Main Chain Hydrogen Bond Interactions in the Binding of Proline-rich Gluten Peptides to the Celiac Disease-associated HLA-DQ2 Molecule*

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Elin Bergseng‡§, Jiang Xia†, Chu-Young Kim‡§, Chaitan Khosla**, and Ludvig M. Sollid‡

From the ‡Institute of Immunology, University of Oslo, Rikshospitalet University Hospital, N-0027 Oslo, Norway and Departments of †Chemistry, ¶Chemical Engineering, and **Biochemistry, Stanford University, Stanford, California 94305-3980

Binding of peptide epitopes to major histocompatibility complex proteins involves multiple hydrogen bond interactions between the peptide main chain and major histocompatibility complex residues. The crystal structure of HLA-DQ2 complexed with the α-gliadin epitope (LQPFPQPELPY) revealed four hydrogen bonds between DQ2 and peptide main chain amides. This is remarkable, given that four of the nine core residues in this peptide are proline residues that cannot engage in amide hydrogen bonding. Preserving main chain hydrogen bond interactions despite the presence of multiple proline residues in gluten peptides is a key element for the HLA-DQ2 association of celiac disease. We have investigated the relative contribution of each main chain hydrogen bond interaction by preparing a series of N-methylated α-epitope analogues and measuring their binding affinity and off-rate constants to DQ2. Additionally, we measured the binding of α-gliadin peptide analogues in which norvaline, which contains a backbone amide hydrogen bond donor, was substituted for each proline. Our results demonstrate that hydrogen bonds at P4 and P2 positions are most important for binding, whereas the hydrogen bonds at P9 and P6 make smaller contributions to the overall binding affinity. There is no evidence for a hydrogen bond between DQ2 and the P1 amide nitrogen in peptides without proline at this position. This is a unique feature of DQ2 and is likely a key parameter for preferential binding of proline-rich gluten peptides and development of celiac disease.

Celiac disease is a complex genetic disorder of the small intestine caused by an inflammatory response to dietary wheat gluten (gliadins and glutenins) and related proteins from rye and barley (1). It is a prevalent disease affecting about 1 in 100 Caucasians (2). The lesion is characterized by villous atrophy, crypt cell hyperplasia, and infiltration of inflammatory cells. The villous atrophy may lead to malabsorption, but various extraintestinal symptoms often dominate the clinical picture (3). There is a strong HLA association in this disorder, and the primary susceptibility is mediated by HLA-DQ2 in the great majority of patients (4). Gluten-reactive T cells that recognize gluten peptides exclusively in the context of DQ2 are found in the gut lesions of DQ2-positive patients (5). This preferential antigen presentation explains the strong HLA association (6). There are several gluten T-cell epitopes that are recognized by intestinal T cells, and these epitopes are particularly rich in proline and glutamine residues (7–9). Most T-cell epitopes harbor glutamate residues that have been deamidated from glutamine residues by the action of tissue transglutaminase (11, 12). Proline residues confer resistance to proteolysis by digestive enzymes (13) and influence the selective targeting of glutamine residues by tissue transglutaminase (14, 15).

Binding of peptides to major histocompatibility complex (MHC)2 class II molecules involves interaction of peptide side chains at the P1, P4, P6, P7, and P9 positions to pockets of the HLA binding site as well as hydrogen bonding between conserved residues of the HLA molecule and main chain carbonyl oxygen (C=O) and amide nitrogen (N-H) groups of the peptide (16). Crystallographic studies demonstrate that the pattern of hydrogen bonding to main chain atoms is similar between MHC alleles, and the involved MHC residues are often conserved across MHC alleles. The hydrogen bonding to the structurally conserved backbone explains why a single MHC class II molecule can accommodate a large number of disparate peptide sequences.

The X-ray crystal structure of DQ2 complexed with the deamidated T-cell epitope α-gliadin QLQPFPQPELPY provided the molecular basis for the superior ability of DQ2 to bind the biased repertoire of proline-rich gluten peptides that have survived gastrointestinal digestion and been deamidated by tissue transglutaminase (17). Despite the inability of proline to act as a hydrogen bond donor, the α-gliadin peptide binds to DQ2 with an extensive hydrogen bonding network. The multiple proline residues in gluten-derived epitopes impose a selectivity filter for MHC binding that is unrelated to side chain interactions because only a limited number of registers will maintain the essential main chain interactions. In the few permissible registers, DQ2 can effectively bind deamidated gluten peptides via its interaction with negatively charged anchor residues at P4, P6, or P7.

Notwithstanding a common backbone hydrogen bonding pattern, there is some variation among different MHC alleles (16). Some of the hydrogen bonds are mediated via polymorphic MHC residues (such as tyrosine β30 and the P7 amide in DR3/CLIP (18), I-Ak/Ova (19), I-Ak/Hel (20), and lysine β71 and the P5 carbonyl in DQ2/gliadin-α1 (17)), whereas some peptide-

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§ To whom correspondence should be addressed. Tel.: 47-23073815; Fax: 47-23073510; E-mail: elin.bergseng@medisin.uio.no.

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2 The abbreviations used are: MHC, major histocompatibility complex; HATU, O-(1-azabenzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium hexafluorophosphate; Boc, t-butoxycarbonyl.
MHC complexes appear not to utilize hydrogen bonds to conserved MHC residues (such as tryptophan β61 and the P8 carbonyl in I-Aβ/Hel (20)). Given this variation, MHC class II molecules may differ in their ability to bind proline-containing peptides with their atypical backbone. DQ2 may have unique characteristics in this regard.

The significance of main chain hydrogen bond interactions in the presentation of proline-rich gluten epitopes by MHC is poorly understood. Detailed knowledge about these interactions is needed to better understand the HLA association in celiac disease. To establish the relative importance of hydrogen bonding between DQ2 and the amide nitrogen atoms of the α1-gliadin epitope (Fig. 1), we prepared and analyzed a series of N-methylated peptides. Together with depsipeptides, N-methylated peptides are invaluable reagents for evaluating the role of backbone hydrogen bonds in protein-ligand interactions (21), and they have therefore also been exploited in MHC structure-function studies (22–24). In addition, we prepared and analyzed several norvaline-containing analogues to assess the potential for amide nitrogen-mediated hydrogen bonding in positions occupied by proline residues in the DQ2-α1-gliadin complex. Our results highlight a critical role for hydrogen bonding at P2 and P4 positions in a proline-rich DQ2 epitope.

**EXPERIMENTAL PROCEDURES**

**Peptide Synthesis—N-Methylated peptides used in this study were synthesized using Boc/HBTU chemistry starting from N-α-t-Boc-L-aminoacyl-phenylacetamidomethyl resin. For N-methylated positions, Boc-protected N-methylated amino acids were used, with HATU as the activation reagent. Triple coupling with prolonged coupling time (7–1 h) pushed the reactions closer to completion. Following cleavage of the peptide resin in trifluoroacetic acid/trifluoromethanesulfonic acid/thioanisole (10:1:1, v/v/v) for 4 h, the crude peptides were precipitated in cold ether and dissolved in 1:1 (v/v) acetonitrile/water. The peptides were purified by reverse-phase high pressure liquid chromatography on a semi-preparative C18 column using a water-acetonitrile gradient in 0.1% (v/v) trifluoroacetic acid. The molecular masses of the peptides were confirmed by liquid chromatography-electrospray mass spectrometry. The exact sequences of all the N-methylated peptides were confirmed by the fragmentation pattern using tandem mass spectrometry analysis. The peptides were lyophilized and stored at −20 °C before use.**

**Competitive HLA-DQ2-Peptide Binding Assay—** Detergent-solubilized HLA-DQ2 (A1*0501, B*0201) molecules were purified from Epstein-Barr virus-transformed B lymphoblastoid cell lines as previously described (25). The indicator peptide (KPLLIIAEDVEGEY, *Mycobacterium bovis* 65-kDa Hsp 243–255Y) was 125I-labeled by the chloramine-T method (26). The labeled indicator peptide (30,000 cpm; 1–5 nM) and various concentrations of unlabeled peptides were incubated with 100–300 nM DQ2 overnight at 37 °C in the presence of a mixture of protease inhibitors (25). Complexes of peptide and DQ2 were separated from unbound peptides by spin column chromatography technique as described previously (27). Radioactivity was counted, and the concentrations of the competing peptides required to give 50% inhibition of the binding of the indicator peptide (IC50) were calculated. The IC50 values were determined by four consecutive titration experiments; first we did a 10-fold titration, then a 4-fold titration, and finally, two 3-fold titration experiments around the estimated IC50 values. The consistency of the results was excellent, and the results from one of the 3-fold titration experiments are presented.

**Dissociation Experiments—** Preformed complexes were prepared by incubating radiolabeled peptide with purified HLA-DQ2 overnight at 37 °C. Conditions were identical to those employed in the binding assay, except that the concentration of radiolabeled peptide was 10-fold higher. The complexes were isolated by spin columns and then incubated at pH 5.2 in the presence of protease inhibitors (as described in the peptide binding assay) at 37 °C. Aliquots were removed at various time points and separated on spin columns. The dissociation kinetics were fit into the one-phase exponential decay function ($Y = A_x \times \exp(-k_x t)$) or the two-phase exponential decay function ($Y = A_x \times \exp(-k_x t) + A_y \times \exp(-k_y t)$) using GraphPad Prism (Version 3.02).

**RESULTS**

**Binding of N-Methylated Peptides—** The importance of hydrogen bonds mediated by the peptide main chain amide groups was investigated by testing the binding of a series of N-methylated variants of the peptides LQPFPPELPEPY and AAIAAVKEEAF. By N-methylation, the N-H groups of the peptide backbone were converted to N-CH3 groups that are unable to engage in hydrogen bonding. The LQPFPPELPEPY peptide was used instead of the LQPFPQPELPEPY peptide because it has a 4-fold higher affinity to DQ2. IC50 values of the two peptide series were measured using a competitive binding assay with a radiolabeled indicator peptide. The experimentally determined IC50 values of these peptides are given in Figs. 2 and 3. N-Methylation at position P2 and P4 in the α1-gliadin peptide resulted in substantially reduced binding affinity (35.6- and 23.3-fold, respectively), indicating that hydrogen bond interactions at these positions contribute significantly to peptide binding. N-Methylation at the P9 position also resulted in an

**FIG. 1.** Schematic representation of the hydrogen bond network between HLA-DQ2 and the backbone of the α1-gliadin peptide. The hydrogen bonds are indicated by dashed lines. The four hydrogen bonds between DQ2 and amide groups of the peptide main chain are marked with gray boxes. The figure is based on Ref. 17.
8.0-fold reduction in binding affinity. In contrast, the high affinity, proline-free AAIAAVKEEAF peptide showed decreased affinity when N-methylated at positions P4 and P9 (10.5- and 5.1-fold, respectively), but not at P2. Of note, the discriminatory effect of N-methylation was more pronounced for the LQPFPEPELPY peptide than the AAIAAVKEEAF peptide.

**Dissociation of N-Methylated Peptides**—The importance of hydrogen bonding was further addressed by dissociation experiments. For the LQPFPEPELPY analogue series, we were unable to form significant amounts of complexes with peptides N-methylated at the P2 and P4 positions, presumably due to their low affinity for DQ2. The dissociation experiment results are given in Fig. 4 and Table I. Peptides that were N-methylated at either position P6 or P9 showed faster dissociation compared with the unmethylated peptide, whereas the peptide N-methylated at position P7 had a dissociation rate similar to that of the unmethylated peptide. Consistent with this result, the DQ2-gluten crystal structure revealed no hydrogen bonding at the P7 position. The YAAIAAVKEEAF peptide, containing a tyrosine at the N terminus for labeling purposes, was synthesized for additional dissociation experiments. More than 60% of the peptide-DQ2 complexes remained intact after 30 days (data not shown). The slow dissociation of this peptide from DQ2 prevented us from proceeding with the testing of N-methylated variants.

**Binding of Norvaline-substituted Peptides**—To probe for the potential for hydrogen bonding at positions occupied by proline residues in the α-gliadin epitope, a series of peptides containing norvaline in place of proline was tested for binding to DQ2 in a competitive binding assay. Norvaline is an acyclic amino acid that is isosteric to proline and can therefore participate in favorable hydrogen bonds that are masked by proline residues. The analogue with a norvaline substitution at position P1 bound to DQ2 with a higher IC50 value, contrary to what is expected when an additional hydrogen bond is present in the binding of the peptide. All other norvaline-substituted peptides (at positions P3, P5, and P8) had moderately (1.5-4-fold) lower IC50 values than the unsubstituted peptide.

**Dissociation of Norvaline-substituted Peptides**—Peptide dissociation experiments were performed to further characterize the hydrogen bonds in the norvaline-substituted peptides. The results are shown in Fig. 6 and Table II. DQ2 complexes with peptides containing a norvaline substitution at P1 or P3 had a half-life comparable to that of the unsubstituted peptide, whereas the P5 substitution resulted in a considerably increased half-life, primarily due to virtual ablation of the fast phase of the dissociation curve.

**DISCUSSION**

The abundance of proline residues in gluten epitopes is a hallmark of celiac disease. This, in turn, has led to an increased appreciation for the possibility that the mechanistic consequences of certain proline-rich motifs may be a key to understanding celiac disease pathogenesis. This enigmatic relationship between proline and celiac disease is perhaps most vividly illustrated by the affinity of gluten epitopes for HLA-DQ2. Although the importance of backbone hydrogen bonding in MHC-ligand interactions is widely appreciated, T-cell epitopes from gluten can have as many as four proline residues, none of which are able to act as backbone hydrogen bond donors. To understand the molecular logic for high affinity binding of such epitopes, we have systematically investigated the effect of disrupting hydrogen bond interactions by N-methylation of non-proline residues and proline-to-norvaline substitutions in the celiac disease-relevant gluten T-cell epitope, α-gliadin. Our results indicate that backbone hydrogen bonds at P2 and P4

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**Figure 2.** IC50 values of N-methylated analogues of the modified α-gliadin peptide LQPFPEPELPY. IC50 is the peptide concentration required to give 50% inhibition of the indicator peptide KPLLIAEDVEGEY. The O in the amino acid sequence denotes N-methylated amino acid.

**Figure 3.** IC50 values for the N-methylated high affinity binder peptide AAIAAVKEEAF. The O in the amino acid sequence denotes N-methylated amino acid.

**Figure 4.** Dissociation of N-methylated analogues of the modified α-gliadin peptide LQPFPEPELPY from DQ2. Remaining complexes of DQ2 and the peptides P1563 LQPFPEPELY (■), P1564 LQPFPEPELOP (∗), and P1550 LQPFPEPELY (●) are plotted against time. The O in the amino acid sequence denotes N-methylated amino acid.

**Table I**

| Peptide | Position tested | T50 % | A f | k f | A s | k s |
|---------|-----------------|-------|-----|-----|-----|-----|
| P1550   | P6              | 99    | 7   | 77  | 0.14| 23  | 0.015|
| P1563   | P7              | 105   | 26  | 44  | 0.07| 56  | 0.010|
| P1564   | P8              | 100   | 26  | 44  | 0.07| 56  | 0.010|

* T50% is defined as the half-life when 50% of the peptide remains bound to DQ2, i.e. x = T50%/T = 0.5 × (A f + A s).

* A f (%) is defined as the proportion of the fast phase in the total population of peptide-DQ2 complexes. A f (%) = A f / (A f + A s) × 100.

* A s (%) is defined as the proportion of the slow phase in the total population of peptide-DQ2 complexes. A s (%) = A s / (A f + A s) × 100.
Peptide Binding to HLA-DQ2

**FIG. 5.** IC$_{50}$ values of norvaline substituted $\alpha$-gliadin peptide. IC$_{50}$ is the peptide concentration required to give 50% inhibition of the indicator peptide KPLLAEDVEGEY. The Z in the amino acid sequence denotes norvaline.

**TABLE II**
Dissociation kinetic parameters of norvaline-substituted $\alpha$-gliadin peptide

| Peptide | Position tested | $T_{90\%}$ | $A_h$ | $k_f$ | $A_i$ | $k_i$ |
|---------|-----------------|-----------|------|------|------|------|
| P1281   |                | $h$       | $%$  | $h^{-1}$ | $%$  | $h^{-1}$ |
| P1546   | P1             | 11        | 87   | 0.08  | 13   | 0.0007 |
| P1546   | P3             | 7         | 74   | 0.15  | 26   | 0.009  |
| P1547   | P3             | 21        | 73   | 0.05  | 27   | 0.004  |
| P1548   | P5             | 182       |      |       | 100  | 0.004  |

$T_{90\%}$ is defined as the half-life when 50% of the peptide remains bound to DQ2, i.e., $x = T_{90\%}$, $T = 0.5 \times (A_f + A_i)$.

$A_h$ is defined as the proportion of the slow phase in the total population of peptide-DQ2 complexes. $A_i = A_h (A_f + A_i) \times 100$.

$A_h$ is defined as the proportion of the slow phase in the total population of peptide-DQ2 complexes. $A_i = A_h (A_f + A_i) \times 100$.

Contribute significantly to the overall binding energy, whereas those at P6 and P9 are less important. Moreover, we found no evidence for a hydrogen bond between DQ2 and the P1 amide nitrogen in a peptide analogue that should be capable of establishing this bond. This property differentiates DQ2 from other human MHC class II molecules and is therefore likely a key parameter for explaining the preferential binding of proline-rich gluten peptides to DQ2.

Several previous studies have addressed the importance of hydrogen bonding to the peptide main chain for binding to MHC class II molecules. These include mutational study of the MHC class II molecules that are as well as binding assay of peptide analogues containing reduced peptide bonds or $N$-methylated amino acids (22, 24, 32, 33). Gliadin T-cell epitopes presented by DQ2 molecules are particularly rich in proline residues. In this study, we examined the relative contribution of individual backbone hydrogen bond interactions by comparing the binding and dissociation of backbone $N$-methylated analogues in the context of HLA-DQ2. $N$-Methylation could affect peptide binding by interfering with the amide group hydrogen bond formation. It could also affect the free energy of binding as the result of introducing a hydrophobic methyl group or impose steric effects. The results must be interpreted with this in mind. The most prominent effect for peptide binding was observed for analogues $N$-methylated at the P2 and P4 positions. This is consistent with the crystal structure of the DQ2-$\alpha$-gliadin complex, which shows hydrogen bonds at these positions. The crystal structure also indicated hydrogen bonds mediated by the amide nitrogen at the P6 and P9 positions. The analogues with $N$-methylation at positions P6 and P9 displayed some reduced binding, and the off-rates of these analogues were clearly increased. Taken together, these results are compatible with the notion that the hydrogen bonds at the P6 and P9 positions are energetically less important than those at the P2 and P4 positions. The DQ2-$\alpha$-gliadin structure gave no indication of a hydrogen bond to the P7 amide. The analogue with $N$-methylation at position P7 had a slightly higher IC$_{50}$ compared with the unmodified peptide, whereas the off-rate was unaltered. In the crystal structure, the amide of P7 residue points directly toward DQ2. Therefore, methylation at the P7 position may cause a steric clash, thereby impairing ligand binding. Whereas results from the $N$-methylated analogues of the $\alpha$-gliadin peptide showed clear discrimination, there was little difference in IC$_{50}$ values for N-methylated analogues of the AAIAAVKEEAF peptide, a peptide designed to bind well to DQ2 that lacks any proline residues. A reason for this could be the high binding affinity and strong interaction of this peptide at several positions in the DQ2 binding site.

Strategic positioning of proline residues that maintains the backbone hydrogen bond network provides an explanation for the observation that proline residues are never found at the P2, P4, or P9 positions in gluten T-cell epitopes bound to DQ2. The localization of proline at the P6 position in some DQ2-restricted gluten T-cell epitopes is, however, in conflict with this scheme. Similarly, one could expect that $N$-methylation at the P6 position would have less effect than $N$-methylation at the P9 position. The IC$_{50}$ values for the analogues with $N$-methylation at P6 and P9 are virtually the same, whereas the off-rate is higher for the analogue with $N$-methylation at P6. A possible explanation for this is that the side chain of proline is a favorable anchor for the P6 pocket, but not for the P9 pocket (34, 35), and that in gluten T-cell epitopes, the effect of the side chain interactions for proline will dominate over the lack of main chain interactions at the P6, but not the P9, position.

In the DQ2-$\alpha$-gliadin complex crystal structure, there is a proline residue positioned at P1, and hence there is no hydrogen bond to the amide nitrogen at this position. All currently available crystal structures of MHC class II molecules (DR1, DR2, DR3, DR4, I-E$k$, DQ8, DQ6, I-A$^b$, I-A$^d$, I-A$^{k\alpha}$) (18–20, 36–45) are complexes with peptides that do not have proline at P1, and in all cases there is a hydrogen bond between the P1 amide nitrogen and the backbone carbonyl
group of the α53 residue. Interestingly, DQ2 has a deletion of the α53 residue, and it is conceivable that DQ2 is unable to establish a hydrogen bond to the P1 amide nitrogen (17). Previous functional assays suggest that the P1 hydrogen bond is critical for binding of peptides to DR molecules. In binding analysis of DR1 and DR4 (0401, a subtype of DR4) for N-methylated peptide series, the weakest binding was found for analogues with N-methylation at the P1 position (24, 32). Similarly, off-rate analysis of DR1-peptide complexes showed the highest off-rate for the peptide with N-methylation at P1 both for DM-catalyzed and non-DM-catalyzed reactions (33). For I-E\(^{\alpha}\), similar binding analysis did not reveal any clear effects for N-methylated analogues representing the P1–P9 positions (22), although I-E\(^{\alpha}\) does not have a deletion at α53. To probe the possibility of hydrogen bond formation between the P1 amide and DQ2, we tested an analogue of the α1-gliadin peptide containing a norvaline substitution at P1. Norvaline and proline have the same number of carbon atoms in their side chains, but in contrast to proline, the side chain of norvaline does not have a cyclic structure. Compared with the unmodified α1-gliadin peptide, the P1 norvaline analogue bound with a higher IC\(_{50}\) value and had the same off-rate. This suggests that DQ2 binds peptides without establishing a hydrogen bond to the P1 amide. The majority of the gluten T-cell epitopes characterized so far (10), including the gluten T-cell epitope characterized by guest on July 25, 2018http://www.jbc.org/Downloaded from

...the T-cell receptor is prevented from making a productive contact to the blocker-DQ2 complex, and the blockers should also be proteolytically stable. How this should be obtained will be the focus of additional studies.

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Peptide Binding to HLA-DQ2
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