr L-Glu (Fig. 3A). The 6,7-dinitro-quinoxaline-2,3-dione (DNQX) is non-NMDA receptor antagonists (6, 7). DNQX was found to have no significant effect on the spontaneous acid secretion

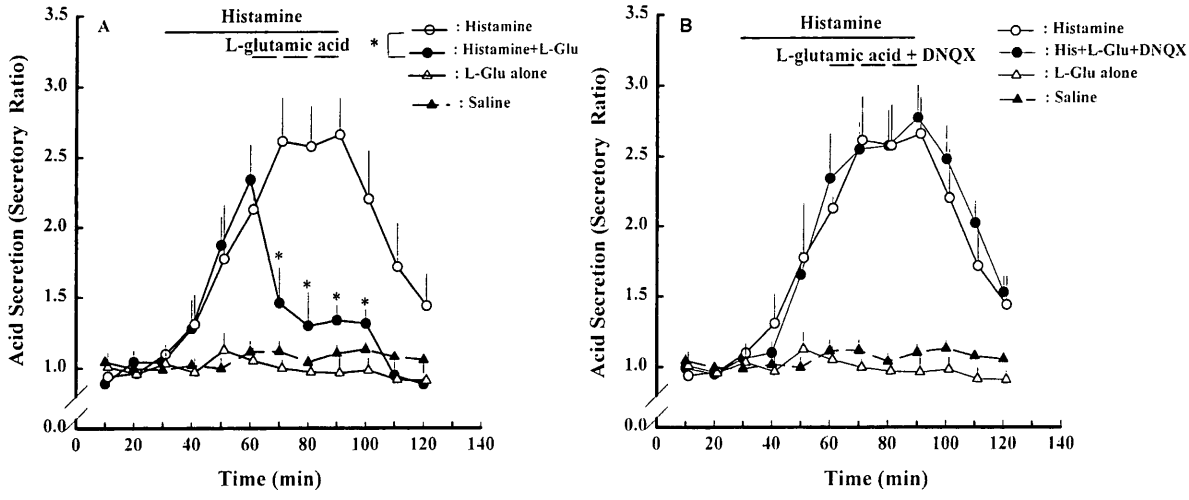

Fig. 3. Effects of L-glutamic acid or/and DNQX on histamine-induced acid secretion in perfused stomach of anesthetized rats. Acid secretion expressed as secretory ratio was plotted against the duration after L-Glu administration in min. Histamine (2 mg/kg/hr) was infused intravenously via the femoral vein. A. Histamine (2 mg/kg/hr) plus L-Glu (750 μg/kg/hr) was infused intravenously at 30 min after histamine infusion. B. Histamine (2 mg/kg/hr) plus L-Glu (750 μg/kg/hr) and DNQX (750 μg/kg/hr) were infused intravenously at 30 min after histamine infusion. Data represent mean ± SEM of values determined for specimens collected every 10-min from 6 to 7 rats. * Significant difference ($p<0.05$) between the responses to histamine alone and to histamine in the presence of L-Glu.

at a dose of 750 μg/kg/hr (data not shown). Furthermore, this inhibitory effect of L-Glu on histamine-stimulated acid secretion was completely reversed by DNQX (750 μg/kg/hr) (Fig. 3B).

Pentagastrin was also employed to stimulate acid secretion in the rat stomach. Pentagastrin at 8 μg/kg/hr stimulated acid secretion to 7-folds at 80 min interval. L-Glu at 750 μg/kg/hr did not block such pentagastrin stimulated acid secretion (Fig. 4).

Effect of L-Glutamic Acid on Cholinergic Agent-Induced Acid Secretion

Oxotremorine, the muscarinic cholinergic receptor agonist, at 1 μg/kg/hr induced an increase in acid secretion and the reaction reached a maximal response about 30 min after the oxotremorine infusion. The maximal secretory response was 3.412 ± 0.286 fold (n = 6) (Fig. 5). Acid secretion induced by 1 μg/kg/hr of oxotremorine was effectively inhibited by L-Glu. The secretion was reduced from about 3.0 fold to 2.0 fold at 90 min after infusion with 750 μg/kg/hr of L-Glu (Fig. 5A). L-Glu also inhibited about 50% of oxotremorine-induced acid secretion. This inhibitory effect of L-Glu on oxotremorine-stimulated acid secretion was blocked by DNQX at 750 μg/kg/hr (Fig. 5B).

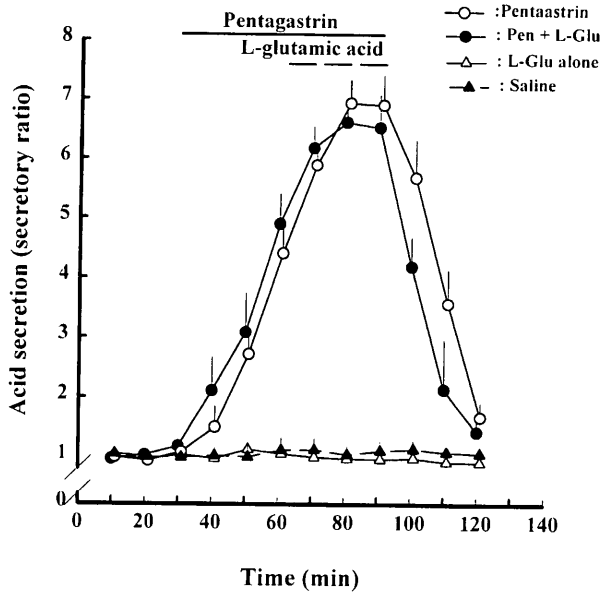

Fig. 4. Effects of L-glutamic acid on pentagastrin-stimulated acid secretion in perfused stomach of anesthetized rats. Acid secretion expressed as secretory ratio was plotted against the time intervals expressed in min. Pentagastrin (8 μg/kg/hr) was infused intravenously via the femoral vein. Pentagastrin (8 μg/kg/hr) plus L-Glu (750 μg/kg/hr) was infused intravenously at 30 min after pentagastrin infusion. Data represent mean ± SEM of values determined for specimens collected every 10-min from 6 to 7 rats.

Effect of L-Glutamic Acid on gastric mucosal blood flow (GMBF)

The use of LDF to study the effect of L-Glu (750 μg/kg, iv.) on gastric mucosal microcirculation was performed in the anesthetized rats. However, in the control studies, bolus intravenous injection of isotonic saline showed no significant action on resting LDF

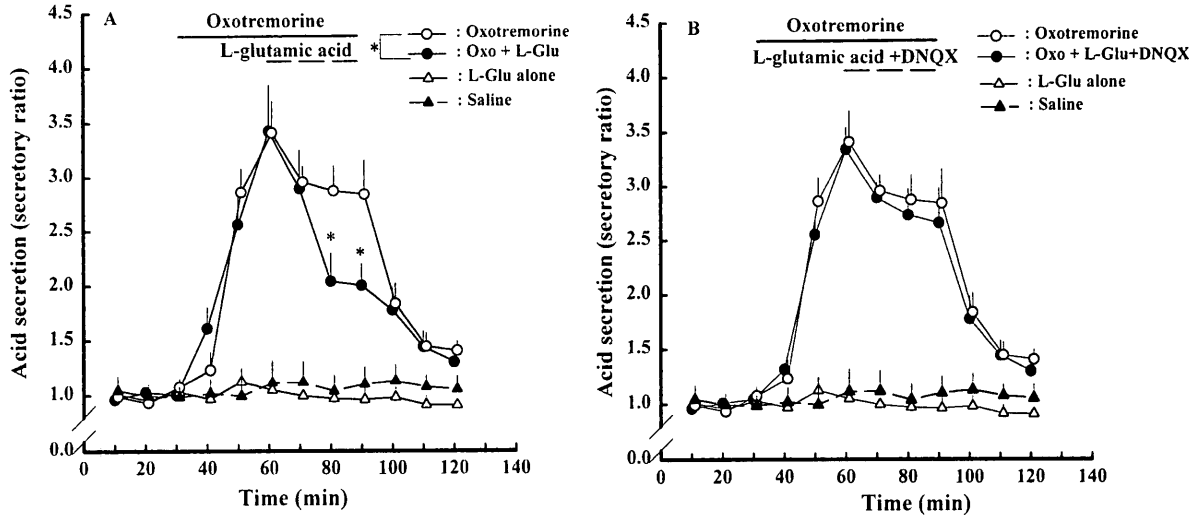

Fig. 5. Effects of L-glutamic acid or/and DNQX on oxotremorine-stimulated acid secretion in perfused stomach of anesthetized rats. Acid secretion expressed as secretory ratio was plotted against the time intervals expressed in min. Oxotremorine (1 μg/kg/hr) was infused intravenously via the femoral vein. A. Oxotremorine (1 μg/kg/hr) plus L-Glu (750 μg/kg/hr) were infused intravenously 30 min after histamine infusion. B. Oxotremorine (1 μg/kg/hr) plus L-Glu (750 μg/kg/hr) and DNQX (750 μg/kg/hr) were infused intravenously 30 min after histamine infusion. Data represent mean ± SEM of values determined or specimens collected every 10-min from 6 to 7 rats. * Significant difference ($p<0.05$) between the response of rats treated with oxotremorine alone and those with oxotremorine and L-Glu.

(n=5). L-Glu did not significantly reduce either mucosal or serosal blood flow of stomach. Intravenous infusion of histamine at 2 mg/kg/min increased GMBF. L-Glu had no influence on histamine-stimulated GBF on both mucosal and serosal blood flow in stomachs (Fig. 6).

Oxotremorine at 1 μg/kg/hr infusion resulted in only a slight increase in GMBF. L-Glu at 750 μg/kg by intravenous injection had little influence on oxotremorine-increased GMBF (data not shown).

Discussion

In this communication we further support the notion that L-Glu may play an important role in the stomach. First of all, L-Glu markedly reduces gastric acid secretion induced by histamine or oxotremorine, but not that by pentagastrin. Secondly, L-Glu alone has little effect on spontaneous acid secretion. Third, this inhibitory effect of L-Glu on histamine- or oxotremorine-stimulated acid secretion can be blocked by DNQX, a non-NMDA receptor antagonist. Forth, the effects of L-Glu on histamine- or oxotremorine-stimulated acid secretion have no influence on histamine- or oxotremorine-induced GMBF.

Central L-Glu administration is known to increase GMBF, but not histamine- or oxotremorine-stimulated acid secretion (29). Therefore, the effects of intravenously administered L-Glu provide evidence for the stimulatory role of peripheral glutamate receptors in the regulation of acid secretion, because little L-Glu across the blood-brain barrier to the brain

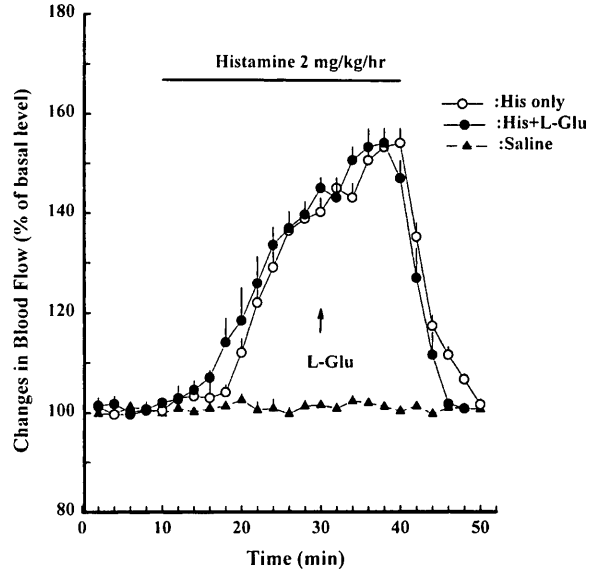

Fig. 6. Effects of L-glutamic acid on histamine-induced increase in mucosal blood flow. Histamine (2 mg/kg/hr) was i.v. infused. L-Glu (750 μg/kg) was i.v. administrated. Control (n=8), normal saline alone. Histamine alone (n=6), and histamine plus L-Glu (n=6). Each point represents mean ± SEM.

(5). Previous studies in this laboratory showed that 10^{-7} M L-Glu in vitro markedly inhibited the histamine-, oxotremorine-, gastrin- and dimethylphenylpiperazinium (DMPP)-stimulated acid secretion (37). Present results indicate that intravenous administration of L-Glu inhibited only histamine-, and oxotremorine-induced acid secretion.

Therefore, it appears that the inhibitory effect of in vitro administration of L-Glu on the stimulated acid secretion is much potent than its effect in vivo. However, they are all mediated through non-NMDA receptors (AMPA receptors).

It is interesting that L-Glu inhibits oxotremorine-induces acid secretion (37, 38). Oxotremorine stimulates acid secretion by binding to M_3 muscarinic receptors (14, 32) on the membrane of the parietals cell. Binding of oxotremorine to its receptors open Ca^{2+} channels and allows Ca^{2+} to enter the cell, increasing level of free Ca^{2+} (18, 19, 31). Furthermore, the inhibition of oxotremorine-induced acid secretion by L-Glu is completely reversed by DNQX, a specific antagonist of AMPA/QA receptors, suggesting that the action of L-Glu is mediated by non-NMDA type ionotropic glutamate receptors, e.g., AMPA/QA receptors and not by metabotropic glutamate receptors.

Several studies have shown that increases in blood flow and acid secretion run parallel after various types of secretory stimuli. These studies measured gastric blood flow (GBF) and/or GMBF (2-4, 10, 12, 15, 16, 27). The relationship between blood flow and acid secretion is not linear, however, as it is also dependent of the O_2 uptake by the stomach. At normal (low) flow rates, the dependence of acid production on blood flow might be demonstrated. As the delivery of oxygen is indispensable for maintenance of the high energy-demanding process of HCl production. The opposite is also true: in cases of blood supply sufficient to fully perfuse all the gastric tissue, acid production may be independent of GMBF, but the latter might become rate-limiting at very high rates of secretion (11, 30).

Histamine seems to increase both GMBF and acid secretion (24). The present finding indicate that L-Glu inhibits histamine-induced acid secretion but not histamine-increased GMBF. Whether these effects are associated with both H_1 (vasodilation) and H_2 receptors (HCl stimulation) is not yet clear; species differences (rat, rabbit, dog) may also influence the results so far. Histamine increased the GBF which was inhibited by diphenhydramine but not by cimetidine, suggesting a stimulation of H_1 receptors by histamine (39). Oxotremorine alone caused only a slight increase in GMBF (28). However, L-Glu had little influence on oxotremorine-increased GMBF.

In conclusion, L-Glu has the ability to inhibit histamine- or oxotremorine- induced acid secretion, but this L-Glu effect can be reversed by DNQX, non-NMDA type of ionotropic glutamate receptors. No significant modulatory fully effect on histamine- or oxotremorine-stimulated increase in GMBF was noted after L-Glu infusion. The relationship between acid secretion and mucosal blood flow is not linear. That the peripheral L-Glu may participate in the modulation of gastric function is the subject of ongoing investigation.

Acknowledgments

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