The following is the abstract of the article discussed in the subsequent letter:

**Prinz, Christian, Robert Zanner, Markus Gerhard, Sabine Mahr, Nina Neumayer, Barbara Höhne-Zell, and Manfred Gratzl.** The mechanism of histamine secretion from gastric enterochromaffin-like cells. Am. J. Physiol. 277 (Cell Physiol. 46): C845–C855, 1999.—Enterochromaffin-like (ECL) cells play a pivotal role in the peripheral regulation of gastric acid secretion as they respond to the functionally important gastrointestinal hormones gastrin and somatostatin and neural mediators such as pituitary adenylate cyclase-activating peptide and galanin. Gastrin is the key stimulus of histamine release from ECL cells in vivo and in vitro. Voltage-gated K⁺ and Ca²⁺ channels have been detected on isolated ECL cells. Exocytosis of histamine following gastrin stimulation and Ca²⁺ entry across the plasma membrane is catalyzed by synaptobrevin and synaptosomal-associated protein of 25 kDa, both characterized as a soluble N-ethylmaleimidesensitive factor attachment protein receptor protein. Histamine release occurs from different cellular pools: pre-existing vacuolar histamine immediately released by Ca²⁺ entry or newly synthesized histamine following induction of histidine decarboxylase (HDC) by gastrin stimulation. Histamine is synthesized by cytoplasmic HDC and accumulated in secretory vesicles by proton-histamine countertransport via the vesicular monoamine transporter subtype 2 (VMAT-2). The promoter region of HDC contains Ca²⁺-, cAMP-, and protein kinase C-responsive elements. The gene promoter for VMAT-2, however, lacks TATA boxes but contains regulatory elements for the hormones glucagon and somatostatin. Histamine secretion from ECL cells is thereby under a complex regulation of hormonal signals and can be targeted at several steps during the process of exocytosis.

The mechanism of histamine secretion from gastric enterochromaffin-like cells

To the Editor: We read with interest the excellent review by Prinz and co-workers (3). However, the lack of references to studies on histamine release from isolated rat (4–6, 8, 9) and pig (2) stomachs is remarkable. In fact the regulation of the enterochromaffin-like (ECL) cell had been elucidated in detail in the isolated rat stomach (10, 11) before we as the first (1) studied the effect of gastrin on histamine release from oxyntic mucosal cells enriched in ECL cells by elutriation. Since histamine from isolated ECL cells is released to the whole medium, small and short-lived histamine release will not be easily detected by such a preparation. Thus Prinz and co-workers in their review quote that histamine release starts after 5 min and reaches its maximum after 60 min (3). However, in the physiological situation this is not the case, since the histamine release starts immediately after gastrin reaches the oxyntic mucosa (7) and declines gradually in spite of continuous stimulation (9).

Moreover, studies on isolated cells cannot in most instances be used to assess the quantitative role of histamine release in the stimulation of acid secretion without combining it with aminopyrine uptake to assess the effect on the parietal cells (1).

In conclusion, isolated ECL cell preparations are not well suited for studying the immediate effects of a stimulant or to assess the concentration response relationship due to low sensitivity. The main reason for writing this letter is, however, that we think it is peculiar not to mention that most aspects of ECL cell regulation had been done when we (1), and later Prinz (2), started to study isolated ECL cells.

REFERENCES


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To the Editor: We agree that several Scandinavian research groups, including the group of Prof. Waldum from Trondheim, Norway, have performed very interesting and excellent studies that helped the understanding of the physiology of enterochromaffin-like (ECL) cells to a great extent. In this regard, the initial studies using isolated ECL cells confirmed the results made by these researchers in other in vivo or in vitro systems. However, since this review was focused on work done in isolated cells, we did not cite all the contributions made in other in vivo or in vitro systems. We disagree, however, with several arguments raised by Waldum and colleagues. First, Dr. Waldum's work on isolated ECL cells was no prerequisite to study purified ECL cells. The procedure introduced by the Waldum group did not yield a preparation of functionally intact ECL cells: “Gastrin at high and unphysiologic concentrations stimulated only faintly the aminopyrine uptake in [isolated] parietal cells and the histamine release from [isolated] ECL cells” (1). Therefore, we did not cite this paper mentioned by Dr. Waldum. However, stimulation of histamine release by gastrin was clearly shown in subsequent papers of our own group (2). Moreover, the technique of elutriation of gastric mucosal cells was established in our laboratory in Munich already in 1990 when we started to work on isolated parietal cells as well as G-cells (3).

Second, isolation and enrichment of gastric mucosal cells, in our point of view, is a very elegant technique to study cellular calcium responses, exocytosis, and histamine release in ECL cells. In previous studies, a 5-min incubation period was chosen because this time interval was the minimal period to yield statistically significant differences in this system. Videoimaging of isolated cells, however, revealed that calcium signals can be detected within 30 s of incubation with gastrin, and histamine release from isolated and permeabilized cells also revealed significant release within 60 s of incubation.

Third, we apologize for not having cited work of the Waldum group in the context of histamine secretion in the gastric mucosa, but we wish to emphasize that this review is focused on the “mechanism of secretion from ECL cells” and is not a review regarding the regulation of histamine or acid secretion. In this review, we summarize the mechanisms of calcium signaling, exocytosis via SNARE proteins, regulation of the VMAT-2 transporters, and electrophysiological properties of rat gastric ECL cells.

REFERENCES


Christian Prinz
Department of Medicine II
Technical University of Munich
D-81675 Munich, Germany