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Gastroprotective oligopeptides

Abstract

The review summarizes current knowledge on oligopeptides (up to 20 amino acid residues) with documented gastroprotective properties and their possible mechanisms of action. The most explored gastroprotective oligopeptides, including opiates, pentadecapeptide BPC 157, proline- and hydroxyproline-containing products of collagen degradation, thymohexin and honluten are overviewed. Due to the modern knowledge oligopeptides realize their effect on the cellular, chromosomal, genomic and molecular levels. The multidirectional mechanisms of gastroprotective effects of oligopeptides are mediated by their involvement in the regulation of genes expression, DNA replication and protein biosynthesis, oxidative and reductive reactions, modulation of activity of hormones and enzymes, vessel permeability, neoangiogenesis, neuro- and immunomodulatory effects, influence on motility, secretion and production of gastric mucous. Hence, application of oligopeptides may be considered as a new promising approach to the prevention and treatment of gastrointestinal disorders.

Keywords: oligopeptides, gastroprotection, gastric lesions

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Introduction

Peptic ulcer disease and its complications still remain a hot issue in modern gastroenterology and one of the constantly important targets for pharmacologic research.[1–3] It is commonly acknowledged that nonsteroidal anti-inflammatory drugs (NSAIDs), being the most commonly prescribed group of drugs worldwide for the management of pain and inflammation, play an important role in provoking gastrointestinal tract ulceration, bleeding and perforation.[1,4,5] This mediates the necessity of the effective gastroprotective measures in patients, who are at risk of gastric ulceration, in particular chronic NSAIDs users. Nowadays for this purpose proton pump inhibitors and H2-antagonists are commonly used, but due to side effects of these drugs the search for new compounds with gastroprotective properties, suitable for longterm use, remains actual.[1,2] Contemporary literature gives accumulating evidence that a number of oligopeptides play an important role in the regulation of the function of gastrointestinal tract and their synthetic analogues were reported to be effective in the prevention and treatment of gastric ulceration.[1,5–12]

That is why the purpose of this review was to summarize the current data on the oligopeptides with documented gastroprotective properties and their possible mechanisms of action.

Discussion

Due to the modern outlook, regulatory peptides are considered to be phylogenetically the oldest form of bioregulation.[13–21] Thus, the mechanisms of peptidergic regulation of homeostasis open huge perspectives for the creation of the essentially new methods for the prevention and treatment of different diseases.[13–16] Interestingly, deep studies of the mechanisms of action of regulatory peptides showed that in many cases life-sustaining processes are regulated not by the total peptide molecules but their short-chained derivatives – oligopeptides that are produced in the course of limited proteolysis from proteins-precursors (cytokines, thymic peptides, immunoglobulins).[13,14,18,20,21] The term “oligopeptide” refers to proteins, composed of not more than 20 amino acid residues.[22] For example, it was shown that the inhibition of pancreatic juice secretion by 28-amino acids-containing hormone ghrelin is realized by its biologically active part – pentapeptide with the sequence of amino acids Gly-Ser-Ser (n-octanoyl)-Phe.[23]

The advantages of the short peptides above their long-chain derivatives are high biological activity, that often many fold exceeds the activity of the peptide-precursor, high tissue specificity, lack of species specificity and lack of immunogenicity.[13,14,15-18,20,21] It was established that low-weighing oligopeptides realize their effect on the cellular, chromosomal, genomic and molecular levels.[13–21] The interaction with DNA was proposed to be the key moment of the realization of the biological effect of the short peptides.[17–19,21] This concept is supported by the data that the alterations in the peptidergic regulation of the body cause changes of the functional status of the cell, resulting in the decrease of gene expression and protein biosynthesis.[13–15,17,18,21] Oligopeptides were shown to be involved in the regulation of intracellular communication processes, nociception, vessel permeability, neoangiogenesis, nervous impulse transduction as well as affect the activity of hormones and enzymes and exhibit neuro- and immunomodulatory effects.[13–21] It is also hypothesized that biological activity of short peptides is mainly associated with their prominent antioxidant properties, although this data is a little bit contradictory as some compounds were reported to have an opposite effect, increasing the processes of oxidation.[2,8,16,24–26]

Due to the recent literary data, the most explored representatives of oligopeptides with gastroprotective properties are met-enkephaline (His-D-Trp-Ala-Trp-D-Phe-Lys-NH2)[27,28] and leu-enkephaline (Tyr-Gly-Gly-Phe-Leu),[27–29] demorphine (H-Tyr-D-Ala-Phe-Gly-Tyr-Pro-Ser-NH2) and sedatine (H-Arg-Tyr-D-Ala-Phe-Gly-OH),[5,30] pentadecapeptide BPC 157 (Gly-Glu-Pro-Pro-Pro-Gly-Lys-Pro-Ala-Asp-Asp-Ala-Gly-Leu-Val);[10,31–33] proline- and hydroxyproline-containing products of collagen degradation (mainly Pro-Glu-Pro, Glu-Pro and Pro-Glu);[34–36] thymohexin (Arg-α-Asp-Lys-Val-Tyr-Arg),[1,8,37] honluten (H-Glu-Asp-Gly-OH), known as T-34,[20,21] vesugen (H-Lys-Glu-Asp-OH), known as T-38.[20]

Due to the modern knowledge, gastroprotective effects of the short peptides are mediated by their antioxidant and anti-inflammatory properties,[1,5,8,10,16,23,32,37] regulatory influence on acid/base secretion,[9,24,25,35] motility,[38,39] activity of the gastrointestinal enzymes,[9,13,16,20,21] production of prostaglandins and nitric oxide as well as the interaction with the neuroendocrine system.[1,12,27,31,33,34] For example, it is known that dipeptide L-carnosine, that for about two decades is used in Japan as antiulcer remedy, exerts its gastroprotective

effect through the stimulation of protective mucous production and increases the activity of antioxidant defense enzymes and heat shock proteins expression in stomach, dose dependently preventing gastric ulceration.[26]

The perspectiveness of the application of oligopeptides in gastroenterology is supported by the data, that a variety of the short peptides are resistant to the influence of gastric and enteric proteinases, what allows to introduce them orally to the patient.[7,10,16,35,36,40] Interestingly, the studies of the short peptide livagen (Lys-Glu-Asp-Ala) showed that this compound was not hydrolyzed even by the peptidases of the small intestine and under the conditions in vitro it was hydrolyzed only for 50%.[40] On the example of glypropline of the structure Glu-Pro-Glu, it was shown that this tripeptide was resistant even to the effect of tripeptidases.[7,35,36,40] The pentadecapeptide BPC 157 was also reported to be especially stable and in vitro studies showed that this compound was not broken down by gastric juice during a 24 hours period.[10,31–33]

Analysis of literary reports on the gastroprotective short peptide compounds we present according the following rubrics:

i. Neuropeptides

ii. Short peptide derivatives of collagen

iii. Thymic peptides

other oligopeptides with gastroprotective properties.

Neuropeptides

In 1979, the team of Y. Taché and coauthors reported for the first time that peptides act in the brain to protect against the development of gastric erosions induced by cold restraint stress in rats.[11,26,41] They injected the 14-amino acid neuropeptide bombesin into the cisterna magna and noted the changes in the autonomic nervous system activity, resulting in the simultaneous inhibition of gastric acid and pepsin secretion and motility.[42] In future decades the involvement of neuropeptides in the regulation of the function of gut was confirmed by numerous papers of other authors.[6,28,29,41,38,39,43] Thus, it was shown that opioid peptides, the most numerous family of neuropeptides, have much broader physiological effects than the regulation of emotions. The elucidation of the biological effects of opioid peptides showed their important role in the integration of nervous, endocrine and immune system, since the receptors to different neuropeptides were found on lymphocytes.[6,28,29,30,39,43,44]

Now it is widely accepted that opioid peptides play an important role in the processes of maintenance of the gastric mucosa integrity.[6,28,29,30,38,39,43,45] The results of chronic experiments on dogs showed that leu-enkephalin in doses 1, 7, and 9 μg/kg affected gastric secretion and excretion on the background of various stimulants. The maximum protective effect of opiates was achieved in a dose of 7μg/kg.[18] Interestingly, the peptide effect on gastric secretion depended on the stimulant used: on the background of carbachol and pentagastrine, the activity of acidic and peptic factors was decreased and the protective factors of gastric juice were increased, whereas under the influence of histamine, leu-enkephalin increased the juice acidity and mucus secretion but decreased the activity of pepsin and the excretion of ammonia from the stomach.[18] It was reported that dalargin (leu-enkephalin) significantly decreased the area of erosive and ulcerative lesions, had a normalizing effect on proliferation of epithelial cells and reduced the degree of oxidative stress.[30] It was also documented that centrally induced gastroprotective effect of neuropeptides may be mediated by a vagal dependent increase of gastric mucosal resistance to injury; activation of vagal cholinergic pathway results in the stimulation of the release of mucosal prostaglandins and nitric oxide.[28]

Recent papers report that acupuncture can promote the repair of gastric mucosal injury and improve gastrointestinal function and the authors link these effects with reducing plasma beta-endorphin level and upregulating hypothalamic beta-endorphin level.[46] It was also noted that endomorphin-2, injected intracerebroventricularly, restored the reduced levels of CGRP and somatostatin in gastric mucosa lesions.[27] The gastroprotective action was reported in beta-endorphin, deltorphin II as well as endomorphin-1 and endomorphin-2, injected intracerebroventricularly. The effects of endomorphin-1 and endomorphin-2 were reported to be involved in the regulation of colonic motility through the activation of multiple subtypes of opioid receptors, possibly including mu(1) (naloxonazine-sensitive), mu(2) and other forms of muORs (beta-FNA-insensitive).[39]

It was also found that both nociceptin and nocistatin reduced the mucosal lesions in the same dose range (0.2-1 nmol i.c.v.), but in higher doses (2-5 nmol i.c.v.) the gastroprotective effect of both peptides was highly diminished. The gastroprotective effects of these substances were reported to be antagonized by naloxone (27 nmol), beta-funaltrexamine (20 nmol), naltrindole (5 nmol) and norbinaltorphimine (14 nmol), the mu, delta- and kappa-opioid receptor antagonists and after bilateral cervical vagotomy.[43] In another study nociceptin on the model of gastric mucosal lesions, induced by 50% ethanol (1 ml/rat intragastrically), administered either intracerebroventricularly (3 μg/rat) or intraperitoneally (10 μg/kg) was shown to reduce significantly macroscopic and histological damage of the stomach.[45] The tetrapeptide epitalone of the structure Ala-Glu-Asp-Glu was documented to cause the structural transformation of the endocrine cells of the pylorical part of the stomach and reconstitution of the adaptation reactions of the body.[13,16] It was declared that the oligopeptide sedatine of the structure H-Arg-Tyr-D-Ala-Phe-Gly-OH decreases the erosive and ulcerative lesions of the stomach, caused by NSAIDs in experimental gastric lesions in rats.[5,30] The studies with the use of the method of autoradiography with 3H-thymidine showed that the administration of sedatin in different doses stimulated DNA synthesis in epithelium of the gastric mucosa.[5,30] Endogenous opioids have been implicated in the process of gastric sensitivity and gastric motor responses, and impairment of antinociceptive opioid pathways, that is hypothesized to contribute to the pathogenesis of functional dyspepsia.[46] It was also reported that endogenous opioids are involved in the control of gastric accommodation and phasic contractility but not in the control of sensitivity to gastric distension or gastric emptying in healthy volunteers.[46] Opioid peptides were also reported to stimulate the secretion of the gastric protective mucous.[27,45] It was shown that nociceptin/orphanin FQ counteracts acute stress-induced gastric mucosal damage by interacting with NOP receptor and by influencing mucous cell activity.[45]

Thus, the modulation of neuropeptides secretion as well as approaches to the exogenous administration of artificially synthesized analogues may be considered promising for the amelioration of the ulcerative lesions of the gastrointestinal tract.

Short peptide derivatives of collagen

The recent decade gives accumulating evidence on the gastroprotective properties of glyprolines, that are short peptide derivative of collagen degradation.[7,9,24,25,35,36,40] The gastroprotective

properties of these substances were reported on different models of experimental ulceration of the stomach.[7,9,24,25] Thus, introduction of glyprolines caused the decrease of the area of gastric lesions induced by stress, ethanol, indomethacin and pylorus ligation.[9,24,25,35,36] It was documented that glyprolins posess not only protective untiulcer properties, but also accelerate ulcer healing.[7,9,24,25,35,36,40]

The most prominent untiulcer effects on all models of ulceration were evaluated in Pro-Gly-Pro and Pro-Gly-Pro-Pro-Gly-Pro.[7,24,25] Due to the literary data the untiulcer effects of Pro-Gly, Pro-Gly-Pro, Gly-Pro-Gly-Pro and Gly-Pro-Gly-Pro-Gly-Pro, administered intraperitoneally, made 71%, 72%, 64% and 60% respectively; and 83%, 64%, 72% and 65% in the case of intragastral administration.[7,9,24,25,35,36,40]

The gastroprotective effect of glyprolines some authors explain by anti-inflammatory action of these substances, their involvement in the regulation of acid and bicarbonate secretion.[7,9,24,25,35,36,40] and ability to accumulate in the gastric mucosa with further involvement in the synthesis of the structural peptides, including collagen.[7,9,24,25,35,36,40] On the model of acetate-induced lesions of the gastric mucos, glyprolines were reported to decrease the severity of inflammation in the zone of ulcer defect both in the period of formation of the ulcerative defect and during healing.[7,9,24,25,35,36,40] The anti-inflammatory effect of glyprolines is proved by significant decrease of the number of polymorphonuclear leukocytes in the ulcer zone.[7,9,24,25,35,36,40]

Accelerating healing of the acetic acid lesions of the stomach on experimental models, glyprolines caused earlier total differentiation of the superficial epithelium and glands of the gastric mucosa, promoted the production of the large amount of fibroblasts in the place of regenerating ulcer and decreased the number of macrophages.[7,9,24,25,35,36,40] The studies conducted in rats with gastric lesions, caused by ethanol application and water-immersion restraint stress provide data that prominent preventive effect of Pro-Gly-Pro and Gly-Pro are determined by antioxidant properties of these substances.[24,25]

It was also shown that dipeptide Gly-Pro, that is the structural constituent of the tripeptide Pro-Gly-Pro exhibited independent physiologic impact on the gastric secretion.[9,35] The pretreatment of rats with Gly-Pro 30 minutes before the exposure to the effect of charbacholine decreased the volume of the gastric juice and tempo of the hydrogen ions secretion. The injection of Gly-Pro to the dogs with primary high level of the gastric secretion caused only the increase of the gastric juice volume, whereas in animals with primarily low secretion the increase of the gastric juice volume by the influence of this peptide was accompanied also by the decrease of the acidity and increase of the proteolytical activity of the enzymes as well as fucose content.[9,35]

The glyprolines of the structure of Pro-Gly-Pro and Gly-Pro also decreased the post-stress disturbances of the secretory activity of the stomach in dogs. Hence, glyprolins introduction increased gastric secretion in the case when it was decreased due to the influence of stressory factor and decreased the increased secretory activity of the stomach under the conditions of its increase.[35] Such regulatory effect of glyprolins towards gastric secretion may be important for the consideration of the clinical trials of these substances on the evaluation of their feasibility and efficacy for the correction of gastric secretion disorders.

Thymic peptides

In the XX century the natural extracts of animal thymus in some countries were popular remedies for the complex treatment of a number of infectious and skin diseases, chronic wounds and other conditions associated with immune system disorders.[1,8,37,47] But high immunogenicity of the natural protein products as well as the risk of prions transmission mediated the search for the artificial analogues of the thymic peptides.[1,48,49] Thus, chemical modification of the thymic hormone thymopoietin in positions 32-37 resulted in the formation of the hydrophylous hexapeptide Arg-α-Asp-Lys-Val-Tyr-Arg (thymohexin) with the molecular weight of 360 Da.[1,8,37,47] Since specific activity of thymopoietin is realized due to only one active part of the molecule with the following sequence of 5 amino acids - Arg-Lys-Asp-Val-Tyr, the change of the sequence of amino acid Lys for Asp and incorporation of Arg into the structure of this compound resulted in the creation of the hexapeptide, which pharmacologic activity was 1000-fold higher compared to the previously obtained complex of thymic hormones, f.i. tactivine.[1,8,37,47] Thymohexin possesses a very broad biological effect: stimulates the proliferation and maturation of T-lymphocytes, increases the fagocytic activity of polymorphonuclear granulocytes and macrophages, increases antibody production, modulates the activity of ATP-dependent transporting proteins of biomembranes.[8] Thymohexin also has significant antioxidant and anti-inflammatory effects.[1,8,37,47] The latter are mediated by its inhibiting influence on the production of TNF-α and some other proinflammatory cytokins.[1,8,37,47]

Administration of thymohexin to the patients suffering from ulcerative and inflammatory diseases of the gastrointestinal tract has been found to improve significantly the treatment outcome.[1,8,37] It has been documented that administration of thymohexin caused 1.6-fold reduction of the period of healing of the mucosal defects, had positive effect on the cytokine regulation, enhanced the normalization of peripheral blood and immunologic reactivity parameters, decreased 1.5-fold the number of relapses, 2-fold decreased the quantity of urgent operations and mortality.[37] The administration of thymohexin to patients, suffering from peptic ulcer disease caused the decrease of the early hydroperoxides for 42% and late – for 45%, whereas in control group the relevant indices decreased for 18% and 16% appropriately. The patients, receiving only base treatment, had no changes in the system of peroxide lipid oxidation.[8]

Our own studies showed that thymohexin pretreatment attenuated gastric lesions, induced by indomethacin (30mg) and epinephrine (2mg/kg), what was concluded based on the decrease of the area of damage and ulceration score. In our studies gastroprotective effect of thymohexin was accompanied by the decrease of nitro-oxidative stress, in particular inducible nitric oxide synthase activity and oxidative mucosal damage.[1,47]

Other oligopeptides with gastroprotective properties

Numerous studies reported that high untiulcer and healing effect of the pentadecapeptide BPC 157 of the structure Gly-Glu-Pro-Pro-Pro-Gly-Lys-Pro-Ala-Asp-Asp-Ala-Gly-Leu-Val on different models of ulceration.[9,31,33] The protective effect of BPC 157 on the model of acetic ulceration coincided with famotidine, but the effective dose of famotidine (40mg/kg) is 50-fold higher compared to BPC 157 (800 ng/kg). At the same time the effect of BPC 157 caused more significant formation of the granulation tissue in the zone of ulcer defect in contrast to famotidine.[31–34]

BPC 157 was reported to exert a regulatory influence on the gastric mucosa through the central nervous system and to regulate the number of G and D cells of the stomach.[33] The other mechanisms of the cytoprotective effect of BPC-157 the authors link to the stimulation of the expression of the early growth gene (EGR-1) and its repressor, binding nervous growth factor 1-A.[10,49] It was also established that BPC 157 maintains the natural homeostasis of GABA and GABA-ergic transmission.[31,32] The interaction of BPC157 with dopamine,[31,32] nitric oxide system[31,34] as well as prostaglandins production was shown.[31]

Tripeptide vesugen, known as T-38, administered in dose of 20ng/ml to irradiated animals, was reported to enhance proliferative processes in the tissue of the intestine, thymus and spleen.[20] The authors related this effect to the influence of T-38 on blood vessels that resulted in the improvement of the tissue trophics and stimulation of cell proliferation.[20] Tripeptide honluten (T-34) was also shown to have antiapoptic effect on the culture of epitheliocytes of human stomach.[21] Both tripeptides T-34 and T-38 (were reported to stimulate protein biosynthesis in cells.[21] In experimental gastric ulceration in rats induced by cistamine-Hcl, treatment with T-34 during 5 days after induction of ulceration significantly decreased the area of stomach ulceration and inflammation of the surrounding tissues compared to control.[21] The reparative effect of T-34 was accompanied by the decrease of expression of NOS, HSP70 and p65 to normal values.[21]

Results of our own studies showed that pretreatment of tripeptide T-34 decreased nitric oxide synthase activity in stomach mucosa in rats with water-immobilisation stress-induced gastric lesions.[49]

Conclusion

The evaluation of the gastroprotective properties of oligopeptides helps to elucidate the deep mechanisms of the regulation of the functions of gastrointestinal tract and processes involved in the maintenance of the gastric mucosa integrity. Certain oligopeptides may be regarded as important endogenous modulators of the state of the gastric mucosa and considered for clinical trials as new promising remedies for the prevention and treatment of gastric ulceration.

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Conflicts of interest

The authors declare there is no conflict of interests.

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