TREATMENT OF GASTRO - DUODENAL ULCERATION AN UPDATE

Essay

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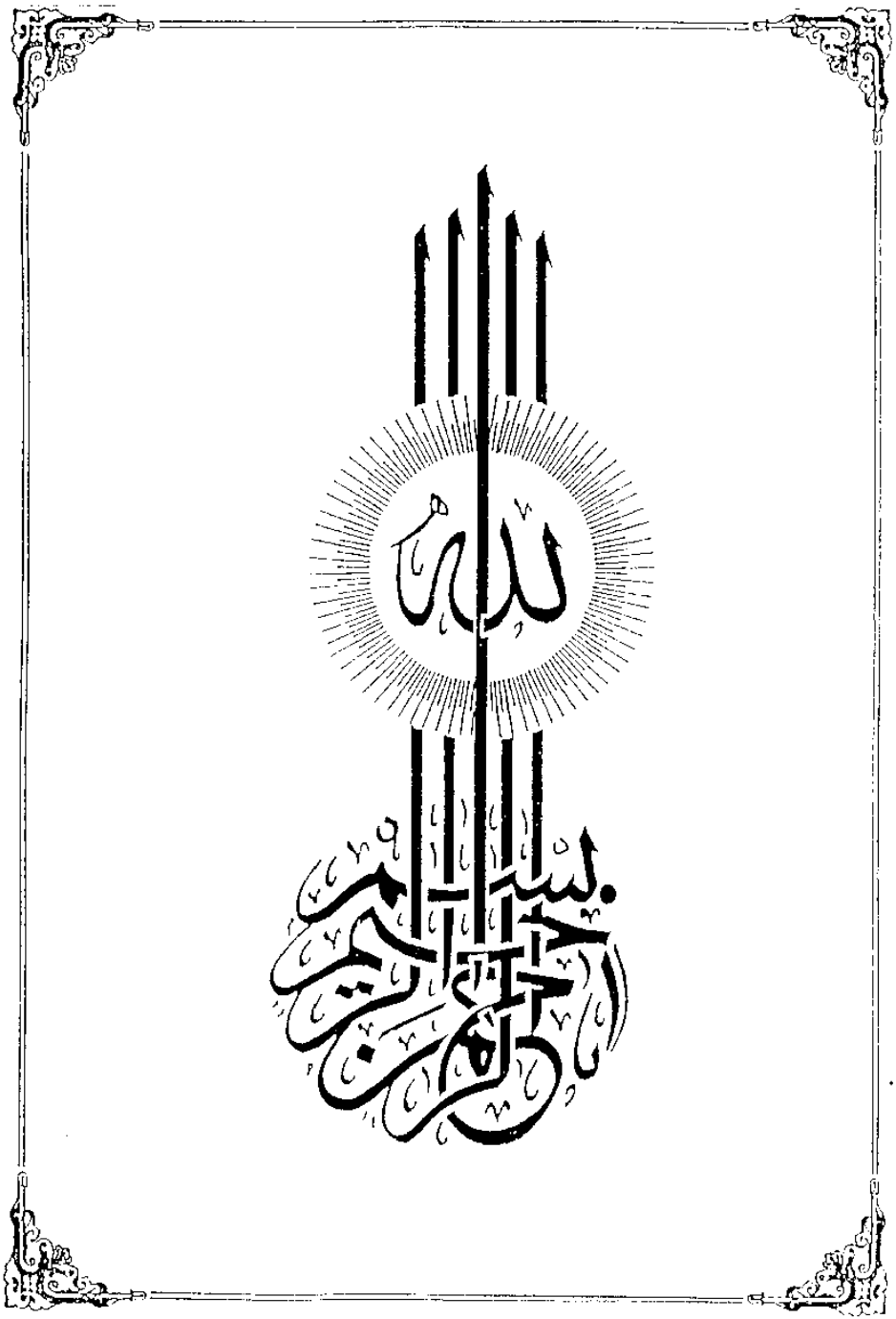

DEDICATION

TO MY FAMILY

ACKNOWLEDGEMENT

Firstly, All thanks are to **God** .

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CONTENTS

INTRODUCTION

The decline in the prevalence of peptic ulceration and the introduction of new medical methods of treatment in recent years have had a major influence on attitude towards surgery. In peptic ulcer surgery a delicate balance has to be achieved between the efficacy of an operation in ulcer healing and the cost of that healing.

Safety must be the prime consideration in the surgeon's mind when performing any surgery, in particular that for peptic ulcer where the possible alternatives of drug therapy might achieve healing with no attendant shot term mortality. Safety is achieved by simplifications of surgical technique and conservativism.

Conservativism with all its safety, however, must be measured in terms of its long term efficacy in maintaining ulcer healing .

The aim of this work is to review the recent literature with special emphasis on the new medical methods of treatment in recent years, an update review of the clinical trials in peptic ulcer surgery and lastly the role of laparoscopic surgery in gastroduodenal ulceration .

REVIEW OF LITERATURE

Chapter 1
Physiology and Pharmacology Of the Parietal Cells

Secretory Mechanisms Of The Parietal Cells

The great majority of the parietal cells are found in the fundus and the corpus of the human gastric mucosa, which consequently is referred to as the oxyntic mucosa. The glands in this region are slightly coiled tubules and the mucosal thickness average is 0.8 mm During secretion, there is a swift stream sweaping down the gland ducts. Although the secretion appears to flow intermitently from the different gastric pits, it seems importantly that, during secretion, water soluble substances in the gastric cavity, for instance drugs, could enter the gland lumen and by diffusion reach the parietal cells. Such diffusion would be delayed by the mucus on the mucosal surface and in the gastric pits (Helander,1988).

The Secretory Canaliculi : They pentrate the various parts of the cytoplasm of the parietal cells . These tortous channels which end on the apical cell surface,are used for the export of Hcl from the interior of the cells into the gland lumen (Helander,1988).

The glycocalyx : It is present on the secretory suface of the parietal cells. This thin layer of neutral mucosubstances, which cover the secretory surface may be of great importance in the protection of parietal cells aganist acid and pepsin in the lumen (Spicer et al, 1987).

The Secretory Surface : During stimulation, the secretory surface (The surface area of the canaliculi and the luminal cell surface) increases by about 75% (Helander et al, 1986). This expansion of the secretory surface area is seen as an increase in the length of the secretory canaliculi with a

concomitant increase in the number and length of microvilli projecting from the surface (Hela nder, 1988).

The Tubulovesicles : They are present in the cytoplasm of the parietal cells. As a result of stimulation, the number of tubulovesicles decreases and their membranes are incorporated into the secretory surface by an exocytotic process. The contents of the tubulovesicles remain unidentified but it is speculated that it may be Hcl or Kcl. After stimulation ceases, the membranes of the seretory surface are recycled to the tubulovesicles. The secretory surface and the tubulovesicular surface are not identical in structure and properties (Helander, 1988).

H+-K+-ATP ase : It is present at the tubulovesicular membrane but not at the secretory membrane. This enzyme is responsible for the final step in the production of Hcl (Smolka et, al, 1983). The tubulovesicular membrane is incorporated into the secretory membrane as a result of stimulation. The particles might corrospond to H+K+-ATP ase (Black et al, 1986).

Recptors : There are 3 types of receptors on the parietal cells :
Receptors for acetylcholine, for histamine and for gastrin (Helander, 1988).

1- Acetylcholine : It is released from unmyelinated parasympathetic nerves in the mucosa and the binding sites were located predominantly on the basolateral membrane of the parietal cells (Nakamura et al, 1985) The efficacy of cholinergic drugs in stimulating acid secretion varies considerably and in humans , there is little or no stimulation at all (Grossman,1989) .

2- Histamine: It is present in endocine cells of human oxyntic mucosa and the receptors for histamine on the parietal cells are of the H2- type

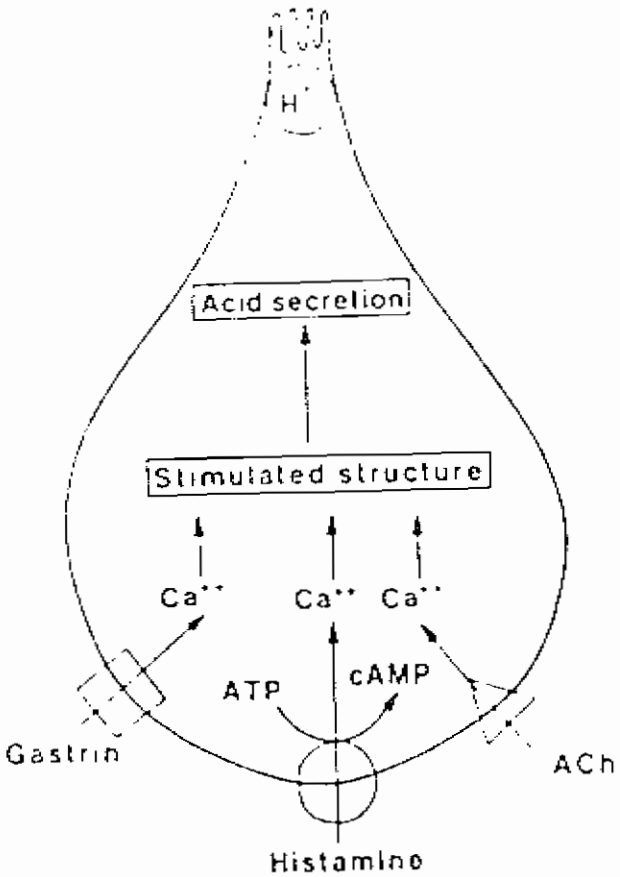

Figure (1):

Model of receptor regulation of acid secretion from the parietal cells (Modified from Soll and Berglindh,1987). Stimulation with acetylcholine,gastrin and histamine -------increase cytoplasmic level of ca++.

Histamine stimulation enhances the production of cAMP from ATP.As a result of stimulation, the parietal cells acquire a stimulated structure and eventually secrete acid.

(Hakanson et al, 1986).The capacity of injected histamine to stimulate gastric acid secretion in man was early establihed (Helander,1988).

3- Gastrin : It is produced by the gastrin cells located primarly in the antrum and duodenum as a classic hormone and it is delivered to parietal cells through the systemic blood vessels. It is suggested that gastrin might be also delivered to the oxyntic mucosa through a portal blood system within the gastric wall (Casale et al, 1981). Gastrin is a strong stimulant of acid secretion (Helander,1988). It has been suggesested that the indirect stimulation by gastrin is more important than the direct one so gastrin would liberate histamine from cells in the oxyntic mucosa such as the enterochromafin like cells (Soll and Berglindh,1987).

The action of acetyl-choline, histamine and gastrin on the parietal cells is not completely clear up to date.Histamine was long ascribed a role as the final common pathway for stimulation, irrespective of what stimulus was applied (Code,1987). This was supported by results from pharmacological inhibition of acid secretion by H2-receptor blockers.These drugs block acid secretion irrespestive of whether acetylcholine ,gastrin or histamine is used as a stimulant (Helander,1988).

Potentiation and inhibition of receptor stimuli : It was early demonstrated that cholinergic stimuli are potentiated by histamine and by gastrin and similarly histamine potentiates the acid response to gastrin (Grossman , 1987) . More recent studies showed a clear potentiation between histamine and acetylcholine (carbachol),as well as between histamine and gastrin. But no data appears to support the possible potentiation between carbachol and gastrin (Soll and Berglindh,1987).

Studies on the inhibition of receptor stimuli have demonstrated that H2 - receptor blockers abolish acid secretion evoked not only by histamine but also by acetylcholine or by gastrin (Grossman. 1989). Similarly, atropine or

vagotomy will inhibit acid secretion due to acetylcholine also histamine and gastrin stimulated secretion (Hirschowiz, 1985). Cimetidine blocks only histamine stimulated acid secretion, leaving carbachol and gastrin stimulated secretions unaffected. Similary, Atropine inhibit carbachol stimulated acid secretion but fails to inhibit the response to histamine and gastrin (Okada and Ueda,1984). These and other studies on potentiation and inhibition of parietel cell receptor stimuli lead to conclude that there is a constant backeground influence from histamine and acetylcholine, even in the non secretory state.Any additional cholinergic,histaminic or gastrinergic stimulation will provoke acid secretion (Helander,1988). The removal of the backeground influence as by H2-receptor blockers or by atropine , will prevent the additional stimuli from provoking acid secretion (Debas,1987). With gastrin,the picture is less clear but the continous presence of gastrin in the blood and its increase when stimulated by food,suggests the central role for gastrin too, as a backeground sensitizing agent (Helander ,1988).

Intracellular stimulation and inhibition :

Following receptor stimulation,a series of events takes place in the cytoplasm of the parietal cells, which results in acid secretion. Post receptor physiology is different for the different secretagogues but many of intracellular sigals are relayed by calcium and or cAMP (Helander, 1988).

1- Calcium : Carbachol increases intracellular calcium due to an influx of extracelluar calcium ions by increasing the plasma membrane permeability to calcium ions (Muallen and Sachs, 1985) also gastrin and histamine increase the intracellular calcium level (Chew, 1986). Since, the increase in the intracellular calcium inos following receptor stimulation depends on the patency of the calcium channels in the plasma membrane, calcuim channel blockers as verapamil might be used to interfere with the production of Hcl,

however the effects of these drugs on the organs as the heart. decrease their clinical use as an acid inhibitors (Sewing and Hannemann, 1983).

2- Cyclic AMP : It is stimulated only by histamine but gastrin and acetylcholine are not effective (Helander, 1988). This is observed when isolated parietal cells are exposed to prostaglandins. which inhibit adenylate cyclase which catalyses the generation of cAMP from ATP, and inhibition of adenylate cyclase leads to a reduction in cAMP accumulation induced by histamine stimulation . Alternatively, prostaglandins might interfere with the binding of histamine to its receptors,and therby attenuate generation of cAMP that nomally follows upon histamine stimulaion(Soll and Berglindh, 1987).

Intermediary events : The increased level of calcium in the cytoplasm interacts with the calcium binding protein - calmodulin - to promote the phosphorylation of certain key proteins and or to activate enzymes which are essential to the formation of Hcl. Similarly,cAMP,acting via protein kinases will modulate cell function through the phosphorylation of target proteins (Helander, 1988).

The final steps : Following stimulation, channels for K+ and cl- become activated in the secretory membrane and these ions can then move passively from the cytoplasm into the canalicular lumen. Subsequently, an electroneutral exchange takes place,substituting K+for H+ , this reaction is stimulated by K+, fuelled by ATP that present in the mitochondria and catalysed by H+-K+-ATP ase which is present in the wall of the secretory canaliculi during stimulation (Helander, 1988). the enzyme H+-K+- ATP ase can be effectively inhibited by substituted bezimidazoles as omeprazole and therby, acid secretion is blocked . Omeprazole is accumulated in tissue compartements with a PH less than 4, where it is traped on its charged and protonated form. In the acid environment, omeprazole is conveted into the