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A NEW CONCEPT FOR HYDROCHLORIC ACID FORMATION.CARBONIC ANHYDRASE ISOENZYMES IMPLICATIONS

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Absract

The collective of Professor Puscas sugests a theory - The pH theory, which presents as a common element of these three receptors (for histamine, acetylcholine and gastrine)the carbonic anhydrase. According to this theory histamine, gastrine and acetylcholine have a dual effect on the parietal cell: one known, that their specific receptor binding, and the second effect, that the activation of CA IV, discovered by Professor Puscas. The results suggest that activation of CA IV, by releasing of H, produces changes in pH, necessary histamine, acetylcholine and gastrine binding to specific membrane receptors. In this case, histamine - the final common path - according to Grossman's theory and Code theory have as common element the CA IV in parietal cell membranes, under pH theory.

Key words : Carbonic anhydrase, pH, gastric acid secretion

1. BACKGROUND

It is well known that gastric acid secretion is regulated by paracrine, endocrine neurocrine mechanisms. Major activators of gastric secretion are histamine, gastrine and acetylcholine and the most important endogenous inhibitors are colecistokinine, somatostatin, prostaglandins and secretine. Excellent research proved the existence of specific receptors on the cell so as parietal cells – as H source- and also enterocromaphyne cells-as histamine source.

With yoate that are controversial data on the mechanism by which gastric acid secretion is activated or inhibited by these agents so far have been established two theories:

1. Theory formulated by Code that considers histamine as the final common mediator. In light of this theory so gastrine would release histamine and also acetylcholine would release histamine by stimulation of enterocromafine cells, histamine, which in turn would initiate the formation of hydrochloric acid by coupling them with H2 receptors of parietal cell.
2. Theory formulated by Grossman and Konturek which postulates that the H2-specific receptors on the parietal cell memmbrana, gastrine receptors and for acetylcholine are coupling with all the major stimuli of gastric acid secretion, respectively histamine,acetylcholine and gastrine. This stimulus-receptor coupling is initiated the formation of hydrochloric acid in parietal cells.

In case that histamine is considered the final common path does not justify this gastrine and acetylcholine receptors on parietal cell membranes. In support of the second theory is required and a potentiation between histamine and gastrine, those between acetylcholine and histamine, interaction described by Soll.

2. CARBONIC ANHYDRASE ISOENZYMES IMPLICATION IN THE MECHANISM OF ACID SECRETION.

Besides these two theories,the collective of Professor Puscas sugests a third theory - The pH theory, which presents as a common element of these three receptors (for histamine, acetylcholine and gastrine)the carbonic anhydrase. According to this theory histamine, gastrine and acetylcholine have a dual effect on the parietal cell: one known, that their specific receptor binding, and the second effect, that the activation of CA IV, discovered by Professor Puscas. The results suggest that activation of CA IV, by releasing of H, produces changes in pH, necessary histamine, acetylcholine and gastrine binding to specific membrane receptors. In this case, histamine - the final common path - according to Grossman's theory and Code theory have as common element the CA IV in parietal cell membranes, under pH theory. Although there is much evidence to support the first two theories, they have not yet elucidated the mechanism of gastric acid secretion inhibition induced by most pharmacological agents such as:
a) acetazolamide and all specific carbonic anhydrase inhibitors - reduce to abolish basal acid output (BAO) and the stimulated (MAO) by histamine, acetylcholine and gastrine.
b) somatostatin - endogenous and exogenous inhibitor of gastric secretion stimulated by histamine, gastrine, acetylcholine is the endogenous antagonist of gastrine. Somatostatin is a powerful inhibitor of CA
c) prostaglandins E1, E2, I2 - inhibit gastric acid secretion stimulated by histamine, acetylcholine, gastrine but they have an incomplete elucitated mechanism. In accordance with in vitro and in vivo researches, prostaglandins are potent inhibitors of the CA of gastric mucosa.
d) Calcitonine - a peptide that inhibits gastric acid secretion stimulated by histamine, acetylcholine and gastrine through a mechanism of action unknown, is a potent inhibitor of CA II and CA IV of gastric mucosal membranes.
e) ATP-ase HK inhibitors such as omeprazole, lansoprazol and Pantoprazole are also potent inhibitors in vitro and in vivo of CA II and CA IV through their active form - sulfenamida.
In 1978 an important focus of research of professor Puscas teamregarding the gastric acid secretion mechanism has been discovered that histamine is a

potent activator of CA in gastric mucosa and in erythrocytes. Further, the researches done in vitro and in vivo have shown that activation of CA by direct mechanism of action is produced not only by histamine but also by gastrine. Furthermore, studies with X-ray crystallography and spectroscopic investigations confirmed the effect of histamine on CA activity directly.
Turn of CA IV from parietal cell membranes produced by the three secretagogue and the absence of this effect in the kidney isoenzyme show an organ specificity for CA IV, those that perpetrated it in the stomach of rinichi.Therefore, these results demonstrate the involvement of membrane CA IV in the formation of HCl, and the major stimuli of gastric acid secretion - histamine, gastrine, acetylcholine increase by direct mechanism, the cytosolic activity of CA II and CA IV from parietal cell membranes. CA inhibitors such as acetazolamide reduce the activity of CA II in erythrocytes and the parietal cell cytosol, and the CA IV activity in gastric parietal cell membranes, in parallel with the reduction of BAO and MAO

3. CONCLUSIONS

These results suggest that each major stimulus of gastric acid secretion or primary messengers, that histamine, gastrine and acetylcholine, which induce secretory changes, acts on parietal cell membrane through a dual mechanism of action:
- First mechanism, well known, which consists in action of the stimulus on its specific receptor, giving of the stimulus-receptor complex formation.
- The second mechanism, it comes to complete the first one. In this second component of the mechanism, the same stimulus directly addresses to CA IV isoenzyme which is located on the entire surface of the parietal cell membrane, so enabling them to provide a suitable pH for stimulus-receptor coupling (in our case histamine, gastrine and acetylcholine with each of their specific receptors), for signal transmission in the cell, resulting the growth of gastric acid secretion.
The results show the same dual mechanism for all major inhibitors of gastric acid secretion. In this way, somatostatin, prostaglandins, benzimidazol substitutes and calcitonina (omeprazole, lansoprazol, Pantoprazole) address both their receptors with the specific coupling and CA IV membrane that is functionally coupled to these receptors.pH increasing has consequences on the stimulus-receptor binding, on the transmission of the signal into the cell and on the reduction of gastric acid secretion.
A proof of the involvement of CA IV of parietal cell membranes in gastric acid secretion is the fact that all isoenzyme activators increase the production of HCl and all its inhibitors decrease it.

The data suggests the functional compounds between CA IV and histamine receptors,gastrine and acetylcholine, those between CA IV and stomatostatine receptors, prostaglandins, calcitonine located on parietal cell membranes.

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