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EFFECTS OF HISTAMINE AND CIMETIDINE ON CHLORIDE SECRETION IN ISOLATED MONKEY GASTRIC MUCOSA

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ABSTRACT The stripped gastric mucosa of Rhesus monkeys were used to study electrical properties and chloride secretion. A potential difference (PD) across the mucosal membrane was seen with serosa being electropositive. The magnitude of PD and short-circuit current (I_{SC}) were found to be close to that of dog gastric mucosa. At resting state, Cl^- was secreted from serosal to mucosal side, and this secretion was greatly stimulated by histamine. Cimetidine completely blocked the stimulating effect of histamine on Cl^- secretion.

KEY WORDS *Macaca mulatta*; gastric mucosa; potentiometry; chlorides (^{36}Cl); histamine; cimetidine

In amphibian[1-3] and mammalian[4,5] gastric mucosa *in vitro*, under resting conditions, there is very little acid secretion but an electropositive potential difference (PD) toward serosal side. Histamine stimulates H^+ secretion and lowers PD[2,5]. There is probably a H_2 receptor at the parietal cells[6]. In the resting state the dog stomach secretes more Cl^- than H^+[5]. The secretion of Cl^- by rat gastric mucosa was blocked by thiocyanate[7]. Cimetidine inhibits H^+ secretion in humans[8] and dogs[8,9]. The monkey is the only species closely related to humans as shown in renal studies[10]. This investigation was intended to use gastric mucosa of Rhesus monkeys to study the gastric secretion, the electrical properties, and the effects of histamine and cimetidine.

MATERIALS AND METHODS

Rhesus monkeys were kindly provided by Dr Robert D'Amato of Procter & Gamble Co. They were retired breeders, over 4-6 yr old and have been recovered from drug screening tests. Monkeys of either sex are anesthetized with iv pentobarbital 20 mg/kg. The gastric fundus was excised. Both the serosa and the muscular layer were stripped. The remained

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mucosal layer was then divided in equal parts and mounted in 2 identical Ussing chambers. Both sides of the layer were bathed in 7 ml of glucose-Ringer solution. The details of procedure have been described[2,11]. The PD was measured with 2 calomel electrodes. An external current was sent to bring the PD to zero and recorded by a Varian Recorder as short-circuit current, Isc. The resistance across the membrane was measured by sending a temporary current of 10 μA across the membrane.

^{36}Cl, in the form of HCl (New England Nuclear Co.) was added to either side of the chamber for 20 min to reach a steady state. Duplicate samples were then collected at 30-min intervals and counted in an automatic β counter and compared with a standard ^{36}Cl solution.

Histamine and cimetidine were commercial products from Sigma Co.

RESULTS

Electrical Properties On isolated gastric mucosa a PD (electropositive to serosal side) was recorded and maintained constant for >3 h. In 11 monkeys the PD was 22±SD 4 mV, the transmucosal resistance was 239±49 Ω-cm^2, and the I_{SC} was 94±21 μA·cm^{-2}. Histamine in serosal bath decreased PD and I_{SC}, and slightly lowered the transmucosal resistance.

Chloride Secretion and Histamine Effect In resting state the mucosa showed a net Cl^- secretion from the serosal to mucosal side. This contributed partially the electropositive PD and I_{SC} recording across the membrane. Histamine added to the serosal bath at a final concentration of 10 m*M* caused a slight reduction of both PD and I_{SC}. Tab 1 summarizes the result from 5 monkeys. In each experiment at least three 30-min Cl^- flux measurements were determined before histamine was added, then two to three 30-min flux measurements were made. Histamine in creased both mucosal-to-serosal (J_{m-s}) and serosal-to-mucosal (J_{s-m}) fluxes of Cl^- ion with the latter being much predominant, resulting in a greater net Cl^- secretion.

Effect of Cimetidine In 4 monkeys cimetidine was added to serosal bath at a final concentration of 1.09 mg/ml (4.3 m*M*) after the mucosa was stimulated by histamine. Both PD and I_{SC} were slightly lower than that during the previous histamine period. Under cimetidine the J_{m-s} was practically unchanged while the J_{s-m} was greatly reduced, resulting in a slight net Cl^- absorption (Tab 2).

Tab 1. Mucosa-to-serosa(J^{Cl}_{m-s}), serosa-to-mucosa(J^{Cl}_{s-m}), net(J^{Cl}_{net}) fluxes of Cl^-, difference between 2 net fluxes (△) and short-circuit current (I_{SC}) across isolated gastric mucosa of 5 monkeys. $\bar{x}$±SD

Condition	J^{Cl}_{m-s}	J^{Cl}_{s-m}	J^{Cl}_{net}	△	I_{SC}
		(μEq/cm²-h)			
Resting state	2.4±1.0	3.9±1.4	−1.4±0.8		4.6±1.3
				↑2	
Hist-stimulated*	3.5±1.3	7.2±2.9	−3.7±1.7		3.2±1.0

*Histamine was added to serosal bath, final concen tration 10 m*M*.

Tab 2. Effect of cimetidine (4.3 m*M*) on histamine (10 m*M*)-stimulated isolated gastric mucosa of 4 monkeys. $\bar{x}$±SD

Condition	J^{Cl}_{m-s}	J^{Cl}_{s-m}	J^{Cl}_{net}	△	I_{SC}
		(μEq/cm²-h)			
Resting state	2.0±0.6	3.1±0.7	−1.2±0.5		4.0±1.0
Hist-stimulated	3.2±1.4	10.8±8.4	−7.6±8.9	↑6	2.9±1.0
Cimetidine	2.5±2.2	2.0±1.4	+0.4±0.7	↓8	2.1±0.8

Tab 3. Comparison of isolated gastric mucosa of 4 mammalian species in resting state

Parameter	Monkey	Dog[5]	Rat[7]	Rabbit[5]
PD(mV)	21.9	48	5.7	4.5
R(Ω-cm²)	239	183	232	121
I_{SC}(μEq/cm²-h)	3.78	6.5	1.33	0.7
J^{Cl}_{net}(μEq/cm²-h)*	-1.45	-0.8	-1.3	-1.0
J^{Na}_{net}(μEq/cm²-h)*	+0.98	+6.6	+0.9	+3.1

* A greater J_{s-m}(-) or a greater J_{m-s}(+)

DISCUSSION

This experiment was the first one to use monkey stomach to study electrical parameters and ion fluxes across gastric mucosa. Tab 3 summarizes a comparison of parameters of isolated gastric mucosa between monkey, dog, rabbit and rat. The Cl^- secretion across the monkey stomach resembles that of dog stomach, but the I_{SC} in monkey stomach is approximately half that of dog stomach. This is probably due partially to the lower net Na^+ absorption.

With amphibian gastric mucosa preparations *in vitro*, even in Cl-free Ringer solution, histamine stimulated H^+ secretion [3], indicating that Cl^- secretion was independent to H^+ secretory process. During iv infusion of histamine on dog stomach both H^+ and Cl^- secretions were augmented[9]. Our data also showed that the Cl^- secretion was twofold greater than in the resting state after histamine was added. Under the effect of cimetidine, both H^+ secretion and gastric volume from dog stomach were much reduced but with little effect on Cl^- secretion at lower doses[9]. Our data demonstrated that cimetidine blocked Cl^- secretion in monkey gastric mucosa completely. Such inhibition by cimetidine is not due to an increase of J_{m-s}, but rather due to a reduction of J_{s-m}.

It is concluded that cimetidine inhibits both H^+ and Cl^- secretion from the mammalian gastric mucosa.

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组胺和西咪替丁对离体猴胃粘膜中氯化物分泌的作用

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提要　研究剥离的恒河猴胃粘膜之电性质及 Cl^- 分泌，观察到从浆膜侧为正的粘膜电位差(PD)和短路电流(I_{SC})与狗胃粘膜之相应数据接近。在静息相，Cl^- 从浆膜侧分泌至粘膜侧，组胺强烈刺激这一过程，加入组胺 H_2 拮抗剂西咪替丁，能完全阻断组胺对 Cl^- 分泌的刺激作用。

关键词　恒河猴；　胃粘膜；　电位测定法；　氯化物(^{36}Cl)；　组胺；　西咪替丁

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