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بعض الوثائق الأصلية تالفة

STUDY OF THE EPIDERMAL GROWTH FACTOR IN PORTAL HYPERTENSIVE GASTROPATHY

Thesis

Submitted to the Faculty of Medicine

University of Alexandria

in partial fulfillment of the

requirement of the degree of

Master of Internal Medicine

By

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2000

ACKNOWLEDGMENT

I would like to express my deepest appreciation and endless gratitude to my great ***Professor Dr. Tarek Moustafa Thabet****, Professor of Internal Medicine, Faculty of Medicine, Alexandria University, for giving me the privilege of working and for his fatherly guidance and encouragement throughout the whole work.*

I owe a special depth of thanks to ***Dr. Osama Ebada Salem****, Assistant Professor of Internal Medicine, Faculty of Medicine, Alexandria University, for his earnest supervision throughout the course of the study and kindness to review each step in this work. He liberally gave me of his time, patience and expertise.*

I would like to acknowledge my gratitude to ***Professor Dr. Amina Hussein Hassab****, Professor of Clinical Pathology, Faculty of Medicine, Alexandria University, for her initial advice, constant guidance, and constructive criticism and stimulating interest in conducting this study.*

I am really also thankful to ***Dr. Layla Kamal Younis****, Assistant Professor of Pathology, Faculty of Medicine, Alexandria University, for her skillful guidance and encouragement.*

I would like to expand my thanks to all staff members of the unit of Gastroenterology, Faculty of Medicine, Alexandria University, to my colleagues, and everyone gave a hand and helped this work to appear in its present form. I am really indebted to those patients who were included in this work for their cooperation.

LIST OF ABBREVIATIONS

ALT: Alanine aminotransferase.

AST: Aspartic aminotransferase.

ATP: Adenosine Triphosphate.

BAO: Basal Acid Output.

BFV: Blood Flow Volume.

c-AMP: Cyclic Adenosine Monophosphate.

CSA: Cross Sectional Area.

CGRP: Calcitonin Gene – Related Peptide.

CCK: Cholecystokinin.

Cag-A: Cytotoxin associated gene – A.

DAG: Diacylglycerol.

DNA: Deoxyribonucleic Acid.

ECL cells: Enterochromaffin Like cells.

ELISA: Enzyme Linked Immune Sorbant Assay.

EGF: Epidermal Growth Factor.

EGFR: Epidermal Growth Factor Receptor.

GTP: Guanosine Triphosphate.

Gs: Stimulatory GTP regulatory protein.

G_I: Inhibitory GTP regulatory protein.

GIP: Gastric Inhibitory Polypeptide.

GAVE: Gastric Antral Vascular Ectasia.

GH: Growth Hormone.

H. Pylori: Helicobacter Pylori.

H & E: Hematoxylin and Eosin.

IP_3: Inositol Triphosphate.

ICAM-1: Inter-Cellular Adhesion Molecule – 1.

IL: Interleukin.

LPS: Lipopolysaccharide.

mRNA: Messenger Ribonucleic Acid.

NSAIDs: Non-Steroidal Anti Inflammatory Drugs.

PCR: Polymerase Chain Reaction.

PG: Prostaglandin.

PP: Pancreatic Polypeptide.

PHG: Portal Hypertensive Gastropathy.

PAF: Platelet Activating Factor.

RUT: Rapid Urease Test.

TPN: Total Parenteral Nutrition.

TNFα: Tumor Necrosis Factor Alpha.

UBT: Urea Breath Test.

UACL: Ulcer Associated Cell Lineage.

VIP: Vasoactive Intestinal Polypeptide.

Vac-A: Vacuolating Cytotoxin.

V max: Maximum blood flow velocity.

V mean: Mean blood flow velocity.

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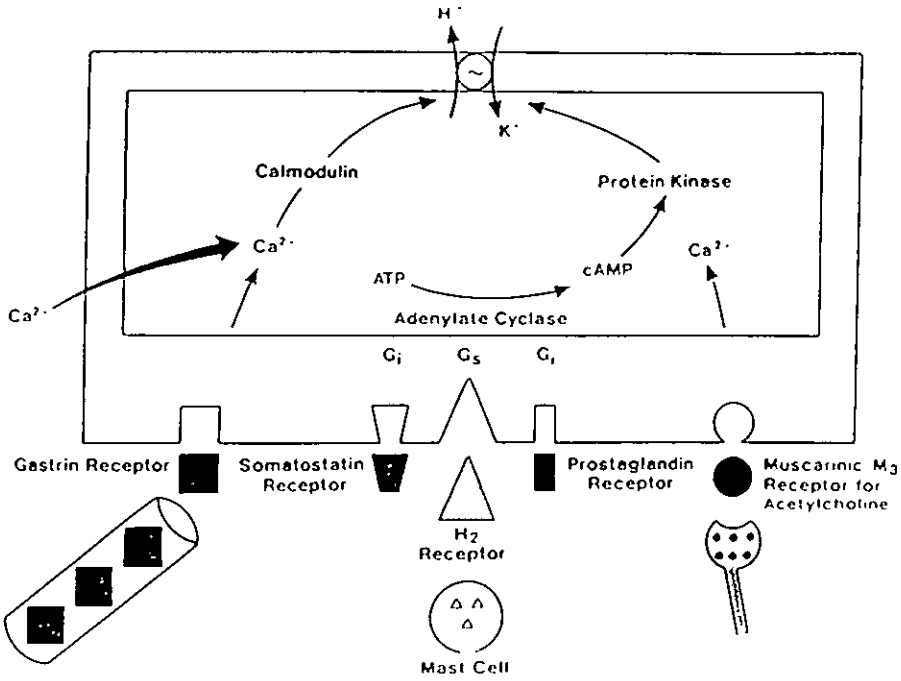
GASTRIC ACID SECRETION

Parietal cells and membrane receptors

The parietal cell is a highly differentiated cell, with an apical membrane directed towards the lumen and a baso-lateral membrane bearing a number of receptors that, when activated by agonists, stimulate the parietal cell to secrete hydrochloric acid.[1] Also at least two receptors mediate the inhibition of acid secretion by the parietal cell.[2] (Fig 1) The main cytoplasmic features are an elaborate system of tubulo-vesicular membranes and an abundance of mitochondria.[1] The intracellular membrane system is considered to store inactive H^+-K^+ ATPase, whereas the mitochondria are required to generate the oxidative energy necessary for acid secretion, the main metabolic function of the cell.[3]

The capacity of hydrochloric acid secretion is enormous, and the parietal cell can generate a maximal luminal pH of 0.8, while maintaining an intracellular pH of 7.1 to 7.2. The apical cell membrane and the intracellular functions of the columnar cell-lined epithelium prevent acid back-diffusion and maintain the acid gradient.[1]

The first stage of acid secretion by parietal cells involves activation by an external stimulus. There are four physiologically relevant stimuli for acid secretion: histamine, acetylcholine, and gastrin which bind to specific receptors on the baso-lateral membrane, and extracellular Ca^{2+}.[1]



re 1 Model demonstrating recep-
on the parietal cell basolateral mem-
. H_2-receptor stimulation activates
latory guanosine triphosphate (GTP)
itory protein (G_s), which subsequently
tes adenylate cyclase. Somatostatin
rostaglandin E_2 inhibit adenylate cy-
via the inhibitory GTP regulatory pro-
G_i)

PARIETAL CELL RECEPTORS

A-Stimulatory receptors

1- Histamine type 2 receptors:

There are now three different subtypes of histamine receptors identified in various tissues, H_1, H_2 and H_3 receptors.[4] The receptors on the baso-lateral membrane of parietal cells are H_2 receptors.[5]

The H_2 receptor is a 70 kDa glycoprotein of marked homology with the super-family of G protein- coupled receptors including the beta adreno-receptors.[6] An extracellular hydrophilic region binds to histamine, a mid hydrophobic region anchors the receptor to the membrane, and an internal portion passes on a trans-membrane signal to the stimulatory guanosine triphosphate (GTP) regulatory protein (Gs) which is then thought to activate adenyle cyclase with the formation of cyclic adenosine monophosphate (cAMP), which acts as a second messenger. Histamine also increases intracellular free calcium, although the precise relevance of this is unclear.[7]

More recently, type 3 histamine receptors (H_3) have been defined that can inhibit both gastrin-induced histamine release and gastric acid secretion in mammals.[7]

2- Muscarinic cholinergic receptors:

Acetylcholine is the physiologic agonist for the muscarinic cholinergic receptors situated on the baso-lateral membrane of the parietal cell. Studies point to the muscarinic receptors on the parietal cell being of the M_3 receptor subclass.[8] In fact in rabbit parietal cell using the polymerase chain reaction (PCR) to identify parietal cell mRNA, only the M_3 receptor mRNA was detected.[9]

An elevation of intracellular Ca^{2+} ion level is believed to be the second messenger mediating the action of cholinergic agents.[10] Receptor binding activates phospholipase C, which generates high levels of inositol triphosphate (IP_3) from membrane phospholipids.[11] IP_3 mobilizes calcium from intracellular stores, which can then activate the calmodulin system. Also diacylglycerol (DAG) is generated from membrane phospholipids by the action of phospholipase C, and this may activate protein kinases.[12] In addition to the induction of membrane inositol phospholipid turnover, the rise in intracellular Ca^{2+} can also result from an influx of extracellular Ca^{2+} secondary to acetylcholine stimulation.[13]

3- Gastrin receptors:

The gastrins are a group of peptide hormones which are involved in the physiology of gastric mucosa and gastric acid secretion at a number of levels.[1] The binding of gastrin receptors on the parietal cell leads to stimulation of acid secretion, a response that is not blocked by H_2 receptor antagonists but is prevented by proglumid (a cholecystokinin / gastrin receptor antagonist) and specific gastrin receptor antagonists.[14] In addition, gastrin enhances the parietal cell response to histamine. There is an increasing evidence that gastrin modifies acid secretion by raising intracellular Ca^{2+} levels as a second messenger.[15]

B-Inhibitory receptors:

At least two receptors on the parietal cell baso-lateral membrane can inhibit acid secretion. Somatostatin and prostaglandin E_2 bind to their specific receptors that act by an inhibitory GTP regulatory protein (G_I) in preventing the activation of adenyle cyclase.[1] Somatostatin receptors are also found in other cell types e.g. enterochromaffin like cells (ECL)