THE MECHANISM OF ACID SECRETION BY GASTRIC MUCOSA

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The mechanism of acid secretion by gastric mucosa has been the subject of much experimentation and speculation in recent years. Many investigations in this field, including those described here, have been prompted by an idea which is generally known as the redox theory of acid secretion.

The redox theory was first proposed by Conway and Brady (1948). According to this theory the hydrogen ions secreted by the oxyntic cells of gastric mucosa come from the hydrogen atoms of the substrates of oxidative metabolism. One way of finding whether the hydrogen ions are so produced, is to determine the ratio between acid secretion and the associated oxygen uptake. If the hydrogen ions secreted by gastric mucosa are produced as a result of oxidoreductions in the oxyntic cells, one should not observe values greater than four for the ratio between acid secretion and the associated oxygen uptake. This ratio is not expected to exceed four, because four is the maximum number of reducing equivalents which can combine with the oxygen molecule.

Much work has been carried out to find the value of the ratio between acid secretion and the associated oxygen uptake by gastric mucosa (Crane and Davies, 1951; Davenport, 1952; Bannister, 1964, 1965a). A central problem in this work is that one can only observe the total oxygen uptake of gastric mucosa, which must be divided in a justifiable way into the oxygen uptake associated with acid secretion, and that due to the non-acid-producing metabolism of the mucosa. It has been possible to achieve this end in isolated gastric mucosae of the frog (Bannister, 1963, 1965a).

The isolated gastric mucosa of the frog is a favourite preparation in the study of the biochemistry of acid secretion because the mucosa of a single stomach is easy to isolate in one piece, and it survives for a long time and secretes acid in vitro. The rate of acid secretion by isolated frog gastric mucosae was found to be a linear function of their rate of oxygen uptake. This was a convenient finding because the ratio between acid secretion and the associated oxygen uptake is given by the slope of the line obtained on plotting acid secretion against oxygen uptake. A number of determinations indicated a mean value of 2.3 + or − 1.0 (S.D.). It would seem that the value of the ratio between acid secretion and the associated oxygen uptake by gastric mucosa does not exceed four, as required by the redox theory of acid secretion (Bannister, 1965a).

The redox theory has two interesting consequences. In the first place, it implies a spatial separation of the hydrogen and hydroxyl ions produced in the respiratory chain. Secondly, it leads to the view that the secretion of hydrogen ions, unlike other active transport processes, does not necessarily require phosphate-bond energy.

Spatial separation of hydrogen and hydroxyl ions is demanded by the organisation and function of the respiratory chain, which is located in the mitochondria. The respiratory chain transports hydrogen atoms and electrons from the substrates of oxidative metabolism to oxygen. The electron transport has the following general sequence: Substrate — pyridine nucleotide — flavoprotein — cytochromes — oxygen. The hydrogen atoms of the substrate being oxidized are released as hydrogen ions in the oxidation of flavoprotein. These hydrogen ions normally combine with hydroxyl ions produced as a result of reduction of oxygen at the terminal part of the respiratory chain.

It would appear that in the oxyntic cell there is a barrier which prevents hydrogen ions but permits electrons to flow from pyridine nucleotide and flavoprotein to the cytochromes (Bannister, 1965b). Acid secretion would seem to be possible only if hydrogen ions are produced on the pyridine nucleotide side of this barrier. If hydrogen ions are produced on the cytochrome side, acid secretion does not take place because the hydrogen ions combine with the hydroxyl ions formed at the end of the respiratory chain.

This view was proposed because when electron transport in gastric mucosa is blocked by means of Amytal, which acts between pyridine nucleotide and flavoprotein, the ability to secrete acid is not restored by restoring electron transport in various ways at the stage of the cytochromes (Bannister, 1965b).

The hydrogen-ion barrier between flavoprotein and the cytochromes is formally equivalent to a *secretory membrane.* It would seem that a structural barrier exists rather than an energy-requiring process which prevents the translocation of hydrogen ions. The evidence for this idea comes from the mechanism of action of the so-called uncoupling agents.

The major mechanism of energy capture in the cell is the process of oxidative phosphorylation. Electron transport in the respiratory chain is associated with considerable release of energy. This energy is partially harnessed by the synthesis of so-called energy-rich bonds, which ultimately take the form of the terminal phosphate bond in adenosine triphosphate (ATP). Uncoupling agents prevent the synthesis of ATP by oxidative phosphorylation.

It has been known for some time that the classical uncoupling agent 2,4-dinitrophenol (DNP) inhibits acid secretion by gastric mucosa. It was thought that this action of DNP meant that hydrogen-ion secretion requires phosphate-bond energy. There is, however, evidence for an alternative view.

It has been shown that DNP catalyses the diffusion of hydrogen ions across biological membranes such as the mitochondrial membrane of animal cells and the plasma membrane of bacteria (Mitchell, 1966). This action would seem to be responsible for the inhibition of acid secretion by DNP (Bannister, 1965b, 1966b).

The efficiency of the secretory membrane, which has been postulated to exist in the oxyntic cell, is measured by the ratio between acid secretion and the associated oxygen uptake. According to the redox theory, this ratio will have values varying from zero to four depending on the efficiency of separation of hydrogen and hydroxyl ions (Bannister, 1966a). The value of the ratio is greatly reduced by DNP.

Uncoupling agents which do not catalyse the diffusion of hydrogen ions across biological membranes should not affect the efficiency of acid secretion in relation to oxygen uptake. As a matter of fact, an uncoupling agent in this category, namely, oligomycin, was found to have no effect on the ratio between acid secretion and the associated oxygen uptake by gastric mucosa (Bannister, 1966b).

In summary, it would seem that separation of hydrogen and hydroxyl ions produced in the respiratory metabolism of the oxyntic cell is a basic feature of the mechanism of acid secretion by gastric mucosa. However, the exact source and site of origin of the hydrogen ions in the oxyntic cell remain to be found. Work on this problem is being carried out. It is directed at finding the activity of the enzymes which could supply the acid secretory process with reducing equivalents, namely, the oxidoreductases.

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