PIRENZEPINE IN DUODENAL ULCER

AN-ENDOSCOPICALLY CONTROLLED

CLINICAL TRIAL

THESIS

SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENT

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BY

EZZ EL-DIN A.ABOU EL NIL

M.B.B.GH.

SUPERVISED BY

PROF.DR.
ALY MONIS

PROF.DR.
SAMY ABDEL FATAH

FACULTY OF MEDICINE

AIN SHAMS UNIVERSITY

CAIRO

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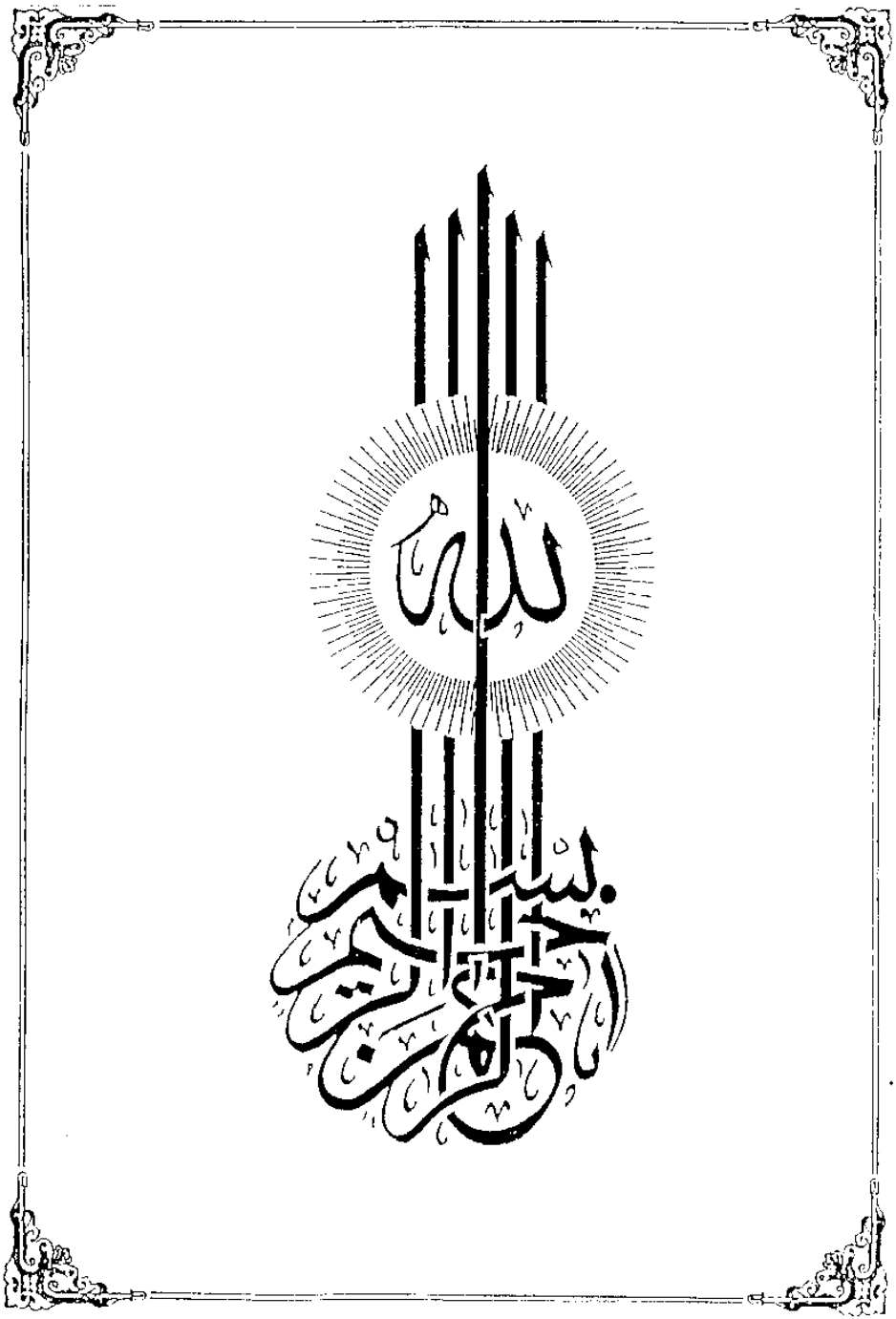

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INTRODUCTION

Peptic ulcer is an important disease.Roughly 10 percent of the population an expect to develop this disease during their lifetime,which amounts to an enourmous loss in terms of money spent on health care,individual's loss of wages and absenteeism.

Twenty years ago,medical treatment of peptic ulceration consisted of bed rest,bland diet and antacid.

Antacids,Anticholinergics,Carbenoxolone and Colloidal bismusth were available in 1960's, but controlled evidence of their efficacy in healing duodenal ulcer was laking.

Fiberoptic endoscopy,controlled trials and the histamine H_2-receptor antagonists arrived at about the same time.It is not suprising,therefore,that Cimetidine and Ranitidine have been more intensively researched than any previous drug.

Cimetidine has appeared unable, in short-term treatment to induce healing in 100% of patients, and Cimetidine non-responders constitute a very intersting and stimulating problem, so,the search for new antiulcer drugs is still justified,in spite of a declining incidence of peptic ulcer disease.

The reported controlled studies with anticholinergic-agents suggest that they can induce healing of duodenal ulcer to the same degree as cimetidine,but at the cost of more frequent side-effects

In the clinical use of anticholinergic drugs most often only one effect is desired in the treatment of peptic ulcer,this is an inhibitory effect on gastric secretion.Much effort has been devoted towards developing antimuscarinic agents with a selective effect on gastric secretion.

Some evidence has been published that demonstrated the presence of receptor subtypes which show different affinity for different antimuscarine drugs.It is probable that the classical antimuscarinics inhibit both M_1 and M_2 receptors,while pirenzepine inhibits M_1 responses at doses far below those required to block M_2-mediated muscarinic effects.In doses of 100-150mg/daily, Pirenzepine is a candidate drug for the short-term treatment of duodenal ulcer.Also,there is some evidence that long-term treatment can decrease reccurence and complications of the ulcer.

This study was carried out in order to investigate the efficacy and the tolerance of Pirenzepine in the short-term treatment of duodenal ulcer.Pirenzepine was compared to placebo.

Review of the literature

CELLULAR MECHANISMS OF ACID SECRETION

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Parietal Cell Receptor:

A variety of stimuli activate acid secretion in the stomach, histamine potentiates the effects of gastrin and acetylcholine on the parietal cells.Acetylcholine also potentiates the responses to gastrin.In this way small amount of stimuli acting together can often produce a near maximal secrotory responses.

Potentiation requires the presence of separate receptors on the target cell for each stimulant (Histamine,Acetylcholine, gastrine),and in the case of acid secretion,is incompatible with the final common mediators hypothesis.

It has been shown that the effects of cimetidine on gastrin and acetylcholine stimulated secretion are due to the inhibition of that part of the secretory response resulting from histamine potention.Similarly,the inhibition of gastrin and histamine-stimulated secretion by atropine is caused by removing the potentiating effects of acetylcholine.(Johnson,1981).A model based on these results is,shown in Fig (1).

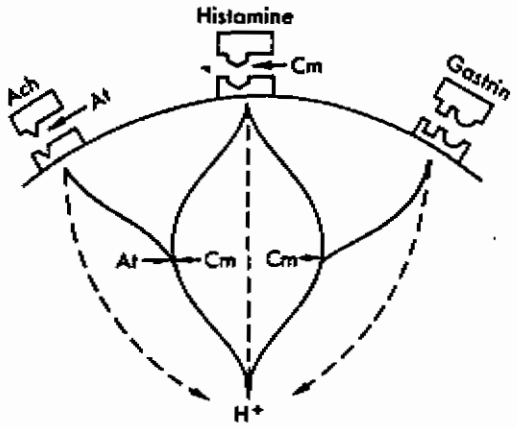

Fig. (1) Diagram of a model explaining the interactions of histamine, gastrin, and acetylcholine on the parietal cell.
(Adapted from A. H. Soll.)

Other receptors:

A part from the activating receptors discussed above, there are also peptide receptors on the parietal cell that appear to inhibit acid secretion.

Somatostatin has been shown to inhibit only histamine-Stimulated acid secretion in rabbit gastric glands (Chew,1983).

SECOND MESSENGERS IN THE PARIETAL CELL

The currently held view of how ligand binding to receptors alters cell function is generally that one of two processes in the plasma membrane is affected. Thus changes in the generation of cyclic AMP by adenylated cyclase,or the permeability of the membrane to Ca^{2+}, results in different levels of intracellular cyclic AMP or intracellular free Ca^{2+},which in turn activates a train of events which alters cell function in various ways.

Cyclic AMP :

Direct measurements have shown that histamine activates adenylate cyclase and causes cyclic AMP concentration to increase.

Phosphodiesterase inhibitors increase acid secretion and cyclic AMP or its anlogues (e.g.dibutyril cyclic AMP)and stimulate the parietal cell (Machen,Rutten and Ekblad,1982).

It is likely that the parietal cell also contains a guanine nucleotide regulatory protein (N Protein).Thus binding of the hormone to the receptor is thought to cause exchange of guanosine diphosphate (G.D.P) for guanosine triphosphate (G.T.P) on the guanyl nucleotide regulatory protein.which then activates the catalytic component of the adenyl cyclase.

A hormone-stimulated GPTase activity (perhaps the N Protein itself) provides an inactivation mechanism by hydrolysing GTP to GDP.The GDP form of the N protein is inactive and thus the receptor complex uncoupled from the cyclase system (Ross and Gilman,1980).

Little is known of the biochemical mechanism whereby cyclic AMP activates the parietal cell.However,as in other cells,it has been shown that the major site of cyclic AMP binding is the regulatory subunit of both type I and type II cyclic AMP-dependent protein phosphokinase (Jackson and Sach,-1982);the sites (? proteins) that are phosphorylated as a result of this binding are as yet unidentified.

Calcium ions:

Both the cholinergic response in rabbit gastric glands and dog parietal cells,and the gastrin response in IMX-treated (isobutil methyl xanthin) gastric glands require extracellular Ca^{2+} (Soll,1981).

Measurements of Ca^{2+} fluxes in these conditions substantiated that an increase in the membrane permeability to Ca^{2+} does occur (Soll,1981.Muallem,1982).

Regulation of cell Ca^{2+} depends on passive Ca^{2+} entery and active Ca^{2+} exit pathways across the basal-lateral membranes,vesicles isolated from the gastric mucosa and enriched

in basal-lateral membrane shown the presence of an ATP-dependant, Calmodulin-activated Ca^{2+} pump :

The effects of intracellular Ca^{2+} change have not been established in the parietal cell.Nevertheless, a Ca^{2+} dependant protein Kinase has been described in the gastric mucosa (Shaltz, Bools and Reimann, 1981),although a functional correlate is still lacking.

Intracellular Ca^{2+} has been shown in other systems to be required for membrane fusion events (Knight and Baker,1982).Such events may be involved in parietal cell activation,thus suggesting an important physiological role for Ca^{2+} .A general model for the regulation of acid secretion by Ca^{2+} at the level of the basal-lateral membrane is shown in Fig.(2).

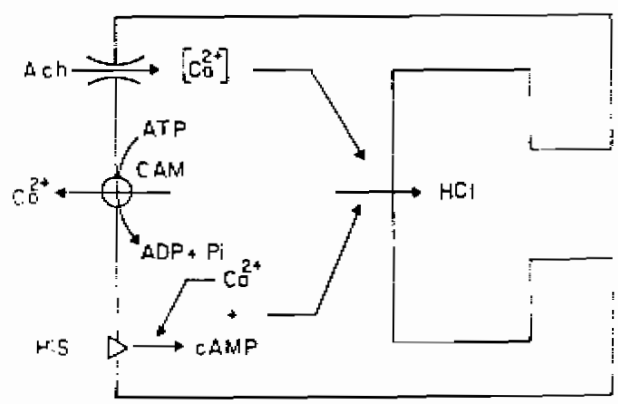

Fig.2. Regulation of acid secretion by Ca^{2+} at the basal-lateral membrane of the parietal cell.Acetylcholine (Ach) is known to cause changes in the Ca^{2+} permeability and a calmoduline (CAM) activated Ca^{2+}.ATPase pumps Ca^{2+} out of the cell.Ca^{2+} may also be involved in the histamine (HIS) response of the parietal cell.

EFFECT OF SECOND MESSENGERS

Activation of the parietal cell to secrete acid is accompanied by several clearly observable effects such as changes in morphology,metabolism,and apical membrane characteristics;

Parietal Cell MorphologY:

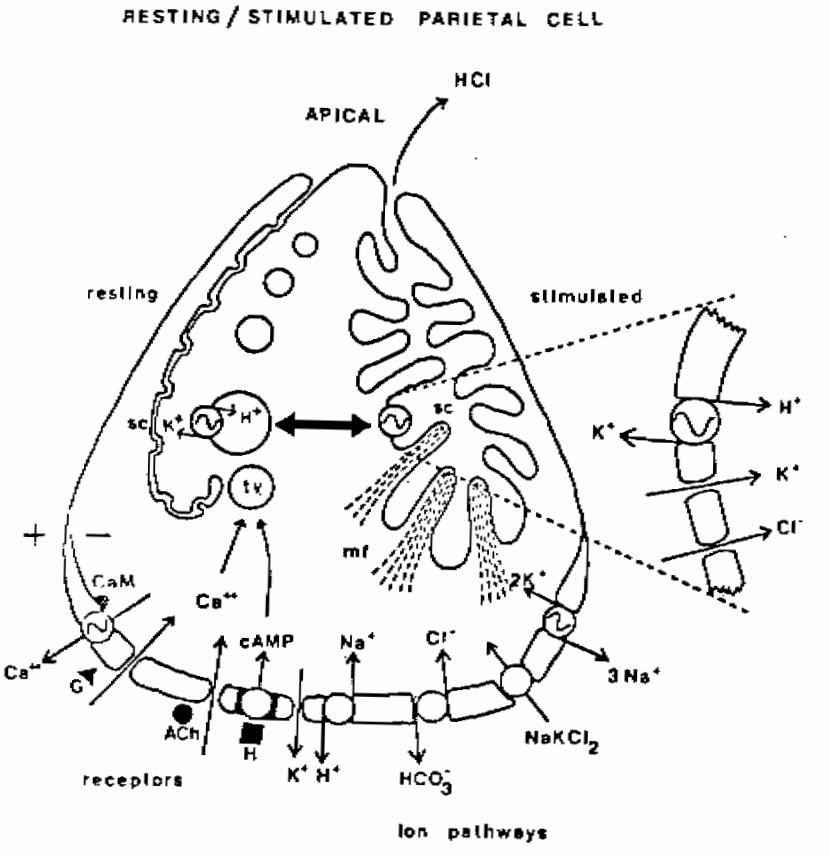

Fig.(3). Schematic model of the parietal cell showing the receptor systems and ion pathways in the basal-lateral membrane, and the apical membrane transition from a resting to a stimulated state. G = gastrin; Ach = acetylcholine; H = histamine; CaM = calmodulin; sc = secretory canaliculus; tv = tubulovesicles; mf = microfilaments.

Parietal Cell Morphology :

- The resting parietal cell has very distinctive features.Its cytoplasm contains the largest number of mitochondria found