Gluten Enteropathy

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Gluten enteropathy, namely Celiac disease (CD), is a hereditary predisposed disease, accompanied by the atrophy of the small intestine mucosa, associated malabsorption syndrome, and the development of various deficiency conditions. Celiac disease is caused by food containing gluten—the proteins of cereals that are the diet of the majority of the world population. Some immunogenic peptides of gluten proteins formed during digestion, mainly gliadins from wheat, rye, and barley, are resistant to proteolysis by human digestive peptidases and cause CD in predisposed people.

Keywords: celiac disease ; peptidases ; gluten ; enzyme therapy ; gluten-free diet

1. Introduction

Celiac disease or gluten-sensitive enteropathy is a classic autoimmune disease, because it is characterized by tissue immunogenic inflammation and occurs in individuals with a specific set of HLA genes, namely those people whose genome contains certain alleles of the T-cell-specific immune response genes—HLA-DQ2 and HLA-DQ8, which are part of the HLA-DR3 genotype. HLA-DQ2 and HLA-DQ8 molecules have a high affinity for deamidated gliadin peptides, and in complex with tissue transglutaminase (TG2), present them to immune cells. TG2 deamidates gliadin peptides to form negatively charged deamidated peptides, leading to enhanced binding to HLA-DQ2 or HLA-DQ8 and subsequent presentation to the immune system, resulting in strong immunogenic inflammation in the intestinal wall. The T-cell-specific immune response is to gliadins, their deamidated fragments (peptides), TG2, and connective tissue proteins that are part of the endomysium and reticulin. Manifestations of autoimmune reaction are the destruction of the small intestinal mucosa and malabsorption of nutrients [1].

Proline- and glutamine-rich peptides derived from α-gliadins (a low-molecular-weight variety of gliadins) and γ-gliadins (cysteine-rich gliadins stabilized by disulfide bonds) containing more than nine amino acid residues are toxic to predisposed people [2][3][4]. For example, the 33-mer α-2 gliadin peptide LQLQPFPQPQLPYPQPQLPYPQPQLPYPQPQPF is a substrate for a TG2 enzyme that modifies glutamine residues to promote pathogenesis. Another 26-mer peptide, FLQPQQPFPQQPQQPYPQQPQQPFPQ, is formed from γ-5 gliadin. Shorter immunogenic proline- and glutamine-rich peptides containing 10–20 amino acid residues (**Table 1**) often are used for model studies [5]. However, it is the 33- and 26-mer peptides, derived from α- and γ-gliadins, respectively, that are particularly strong activators of T-cells and therefore strongly correlate with the onset and development of CD [2][3].

Table 1. Peptide sequences of wheat gliadins that are resistant to proteolysis.

Size	Peptide Sequence	Origin	Position	Composition (Pro, Gln), %
33-mer	LQLQPFPQPQLPYPQPQLPYPQPQLPYPQPQPF	α-2 gliadin	56–88	Pro 40, Gln 30
26-mer	FLQPQQPFPQQPQQPYPQQPQQPFPQ	γ-5 gliadin	26–51	Pro 35, Gln 46
20-mer	LQPQQPFPQQPQQPYPQQPQ	γ-5 gliadin	60–79	Pro 35, Gln 50
20-mer	QQQQPPFSQQQQSPFSQQQQ	glutenin		Pro 15, Gln 60
19-mer	LGQQQPFPPQQPYPQPQPF	α-gliadin	31–49	Pro 37, Gln 37
17-mer	QLQPFPQPELPYPQPQS	α-gliadin	57–73	Pro 35, Gln 29
15-mer	VQGQGIIQPQQPAQL	γ-gliadin		Pro 13, Gln 40
15-mer	QQPPFSQQQQQPLPQ	glutenin		Pro 27, Gln 53
14-mer	PQPQLPYPQPQLPY	α-2 gliadin	62–75	Pro 43, Gln 29
13-mer	LGQQQPFPPQQPY	α-gliadin	31–43	Pro 31, Gln 38

Size	Peptide Sequence	Origin	Position	Composition (Pro, Gln), %
12-mer	FSQPQQQFPQPQ	γ-5 gliadin	102–113	Pro 25, Gln 50
12-mer	QLQPFPQPQLPY	α-9 gliadin	57–68	Pro 33, Gln 33
10-mer	QPQQSFPQQQ	γ-gliadin		Pro 20, Gln 60

The intensity of the inflammatory process in CD varies from an increased content of intraepithelial lymphocytes in the epithelium of the villi of the small intestine to atrophy of the mucous membrane. Due to the complexity of the diagnosis, which was previously based on the results of a biopsy, CD was considered a rare disease that was mostly found in Europeans and manifested during the first years of life. Later, sensitive and specific serological tests permitted estimates of the actual number of patients [6]. Screening studies have shown that this disease is not age-related, can occur at any time, and is much more common than previously thought, namely 1% of the world's population. In most patients, CD occurs with mild symptoms or has atypical clinical manifestations. A persistent epidemiological pattern is the steady increase in gluten intolerance in humans [7][8]. The reasons for this can be the following factors: the increase in gluten consumption worldwide; early introduction of complementary foods containing cereals in children of the first year of life against the background of a decrease in the duration of breastfeeding; the emergence of new varieties of wheat with a high content of gluten; and accelerated methods in the production of bakery products (reducing the fermentation period) that increase the content of toxic gluten peptides [9]. Malabsorption is the classic manifestation of CD. At the same time, the following symptoms are observed: chronic diarrhea, flatulence, weight loss, and vitamin and microelement deficiencies. Over time, there is a high risk of developing cancer and other autoimmune diseases, as well as nervous disorders [10][11][12].

Currently, there is no cure for CD. A strict gluten-free diet (GFD) is the only effective way to maintain the health of CD patients. In most patients with gluten sensitivity, the introduction of GFD leads to at least partial healing of the duodenal mucosa, improvement of most symptoms associated with gluten consumption, and a decrease in the titers of specific antibodies in gluten disease. However, in many patients, even with long-term strict adherence to GFD, symptoms may persist, including inflammatory and architectural changes in the small intestine mucosa and positive antibody levels [13][14]. A number of factors may contribute to an incomplete response to a GFD. It is difficult to avoid cross-contamination during food production because gluten is widely used in the food industry. Food labeling may be inaccurate, misleading, or incorrect. In a double-blind clinical trial, patients with CD in remission who were given 50 mg of gluten daily experienced a 20% reduction in villus height/crypt depth compared to a daily placebo or 10 mg of gluten [15]. This indicates that even traces of gluten can cause chronic mucosal damage. The acceptable (safe) limit of gluten may vary from patient to patient and may correspond to 10–100 mg per day, even though a slice of wheat bread contains approximately 3–4 g of gluten [16]. Sticking to such a strict diet is difficult; generally, it is more expensive, less accessible, severely restricts food choice, may result in products with off-taste, and may lead to asocialized individuals (especially in adolescents) and depressive states [17]. Moreover, there is a lack of vitamins and minerals, as well as a tendency to anemia and osteoporosis, in patients on GFDs. In most cases, unintended gluten exposure can occur in patients as a result of the consumption of 10–1000 mg of "hidden" gluten contained in common food ingredients such as sauces, salad dressings, food starches, malt extract thickeners, and other flavors, and sometimes simply as a result of cross-contamination during cooking. Thus, the complete elimination of gluten is, at best, a difficult task. Despite attempts to adhere to GFD, long-term treatment of patients with gluten disease often results in severe atrophy of the villi [14]. It is possible that many patients are inadvertently consuming hundreds of milligrams (or more) of gluten per day. Therefore, there is a need to develop a non-dietary (pharmacological) therapy that would either supplement or replace GFD and neutralize up to 1 g of gluten while the food is still in the stomach.

Various therapeutic strategies are being developed to combat CD. Enzyme therapy is especially promising, as a supplement to food in the form of a peptidase preparation that efficiently degrades prolamins peptides [18]. This approach is based on a direct effect on the pathogenic substance, namely, uncleaved peptides with a large number of proline and glutamine residues that are not digested by typical stomach enzymes.

2. Peptidases that Effectively Hydrolyze Prolamins and Their Immunogenic (Toxic) Peptides

Since immunogenic gliadin peptides are rich in proline residues, PSPs can be used to cleave bonds formed by the Pro residue in proteins and peptides [18]. PSPs characterized thus far have different substrate specificity (**Table 2**). Most PSPs are exopeptidases: dipeptidyl peptidase (DPP) 2, DPP 4, DPP 8, DPP 9, prolyl carboxy peptidase (PRCP), aminopeptidase P (APP) 1, APP2, APP3, and prolidase. PSP endopeptidases, prolyl oligo peptidases (POP) and prolyl

endo peptidases (PEP), usually have higher efficacy. Fibroblast activation protein (FAP) possesses both exo- and endopeptidase activity. All PSPs belong to one of two classes of peptidases—either serine or metallopeptidases. PSPs that are effective in detoxifying the immunotoxic prolamin peptides are found in various organisms belonging to different kingdoms of wildlife.

Table 2. Specificity of proline-specific peptidases.

Number	Peptidase Class	Enzymes	Substrates [1]
1	Serine peptidases	Prolyloligopeptidase (POP), prolylendopeptidase (PEP), fibroblast activation protein (FAP)	(Xaa)*n*-Xbb-Pro↓Xbb-(Xaa)$_n$, *n* = 1–13 (the length of the peptide is approximately 30 amino acid residues)
2		Dipeptidylpeptidases (DPP) 2, DPP 4, DPP 8, DPP 9, FAP	Xbb-Pro↓Xbb-(Xaa)$_n$, *n* = 2–12
3		Prolylcarboxypeptidase (PRCP)	(Xaa)$_n$-Xbb-Pro↓Xbb, *n*—any number
4	Metallopeptidases	Aminopeptidases P (APP) 1, APP2, APP3	Xbb↓Pro(Xaa)$_n$, *n* = 1–9
5		Prolidase	Xbb↓Pro

[1] Xaa—any amino acid; Xbb—any amino acid, except Pro.

In addition to proline, the other most common amino acid residue in cereal prolamins is glutamine, so that peptidases with specificity toward this residue also are needed. The activity of cysteine post-glutamine cleaving peptidases (PGP) was detected in the larval midgut tissue of the Tenebrionidae beetles *Tenebrio molitor* and *Tribolium castaneum* using highly specific peptide substrates Z-Ala-Ala-Gln-pNA, Glp-Phe-Gln-pNA, and Glp-Phe-Gln-AMC, where Z is benzyloxycarbonyl, Glp—pyroglutamyl, pNa—*p*-nitroanilide, and AMC—4-amino-7-methylcoumaride [19][20][21]. Post-glutamine cleaving activity has also been found in studies of the hydrolysis of proline- and glutamine-rich immunogenic peptides by subtilisin-like peptidases of bacteria [22] and cysteine peptidases of plants [23][24].

3. Conclusions

Hydrolysis of proline/glutamine-rich proteins is difficult because most broad-spectrum peptidases are unable to cleave the peptide bonds formed by proline and glutamine residues. However, proline/glutamine-rich proteins such as prolamins become pathogenic under certain physiological conditions, but their proteolysis can provide a therapeutic effect. Thus, prolamins and their immunogenic peptides in human food cause an autoimmune response in predisposed people, leading to the development of CD. This review summarized the use of various PSPs for the hydrolysis of these proteins. Among them, the greatest attention is paid to the study of POP and PEP, since these peptidases hydrolyze long protein sequences into shorter fragments. However, a sufficiently complete hydrolysis was possible only with the combined use of several different PSPs. Promising results are found in studies of mixed complexes of PSPs and subtilisin-like or cysteine peptidases with PGP activity.

With that, a number of questions remain unanswered or insufficiently studied related to the effective use of peptidases to reduce the toxic effects of prolamins and their immunogenic peptides. In addition, it is necessary to evaluate whether the enzymatic pretreatment of wheat flour and the removal of harmful components for CD may lead to the loss of characteristics that make gluten-containing products preferable for food production. Before incorporating commercially available enzyme preparations to reduce gluten sensitivity, such as those containing various glutenases derived from bacteria or fungi, it is important to gather the available scientific data on their effectiveness and safety.

The use of these enzymes cannot be recommended to compensate for the intake of large quantities of gluten (consumed unintentionally or intentionally). Despite the fact that their effectiveness can be quite high, even a small amount of gluten or its peptides that reach the duodenum can be harmful to CD patients. In addition, the effectiveness of the enzymes in vitro is affected by the composition of the food, and this effect has not yet been properly investigated in vivo.

The available biochemical data on a particular enzyme may help to select a promising candidate for possible enzyme preparations, but further clinical trials are needed to confirm the therapeutic effectiveness of the selected enzyme in the treatment of gluten intolerance. So far, an analysis of the results suggests that enzyme therapy alone is not sufficient for

the treatment of CD. Such therapy is probably not able to neutralize the large amount of gluten present on average in the human diet based on wheat or similar cereals. However, enzyme therapy can reduce the gluten-induced effects observed in the background of GFD practices that occur by the unintentional consumption of small amounts of gluten, that is, to act as a pharmacological supplement to GFD.

References

1. Sollid, L.M. Molecular basis of celiac disease. Annu. Rev. Immunol. 2000, 18, 53–81.
2. Shan, L.; Molberg, O.; Parrot, I.; Hausch, F.; Filiz, F.; Gray, G.M.; Sollid, L.M.; Khosla, C. Structural basis for gluten intol erance in celiac sprue. Science 2002, 297, 2275–2279.
3. Shan, L.; Qiao, S.W.; Arentz-Hansen, H.; Molberg, O.; Gray, G.M.; Sollid, L.M.; Khosla, C.J. Identification and analysis of multivalent proteolytically resistant peptides from gluten: Implications for celiac sprue. Proteome Res. 2005, 4, 1732–1741.
4. Wieser, H. The precipitating factor in coeliac disease. Baillieres Clin. Gastroenterol. 1995, 9, 191–207.
5. Loponen, J. Prolamin Degradation in Sourdoughs. Ph.D. Thesis, University of Helsinki, Helsinki, Finland, 20 December 2006.
6. Lionetti, E.; Catassi, C. New clues in celiac disease epidemiology, pathogenesis, clinical manifestations, and treatment. Int. Rev. Immunol. 2011, 30, 219–231.
7. Lohi, S.; Mustalahti, K.; Kaukinen, K.; Laurila, K.; Collin, P.; Rissane, H.; Lohi, O.; Bravi, E.; Gasparin, M.; Reunanen, A.; et al. Increasing prevalence of coeliac disease over time. Aliment. Pharmacol. Ther. 2007, 26, 1217–1225.
8. Catassi, C.; Kryszak, D.; Bhatti, B.; Sturgeon, C.; Helzlsouer, K.; Clipp, S.L.; Gelfond, D.; Puppa, E.; Sferruzza, A.; Fas ano, A. Natural history of celiac disease autoimmunity in a USA cohort followed since 1974. Ann. Med. 2010, 42, 530–5 38.
9. Shumilov, P.V.; Muhina, Y.G.; Netrebenko, O.K.; Ryazanova, O.V.; Schigaleva, N.E.; Kovalenko, A.A.; Levina, E.E.; Pon omareva, A.P. Modern understanding of celiac disease pathogenetic mechanisms: Defining role in course clinical varia nts. Pediatriya 2016, 95, 110–121.
10. Grossman, G. Neurological complications of coeliac disease: What is the evidence? Pract. Neurol. 2008, 8, 77–89.
11. Ford, R.P. The gluten syndrome: A neurological disease. Med. Hypotheses 2009, 73, 438–440.
12. Verdu, E.F.; Armstrong, D.; Murray, J.A. Between celiac disease and irritable bowel syndrome: The “no man’s land” of g luten sensitivity. Am. J. Gastroenterol. 2009, 104, 1587–1594.
13. Midhagen, C.; Hallert, C. High rate of gastrointestinal symptoms in celiac disease patients living on a gluten-free diet: C ontrolled study. Am J Gastroenterol. 2003, 98, 2023–2026.
14. Ilus, T.; Lähdeaho, M.L.; Salmi, T.; Katri, H.; Jukka, P.; Päivi, S.; Heini, H.; Markku, M.; Pekka, C.; Katri, K. Persistent du odenal intraepithelial lymphocytosis despite a long-term strict gluten-free diet in celiac disease. Am. J. Gastroenterol. 2 012, 107, 1563–1569.
15. Catassi, C.; Fabiani, E.; Iacono, G.; D’Agate, C.; Francavilla, R.; Biagi, F.; Volta, U.; Accomando, S.; Picarelli, A.; De Viti s, I.; et al. A prospective, double-blind, placebo-controlled trial to establish a safe gluten threshold for patients with celia c disease. Am. J. Clin. Nutr. 2007, 85, 160–166.
16. Hischenhuber, C.; Crevel, R.; Jarry, B.; Maki, M.; Moneret-Vautrin, D.A.; Romano, A.; Troncone, R.; Ward, R. Review ar ticle: Safe amounts of gluten for patients with wheat allergy or coeliac disease. Aliment. Pharmacol. Ther. 2006, 23, 559 –575.
17. Hopkins, S.; Soon, J.M. Nutritional quality, cost and availability of gluten-free food in England. Br. Food J. 2019, 121, 28 67–2882.
18. Wieser, H.; Koehler, P. Detoxification of gluten by means of enzymatic treatment. J. AOAC Int. 2012, 95, 356–363.
19. Goptar, I.A.; Semashko, T.A.; Danilenko, S.A.; Lysogorskaya, E.N.; Oksenoit, E.S.; Zhuzhikov, D.P.; Belozersky, M.A.; Dunaevsky, Y.E.; Oppert, B.; Filippova, I.Y.; et al. Cysteine digestive peptidases function as post-glutamine cleaving en zymes in tenebrionid stored-product pests. Comp. Biochem. Physiol. B Biochem. Mol. Biol. 2012, 161, 148–154.
20. Filippova, I.Y.; Dvoryakova, E.A.; Sokolenko, N.I.; Simonyan, T.R.; Tereshchenkova, V.F.; Zhiganov, N.I.; Dunaevsky, Y. E.; Belozersky, M.A.; Oppert, B.; Elpidina, E.N. New glutamine-containing substrates for the assay of cysteine peptidas es from the C1 papain family. Front. Mol. Biosci. 2020, 7, 578758.

21. Dvoryakova, E.A.; Vinokurov, K.S.; Tereshchenkova, V.F.; Dunaevsky, Y.E.; Belozersky, M.A.; Oppert, B.; Filippova, I.Y.; Elpidina, E.N. Primary digestive cathepsins L of Tribolium castaneum larvae: Proteomic identification, properties, comparison with human lysosomal cathepsin L. Insect Biochem. Mol. Biol. 2021, submitted.
22. Wei, G.; Tian, N.; Siezen, R.; Schuppa, D.; Helmerhorst, E.J. Identification of food-grade subtilisins as gluten-degrading enzymes to treat celiac disease. Am. J. Physiol. Gastrointest. Liver Physiol. 2016, 311, G571–G580.
23. Bethune, M.T.; Strop, P.; Tang, Y.; Sollid, L.M.; Khosla, C. Heterologous expression, purification, refolding, and structural-functional characterization of EP-B2, a self-activating barley cysteine endoprotease. Chem. Biol. 2006, 13, 637–647.
24. Savvateeva, L.V.; Gorokhovets, N.V.; Makarov, V.A.; Serebryakova, M.V.; Solovyev, A.G.; Morozov, S.Y.; Reddy, V.P.; Zernii, E.Y.; Zamyatnin, A.A., Jr.; Aliev, G. Glutenase and collagenase activities of wheat cysteine protease Triticain-α: Feasibility for enzymatic therapy assays. Int. J. Biochem. Cell. Biol. 2015, 62, 115–124.

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