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Mechanisms of pathological changes development in periodontium tissues during long-term omeprazole administration

Mechanizm rozwoju zmian patologicznych w tkance przyzębia podczas długotrwałego podawania omeprazolu

INTRODUCTION

Now the world sees a significant prevalence of diseases of digestive system. According to WHO data diseases of the digestive system organs take the third place after cardiovascular diseases and cancer. For the treatment of acid-dependent diseases proton pump inhibitors (PPI) are used: omeprazole, lanzoprazole. They block the final stage of HCl secretion by inhibition of H^+/K^+-ATP-ase [8], which leads to hypergastrinemia. The question about mechanisms of pathological changes development in proximal part of gastrointestinal tract is still not solved [3].

The aim of our research was to study the influence of long-term omeprazole administration on periodontium tissues.

MATERIAL AND METHODS

Experiments were carried out observing of recommendations about carrying out of medical-biological researches according to the European convention on 29 rats-males of the "Wistar" line, weight of 180–250 g. Euthanasia of animals was carried out under urethane anaesthesia by bloodletting. Omeprazole ("Sigma", USA) was injected intraperitoneally to experimental rats in a dose of 14 mg/kg daily for 28 days, to control rats during this time 0.2 ml of water was injected. Objects of the research were soft periodontium tissues and blood of the animals. In periodontium tissues the activity of NO-synthase (NOS) (EC: 1.14.13.39) [5], content of nitrite-anions [5], collagenolytic activity (EC: 3.4.24.7) (MMP-1) [6], the content of oxyproline [13], middle mass molecules (MMM) [3], oxidative-modified proteins [2], fucose [11] and glycosaminoglycans (GAG) [11] were determined. In blood plasma gastrin concentration was determined by a radioimmunoassay technique, using an analytical kit of "MP Biomedicals, LLC", USA. We determined that gastrin

concentration in blood plasma of rats of the control group was 59.0±35.05 pg/ml, in the experimental animals – 170.7±90.7 pg/ml. Thus, hypergastrinemia is observed.

RESULTS AND DISCUSSION

Nitric oxide is an important regulator of endo- and intercellular processes in living organisms. With the participation of NO-synthase enzyme L-arginine converted to L-citrulline releasing of NO. For investigation of NO-ergic system of rats periodontium tissues at omeprazole-induced hypergastrinemia determined NOS activity and content of NO_2^-, which is the end product of NO exchange. (Tab. 1).

Table 1 shows that long-term PPI administration to animals for 28 days leads to a decrease 1.2 times the activity of NOS in soft periodontium tissues compared with control. NO_2^- content in soft periodontium tissues under these conditions increases 1.06 times compared with the control group of animals.

Table 1. NOS activity and content of NO_2^- in soft periodontium tissues of rats (M±m)

Groups of animals	NO-synthase activity, nmol[NO_2^-]/g*min	Content of NO_2^-, mmol/g
Control (n=12)	0.123±0.020	0.062±0.012
Omeprazole 28 days (n=17)	0.103±0.031	0.066±0.010
	$P_{1-2}>0.05$	$P_{1-2}>0.05$

n – number of animals

Thus, long-term PPI administration leads to increased amount of nitrite-anions on the background of NOS activity decreasing, which testifies to disbalance of NO-ergic system of periodontium tissues.

Oxyproline is one of the basic collagen amino acids, which allows to consider it a marker that reflects the catabolism of this protein by MMP-1 [5]. We determined, at omeprazole-induced hypergastrinemia, a reliable increase by 1.06 times MMP-1 activity and 1.1 times the content of free oxyproline in experimental rats soft periodontium tissues compared with control (Tab. 2). Therefore, hypergastrinemia activates collagenolysis in soft periodontium tissues.

Table 2. Collagenolytic activity and content of free oxyproline in soft periodontium tissues (M±m)

Groups of animals	Collagenolytic activity, μmol/g/min	Oxyproline content, μmol/g
Control (n=12)	2.590±0.040	5.630±0.120
Omeprazole 28 days (n=17)	2.760±0.040	6.150±0.200
	$P_{1-2}<0.05$	$P_{1-2}<0.05$

n – numbers of animals

Free-radical oxidation leads to oxidative modification of proteins and reflects the universal mechanisms of different origin damage [7] (Table 3).

Table 3. Content of oxidative-modified proteins and MMM in soft periodontium tissues (M±m)

Groups of animals	Content of oxidative-modified proteins, c.u.	Content of middle mass molecules, c.u.
Control (n=12)	0.059±0.008	0.174±0.002
Omeprazole 28 days (n=17)	0.211±0.007	0.185±0.004
	P_{1-2}<0.05	P_{1-2}<0.05

n – number of animals

Table 3 shows that at omeprazole-induced hypergastrinemia content of oxidative-modified proteins is increased 3.6 times ($p<0.05$), the amount of MMM is increased 1.6 times ($p<0.05$) in soft periodontium tissues compared with the control group of animals (tab. 3). Activation of free-radical oxidation leads to an increase of MMM content which is a consequence of endogenous intoxication [4].

The basis of periodontium tissues is the connective tissue, its amorphous phase is represented by proteoglycans and glycoproteids. Activation of the connective tissue components catabolism is reflected by increasing of GAG and free fucose amounts in tissues and liquids of body. We determined that in omeprazole-induced hypergastrinemia the amount of GAG is increased 1.2 times and the amount of free fucose is increased in soft periodontium tissues of rats compared with control (tab. 4).

Table 4. Content of GAG and fucose in soft periodontium tissues of rats (M±m)

Groups of animals	GAG content, μmol/g	Fucose content, μmol/g
Control (n=12)	1.117±0.067	1.757±0.259
Omerazole 28 days (n=17)	1.526±0.106	2.152±0.290
	P_{1-2}<0.05	P_{1-2}>0.05

n – number of animals

CONCLUSION

Under the long-term administration of omeprazole in the soft periodontium tissues pathological changes appear: disbalance of NO-ergic system, activation of free-radical oxidation, increase of MMM concentration, activation of MMP-1 and, consequently, intensification of destruction of collagen and noncollagen proteins of periodontium connective tissue.

REFERENCES

1. Askerova T.A. et al.: Diagnosticheskaya znachimost opredeleniya svobodnogo oksiprolina pri nasledstevennuh i priobretennuh kollagenozah. Lab. Diag., 9, 15, 2009.
2. Dubinina E.E. et al.: Okislitelnaya modifikacia belkov syvorotki cheloveka. Metod ee opredelenija. Voprosy Medicinskoj Himii, 1, 24, 1995.
3. Gabrielyan N.I. et al.: Opyt ispolzovaniya pokazatelja srednih molekul v krovi dlya diagnostiki nefrologicheskih zabolevanij u detej. Lab. Delo, 3, 131, 1983.
4. Gromashevskaya L.L.: "Srednye molekuly" kak odin iz pokazatelej metabolicheskoj intoksikacii v organizme. Lab. Diag., 1, 11, 1997.
5. Hevel I.M.: Purification of the inducible murene macrophage nitric oxide synthase. J. Biol. Chem., 266, 22789, 1991.
6. Mandl. I. et al.: Collagenolytic activity determination. J. Clin. Invest., 32, 1323, 1953.
7. Meerson F.Z.: Obshij mehanizm adaptacii i rol v nem stress-reakcii, osnovnye stadii processa. M.: Nauka, 77, 1986.
8. Olbe L. et al.: Effect of omeprazole on gastric acid secretion and plasma gastrin in man. Scand. J. Gastroenterol., 166, 27, 1989.
9. Radchuk O.M. et al.: Morphometrichni pokazniki sluzovoi obolonki kushki za ymov gipergastrinemii ta pri vvedenni multiprobiotiku "Symbiter acidophilic". Annual Reports. Academy of Sciences of Ukraine, 1, 144, 2009.
10. Renga M. et al.: Rectal cell proliferation and colon cancer risk in patients with hypergastrinemia. Gut, 41, 330, 1997.
11. Sharaev P.N.: Metod opredeleniya glikozaminoglikanov v biologicheskih judkostjah. Lab. Delo, 5, 530, 1987.
12. Sharaev P.N. et al.: Metod opredelenija fukozu, nesvjazannoj s belkami. Klin. Labor. Diagnostika, 4, 17, 1997.
13. Tetyanets S.S.: Metod opredelenija svobodnogo oksiprolina v sivorotke krovi. Lab. Diag., 1, 61, 1985.
14. Tsyryuk O.I. et al.: Vpliv omeprazol-vuklukanoi gipergastrunemii na bazalny shlynkovy sekreciu u shyriv. Visnik Problem Biologii ta Medicini, 3, 38, 2001.

SUMMARY

Under the long-term administration of omeprazole pathological changes appear in soft periodontium tissues, namely: disbalance of NO-ergic system, activation of free-radical oxidation, increase of MMM concentration, activation of MMP-1 and, consequently, intensification of collagen proteins destruction and increase of catabolism of connective tissue amorphous phase components of periodontium.

Keywords: periodontium, omeprazole, hypoacidity, hypergastrinemia

STRESZCZENIE

W trakcie długotrwałego podawania omeprazolu w tkance miękkiej przyzębia pojawiają się zmiany patologiczne w postaci zaburzenia systemu NO-ergicznego, aktywacji utleniania wolnych rodników, wzrostu stężenia MMM, aktywacji MMP-1 i, w efekcie, intensyfikacji procesów destrukcji białek kolagenu oraz wzrostu katabolizmu składników fazy amorficznej tkanki łącznej przyzębia.

Słowa kluczowe: przyzębie, omeprazol, nadkwaśność, hypergastrynemia