Content of Acetylcholine and Gastrin in Biological Fluids and Tissues in Patients with Stomach Polyposis

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Abstract: In recent years, much attention has been paid to the role of hormones and biogenic amines, contained in the gastric mucosa, in the regulation of gastric secretion. At the same time, monoamines ratio plays a significant role in changing the activity of gastric juice and impaired regulatory mechanisms of the stomach. These disorders are caused by various reasons, resulting in insufficient secretory function of the stomach. Unfortunately, there are not enough data on the significance of these factors in polyps' formation. This led us to conduct a comprehensive study of gastrointestinal hormones and biogenic amines in patients with gastric polyps of different locations, sizes and shapes. We believe that our study will come closer to understanding the mechanisms of polyps' formation and its cancerous transformation.

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1. Introduction

Nowadays it was found that a number of neurohumoral systems and local mechanisms take part in the regulation of coordinated activity of all structural formations of gastric mucosa. [2, 8].The leading role of all the currently known monoamines in the regulation of digestion belongs to acetylcholine – the mediator of parasympathetic nervous system and general stimulant of the gastric glands [3, 4].

Originally peripheral action of acetylcholine seemed straightforward, independent of any endogenous stimulants. But in gastric juice obtained after insulin stimulation of the vagus nerve, a high concentration of hydrochloric acid and increase of digestive power of pepsinogen were revealed, and also a significant amount of mucus was found in it. After injection of histamine, acetylcholine and pepsinogen content in the gastric juice became insignificant. It must be assumed that the difference in the content of acetylcholine in the «insulin» and «histamine» juice is caused by the release of the mediator upon stimulation of the vagus nerve by insulin [6].

On the other hand, the concentration of pepsin and its release in response to stimulation of histamine decreases after injection of atropine [1], which is indicating participation of cholinergic component in the secretory effect of histamine.

However, secretion of gastric juice increases on the background of atropine action after injection of gastrin. This raises doubts about the only direct action of acetylcholine on the secretory cell. Despite the contradictory and controversial views in the literature data, the vagus nerve is currently recognized as the main secretory nerve of the digestive tract, stimulating the secretion of the gastric glands in all phases of the secretory process [5, 7].

It is known, that decreased secretion of hydrochloric acid and pepsin was noted in patients with gastric polyposis, both before and after stimulation [9, 10, 11, 12].

2. Material and Methods

In light of the above, we have carried out a study of acetylcholine and gastrin in the serum, in gastric juice, mucosa and tissues of polyp, and gastric secretory function and proteolytic activity of gastric juice in 22 patients (4 women and 18 men with stomach polyposis aged 42 to 68). These patients were divided into groups depending on the location of polyps, their number and malignancy.

In addition, clinical observation was subjected to 7 patients who underwent gastric resection for malignancy of polyps, and to those with chronic hyperplastic gastritis. Twenty healthy people were used as a control group to determine the normal values of the studied parameters.

3. Results

Determination of acetylcholine concentration in the serum showed, that the concentration of acetylcholine in serum was lower in all groups of

patients (85.0 ± 12.2 μg/ml) than in control group (128.7 ± 14.8 μg/ml).

Concentration of acetylcholine was reduced by more than 2 times compared to the control group in patients after gastrectomy for malignancy of polyps, reaching an average level of 54.9 ± 9.1 μg/ml, (P> 0.1). In this test, there were no significant differences in patients with single or multiple gastric polyps, but a slight tendency to acetylcholine decrease was noted with an increase in the number of polyps.

For a more accurate evaluation of disorders of stomach parasympathetic innervation in the above groups of patients, the acetylcholine concentration has been studied in the gastric juice and gastric mucosal tissue.

Some deviation from the standard value of acetylcholine in mucosa could be due to a small amount of tissue obtained for research using gastrobiopsy. However, attention is drawn to the 2 times higher concentration of acetylcholine in mucosa as compared with its content in polyp tissue. Only when malignancy of polyps the concentration of acetylcholine was reduced in the gastric mucosa. In patients with multiple and malignant polyps, the concentration of acetylcholine in polyp tissue was lower than in single polyp - respectively 489.0 ± 89.5 and 329.0 ± 65.0 μg/g. A significant difference in the concentration of acetylcholine is not revealed at various localizations of polyps.

Estimation of acetylcholine in gastric juice indicated that its concentration in patients with solitary and multiple polyps differs slightly from the control level.

In patients with malignant polyps its decline was more notable, and amounted to 133 ± 25.4 μg/ml (P<0.1). As regards basal gastric secretion of acetylcholine, it was dramatically reduced in patients of all three groups, reaching a minimum value 2.6 ± 0.6 mg/hour (P>0.01) in patients with malignant polyps.

4. Discussions

Thus, a certain concentration of acetylcholine in the serum indicates a content violation of this mediator in patients suffering from stomach polyposis. Moreover, reducing the concentration of acetylcholine in serum, polyp tissue and in gastric mucosa promotes dystrophic changes of the gastric mucosa, polyps' formation and its malignant transformation.

Regulatory and trophic effects of gastrin may be detected in stomach polyps. Therefore, we studied the basal level of gastrin and change in its concentration in the serum of patients with single and multiple polyps. Basal level of gastrin in patients with single gastric polyps is 155.0 ± 26.7 pg/ml, i.e. greatly exceeds that in healthy individuals (87.4 ± 2.8 pg/ml).

This difference is even more pronounced when comparing this indicator in healthy persons and in patients with multiple gastric polyps (176.3 ± 28.3 pg/ml) (P<0.02).

Gastrin level in the blood of patients continues to increase from 15 to 60 minutes in response to a standard dietary exposure and even after it, while there is a tendency to decrease in gastrinemia after 45 minutes in healthy persons. In addition, hypergastrinemia in patients with multiple polyps is expressed and more durable after dietary exposure. Content of gastrin in blood on an empty stomach in patients with polyps in diameter from 0.5 to 1.0 cm was more significant than that in healthy persons and patients with polyps less than 0.5 cm. Differences were more pronounced after dietary exposure, and hypergastrinemia continued to grow reaching 384.9 ± 83.1 pg/ml (P<0.01) in 60 minutes. The highest basal level of gastrin appeared in the serum of patients with polyps in diameter of 1.0 cm and amounted to 206.4 ± 43.4 pg/ml (P<0.05). Standard dietary exposure in these patients caused maximum hypergastrinemia and it reached 439.8 ± 113.8 pg/ml (P> 0.05), but there was a trend towards reduction in 60 minutes.

Thus, there is a definite relationship between the size of stomach polyps and the disorder degree of the functional state of gastrin-secreting cells in patients with stomach polyposis, which is manifested in the increase in the baseline gastrin level in serum and in growth under the influence of dietary exposure. The baseline gastrin level was significantly lower in patients with polyps in the cardiosubcardial part of the stomach, than in the control group. In addition, dietary exposure did not cause a clear increase in serum gastrin in these patients. In patients with polyps of the stomach body, the initial level of gastrin was 118.1 ± 17.2 pg/ml (P<0.05), which significantly exceeded patients of the previous category and in healthy individuals. Dietary exposure resulted in a gradual, quite clear increase in gastrin level (230.6 ± 40.1 pg/ml (P<0.02), a decrease which was observed in only 60 minutes after exposure.

The highest initial concentration of serum gastrin was in patients with polyps of pyloric antrum and it amounted to 327.9 ± 39.2 pg/ml (P>0.05). The most severe hypergastrinemia in response to dietary exposure was revealed in those patients. Though in 60 minutes, the concentration of gastrin in the blood increased even up to 652.8 ± 83.1 pg/ml (P>0.05).

It should be noted, that the different functional state of gastrin-secreting cells in gastric mucosa can be detected in patients with various localization of stomach polyps. If suppression of secretory function of these cells, resulting in a noticeable decrease in

production of gastrin, registered in polyps of the cardiosubcardial part of the stomach, then the gastrin-secreting function of these cells is more strengthened in the lower localization of the polyps. If the disease duration was up to 1 year, the increase in gastrinemia was more significant in patients with stomach polyposis than in healthy individuals. Dietary exposure in these patients causes pronounced and prolonged increase in the concentration of gastrin in the serum. The initial level of gastrin in patients suffering from stomach polyposis from 1 to 3 years is more significant than that of the previous patients. But if after dietary exposure of this group of patients, the results lead to a more pronounced hypergastrinemia then its duration is less, with wavy nature, i.e. an alternation of ups and downs of the gastrin concentration in the patients' blood was registered. It can be stated, that the growing hypergastrinemia, depending on the duration of the disease, contributes to an increase in the number and size of stomach polyps. The basal gastrin level in the blood of patients with benign polyps is 2 times higher than that of healthy individuals. Moreover, in response to standard dietary exposure, the gastrin content increases sharply and continues to increase to 398.6 ± 59.6 pg/ml ($P<0.05$), even in 60 minutes and after exposure. It should be noted, that when comparing the gastrin content in the blood of patients with benign and malignant polyps, it was lower in the group with malignant polyps. These indicators are recorded both before and after dietary exposure. A similar phenomenon may be caused by the influence of the tumor tissue on gastrin-secreting cells of the gastric mucosa, which entails a reduction of gastrinemia compared to patients with benign polyps. Simultaneously, we investigated the content of gastrin in gastric mucosa, polyps' tissue and gastric juice in 7 patients (including 5 patients with polyps of antral localization and 2 patients with polyps of fundic localization). The gastrin content in the antral mucosa was 81.2 ± 8.1 μg/g, which is almost twice as higher than in healthy individuals and patients with polyps of fundic localization. The gastrin content appeared negligible in polyps' tissue compared to its content in the gastric mucosa (3.6 ± 0.6 μg/g).

Our results suggest that gastrin content in the gastric juice of patients with stomach polyposis (69.5 ± 7.8 pg/ml) was slightly lower than in healthy individuals (185.0 ± 28.0 pg/ml). To justify each method of study in patients with stomach polyposis, it was necessary to estimate the effect of neuro-humoral factors in the regulation of gastric secretion, so it was necessary to examine both the quantitative and functional state of G-cells in mucosa, as well as their relationship with the gastrin level in the blood of patients with stomach polyposis.

We have carried out quantification of G-cells in the mucosa of the antrum and stomach body, as well as in polyps' mucosa in 17 patients with polyposis. In the presence of severe basal hypergastrinemia in patients with stomach polyposis, the number of G-cells in 1 mm² of antral mucosa reached 338.9±22.7 μg/g. This value slightly exceeds the indicator in apparently healthy individuals. The quantity of G-cells is determined in the mucosa of the stomach body in 7 patients, but the gastrin-secreting cells in these patients were significantly lower than in the antrum. Gastrin-secreting cells in the polyps' mucosa were found in only 5 of the 7 patients. The number of these cells was equal only to 46.4 ± 27.0 μg/g.

Above data indicates that hypergastrinemia caused, not only by the increased functional activity of gastrin-secreting cells in antrum polyposis, but also by the increase in their number in the antral mucosa. We can assume that hypergastrinemia, revealed in patients with polyposis of the stomach body, is caused only by increasing the functional activity of the G- cells.

Indicators of total acidity in these patients showed that gastric achylia was found in 67.6% of patients and an acidity decrease was revealed in 27.3% of patients. However, achylia was detected in 72.4% of patients with benign polyps and in 92.4% of patients with malignant polyps.

Free hydrochloric acid was absent in 66.4% of patients, and a reduction of its concentration (from 1 to 10 titrated units) was noted in 28.7% of patients. In patients with benign polyps free hydrochloric acid was absent in 63.3% of cases, while in patients with malignant polyps it was not found in 77.01% of cases.

A study of the glandular apparatus in the fundic gland area was undertaken and the density of lymphoid plasmocytic infiltration was estimated in some patients (44 people) along with a morphological study of removed polyps and surrounding mucosa.

Slight lymphocytic infiltration with the number of cells from 30 to 70 in sight was noted in the stroma of polyps. Predominantly moderate but uneven expressed round cell infiltration with the number of 70-200-500 in sight was observed in the lamina propria of gastric mucosa.

The average number of epithelial cells in the fundic gland in 19 patients was equal to 20-32, and in 23 patients it ranged from 32 to 46, while the normal rate is from 70 to 100. Epithelial formula was usually characterized by a marked reduction in the percentage of chief and parietal stomach cells.

The chief cells were less than 10% (at normal rate of 40-49%) in 5 cases; it ranged from 10 to 20% in 12 cases, and from 20 to 25% in 25 cases.

In 27 observations parietal cells amounted from 10 to 15% (at normal rate of 20-29%); accessory and indifferent cells mostly were 20-40%. Moreover, deep deep gastric pits with increased cell numbers from 70 to 140 were detected in a significant number of observations, especially in the formation of foci of intestinal metaplasia.

Thus, the morphometric study of the gastric mucosa revealed a significant decrease in the number of parietal and chief cells in the event of gastric polyps, accompanied by achylia of gastric secretion. Furthermore, a reduction in the proteolytic activity of gastric juice is revealed, which might indicate lower level of enzymes with proteolytic activity at pH from 1.0 to 5.0, as well as their disability.

The electrophoretic study of proteins in gastric juice also shows a decrease in the amount of protein fractions that do not increase after stimulation. We did not reveal any certain differences in the protein spectrum in different groups of patients, but it was noted, that in patients with multiple and malignant stomach polyps the number of fractions and proteolytic activity were even lower.

In conclusion, all data show that the reduction of gastric secretion and production of defective gastric acid having low proteolytic activity caused by disorders of trophic processes in the gastric mucosa due to hypergastrinemia in the blood and decrease of acetylcholine, regulating gastric secretion.

General conclusions:

1. Increased activity of gastrin-secreting cells observed in patients with gastric polyposis, accompanied with hypergastrinemia in serum and an abrupt decrease of acetylcholine concentration in biological fluids and tissues in parallel with an increase in the number, size of polyps and their malignancy.
2. Determination of gastrin and acetylcholine concentration in biological fluids and tissues of the stomach may be used as a test to determine the stage and prevalence of gastric polyposis.
3. The development of secretory insufficiency caused by the degenerative processes in the gastric mucosa was indicated in patients with gastric polyposis, accompanied by a decrease in the number of parietal and chief cells, and the number of protein fractions and their amounts in the gastric juice.
4. Reduction of the proteolytic activity of gastric mucosa and juice leads to a decrease in the number of protein fractions and to an increase in the amount of multiple and malignant polyps in patients.

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References

1. Konturek SJ, Bielanski W, Konturek PC, Brzozowski T. Endogenous gastric mediators: patho-physiological role and measurements. Curr Protoc Toxicol. 2010 Aug;Chapter 21:Unit 21.6.
2. Waldum HL, Hauso O, Fossmark R. The regulation of gastric acid secretion - clinical perspectives. Acta Physiol (Oxf). 2013 Nov 26.
3. Li H, Guo Y, Xiao L, Chen B. A fluorometric biosensor based on H₂O₂-sensitive nanoclusters for the detection of acetylcholine. Biosens Bioelectron. 2014 Apr 2;59C:289-292.
4. Carmack SW, Genta RM, Graham DY, Lauwers GY. Management of gastric polyps: a pathology-based guide for gastroenterologists. Nat Rev Gastroenterol Hepatol. 2009 Jun;6(6):331-41.
5. Tahara T, Shibata T, Okubo M, Yamashita H, Yoshioka D, Yonemura J, Maruyama N, Kamano T, Kamiya Y, Fujita H, Nakagawa Y, Nagasaka M, Iwata M, Yamada H, Nakamura M, Arisawa T, Hirata I. Examination of serum pepsinogen in functional dyspepsia. Hepatogastroenterology. 2012 Nov-Dec;59(120):2516-22.
6. Pino-Ángeles A, Reyes-Palomares A, Melgarejo E, Sánchez-Jiménez F. Histamine: an undercover agent in multiple rare diseases? J Cell Mol Med. 2012 Sep;16(9):1947-60.
7. Schubert ML. Gastric secretion. Curr Opin Gastroenterol. 2011 Oct;27(6):536-42.
8. Chu S, Schubert ML. Gastric secretion. Curr Opin Gastroenterol. 2013 Nov;29(6):636-41.
9. Datkhayev U., Shopabayeva A., Zhakipbekov K., Yermekbayeva D., Orazbekov E., Turgumbayeva A. Basic aspects of the organization of the pharmaceutical industry. Life Sci J 2013; 10(7s): 677-683] (ISSN:1097-8135). http://www.lifesciencesite.com. 106.
10. Botabayeva R., Shertaeva C., Blinova O., Datkhayev U., Shopabaeva A., Zhanabayev N., Zhakipbekov K. Methodical approaches to a strategy of diversification to advance domestic production of medicines. Life Sci J 2013;10(12s):302-309. (ISSN:1097-8135). http://www.lifesciencesite.com. 53.
11. Zhumabayev N., Makhatov B., Makhatova A., Magay T., Zhakipbekov K., Sapakbay M., Makhatova B. The use of mathematical methods of analysis in the pharmaceutical area of Kazakhstan. Life Sci J 2013;10(10s):36-40. (ISSN:1097-8135). http://www.lifesciencesite.com. 7.
12. Utegenova G., Blinova O., Sherta eva C., Tulemissov S., Sapakbay M., Umurzakhova G., Zhakipbekov K. About the standards of development and the placement of pharmacy network in the Republic of Kazakhstan. Life Sci J 2013; 10(12s):664-672. (ISSN: 1097-8135). http://www.lifesciencesite.com. 107.