THE EFFECT OF ESTROGEN AND TESTOSTERONE ON GASTRIC MUCOSAL INTEGRITY AND GASTRIC SECRETION: POSSIBLE ROLE FOR NITRIC OXIDE

Thesis
Submitted for the Partial Fulfillment of M.D. in physiology

By
ENAS MOHAMED KASEM
(M.Sc. in physiology)

supervisors

PROF. DR. AHMED IBRAHIM AGAMY
Professor of physiology
Benha Faculty of Medicine

PROF. DR. NASR ARAFAT BELACY
Professor of physiology
Benha Faculty of Medicine

PROF. DR. MOHAMED SALEM
Professor of physiology
Benha Faculty of Medicine

DR. WAOEL ARAFAT EL-MANSY
Lecturer of physiology
Benha Faculty of Medicine

PHYSIOLOGY DEPARTMENT
BENHA FACULTY OF MEDICINE
ZAGAZIG UNIVERSITY

2004
GASTRIC SECRETION

The stomach secretes the gastric juice, which is a mixture of the secretions of the surface epithelial cells and the secretions of the cells of the gastric glands, which include mucous cells, chief cells and parietal cells.

Among the important components of the gastric juice is hydrochloric acid (HCl), salts, pepsins, water, mucus, bicarbonate and intrinsic factor. Secretion of all these components increases after a meal. *(Feldman 1993)*

Ionic composition of the gastric juice:

This depends on the rate of secretion, the higher the secretory rate the higher is the concentration of hydrogen ions (H\(^+\)). At lower rates hydrogen decreases and sodium (Na\(^+\)) increases but potassium (K\(^+\)) concentration is always higher than that in plasma. At all rates of secretion chloride (Cl\(^-\)) ion is the major anion of gastric juice.

Gastric secretion is divided into:

1- Gastric acid secretion (secretion of HCl acid)
2- Gastric mucus secretion
3- Pepsinogen secretion
4- Gastric alkaline secretion (secretion of bicarbonate) *(Feldman 1993)*

Gastric Acid Secretion

Rate of gastric acid secretion:

This varies considerably among individuals due to variations in the total number of parietal cells. In humans basal (unstimulated) rates of
gastric acid production ranges from 1-5 mEq/hr and during maximal stimulation it rises to 6-40 mEq/hr.

**Cellular Mechanism of Gastric Acid Secretion**

- HCl acid is actively secreted by the parietal cells as hydrogen ion is pumped against a very high concentration gradient about one million fold (from pH 7 in the cytosol of the parietal cell to pH 1 in the lumen of the gastric gland). In addition due to the electronegativity of the lumen of the stomach by 30 to 80 millivolt relative to the serosa, chloride ions enter the lumen against both chemical and electrical potential differences so energy is required for transport of both H⁺ and Cl⁻ ions into the gastric juice (*Rabon and Reuben 1990*).

- The hydrogen ion is pumped out of the cell in exchange for K⁺ by a hydrogen-potassium ATPase (Adenosine triphosphatase) pump present in the apical membrane of the parietal cell. This ATPase is the primary H⁺ pump. Both H⁺ and K⁺ are pumped against their electrochemical potential gradients. (*Rabon and Reuben 1990*)

**The Source of Hydrogen Ion:**

This hydrogen ion is derived from the dissociation of carbonic acid (H₂CO₃) which results from the combination of water and carbon dioxide (CO₂) under the effect of Carbonic Anhydrase Enzyme (CAE). (CO₂) either results from cell metabolism or diffuses from blood into the cell.

* As a result of hydrogen ion pumping out of the cell an excess of bicarbonate ion resulting from the dissociation of H₂CO₃ acid accumulate in the cell and flow down their electrochemical gradient across the basolateral plasma membrane via a protein carrier causing the alkaline tide. The protein carrier that mediates HCO₃⁻ efflux is called the Cl⁻/HCO₃⁻ counter-transporter which also transports Cl⁻ in the opposite
direction against its electrochemical potential gradient into the cell. The energy for this active transport of Cl⁻ ion comes from the downhill movement of HCO₃⁻ ions across the basolateral membrane. * As a result of the above Cl⁻ ion is concentrated in the cytoplasm of the parietal cell and will then leave it at the apical membrane via an electrogenic anion channel (Sachs 1994).

The basolateral membrane of the parietal cell contains two types of potassium channels. One type is activated by cAMP (Cyclic Adenosine MonoPhosphate) and the other type is activated by calcium (Ca²⁺). Activation of the basolateral K⁺ channels hyperpolarizes the cell and thereby increases the driving force for Cl⁻ to leave the cell. The K⁺ channels also mediate the efflux of K⁺ which accumulates in the parietal cell via the activity of the H⁺ -K⁺ ATPase.

(Sachs 1994)

**Regulation of gastric acid secretion:**

**Physiological agonists of HCl acid secretion:** gastric acid secretion is mainly under the control of the following which include:

- **Acetylcholine (Ach):** is a neurotransmitter which is released near the parietal cells from cholinergic nerve terminals and binds to muscarinic (M₃) receptors on the surface of parietal cells. It acts by opening calcium channels in the apical surface and promotes release of Ca²⁺ from intracellular stores thus elevating intracellular calcium concentration (Shamburek and Schubert 1992).

- **Histamine:** which is a paracrine agonist synthesized, stored and released from EnteroChromaffin – Like cells (ECL) present in the gastric mucosa and from mast cells. It diffuses to the parietal cell and binds to histaminergic (H₂) receptors on parietal cell surface
resulting in activation of adenylate cyclase enzyme and increases intracellular concentration of cAMP (Soll and Berglindh 1994).

- **Gastrin**: which is a hormone produced and released from G-cells of the gastric antrum and reaches the parietal cells via the blood stream and binds to CCK – B (cholecystokinin-B) receptor on the surface of parietal cell and releases intracellular calcium from its stores thus elevating intracellular calcium concentration (Chew 1991). Gastrin is not as potent as Ach or histamine but a major component of the response to gastrin may result from gastrin-stimulated release of histamine. Thus HCl acid secretion is controlled by neurocrine, endocrine and paracrine mechanisms.

- The elevated intracellular concentrations of cAMP or calcium stimulate HCl acid secretion by activating basolateral K+ channels and apical Cl- channels. They also cause more H+- K+ ATPase molecules and Cl- – channels to be inserted into the apical plasma membrane. (Gerber and Payne 1992).

**Endogenous inhibitors of HCl acid secretion:** Inhibitors of gastric acid secretion include:

- **Somatostatin**: which is released from D-cells near the bases of gastric glands is probably a physiological inhibitor of acid secretion by parietal cells. It may also inhibit the release of histamine by ECL cells.

- **Prostaglandins of E and I series.**

- **Epidermal Growth Factor (EGF)**

  They act by inhibiting adenylate cyclase enzyme and decreases the intracellular cAMP concentration.

**Importance of gastric HCl acid:**

- Gastric HCl converts pepsinogens to active pepsins and provides an acid pH at which pepsins are active.