ニワトリにおけるコリン作働性胃酸分泌におよぼすproglumideおよびmetiamideの影響

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Effects of Proglumide and Metiamide on Vagally Stimulated Gastric Acid Secretion in Chickens

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Abstract. Effects of atropine (ATR, 0.5 mg/kg, i.v.), proglumide (PGM, 100 mg/kg, i.v.) and metiamide (MTM, 0.4 mg/kg, i.v.) on gastric acid secretion induced by vagal stimulation, carbamylcholine (CCh, 5 μg/kg, i.v.), tetragastrin (TG, 5 μg/kg, i.v.) and histamine (Hist, 10 μg/kg, i.v.) injections were examined by means of continuous pH recording of proventricular effluent in urethan anesthetized chickens. Birds were operated for fitting an esophageal cannula and gastric fistel, artificial respiration, bilateral vagotomy and instillation of physiological saline solution. Electrical stimulation (0.1 msec duration, 30 volts, 50 Hz, for 40 to 60 sec) was applied to Trunks communis n. vagi at the proximal region of the proventriculus where the proventricular rami (Rr. gastrici glandulares) branched. The vagal stimulation and the administration of CCh produced a biphasic profile of pH fall response consisting of an early transient and a secondary lasting phases. The transient response was larger in the degree of pH fall than the lasting one, and was inhibited by ATR but not by PGM and MTM. The lasting response was reduced by all of the three inhibitors. PGM and MTM inhibited pH fall responses induced by TG and Hist, respectively. These results show that the vagally stimulated acid secretion consists of an early transient response which is major component and a secondary lasting response which is minor component. It is suggested that the transient response is directly mediated by cholinergic transmission and the lasting response is possibly mediated by endogenous gastrin and histamine in the pathways sensitive to PGM and MTM.

It has been reported that the gastric acid secretion is mainly stimulated by endogenous gastrin which is present in the blood stream for the vagal excitation in mammals [5]. In the chickens, there have been some reports on the presence of gastrin in the gizzard [9], duodenum [6, 9] and intestine [9]. However, it has been reported that the role of the endogenous gastrin on acid secretion induced by vagal stimulation is doubtful in chickens from the lack of an inhibitory effect of proglumide on enhancement of gastric acid secretion evoked by vagal stimulation [7].

The present experiments were carried out to elucidate the effects of proglumide, an antigastrinic agent [10], and metiamide, a histamine H_2 receptor blocking agent [1], on cholinergically stimulated gastric acid secretion in anesthetized chickens.

Materials and Methods

Male chickens of Lameat strain (Nikkei Shokusan), weighing 3.5 to 4.8 kg, were used in this experiment. Gastric acid secretion was measured by continuous pH recording of proventricular effluent in chickens [7, 8] with some modifications of the original methods for rats [2]. All the birds were starved for 24 hr prior to use in the experiments

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and were anesthetized by a single intraperitoneal injection of urethan (1.7 g/kg). After anesthesis, birds were operated for artificial respiration with air, bilateral vagotomy, instillation of physiological saline solution and kept warm by electric heating matt and 60 watt incandescent light. The operative technique for proventricular perfusion has been described in detail in the previous paper [8].

The proventricular lumen was continuously perfused with a diluted sodium hydroxide solution (1.25×10^{-4} N) by using Manostatt cassette pump (Manostatt) at a flow rate of 2.0 to 3.0 m*l*/min. The pH of the perfusate emerging from the proventriculus was monitored by a pH meter (Labomate, Beckman and Toshiba) and recorded by a servo recorder (Technicorder Type 3047, Yokokawa). The basilic vein (V. basilica) was cannulated with a stainless steel tube connected to a silicone rubber tube which was connected to a syringe with a three way cock for the purpose of drug application.

Nerve stimulation was electrically performed with a stimulater (MSE-3R, Nihon Kohden Kohgyo). The stimulation was applied to Trunks communis n. vagi [11] at the proximal region of the proventriculus (0.1 msec duration, 30 volts, 50 Hz, for 40 to 60 sec).

All drugs were administered intravenously. The first injection was usually made 60 min after completing the operation. Drugs were injected in a volume of 0.35 to 0.48 m*l* followed by a washing injection of 1.0 m*l* saline solution.

Drugs used: carbamylcholine chloride (CCh) (Tokyo Kasei); histamine dihydrochoride (Hist) and atropine sulfate (ATR) (Wako Pure Chemicals); tetragastrin (TG) (Sana Yakuhin); proglumide (PGM) (donated by Kaken Kagaku); metiamide (MTM) (donated by Smith, Kleine and Fujisawa).

Results

Effects of vagal stimulation on continuous pH recording of proventricular perfusate was examined and the results are presented in Fig. 1. The electrical stimulation to the vagus nerve evoked a biphasic profile of pH fall response consisting of an early transient phase (TP) and a secondary lasting phase (LP). The TP response was larger in the degree of pH fall than the LP response. The biphasic response to the nerve stimulation was reproducible with 60 min or more intervals. ATR (0.5 mg/kg, i.v.) administered 10 min before the stimulation inhibited the biphasic response. PGM (100 mg/kg, i.v.) or MTM (0.4 mg/kg, i.v.) applied 10 min before the stimulation considerably reduced LP of the response but almost no effect on TP.

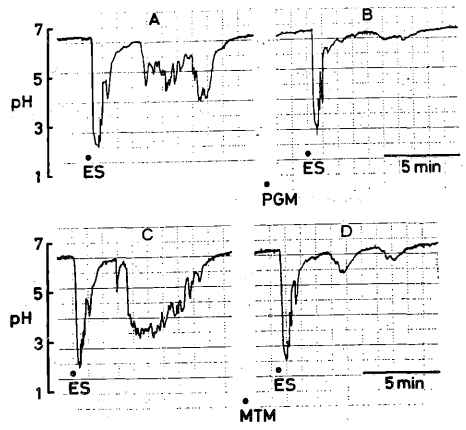

Fig. 1. Typical results for the effects of PGM (upper) and MTM (lower) on pH fall responses of proventricular perfusate induced by vagal stimulation (0.1 msec duration, 30 volts, 50 Hz, for 60 sec) on Trunks communis n. vagi at the proximal region of the proventriculus in chickens. ES, electrical stimulation; PGM (100 mg/kg, i.v.) or MTM (0.4 mg/kg, i.v.) was administered 10 min before the second stimulation applied 60 min after the first stimulation; A and C, control; B and D, after PGM and MTM, respectively.

The pH fall response were observed in chickens administered CCh (5 μg/kg, i.v.). The responses were divisible into two phases consisting of an early transient (TP) and a secondary lasting (LP) ones (Fig. 2) similar to the case in the vagal stimulation. The TP response was larger in the degree of pH fall than the LP response. The biphasic response evoked by CCh was blocked by ATR (0.5 mg/kg, i.v.) administered 10 min before CCh application. PGM (100 mg/kg, i.v.) or MTM (0.4 mg/kg, i.v.) applied 10 min before CCh administration considerably reduced CCh-induced LP of the response but was almost no effect on CCh-induced TP response. The inhibition of

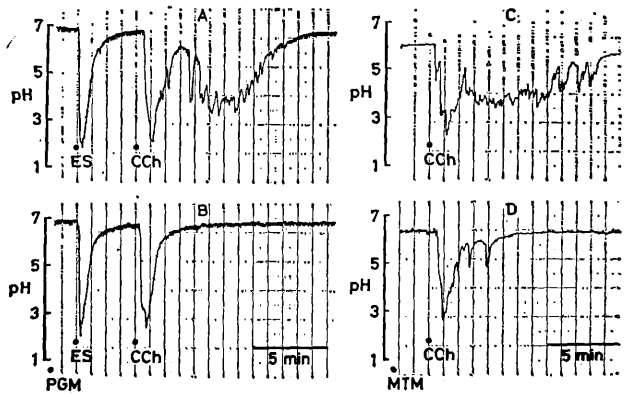

Fig. 2. Typical results for the effects of PGM and MTM on pH fall responses of proventricular perfusate induced by CCh in chickens.

ES, electrical stimulation with pulses of 0.1msec duration, 30 volts, 50 Hz and for 5 sec on Trunks communis n. vagi at the proximal region of the proventriculus; CCh, 5 μg/kg, i.v.; PGM (100 mg/kg, i.v.) or MTM (0.4 mg/kg, i.v.) was administered 10 min before the second application of CCh applied 60 min after the first administration of CCh; A and C, control; B and D, after PGM and MTM, respectively.

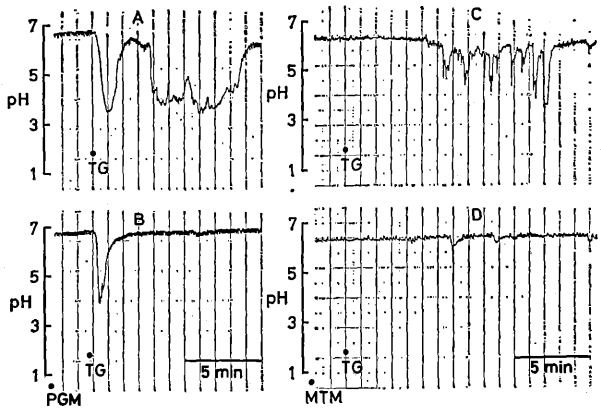

Fig. 3. Typical results for the effects of PGM and MTM on pH fall responses of proventricular perfusate evoked by TG in chickens.

TG, 5 μg/kg, i.v.; PGM (100 mg/kg, i.v.) or MTM (0.4 mg/kg, i.v.) was administered 10 min before the second application of TG administered 60 min after the first treatment with TG; A and C, control; B and D, after PGM and MTM, respectively.

LP by PGM or MTM was disappeared 60 min after the administration.

TG (5 μg/kg, i.v.) produced a pH fall response (Fig. 3). TG-induced pH fall also consisted of biphasic profile in many chickens (Fig. 3, A). In some birds, however, the transient phase of pH fall was lacking in the pH profile induced by TG (Fig. 3, C). TG-induced TP was relatively smaller in the degree of pH fall than cholinergically induced one. The both types of pH fall induced by TG was hardly affected by ATR (0.5 mg/kg, i.v.) had been administered 10 min before TG application. PGM (100

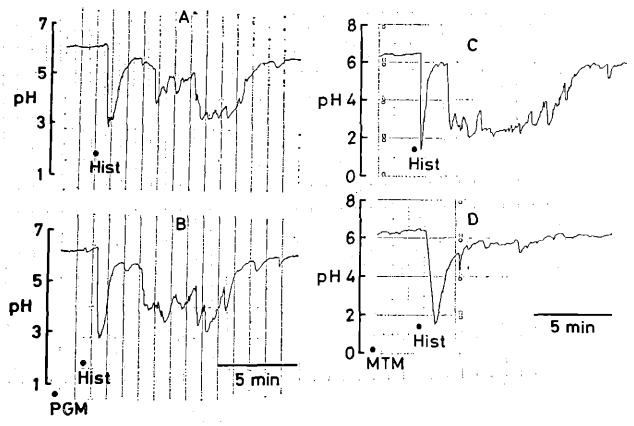

Fig. 4. Typical results for the effects of PGM and MTM on pH fall responses of proventricular perfusate elicited by Hist in chickens.

Hist, 10 μg/kg, i.v.; PGM (100 mg/kg, i.v.) or MTM (0.4 mg/kg, i.v.) was administered 10 min before the second treatment with Hist administered 60 min after the first application of Hist; A and C, control; B and D, after PGM and MTM, respectively.

mg/kg, i.v.) or MTM (0.4 mg/kg, i.v.) applied 10 min before administration of TG inhibited almost completely the secondary lasting pH fall produced by TG but only weakly the TG-evoked transient response.

Fig. 4 shows the effect of Hist (10 μg/kg, i.v.) on the pH of proventricular perfusate. Hist caused a biphasic pH fall similar to the case of the vagal stimulation or CCh treatment in all birds tested. Hist-evoked LP of pH fall response was inhibited only by MTM (0.4 mg/kg, i.v.) had been applied 10 min before treatment with Hist. TP of pH fall evoked by Hist was hardly affected by any of these inhibitors.

Discussion

Present experiments indicated that the vagally or CCh induced acid secretion had a biphasic profile consisting of TP and LP. TP was larger in the degree of pH fall than LP, suggesting that TP is a major component of the cholinergically evoked acid secretion and LP is a minor one. All the response to cholinergic stimulation was inhibited by treatment with ATR. The major component of the response was not inhibited by PGM and MTM. It seems, therefore, that TP is directly induced through cholinergic pathway on the secretory cell, oxyntico-peptic cell.

The LP was reduced by treatments with PGM, an antigastrinic [10], and MTM, a histamine H_2 receptor blocking agent [1], suggesting that the minor component is mediated by pathways which may include endogenous gastrin and histamine and therefore are sensitive to PGM and MTM in the chicken. The inhibitory effect of MTM on cholinergic enhancement of acid secretion in chicken is consistent with the findings in chicken by Goto and Watanabe, 1976 [3], 1978 [4] in which a stimulatory effect of methacholine was reduced by burimamide and cimetidine, histamine H_2 receptor blocking agents.

It has been known that the endogenous gastrin is present in the mucosal layer of the gizzard and intestinal tract [6, 9], although

the role of the endogenous gastrin on vagally stimulated acid secretion remains unclear since any inhibitory effect of PGM on acid secretion evoked by vagal stimulation for brief period (5 to 10 sec) at the cervical region has not been demonstrated [7]. In the present experiments, prolonging the stimulation period (40 sec or more) was needed for the minor component of acid secretion to occur in the chicken. The stimulation of the vagus on Trunks communis n. vagi at the proximal region of the proventriculus made it possible to prolonging the stimulation period without given any stressful effects on the birds. These findings suggested the possibility that endogenous gastrin in the gizzard and intestinal tract might be released by cholinergic mechanism.

From the results, it is concluded that two or more pathways are included in cholinergically induced acid secretion. One is directly induced by cholinergic stimulation on the oxyntico-peptic cell in the proventriculus, which supports the major part of secretion. The others are pathways mediated by gastrinergic and histaminergic mechanisms, which are stimulated directly and/or indirectly through cholinergic transmission, but their roles in the secretion is minor.

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要　約

ニワトリにおけるコリン作働性胃酸分泌におよぼす proglumide および metiamide の影響: 西村昌数・朴駿鎏・中川治人・浦川紀元（東京大学農学部家畜薬理学教室）——ニワトリの腺胃における胃酸分泌に対する迷走神経刺激およびカルバコール（CCh, 5 μg/kg, i.v.）の促進作用におよぼすアトロピン（ATR, 0.5 mg/kg, i.v.），プログルミド（PGM, 100 mg/kg, i.v.）およびメチアミド（MTM, 0.4 mg/kg, i.v.）の影響を検討した．ニワトリ（ラミート種，雄，3.5～4.8 kg）にウレタン麻酔，人工呼吸，両側迷走神経切除，生理食塩水の補液および保温を施し，その腺胃に急性フィステルを装着し，胃内灌流液の pH を連続記録した．食道腺胃移行部で迷走神経を電気刺激（50 Hz, 0.1 msec, 30 volt, 40～60 sec）した．迷走神経刺激および CCh の適用は，一過性（transient phase; TP）およびこれに続く持続性（lasting phase; LPの2相から成る低 pH 下反応をもたらした．TP 反応は ATR により抑制されたが，PGM および MTM によっては影響されなかった．LP 反応は ATR, PGM および MTM のいずれによっても抑制された．PGM および MTM は，それぞれテトラガストリン（5 μg/kg, i.v.）およびヒスタミン（10 μg/kg, i.v.）による pH 低下反応を抑制した．以上の成績から，ニワトリにおけるコリン作働性の胃酸分泌促進には，プログルミドおよびメチアミド感受性の過程が部分的に含まれることが考えられ，このことは，コリン作働性の胃酸分泌促進に内因性のガストリンおよびヒスタミンが関与する可能性を示唆している．