We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,300

Open access books available

172,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Biochemical Examination of the Human Gastrointestinal Tract

Gyula Mozsik and Imre Szabó

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/60102>

The forthcoming biochemical observations were from the resectates of the patients who underwent surgical intervention because of peptic ulcer disease. These observations were done during 1969–1976, when only the parasympatholytics were used in the medical treatment of patients with peptic ulcer.

The resectates of the gastrointestinal tract were divided into two parts: one was used for classical histopathological examinations (with the permission from Professor György Romhányi, Head of the Department of Pathology and of Professor Tihamer Gy. Karlinger, Head of First Department of Surgery, Pécs University, Hungary),, awhile the other part was used for biochemical examinations. Different parts from the mucosa and musculature were separated from each other immediately after the surgical resection of the GI tract, and these parts were put immediately into liquid nitrogen.

All biochemical parameters of the GI tissue samples (normal and ulcerated antral, duodenal and jejunal mucosa and three gastric fundic mucosa and musculature, if we received fundic tissues) were maintained in the same time in all the received tissue samples.

It is very important to emphasize that, on the one hand, all biochemical parameters maintained from the same tissue samples, and on the other hand, all tissue samples were biochemically examined. It is also important to note that the weight of these tissue samples was about 0.25–0.5 g wet tissue (these examinations cannot be carried out from biopsy materials).

The methodologies were detailed in the original published papers.

These patients had typical ulcer histories and endoscopic pictures. These patients received medical treatment (by dominant internists) for about 4 weeks before surgery. The patients who were suspected to have malignant ulcers did not receive any tissue samples from the resectates (because of necessary histopathological examinations).

7.1. Correlation between the gastric fundic mucosal Na⁺-K⁺-dependent ATPase activity versus gastric basal acid output (BAO) in humans

In the gastric basal acid output (BAO) and maximal acid output (MAO), there are different associations with cations and protein secretion from the serosa to the mucosa: the H⁺, chloride, K⁺, Mg²⁺, Ca²⁺ and albumin increase significantly, while the Na indicates a decrease (Myren, 1968; Semb and Myren, 1968; Wright and Hirschowitz, 1976). These called for attention to study the correlations between the classical membrane-bound ATP-dependent energy systems and gastric BAO and MAO.

There was no doubt that after the administration of pentagastrin or histamine (given in doses) to produce gastric MAO values, the changes in the contents of the gastric juice cations became much higher than those in gastric BAO. These data also suggested that there is some correlation between the membrane-bound ATP-dependent energy systems and the gastric BAO and MAO values.

In 45 patients with peptic ulcer (20 patients with gastric and 25 patients with duodenal ulcer), the gastric H⁺ was measured without the administration of any drug (basal acid output, BAO), and its value was expressed in mEq/L. These patients underwent resection of the stomach for peptic ulcer. During the surgery, a piece was cut from the fundic part of the stomach. The gastric mucosa and the muscular layer were separated from each other, and the membrane ATPase was prepared from fundic gastric mucosa with differential centrifugation (20.000 × g and 40.000 × g) and treatment with 2.0 M NaI solution as per our method (Mózsik and Øye, 1969). The membrane ATPase activity was measured in an incubation system at 37 °C by the liberation of inorganic phosphorus (Mózsik, 1969b). The Na⁺-K⁺-dependent ATPase activity was calculated as the difference between the total (obtained in the presence of Mg²⁺, Na⁺ and K⁺) and Mg²⁺-dependent system (obtained in the presence of Mg²⁺) (Figure 45).

The Na⁺-K⁺-dependent ATPase differs from the H⁺-K⁺-dependent ATPase, independently from the similarities of protein structures (see Sections 5.1, 5.2), and the mitochondrial ATP is a common substrate for both these enzymes. Our enzyme was prepared from the whole gastric fundic mucosa; H⁺-K⁺-ATPase is located only in the parietal cells, which are highly specialized epithelial cells in the inner cell lining of the stomach. H⁺-K⁺-ATPase can be separated from the Na⁺-K⁺-pump enzyme based on specific immunological studies (Saccomani et al., 1979b; Yao and Forte, 2004; Dunbar and Caplan, 2001; Sachs et al., 1995; https://www.nlm.nih.gov/cgi/mesh/2011/MB_cgi?&term=Potassium+Hydrogen+ATPase).

There is no doubt that both the active transport of Na⁺ and K⁺ (Na pump) and the gastric acid secretion are energy-dependent processes (obtained from the ATP transformation into ADP); however, the sodium pump is a general function of all cells, while the H⁺-K⁺-ATPase is responsible only for gastric acid secretion.

We never participated in the study of H⁺-K⁺-ATPase; however, it is true that the presence of Na⁺-K⁺-ATPase was proved earlier in the rat and human gastrointestinal (gastric) mucosa (Mózsik and Øye, 1969).

Figure 45. Correlation between the Na⁺-K⁺-dependent ATPase activity from human fundic mucosa (ordinate) and basal acid output (BAO) (abscissa) in 45 patients with peptic ulcer. The enzyme activities are expressed as P_i (μMol/mg protein/hour). [Mózsik, Nagy, Tárnok, Vizi F, Kutas J: Experientia (Basel) 30: 1024–1025, 1974 (with kind permission).]

We used the Na⁺-K⁺-dependent ATPase system as a key enzyme participating in the regulation of cell functions, of course, in the gastric mucosal cells. The function of Na⁺-K⁺-ATPase represents only one side of the ATP splitting process (as energy source), while the actual level of tissue ATP indicates the other side of energy source system (namely, the ATP resynthesis). These processes occur together in all cells and tissues. Both Na⁺ and K⁺ are involved in both the classical sodium pump and the gastric acid secretion.

Our results presented here are related dominantly to the function of the classical sodium pump in the human gastric mucosa. It is interesting and important to note that the activity of Na⁺-K⁺-dependent ATPase is closely associated with the gastric acid secretion.

7.2. Interaction of cholinergic function with Mg²⁺-Na⁺-K⁺-dependent ATPase system of cells in the human fundic gastric mucosa

This section deals with the effects of some cholinergic and anticholinergic drugs on the membrane-bound ATPase enzyme (Mózsik et al., 1974c).

Figure 46. Effects of acetylcholine (Ach), carbamylcholine (Carb.ch.) and neostigmine (Neostig.) on the total ATPase activity in the human gastric fundic mucosa. The enzyme activity is expressed in percentage of total ATPase activity (=100%) without any drug [Mózsik, Nagy, Kutas, Tárnok: Scand. J. Gastroenterol. 9: 741–745, 1974 (with kind permission).]

Figure 47. Effects of acetylcholine on Mg²⁺-dependent, total and Na⁺-K⁺-dependent ATPase prepared from the human gastric fundic mucosa. The results are presented in percentage of total ATPase (=100%) activity without the administration of any drugs. [Mózsik, Nagy, Kutas, Tárnok: Scand. J. Gastroenterol. 9: 741–745, 1974 (with kind permission).]

Figure 48. Effects of atropine on Mg^{2+} -dependent, total and $Na^{+}-K^{+}$ -dependent ATPase prepared from the human gastric fundic mucosa. The results are presented in percentage of total ATPase (=100%) activity without the administration of any drugs. [Mózsik, Nagy, Kutas, Tárnok: Scand. J. Gastroenterol. 9: 741-745, 1974 (with kind permission).]

Figure 49. Comparative inhibitory effect of different parasympatholytics on the total membrane ATPase prepared from the human gastric fundic mucosa. The results are presented in percentage of total ATPase (=100%) activity without the administration of any drugs. [Mózsik, Nagy, Kutas, Tárnok: Scand. J. Gastroenterol. 9: 741-745, 1974 (with kind permission).]

Figure 50. Comparative inhibitory effect of different parasympatholytics on the total membrane ATPase activity prepared from the human gastric fundic mucosa. The results are presented in per cent of total ATPase (= 100 per cent) activity without application of any drugs. (Mózsik, Nagy, Kutas, Tárnok: Scand. J. Gastroenterol. 9: 741-745, 1974) (with kind permission).

Cumulative dose-response curves for parasympatholytics

Figure 51. Cumulative dose-response curves for parasympatholytics inhibiting the $\text{Na}^+\text{-K}^+$ -dependent ATPase prepared from the human gastric fundic mucosa. The intrinsic activity (α) of atropine was found to be equal to 1.0 on $\text{Na}^+\text{-K}^+$ -dependent ATPase activity. Each point represents the average of 10 measurements (chemical structures: isopropamide, 2,2-diphenyl-4-diiso-propylamino-methylodide; Gastrixon^R, methyl-tropinium-bromide-xanthene-9-carboxylate). [Mózsik, Kutas, Nagy, Tárnok, Vizi: Acta Physiol. Sand. Special Suppl. 199-208, 1978 (with kind permission).]

Parasympatholytics	Affinity (pD ₂)	Intrinsic activity (α)
Atropine	9.50	1.00
Isopropamide	7.50	0.36
Gastrixon ^R	6.40	0.43

Table 31. Values of affinity (pD₂) and intrinsic activities (α) for parasympatholytics inhibiting the Na⁺-K⁺-dependent ATPase prepared from the human gastric fundic mucosa. The intrinsic activity of atropine was found to be equal to 1.0.

The results presented above indicate clearly the following:

1. During the cholinergic activation, the enzyme system of sodium pump (the transformation of ATP into ADP by membrane ATPase) is in working state (acetylcholine, carbamylcholine, neostigmine);
2. The parasympatholytics inhibit the function of membrane ATPase prepared from the human gastric fundic mucosa;
3. The different parasympatholytics produced different extents on the inhibition of membrane ATPase activity.

7.3. Inhibitory effects of histamine, pentagastrin, PGE₁ and PGE₂ on Na⁺-K⁺-dependent ATPase prepared from human gastric mucosa

The gastric acid secretory responses are characterized by the so-called basal acid secretory responses (e.g., without the administration of any drug to stimulate the gastric acid secretion) (basal acid output, BAO) and maximal gastric acid secretory responses (maximal acid output, MAO). The MAO can be produced by the administration of histamine (0.04 mg/kg body weight, given subcutaneously) (Kay's test) or pentagastrin (6 µg/kg given subcutaneously).

The effect of histamine was studied on the typical membrane ATPase prepared from the gastric fundic mucosa of patients with gastric (8 patients) and duodenal (6 patients) ulcer, before resection of their stomach: BAO value = 3.86 ± 1.14 mEg/h and MAO = 16.30 ± 2.25 mEg/h.

Histamine was used in 10⁻⁷ M concentration to test its effect only on Mg²⁺-dependent part and Na⁺-K⁺-dependent part (Figure 52).

Figure 52. Histamine (10^{-7} M) effects on only Mg^{2+} -dependent ATPase and on Na^{+} - K^{+} -dependent ATPase activity. The results (means $\pm$ SEM) are presented as per cent of control values. (Mózsik, Nagy, Tárnok, Jávör, Kutas: Pharmacology 12: 193-200, 1974) (with kind permission).

Figure 53. Inhibition of total ATPase from the human gastric fundic mucosa by histamine. The results of 14 patients are expressed in means $\pm$ SEM. The left ordinate shows the enzyme activity ($\mu\text{mol } P_i/\text{mg}$ membrane protein/h, while the abscissa indicates the histamine concentration (M). The right side of the figure demonstrates the “chemical marker behavior” of this membrane fraction taken from 14 patients’ gastric fundic mucosa. [Mózsik, Nagy, Tárnok, Jávör, Kutas: Pharmacology 12: 193-200, 1974 (with kind permission).]

The inhibition of total membrane ATPase activity was caused by histamine in a concentration of 10^{-7} to 10^{-3} M.

Similar observations were noted in pentagastrin, and the same type of inhibition of membrane ATPase was obtained as that of histamine.

The effects of prostaglandin E_1 and E_2 were studied on the Mg^{2+} - dependent and Na^+-K^+ -dependent ATPase prepared from the human gastric fundic mucosa (Figures 54, 55), and significant inhibitory actions were produced by PGE_1 and PGE_2 in concentrations of 10^{-10} to 10^{-6} M.

Figure 54. Inhibitory effects of prostaglandin E_1 (top) and E_2 (bottom) on Mg^{2+} -dependent ATPase prepared from the human gastric fundic mucosa. The results are expressed as percentage value of total ATPase activity (=100%). The abscissa indicates the concentrations of prostaglandins (M). Each point represents the means $\pm$ SEM of 10 observations. [Mózsik, Kutas, Nagy, Németh: Eur. J. Pharmacol. 29: 133–137, 1974 (with kind permission).]

7.4. Correlations between the magnitudes of drug actions versus magnitudes of Na^+-K^+ -dependent ATPase prepared from the human gastric fundic mucosa and from the small intestinal mucosa

It was clear to conclude that the magnitudes of drugs actions depend on the membrane enzyme activity. Because the membrane ATPase activity significantly changes on the activity of target organ, the drug actions depend on the activity of the target organ (Nagy et al., 1976, 1981 a, b).

Figure 55. Inhibitory effects of prostaglandin E₁ (top) and E₂ (bottom) on Na⁺-K⁺-dependent ATPase prepared from the human gastric fundic mucosa. The results are expressed as percentage value of total ATPase activity (=100%). The abscissa indicates the concentrations of prostaglandins (M). Each point represents the means ± SEM of 10 observations. [Mózsik, Kutas, Nagy, Németh: Eur. J. Pharmacol. 29: 133–137, 1974 (with kind permission).]

Drug:	Drug effect:	Tested dose:	r:	Regression line:	p value:	n:
AcH	stimulation	10 ⁻⁴ M	0.98	Y=0.5X-0.8	≪0.001	7
Atropine	inhibition	10 ⁻⁷ M	0.97	Y=1.35X+0.49	≪0.001	19
cAMP	inhibition	10 ⁻⁹ M	0.78	Y=1.34X-1.63	≪0.05	8
Epinephrine	inhibition	10 ⁻⁷ M	0.68	Y=1.10X+0.12	≪0.05	10
Histamine	inhibition	10 ⁻⁷ M	0.87	Y=0.96X+0.88	≪0.01	9
Ouabain	inhibition	10 ⁻⁷ M	0.93	Y=1.03X+0.20	≪0.001	45
	inhibition	10 ⁻⁴ M	0.93	Y=1.20X+1.03	≪0.001	45
Pentagastrin	inhibition	10 ⁻⁷ M	0.94	Y=0.85X+0.11	≪0.02	10

Affinity (pD₂) values: Ach=5.50 ; Atr.=9.50; cAMP=11.30 ;
Epinephr.=8.60 ; Hist.=9.70 ; Pentagast.=10.55 ;
Ouabain=7.50 (9.20 – 6.50)

Table 32. Correlations between the magnitudes of drug actions and the magnitudes of Na⁺-K⁺-ATPase prepared from the human gastric fundic mucosa.

7.5. Correlations between the magnitudes Na⁺-K⁺-dependent ATPase, tissue levels of ATP, ADP in the human gastric fundic mucosa versus values of gastric basal acid ouput (BAO) in humans

We prepared the membrane ATPase from the human gastric fundic mucosa and, simultaneously, directly measured the tissue level of ATP, ADP, lipid phosphates, ribonucleic acid and deoxyribonucleic acid. The tissue levels of ATP, ADP, lipid phosphates and ribonucleic acid

were expressed in accordance to 1.0 mg deoxyribonucleic acid (DNA). The membrane ATPase activity was assayed (Mózsik and Øye, 1969) by *in vitro* method (Figures 56, 58). The different correlations were expressed in consequence of mathematical analyses: BAO versus $\text{Na}^+\text{-K}^+$ -dependent ATPase ($r = 0.88$, $n = 45$; $P < 0.001$); BAO versus tissue level of ATP ($r = 0.53$, $n = 28$, $P < 0.01$); ATP versus $\text{Na}^+\text{-K}^+\text{-ATPase}$ ($r = 0.55$, $n = 32$, $P < 0.001$); ATP versus ADP ($r = 0.99$, $n = 32$, $P < 0.001$); BAO versus ADP ($r = 0.59$, $n = 28$, $P < 0.001$) (Mózsik et al., 1979 a, b, 1981d, 1978b) (Figure 56).

Figure 56. Biochemical regulatory pathways between $\text{Na}^+\text{-K}^+$ -dependent ATPase, tissue levels of ATP, ADP in the human gastric fundic mucosa dependent on the gastric BAO values (means $\pm$ SEM). [Mózsik, Tárnok, Kutas (1981) in Gáti, Szollár, Ungváry (eds.) Advances in Physiological Sciences Vol. 12. Nutrition, Digestion, Metabolism. pp. 117-128. 1981 (with kind permission).]

7.6. Correlation between gastric basal acid output (BAO) versus gastric maximal acid output (MAO) in humans

Figure 57. Correlation between the gastric basal acid output (BAO) versus gastric maximal acid output (MAO) in patients examined biochemically. [Mózsik, Vizi, Nagy, Bero, Tárnok, Kutas (1976): $\text{Na}^+\text{-K}^+$ -dependent ATPase system and the H^+ secretion by the human gastric mucosa. In: Mózsik Gy., Javor T. (eds.) Progress in Peptic Ulcer. Budapest, Akadémiai Kiadó, pp. 37-72 (with kind permission).]

Figure 58. Biochemical regulatory pathways between $\text{Na}^+ - \text{K}^+$ -dependent ATPase, tissue levels of ATP, ADP in the human gastric fundic mucosa dependent on the gastric maximal acid output (MAO) values. For further explanation, see Figure 56 (with kind permission).

7.7. Correlations between $\text{Na}^+ - \text{K}^+$ -dependent ATPase activity, tissue level of ATP, ADP in the human gastric fundic mucosa versus gastric maximal acid output (MAO) in humans

Figure 58 indicates the results of different correlation calculations versus MAO values.

We found positive and significant correlations between the following parameters:

- a. MAO versus $\text{Na}^+ - \text{K}^+$ -dependent ATPase;
- b. MAO versus tissue level of ATP;
- c. $\text{Na}^+ - \text{K}^+$ -dependent ATPase versus ATP;
- d. ATP versus ADP;
- e. MAO versus ADP. (Andrási, 1997; Bódis et al., 1977 a, b; Levine, 1971; Mózsik et al., 1978b).

7.8. Affinity and intrinsic activity curves of acetylcholine, histamine and pentagastrin on the $\text{Na}^+ - \text{K}^+$ -dependent ATPase prepared and on the adenylate cyclase prepared from human gastric mucosa

The contradictory effects of drugs on $\text{Na}^+ - \text{K}^+$ -dependent ATPase and adenylate cyclase were demonstrated earlier (Mózsik, 1969 a, b, 1970, 1974 a, b, 1979 b, c, e).

Table 33 indicates affinity (pD_2) and intrinsic activity (pA_2) curves for the actions of acetylcholine, histamine and pentagastrin. The table also indicates the contradictory actions of these agents on $\text{Na}^+ - \text{K}^+$ -dependent and adenyl cyclase systems.

We hypothesized a feedback system between the membrane ATPase and adenylate cyclase in the development of gastric BAO and MAO (Figure 59).

Mediators	Actions	Affinity values (pD ₂)	Intrinsic activities (α)	Intrinsic activities (pA ₂)
<u>ATP – membrane ATP-ase – ADP</u>				
Ach	Stimulation	5.50	1.00 _{Ach}	5.50
Histamine	Inhibition	9.70	1.00 _{Ouabain}	9.70
Pentagastrin	Inhibition	10.55	0.87 _{Ouabain}	10.55
<u>ATP – adenylate cyclase – cAMP</u>				
Ach	Inhibition	5.30	-0.70 _{Pentagastrin}	5.30
Histamine	Stimulation	9.30	1.00 _{Pentagastrin}	9.30
Pentagastrin	Stimulation	9.40	1.00	9.40

Table 33. Actions of acetylcholine, histamine and pentagastrin in human beings.

Figure 59. Our suggestion to demonstrate the correlations between the ATP-dependent membrane-bound energy systems and the gastric BAO and MAO values regulated by acetylcholine, pentagastrin and histamine. [Mózsik, Debrece- ni, Juricskay, Karádi, Nagy (1997) In: Gaginella T.S., Mózsik Gy., Rainsford K.D. (eds) Biochemical Pharmacology as an Approach to Gastrointestinal Disorders, Kluwer Academic Publishers, Dordrecht, Boston, London. pp. 199–222 (with kind permission).]

7.9. Energetical and biochemical gradients between the gastric fundic, antral and duodenal mucosa in dependence of gastric BAO values in peptic ulcer patients

7.9.1. Energetical and biochemical gradients in the gastric fundic mucosa and musculature in peptic ulcer patients in dependence of gastric basal secretory responses

The biochemical examinations were carried out in resecates of stomach (fundus, antrum) and small intestine (duodenum, jejunum) in patients with chronic peptic ulcer, who underwent surgical intervention.

The gastric BAO and MAO (subcutaneously given 6 µg/kg body weight of pentagastrin) were measured before the surgical intervention.

The examined patients were divided into three groups, according to the BAO values (Table 34). These patients underwent resection of stomach (and some part from duodenum; in patients with jejunal ulcer, who underwent surgery previously, Billroth II-type gastric resection was carried out, and jejunal ulcer appeared later). Immediately after resection, different tissue samples were separated from the obtained tissues, and they were put into liquid nitrogen.

Groups of patients	Basal acid outputs (BAO)	Maximal acid outputs (MAO)
BAO < 2.0 mEq/ h	0.27 ± 0.01 (n = 12)	7.95 ± 1.38 (n = 12)
BAO 2.00 to 4.0 mEq/h	2.81 ± 0.10 (n = 9)	15.69 ± 0.76 (n=9)
BAO > 4.0 mEq/h	5.33 ± 0.24 (n = 11)	18.76 ± 2.15 (n=11)

Table 34. Gastric secretory responses in patients in whom the biochemical examinations were carried out. The gastric acid secretory responses are presented in mEq/h (means ± SEM), *n* indicates the number of patients. [Mózsik, Vizi, Kutas: Scand. J. Gastroenterol. 11: 205–211, 1976 (with kind permission).]

The following biochemical examinations were carried out from different tissue samples:

1. Determination of membrane (Mg^{2+} – Na^{+} – K^{+} -dependent) ATPase;
2. Separation and determination of adenine–adenosine, adenosine triphosphate (ATP), adenosine diphosphate (ADP) and adenosine monophosphate (AMP);
3. Separation and determination of lipid phosphates;
4. Separation and determination of nucleic acids.

The details of these methodological problems are presented in a paper (Mózsik et al., 1976b).

It is important to note and emphasize the following:

1. The number of biochemically evaluated tissue samples in different figures is different (e.g., in case of gastric fundic mucosa vs. musculature), which is dependent on the *in situ* situation at the time of surgical intervention;
2. We had no possibility for direct measurement of cyclic AMP from these tissue samples in these series of observations;
3. All biochemical examinations (including the preparative works) were carried out in all tissue samples obtained in one patient.

Figure 60. Tissue levels of adenosine triphosphate (ATP) in the gastric fundic mucosa and musculature prepared from patients with peptic ulcer depending on the gastric acid secretory responses. The results are presented in nmol/mg DNA (means ± SEM). The results are based on the results published in a paper (Mózsik, Vizi, Kutas: Scand. J. Gastroenterol. 11: 205–211, 1976) (with some modification).

Figure 61. Tissue levels of ribonucleic acid (RNA) in the gastric fundic mucosa and musculature prepared from patients with peptic ulcer depending on the gastric acid secretory responses. The results are presented in mg RNA/mg DNA (means ± SEM). The results are based on the results published in a paper (Mózsik, Vizi, Kutas: Scand. J. Gastroenterol. 11: 205–211, 1976) (with some modification). The numbers in parenthesis indicate the number of patients.

ATP-MEMBRANE ATP-ASE -ADP SYSTEM IN THE HUMAN GASTRIC CORPUS MUCOSA AND MUSCULATURE ON DEPENDENCE OF GASTRIC SECRETORY RESPONSES

CORPUS MUCOSA					
ATP ⁺	48±17	(12)	213±69	(9)	447±46 (11)
↓					
ASES					
↓					
Mg ²⁺ -dependent ⁺⁺	0.95±0.14	(62)	2.56±0.43	(28)	3.90±0.56
Mg ²⁺ -Na ⁺ -K ⁺ -dependent ⁺⁺	2.19±0.27		4.54±0.60		9.14±1.19
Na ⁺ -K ⁺ -dependent ⁺⁺	1.24±0.19		2.04±0.34		5.24±0.72
ADP ⁺	65±23	(12)	211±40	(9)	446±60 (11)
CORPUS MUSCULATURE					
ATP ⁺	99±37	(12)	49±11	(9)	39±10 (6)
↓					
ASES					
↓					
Mg ²⁺ -dependent ⁺⁺	1.17±0.30	(33)	0.77±0.29	(6)	1.10±0.20
Mg ²⁺ -Na ⁺ -K ⁺ -dependent ⁺⁺	2.03±0.39		1.47±0.51		1.83±0.20
Na ⁺ -K ⁺ -dependent ⁺⁺	0.86±0.21		0.70±0.26		0.73±0.26
ADP ⁺	123±38	(12)	74±14	(9)	33±7 (6)
BAO (mmol·hr ⁻¹): ← BAO<20 ← 2-4 → BAO>4 →					
+=nmol·mgDNA ⁻¹ (means±SEM) ; ++= μmol of P _i ·mg membr. prot. ⁻¹ ·hr ⁻¹ (means±SEM)					

Figure 62. ATP-membrane ATPase-ADP system in the human gastric fundic mucosa and musculature prepared in the stomach resectates obtained from patients with peptic ulcer. The results are based on the results published in a paper (Mózsik, Vizi, Kutas: Scand. J. Gastroenterol. 11: 205-211, 1976 and Mózsik, Vizi, Kutas: Scand. J. Gastroenterol. 12: 461-464, 1977) (with some modification). The numbers in parenthesis indicate the number of patients.

ATP MEMBRANE ATP-ASE-ADP SYSTEM IN THE HUMAN ANTRAL MUCOSA AND MUSCULATURE ON DEPENDENCE OF GASTRIC SECRETORY RESPONSES

ANTRUM MUCOSA					
ATP ⁺	46±24	(12)	32±5	(9)	16±2 (11)
↓					
ASES					
↓					
Mg ²⁺ -dependent ⁺⁺	2.00±0.35	(51)	1.60±0.20	(6)	1.56±0.42
Mg ²⁺ -Na ⁺ -K ⁺ -dependent ⁺⁺	2.65±0.40		2.40±0.30		2.52±0.69
Na ⁺ -K ⁺ -dependent ⁺⁺	0.65±0.10		0.86±0.30		0.96±0.22
ADP ⁺	64±25	(12)	25±2	(9)	31±8 (11)
ANTRUM MUSCULATURE					
ATP ⁺	107±41	(6)	88±28	(9)	37±3 (6)
↓					
ASES					
↓					
Mg ²⁺ -dependent ⁺⁺	1.54±0.30	(21)	1.33±0.20	(6)	1.01±0.33
Mg ²⁺ -Na ⁺ -K ⁺ -dependent ⁺⁺	3.36±0.31		3.10±0.30		2.02±0.50
Na ⁺ -K ⁺ -dependent ⁺⁺	1.82±0.12		1.73±0.29		1.01±0.30
ADP ⁺	129±56	(6)	138±38	(9)	23±2 (6)
BAO (mmol·hr ⁻¹): ← BAO<2.0 ← 2-4 → BAO>4 →					
+=nmol·mg DNA ⁻¹ (means±SEM) ; ++= μmol of P _i ·mg membr. prot. ⁻¹ ·hr ⁻¹ (means±SEM)					

Figure 63. Correlations between the membrane ATPase activity, tissue levels of ATP and ADP in the human gastric fundic mucosa and musculature in patients with different gastric (hypacid, normacid and hyperacid) secretory responses depending on the gastric basal acid output (BAO) (means ± SEM). The results are based on the results published in a paper (Mózsik, Vizi, Kutas: Scand. J. Gastroenterol. 11: 205-211, 1976 and Mózsik, Vizi, Kutas: Scand. J. Gastroenterol. 12: 461-464, 1977) (with some modification).

MAIN CHANGES IN METABOLISM OF GASTRIC MUCOSA (A)
AND MUSCULATURE (B) IN PATIENTS WITH DIFFERENT
GASTRIC SECRETORY RESPONSES (BAO)
(means $\pm$ SEM)

BAO (mmol $\cdot$ hr $^{-1}$)	< 2 (n=12)		2-4 (n=9)		> 4 (n=11)	
	A	B	A	B	A	B
CORPUS						
^a ATP $\cdot$ ADP $^{-1}$	0.74 $\pm$ 0.05	0.80 $\pm$ 0.06	1.01 $\pm$ 0.07	0.66 $\pm$ 0.05	1.00 $\pm$ 0.02	1.18 $\pm$ 0.07
^b Lipid $\cdot$ P $\cdot$ DNA $^{-1}$	0.36 $\pm$ 0.04	0.43 $\pm$ 0.04	4.04 $\pm$ 0.10	0.33 $\pm$ 0.04	13.58 $\pm$ 0.70	1.40 $\pm$ 0.30
^b RNA $\cdot$ DNA $^{-1}$	1.74 $\pm$ 0.08	2.03 $\pm$ 0.15	2.00 $\pm$ 0.24	1.24 $\pm$ 0.06	15.28 $\pm$ 1.00	7.14 $\pm$ 0.84
^a „energy charge”	0.43 $\pm$ 0.04	0.46 $\pm$ 0.03	0.33 $\pm$ 0.04	0.42 $\pm$ 0.03	0.03 $\pm$ 0.01	0.14 $\pm$ 0.02
ANTRUM						
^a ATP $\cdot$ ADP $^{-1}$	0.72 $\pm$ 0.06	0.83 $\pm$ 0.06	1.29 $\pm$ 0.08	0.64 $\pm$ 0.05	0.52 $\pm$ 0.04	1.60 $\pm$ 0.10
^b Lipid $\cdot$ P $\cdot$ DNA $^{-1}$	0.16 $\pm$ 0.05	0.85 $\pm$ 0.08	0.26 $\pm$ 0.06	0.31 $\pm$ 0.04	0.43 $\pm$ 0.03	0.34 $\pm$ 0.04
^b RNA $\cdot$ DNA $^{-1}$	1.39 $\pm$ 0.10	1.75 $\pm$ 0.11	1.05 $\pm$ 0.05	2.96 $\pm$ 0.02	2.03 $\pm$ 0.15	1.24 $\pm$ 0.06
^a „energy charge”	0.45 $\pm$ 0.04	0.51 $\pm$ 0.04	0.39 $\pm$ 0.03	0.46 $\pm$ 0.07	0.07 $\pm$ 0.01	0.27 $\pm$ 0.03

^a = values are in nmoles $\cdot$ mg DNA $^{-1}$; ^b = values are in mg $\cdot$ mg DNA $^{-1}$
 „energy charge” = (ATP + 0.5 ADP) $\cdot$ (ATP + ADP + AMP) $^{-1}$

Figure 64. The changes in the biochemistry of gastric fundic mucosa and musculature in patients with different gastric BAO values. The results are expressed as means $\pm$ SEM/1.0 mg deoxyribonucleic acid (DNA) (means $\pm$ SEM). The results are based on the results published in a paper (Mózsik, Vizi, Kutas: Scand. J. Gastroenterol. 11: 205–211, 1976 and Mózsik, Vizi, Kutas: Scand. J. Gastroenterol. 12: 461–464, 1977) (with some modification). The numbers in parenthesis indicate the number of patients.

7.9.2. Energetical and biochemical gradients in the gastric antral and duodenal mucosa and musculature in patients with peptic ulcer in dependence of gastric basal acid secretory responses

There was an energy gradient in the corpus, antrum and duodenum mucosa depending on the gastric basal and maximal acid secretory activities (Mózsik et al., 1976 a, b, c, 1979 b, 1981a) (Figures 65–66; Tables 35–37).

BIOCHEMICAL CONSTITUENTS OF HUMAN CORPUS,
ANTRAL AND DUODENAL MUCOSA

Figure 65. Biochemical parameters in the corpus, antrum and duodenum in patients with gastric hyp acidity (BAO, MAO) (means $\pm$ SEM) (Mózsik, Vizi, Kutas: Scand. J. Gastroenterol. 12: 461–464, 1976) (with some modification).

BIOCHEMICAL CONSTITUENTS OF HUMAN CORPUS, ANTRAL AND DUODENAL MUCOSA

Figure 66. Biochemical gradients in the gastric fundic, antral and duodenal mucosa in patients with hyperacidity (means ± SEM). (Mózsik, Vizi, Kutas: Scand. J. Gastroenterol. 12: 461–464, 1976) (with some modification).

	Corpus (12) ^b	Antrum (12) ^b	Duodenum (12) ^b	p ¹ ^c	p ² ^c	p ³ ^c
ATP ^d	48 ± 17	46 ± 24	24 ± 14	NS ^e	NS	NS
ADP ^d	65 ± 23	64 ± 25	51 ± 28	NS	NS	NS
ATP/ADP	0.74 ± 0.05	0.72 ± 0.06	0.47 ± 0.06	NS	<0.01	<0.01
AMP ^d	60 ± 17	63 ± 12	34 ± 16	NS	NS	NS
ATP+ADP+AMP ^d	173 ± 25	173 ± 18	109 ± 12	NS	<0.01	<0.02
Energy charge ^f	0.43 ± 0.04	0.45 ± 0.04	0.45 ± 0.08	NS	NS	NS
Adenine-adenosine ^d	718 ± 179	549 ± 229	435 ± 207	NS	NS	NS
Lipid-P ^g	358 ± 46	163 ± 50	306 ± 43	<0.02	NS	NS
RNA ^g	1741 ± 81	1397 ± 107	1133 ± 41	=0.02	=0.04	<0.001

^a ATP,adenosine triphosphate; ADP,adenosine diphosphate; AMP,adenosine monophosphate; lipid-P, lipid phosphates; RNA,ribonucleic acid.

^b Numbers in parentheses indicate numbers of patients.

^c p¹,corpus versus antrum; p²,antrum versus duodenum; p³,corpus versus duodenum.

^d Values=nanomoles of substrates per 1.0 mg deoxyribonucleic acid (means ± S.E.M.).

^e Not significant.

^f Adenylate pool energy charge (ATP+0.5 ADP/ATP+ADP+AMP).

^g Values=micrograms of substrates per 1.0 mg deoxyribonucleic acid (means ± S.E.M.).

Table 35. Substrate levels in the gastric mucosa of the corpus, antrum and duodenum of patients with BAO values <2.0 mEq/h (BAO = 0.27 ± 0.27 ; MAO = 9.75 ± 1.38)^a. [Mózsik, Vizi, Kutas: Scand. J. Gastroenterol. 12: 461–464, 1977 (with kind permission).]

	Corpus (9) ^b	Antrum (9) ^b	Duodenum (9) ^b	p ¹ ^c	p ² ^c	p ³ ^c
ATP ^d	213±69	32±5	25±3	=0.02	NS ^e	=0.02
ADP ^d	211±40	25±2	29±6	<0.001	NS	<0.001
ATP/ADP	1.01±0.07	1.29±0.08	0.86±0.07	NS	<0.001	NS
AMP ^d	545±75	57±15	60±7	<0.001	NS	<0.001
ATP+ADP+AMP ^d	969±100	114±18	114±11	<0.001	NS	<0.001
Energy charge ^f	0.33±0.04	0.39±0.03	0.43±0.11	NS	NS	NS
Adenine-adenosine ^d	4327±1908	353±39	326±48	<0.001	NS	<0.001
Lipid-P ^g	4047±108	269±60	261±50	<0.001	NS	<0.001
RNA ^g	2008±543	1050±53	933±32	NS	NS	=0.06

^a ATP,adenosine triphosphate; ADP,adenosine diphosphate; AMP,adenosine monophosphate; lipid-P, lipid phosphates; RNA, ribonucleic acid.

^b Numbers in parentheses indicate numbers of patients.

^c p¹,corpus versus antrum; p²,antrum versus duodenum; p³,corpus versus duodenum.

^d Values=nanomoles of substrates per 1.0 mg deoxyribonucleic acid (means±S.E.M.).

^e Not significant.

^f Adenylate pool energy charge (ATP+0.5 ADP/ATP+ADP+AMP).

^g Values=micrograms of substrates per 1.0 mg deoxyribonucleic acid (means±S.E.M.).

Table 36. Substrate levels in the gastric mucosa of the corpus, antrum and duodenum of patients with 2.0<BAO<4.0 mEq/h (BAO = 2.81 ± 0.10; MAO = 15.69 ± 0.76)^a. [Mózsik, Vizi, Kutas: Scand. J. Gastroenterol. 12: 461–464, 1977 (with kind permission).]

	Corpus (11) ^b	Antrum (11) ^b	Duodenum (11) ^b	p ¹ ^c	p ² ^c	p ³ ^c
ATP ^d	447±46	16±4	60±2	<0.001	<0.001	<0.001
ADP ^d	446±60	31±8	63±6	<0.001	<0.001	<0.001
ATP/ADP	1.00±0.02	0.52±0.04	0.95±0.10	<0.001	<0.001	NS ^e
AMP ^d	19606±720	381±70	38±6	<0.001	<0.001	<0.001
ATP+ADP+AMP ^d	20449±200	428±38	224±21	<0.001	<0.001	<0.001
Energy charge ^f	0.03±0.01	0.07±0.01	0.40±0.07	NS	<0.001	<0.001
Adenine-adenosine ^d	13394±569	3212±1311	370±27	<0.001	=0.05	<0.001
Lipid-P ^g	13588±708	1406±300	91±18	<0.001	<0.001	<0.001
RNA ^g	15289±1000	7141±847	1961±21	<0.001	<0.001	<0.001

^a ATP,adenosine triphosphate; ADP,adenosine diphosphate; AMP,adenosine monophosphate; lipid-P, lipid phosphates; RNA,ribonucleic acid.

^b Numbers in parentheses indicate numbers of patients.

^c p¹,corpus versus antrum; p²,antrum versus duodenum; p³,corpus versus duodenum.

^d Values=nanomoles of substrates per 1.0 mg deoxyribonucleic acid (means±S.E.M.).

^e Not significant.

^f Adenylate pool energy charge (ATP+0.5 ADP/ATP+ADP+AMP).

^g Values=micrograms of substrates per 1.0 mg deoxyribonucleic acid (means±S.E.M.).

Table 37. Substrate levels in the gastric mucosa of the corpus, antrum and duodenum of patients with BAO values >4.0 mEq/h (BAO = 5.33 ± 0.24; MAO = 18.76 ± 2.15)^a. [(Mózsik, Vizi, Kutas: Scand. J. Gastroenterol. 12: 461–464, 1977 (with kind permission).]

7.10. Comparative biochemistry of ulcerated and non-ulcerated mucosal tissues in peptic (antral, duodenal, jejunal) ulcer patients

The membrane ATPase activity and tissue levels of ATP and ADP were measured around the gastric antral, duodenal and jejunal ulcer patients (after partial gastrectomy).

The ATPase activity and tissue levels of ATP and ADP were significantly higher around the gastric antral, duodenal and jejunal mucosa than those obtained in the non-ulcerated (control) mucosa (Mózsik et al., 1976 d, f, 1981 a, c, 1987 a, b, 2000) (Figures 65, 66; Tables 35–37).

7.10.1. Mucosal biochemistry of chronic ulcerated and non-ulcerated antral mucosa in patients with chronic antral ulcer

Figure 67. Changes in the extents of ATP–ADP transformation in the antral mucosa of patients with chronic antral ulcer in the ulcerated and non-ulcerated (control) mucosa (means $\pm$ SEM). [Mózsik, Kutas, Nagy, Tárnok, 1979; Mózsik, Kutas, Nagy, Tárnok, Acta Medica Acad. Sci. Hung. 36: 1–29, 1979 and Acta Medica Acad. Sci. Hung. 38: 129–134, 1984 (with kind permission).]

7.10.2. Mucosal biochemistry of ulcerated and non-ulcerated duodenal mucosa in patients with chronic duodenal ulcer

Figure 68. Changes in the extent of ATP–ADP transformation in the duodenal mucosa of patients with chronic duodenal ulcer, in the ulcerated and non-ulcerated duodenal mucosa (means $\pm$ SEM). [Mózsik, Kutas, Nagy, Tárnok: Acta Medica Acad. Sci. Hung. 37: 39–49, 1979 (with kind permission).]

7.10.3. Mucosal biochemistry of ulcerated and non-ulcerated jejunal mucosa in patients with chronic jejunal ulcer

It was clear to conclude that the magnitudes of drugs actions depend on the membrane enzyme activity. Because the membrane ATPase activity significantly changes on the activity of target organ, the drug actions depend on the activity of the target organ (Nagy et al., 1976, 1981 a, b).

Figure 69. Changes in the extent of ATP–ADP transformation in the jejunal mucosa of patients who underwent partial gastrectomy (according to the method of Billroth II) around the jejunal ulcerated mucosa and non-ulcerated jejunal mucosa (means ± SEM). [Mózsik, Nagy, Tárnok, Kutas: Acta Medica Acad. Sci. Hung. 38, 129–134, 1981 (with kind permission).]

7.10.4. Exclusion of tissue hypoxia in the tissues around the chronic gastric, duodenal and jejunal mucosa in patients

Figures 70 and 71 clearly indicate that the tissue levels of mucosal levels of ATP and ADP are significantly higher in the ulcerated antral, duodenal and jejunal mucosa than those obtained in the control (non-ulcerated) mucosa specimen (the measurements were done simultaneously in patients).

As we indicated earlier, the membrane ATPase activity was also significantly higher in these ulcerated mucosa specimens than that in the control (non-ulcerated) mucosa. Against these biochemical changes, the values of “energy charge” remained the same (Figure 72).

These results demonstrated earlier in Figures 70–72 clearly indicate the following:

1. The extent of ATP–ADP breakdown is significantly higher in the ulcerated antral, duodenal and jejunal mucosa specimens than that in the control (non-ulcerated) mucosa specimens. This fact can be proven by the increased membrane ATPase activity and by increased level of ADP;
2. No impaired phosphorylation can be found in the ulcerated mucosa specimens, which can be proven by increased tissue levels of ATP in time when the ATP–ADP breakdown was significantly increased (significantly higher membrane ATPase activity and increased level of ADP);

Figure 70. Comparative demonstration in the changes of the tissue levels of ATP in the ulcerated versus non-ulcerated antral, duodenal and jejunal mucosa (the musculature is located under the examined mucosa tissues) (means ± SEM). [Mózsik et al., in Mózsik, Hänninen, Jávör (eds.) *Advances in Physiological Sciences*. Vol. 29. *Gastrointestinal Defence Mechanism*, Pergamon Press, Oxford-Akadémiai Kiadó, Budapest. pp. 213–288, 1981 (with kind permission).]

Figure 71. Comparative demonstration in the changes of tissue levels of ADP in the ulcerated and non-ulcerated antral, duodenal and jejunal mucosa (the musculature is located under the examined mucosa tissues). (Mózsik et al., In: Mózsik, Hänninen, Jávör (eds.) *Advances in Physiological Sciences*. Vol. 29. *Gastrointestinal Defence Mechanism*, Pergamon Press, Oxford- Akadémiai Kiadó, Budapest. pp. 213–288, 1981). For further explanation, see Figure 70.

„ENERGY CHARGES“ IN PATIENTS WITH CHRONIC PEPTIC ULCER*

„ENERGY CHARGE“ = $\text{ATP} + 0.5\text{ADP} + \text{ATP} + \text{ADP} + \text{AMP}^{-1}$
(ATKINSON D. E. BIOCHEMISTRY 7, 4030, 1968)

Figure 72. Critical evaluation of the “energy charge” in the mucosa around the chronic antral, duodenal and jejunal mucosa versus Non-ulcerated mucosa (the musculature located under the studies mucosa tissues). [Mózsik et al., in Mózsik, Hänninen, Jávör (eds.) *Advances in Physiological Sciences*. Vol.29. *Gastrointestinal Defence Mechanism*, Pergamon Press, Oxford- Akadémiai Kiadó, Budapest. pp. 213–288, 1981 (with kind permission).] For further explanation, see Figure 70.

3. The extent of ATP–cAMP transformation was significantly higher in the ulcerated antral, duodenal and jejunal mucosa around the chronic ulcer;
4. The tissue levels of ATP were significantly higher in the mucosa – around the chronic antral, duodenal and jejunal ulcer – than those in the control (non-ulcerated) mucosa, while the extents of both ATP–ADP and ATP–cAMP transformations were increased in the ulcerated antral mucosa specimens;
5. The higher ATP tissue levels (in time when the ATP breakdown was increased in both directions) can be obtained by the intact oxidative phosphorylation pathway;
6. The biochemical components of gastric mucosal tissue were expressed in accordance to 1.0 mg DNA, which represents the same number of cells (Figure 297). The values of adenine–adenosine, ATP, ADP and AMP were increased in the gastric fundic mucosa in patients with increased gastric secretory responses (BAO, MAO) and in the mucosa around chronic antral, duodenal and jejunal ulcers.

No physiological data are available in the literature to prove the presence of decreased GMBF in the gastric fundic mucosa in patients with gastric hyperacidity, and nobody found an increased tissue level of lactate. All experts accept the increased energy turnover (increased extents of ATP–ADP and ATP–cAMP transformation) in these gastric fundic mucosa specimens.

The results of animal experiments clearly indicated that the biochemical components differ significantly in the glandular stomach in comparison with the values in the forestomach. When we analyzed the time -sequence of biochemical changes, development of gastric hyperacidity and ulcer development, we first obtained the gastric hyperacidity and then the ulcer development. The same tendency was obtained in the changes of gastric mucosal biochemistry in both parts of the stomach, and these changes appeared before the development of gastric hyperacidity in 24-hour pylorus-ligated rats (Mózsik and Vizi, 1976 a, b).

A significant biochemical gradient was biochemically proved in the gastric fundic, antral, duodenal and jejunal mucosa depending on the gastric secretory responses (BAO, MAO).

Author details

Gyula Mózsik^{1*} and Imre Szabó²

*Address all correspondence to: gyula.mozsik@aok.pte.hu

1 First Department of Medicine, Medical and Health Centre, University of Pécs, Hungary

2 Associate Professor at the First Department of Medicine, University of Pécs, Hungary

IntechOpen