(Gd^{3+}) Complexation with oligopeptide (SFVG) and Amyloid Peptide ($A\beta_{13–23}$) in Aqueous Solution by NMR spectroscopy

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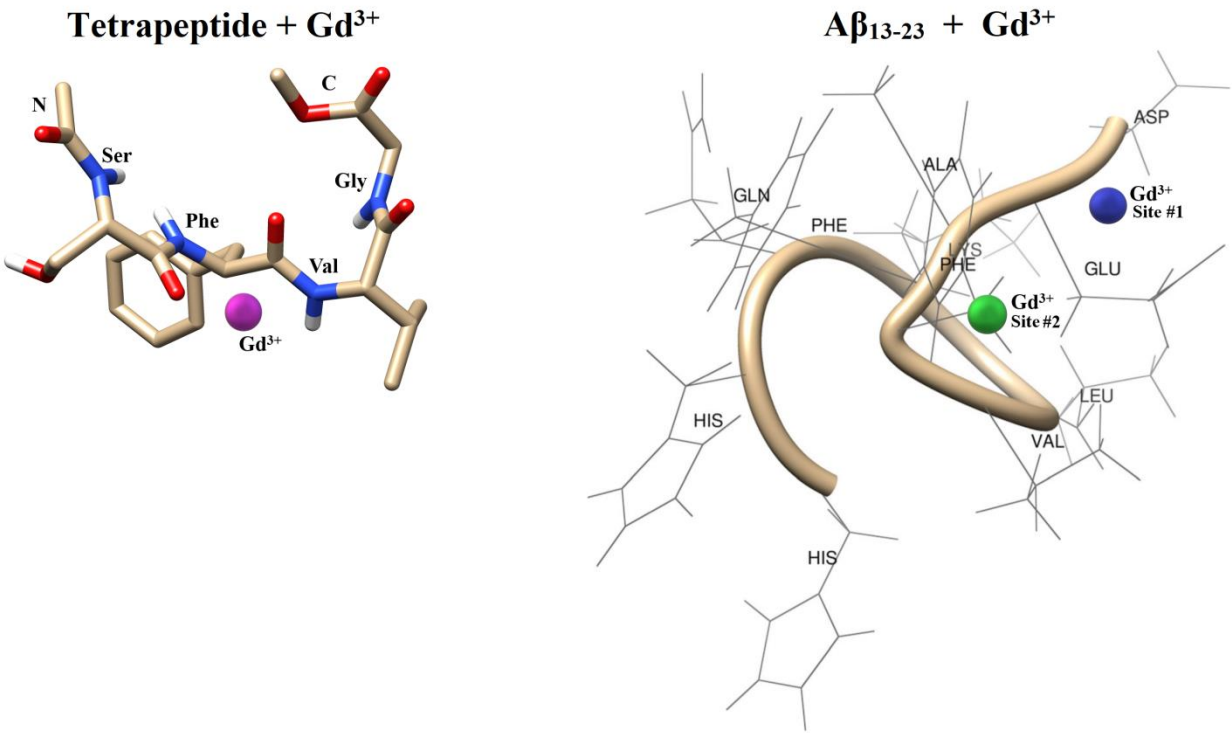
Abstract

Gadolinium (III) ion, which belongs to the subgroup of transition metal ions, has practical importance for magnetic resonance imaging (MRI) with contrast. The accumulation of complexes of transition metal ions with amyloid peptides in the human body leads to the formation of insoluble plaques, which are presumably one of the causes of Alzheimer's disease. This paper presents the results of studying the interaction of the gadolinium (III) ion with a fragment of amyloid protein $A\beta_{40}$ in aqueous solutions using nuclear magnetic resonance spectroscopy. Tetrapeptide (SFVG) was used as the simplified model of metal-peptide interaction research. Beta-amyloid peptide ($A\beta_{13-23}$) was chosen as the amyloid protein $A\beta_{40}$ fragment model. Analysis of ^{1}H NMR spectra revealed that the interaction exists for both types of molecules. It was also suggested the possible location of gadolinium (III) ion in the studied molecules.

Keywords NMR spectroscopy, Amyloid peptide ($A\beta_{13-23}$), tetrapeptide (SFVG), Gadolinium (III) chloride

Graphical abstract



1. Introduction

It is known to date that one of the possible causes of Alzheimer's disease is the accumulation of β-amyloid plaques and neurofibrillary tangles in the brain tissue [1-3]. The plaques are composed of fibrils formed as a result of the aggregation of amyloid Aβ peptides [4]. Transition metal ions such as Zn^{2+}, Cu^{2+} and Mn^{2+} are possible pathogenic agents leading to Alzheimer's disease due to their accumulation in amyloid deposits (amyloid proteins)[5,6]. The interaction of transition metal ions with peptides leads to a strong change in the conformation of the peptide, which promotes the aggregation of Aβ-peptides and the formation of plaques [4-7]. Gadolinium also belongs to the group of transition metal ions and, possibly, it changes the conformation of the amyloid peptide in the same way as other ions of the same group. Paramagnetic gadolinium ions are used as contrast agents for magnetic resonance imaging (MRI) due to their low toxicity and good solubility compared to other ions of this group [8, 9]. MRI is a medical application of nuclear magnetic resonance (NMR) that is used for medical imaging to form pictures of the anatomy and the physiological processes of the body[10]. Transition metal complexes are biologically active molecules with wide clinical applications as antitumor and antiviral agents [11].

The aggregation of amyloid beta peptides plays an important role in the occurrence of Alzheimer's disease (AD) and Parkinson's disease (PD). The aggregation of amyloid peptides may result from disruption of the ubiquitin(Ub)-proteasome system (UbPS) inside the cell, since in many cases Ub and proteasomes are found in the composition of AD and PD aggregates [12]. During the lifecycle inside the neuron, "broken" proteins are not recognized by the UbPS and are therefore not decomposed into separate harmless fragments of amino acid. There is an accumulation of defective peptide within the neuron and its function is disrupted. Aggregated proteins are known to themselves disrupt the functioning of proteasome [12]. With a certain degree of reliability, it was possible to establish the relationship between the development of the disease and UbPS dysfunction only in some types of hereditary Parkinson's and Alzheimer's diseases [12].

It was previously established how the transition metal ions Mn^{2+} and Co^{2+} affect the structure of the amyloid peptide $A\beta_{13-23}$ by using methods of NMR spectroscopy and molecular dynamics computer programs[13, 14]. The manganese ion is initially present in the human body at low concentrations. It is significantly important in the work of our body, and only when certain threshold concentration of these ions is exceeded does pathology appear [15]. Normally, the body should not contain gadolinium ions. However, the ion can enter the body by accident or during magnetic resonance imaging with contrast enhancement, where the patient is injected intravenously with a special drug containing this paramagnetic ion [8, 9]. Recent studies have discussed the accumulation of gadolinium ions in the body of patients following contrast MRI [16-19].

In this study, our goal was to determine whether the interaction of gadolinium ion with the protein molecules of tetrapeptide (SFVG) and the fragment of amyloid protein ($A\beta_{13-23}$) in an aqueous solution possible by using 1D (^1H) NMR spectroscopy. If interaction is possible, then it is necessary to determine where this interaction can be located.

Analysis of ^1H spectra revealed that the above interaction exists for both types of molecules. An assumption has been made as to the possible site of the gadolinium ion for both types of molecules.

2. Materials and methods

2.1. Materials

To test our method, it was initially necessary to choose a simple protein model consisting of several different amino acid residues. We chose a specially synthesized N-Ac-Ser-Phe-Val-Gly-OMe (SFVG) tetrapeptide on Figure 1 consisting of 4 amino acid residues Ser-Phe-Val-Gly. This peptide contains acid residues with polar, non-polar and aromatic R-groups, each of which can interact differently with the positive gadolinium ion Gd^{3+}.

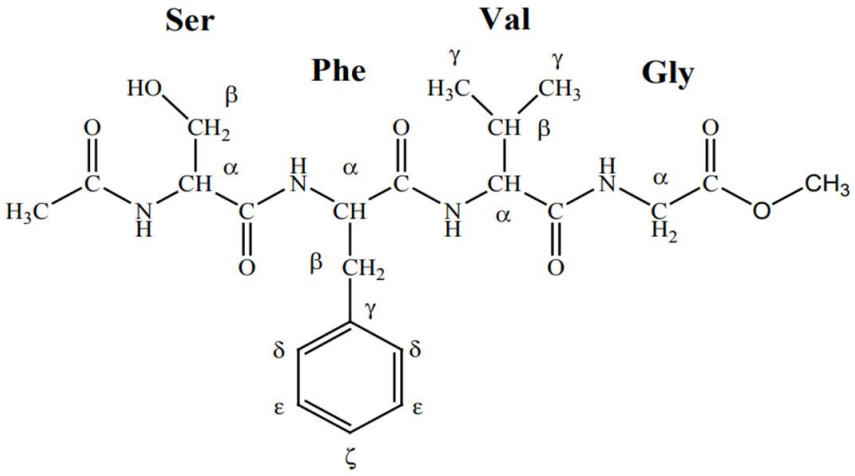


Figure 1 - Chemical structure of tetrapeptide NAc-Ser-Phe-Val-Gly-OMe (SFVG).

Having worked out the signal analysis technique using the example of SFVG, we then moved on to a more complex peptide $A\beta_{13\text{-}23}$. Beta-amyloid peptide $A\beta_{13\text{-}23}$ on Figure 2 consists of eleven amino acid residues His-His-Gln-Lys-Leu-Val-Phe-Phe-Ala-Glu-Asp. In this peptide, R-groups of amino acid residues Glu (E_{22}) and Asp (D_{23}) are negatively charged, R-group of amino acid residue Lys (K_{16}) is positively charged. R-group of amino acid residue Gln (Q_{15}) is polar and uncharged, while other R-groups of amino acid residues are non-polar and uncharged.

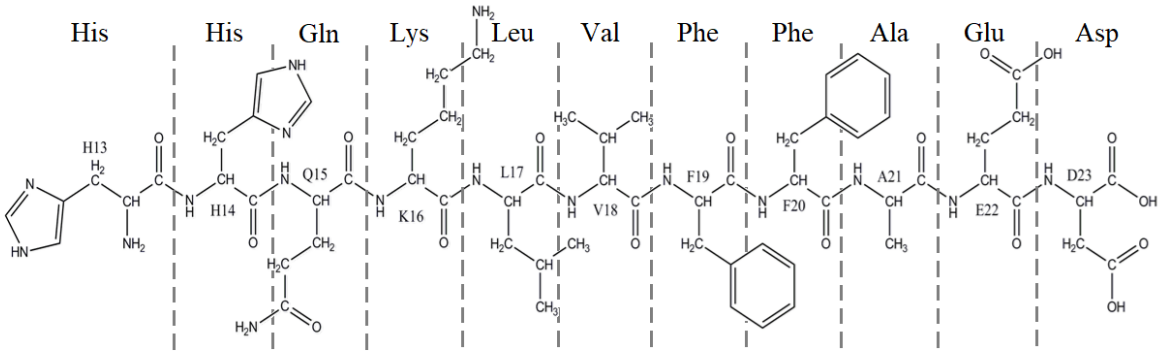


Figure 2 - Chemical structure of beta-amyloid peptide $A\beta_{13\text{-}23}$.

From the point of view of physiology, SFVG and $A\beta_{13-23}$ can be linked using the theory that during the normal operation of the UbPS[20], the $A\beta_{1-40}$ protein can be decomposed into fragments consisting of 3-4 amino acid residues, one of which may be a peptide similar to SFVG. Thus, the essence of our study can be explained by the interaction of the Gd^{3+} ion with the cleavage product of $A\beta_{1-40}$.

2.2. Methods

Registration of ^1H NMR spectra of tetrapeptide SFVG in phosphate buffer (20 mM, 90% H_2O + 10% D_2O, pH = 7.3) and amyloid peptide $A\beta_{13-23}$ in borate buffer solution (20 mM, 90% H_2O + 10% D_2O, pH = 7.3) at a temperature of 293 K with and without addition of $GdCl_3$ were carried out using pulsed NMR spectrometer Avance III HD-700 MHz (Bruker, Avance III 700).

^1H NMR spectra were recorded using 90° pulses, the delay between pulses was 2 s, the spectral width was 12 ppm and a minimum of sixteen scans. To suppress the water signal, the WATERGATE pulse sequence was used. The TOPSPIN software (3.0) was used to obtain the spectra and the MestReNova software was used to analyze and process the spectra. The assignment of spectral lines in ^1H NMR spectra was performed by using high resolution NMR spectroscopy methods of 1D (^1H) experiment [21, 22].

All samples were prepared in standard 5-mm NMR tubes. Concentrations of the substances were 9.6 mM (SFVG), 1.5 mM ($A\beta_{13-23}$) and 0.1 – 0.4 mM ($GdCl_3$). The solution volume were 0.5 ml. The deuterium signals of the solvent were used for the stabilization of magnetic field.

3. Results and discussions

3.1. ^1H NMR experiment of SFVG with Gd^{3+} ion in phosphate solution

^1H NMR spectra of SFVG tetrapeptide dissolved in phosphate buffer (90% H_2O + 10% D_2O, 500 μl) with and without gadolinium ion Gd^{3+} are shown in Figure 3. Proton signals from the obtained spectra were determined by taking into account the literature data [23, 24]. The chemical structure of the SFVG tetrapeptide is shown in Figure 1. The obtained ^1H NMR chemical shifts for the SFVG tetrapeptide dissolved in phosphate buffer (pH = 7.3) with and without gadolinium ion Gd^{3+} are shown in Table 1.

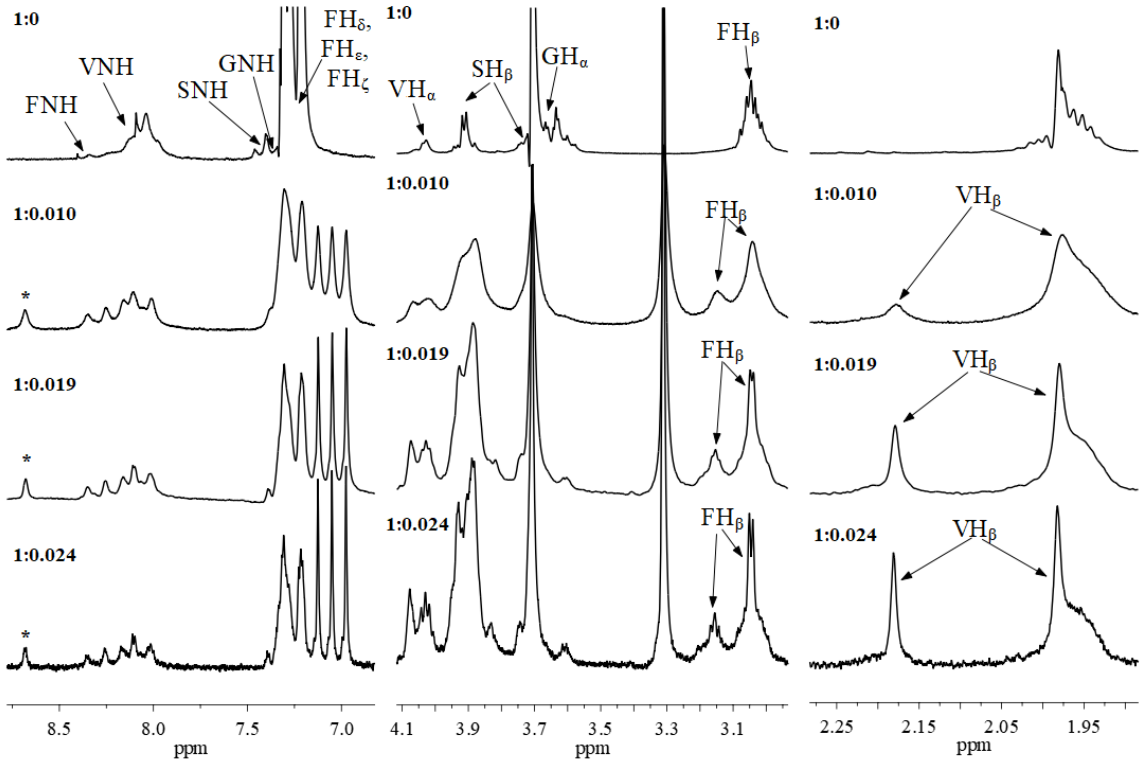


Figure 3 - Fragment (8.8 – 6.8 ppm; 4.0 – 2.8 ppm; 2.2 – 1.9 ppm) of a series of one-dimensional ^{1}H NMR spectra of tetrapeptide NAc-Ser-Phe-Val-Gly-OMe with different molar concentration ratios of peptide – Gd^{3+} ion in phosphate buffer solution (90% H_2O + 10% D_2O, 500 µl), * - signals from impurities.

Table 1 - Chemical shifts (δ) ^{1}H NMR of the studied compound of tetrapeptide NAc-Ser-Phe-Val-Gly-OMe in a solution of 20 mM phosphate buffer (90% H_2O + 10% D_2O) with different molar concentration of gadolinium ion Gd^{3+} at pH = 7.3, 293 K.

Amino acid residue	NH (ppm)	Hα (ppm)	Hβ (ppm)	Hγ (ppm)	Hδ,ε (ppm)
Ser	7.46 (7.46) [7.46]	4.38 (4.31) [4.31]	3.91; 3.74 (3.90b; 3.74) [3.91b; 3.74]	-	-
Phe	8.38 (8.29b) [8.30b]	4.68 (4.68) [4.68]	3.05 (3.15b; 3.04b) [3.16b; 3.04b]	-	7.32-7.16 (7.32-7.16) [7.32-7.16]
Val	8.07 (8.05) [8.05]	4.04 (4.05b) [4.06b]	1.98b (2.18; 1.98b) [2.18; 1.98b]	0.86 (0.86b) [0.86b]	-
Gly	7.40 (7.38) [7.38]	3.65; 3.59 (3.62b) [3.61b]	-	-	-
b – broadened signal, ( ) – spectrum with a molar concentration of 0.100 Mm Gd^{3+} , peptide/ion molar ratio (1:0.010) [ ] – spectrum with a molar concentration of 0.234 Mm Gd^{3+} , peptide/ion molar ratio (1:0.024)					

The ^{1}H NMR spectra of SFVG tetrapeptide in in phosphate buffer solution without and with Gd^{3+} ion have several differences and the following changes were observed: complete

broadening of all resonance signals (which was also observed for other similar compounds in complexes with transition metals [13,14]); A negative shift from -0.11 to -0.24 ppm for signals of phenylalanine protons ($H_\delta F$, $H_\varepsilon F$, $H_\zeta F$) upon addition of 0.100 mM gadolinium salt Gd^{3+} Cl_3^{1-} in Figure 3 (with a further increase of salt concentration, signals were broadened without changing their position); Splitting into 2 signals of serine beta protons ($H_\beta S$) emerges from 0.191 mM salt concentration; Splitting into 2 signals of phenylalanine beta protons ($H_\beta F$) with the initial addition of salt (also, with an increase in concentration, just a broadening of signals was observed); positive shift +0.16 ppm of valine beta proton ($H_\beta V$) upon the initial addition of gadolinium salt (with a larger addition the spectral lines broadened).

The change in the proton spectrum is explained as follows: in fact, there is not a signal shift of the valine proton β-CH (Val) ($H_\beta V$), but a signal splitting is appears due to a two conformations that are explained by the anisotropy of rotation of methyl groups $C_\gamma H_3$ around the $C_\alpha H$ - $C_\beta H$ bond, which manifests itself in the presence of gadolinium ion Gd^{3+}; Signal splitting of phenylalanine β-CH_2 proton ($H_\beta F$) can be explained by the retardation of rotation of the phenol ring around the $C_\alpha H$ - $C_\beta H_2$ bond due to the presence of Gd^{3+} ion that leads to the conclusion of two possible conformations: complex of peptide with gadolinium ion and peptide without gadolinium ion.

Thus, we assume that Gd^{3+} is possibly localized in the tetrapeptide between amino acid residues of Phe and Val in Figures 4, 5. 3D model of the tetrapeptide in Fig. 5 was used from the literature data [23].

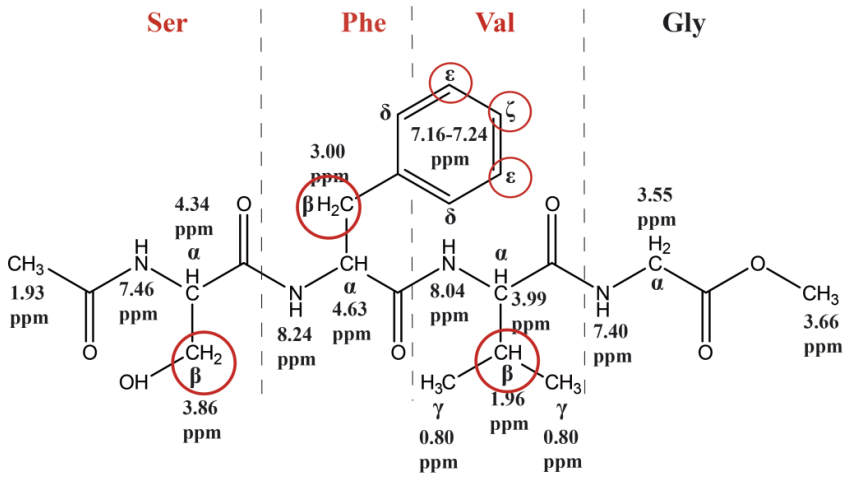


Figure 4 - Chemical structure of tetrapeptide NAc-Ser-Phe-Val-Gly-OMe and the regions of amino acid residues involved in the interaction with the Gd^{3+} ion. Fragments participating in the interaction are circled in red. The corresponding amino acid residues are highlighted in red.

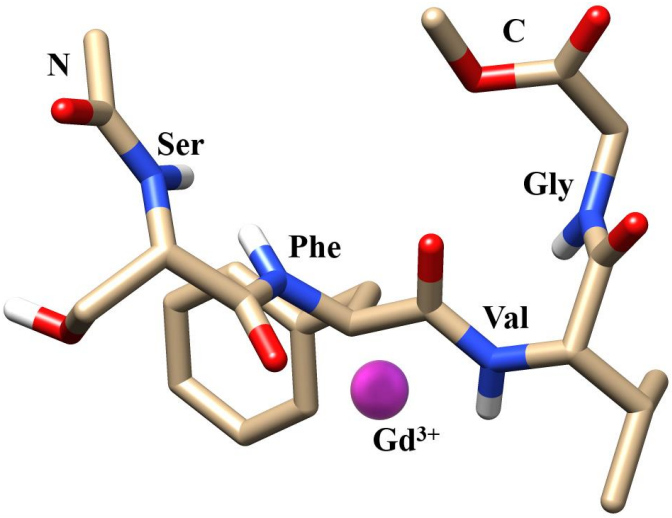


Figure 5 - Model of the interaction of gadolinium (III) ion with tetrapeptide NAc-Ser-Phe-Val-Gly-OMe.

3.2. ^{1}H NMR experiment of amyloid peptide Aβ$_{13-23}$ with Gd^{3+} ion in borate solution

^{1}H NMR spectra of amyloid peptide Aβ$_{13-23}$ dissolved in borate buffer (90% H_2O + 10% D_2O, 500 µl) with and without gadolinium ion Gd^{3+} are shown in Figures 6, 7. Proton signals from the obtained spectra were determined by taking into account the literature data [13, 14, 25]. The chemical structure of the amyloid peptide Aβ$_{13-23}$ is shown in Figure 2. The obtained ^{1}H NMR chemical shifts for the amyloid peptide Aβ$_{13-23}$ dissolved in a borate buffer with and without gadolinium ion Gd^{3+} are shown in Table 2.

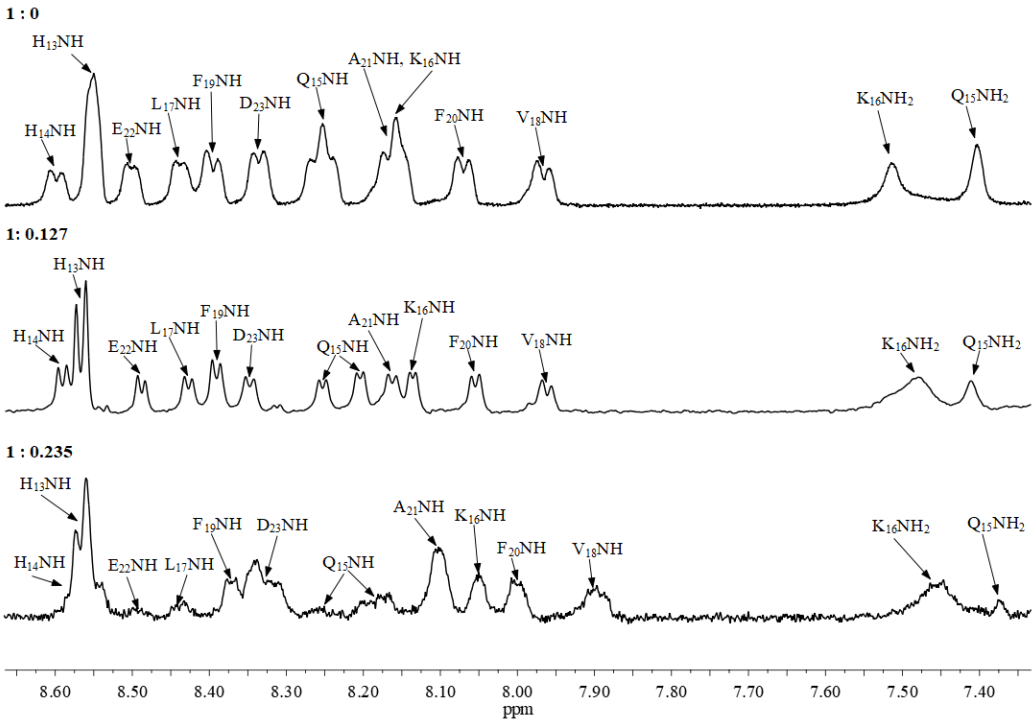


Figure 6 - Amide region of ^{1}H NMR spectra of Aβ$_{13-23}$ in borate buffer solution (90% H_2O + 10% D_2O, 500 µl) with different molar concentration ratios of peptide – Gd^{3+} ion.

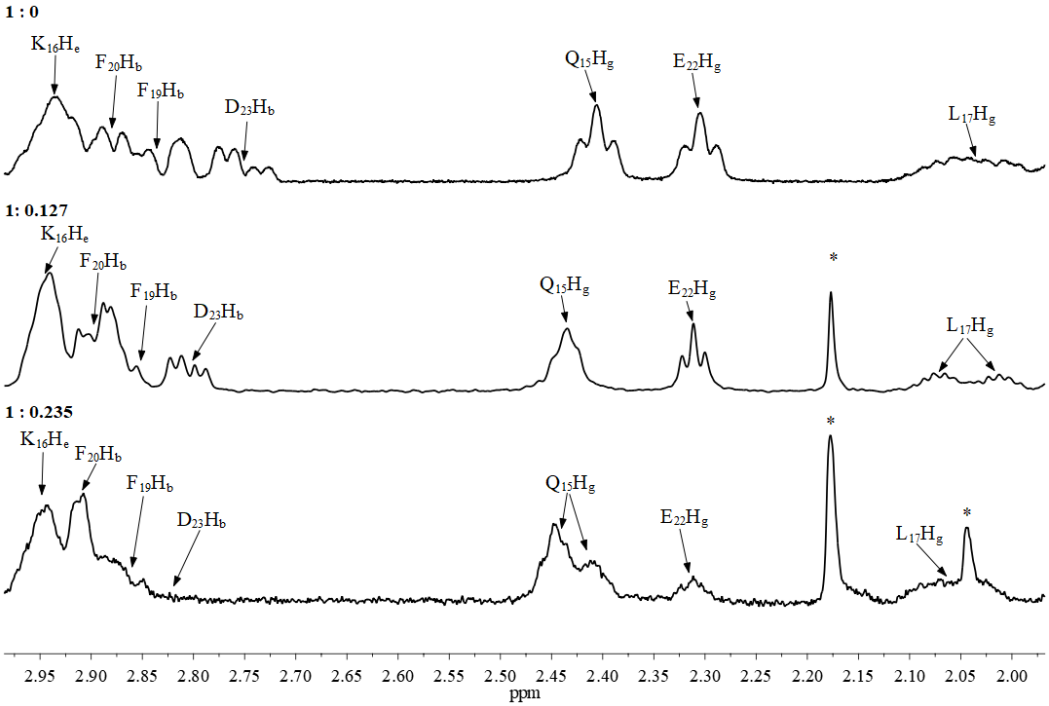


Figure 7 - ^{1}H NMR spectra of $A\beta_{13\text{-}23}$(Signal region 3.0 - 2.2 ppm) in a borate buffer solution (90% H_2O + 10% D_2O, 500 μl) with different molar concentration ratios of peptide – Gd^{3+} ion, * - signals from impurities.

Table 2 - Chemical shifts (δ) ^{1}H NMR of the studied compound of $A\beta_{13-23}$ peptide in a solution of 20 mM borate buffer (90% H_2O + 10% D_2O) with different molar concentration of gadolinium ion Gd^{3+} at pH = 7.3, 293 K.

Amino acid residue	NH (ppm)	H*α* (ppm)	H*β* (ppm)	*Hγ* (ppm)	Etc. (ppm)
H_{13}	8.55 (8.57 (d)) [8.57(d)]	4.67	3.15, 3.03 (3.16(m), 3.03(m)) [3.16(b), 3.03(b)]		
H_{14}	8.60 (8.59 (d)) [8.59(b)]	4.60	3.22, 3.10 (3.23(m), 3.11(m)) [3.23(b), 3.11(b)]		7.27, 7.22 (7.27, 7.22) [7.27, 7.22]
Q_{15}	8.25 (8.25(d), 8.20(d)) [8.25(b), 8.18(b)]	4.24 (4.24) [4.24(b)]	2.00, 1.94 (2.01, 1.94) [2.01(b), 1.93(b)]	2.40 (2.44) [2.45]	NH_2: 7.40; 7.41(b); [7.37(b)]; Hδ: 7.06
K_{16}	8.16 (8.13(d)) [8.05(b)]	4.58	1.70 (1.75, 1.71) [1.75, 1.71]	1.40 (1.40) [1.40]	$H_δ$: 1.64; (1.64); [1.64]; Hε: 2.93; (2.94); [2.95]; NH_2: 7.51; 7.48(b); [7.45(b)]
L_{17}	8.44 (8.43(d)) [8.43(b)]	4.28 (4.29) [4.30(b)]	1.53 (1.53) [1.53]	2.04 (2.07(d), 2.01(d)) [2.06(b)]	Hδ: 0.86(d), 0.80; (0.86(d), 0.80); [0.86(d),0.80];
V_{18}	7.96 (7.96) [7.90(b)]	3.98 (3.98) [3.99(b)]	1.86 (1.86) [1.86(b)]	0.78, 0.71 (0.78, 0.71) [0.78, 0.71]	
F_{19}	8.40 (8.39) [8.37(b)]	4.20 (4.20) [4.20]	2.90, 2,83 (2.89(b)) [2.89(b)]		7.17, 7.12 (7.17, 7.12) [7.17, 7.12]
F_{20}	8.07 (8.05) [8.00(b)]	4.58	3.00(d), 2.88(d) (3.00(m), 2.89(m)) [3.00(m),2.90(b)]		7.18, 7.13 (7.18, 7.13) [7.18, 7.13]
A_{21}	8.17 (8.16(d)) [8.10(b)]	4.17 (4.17) [4.19(b)]	1.30 (1.30(d)) [1.29(d)]		
E_{22}	8.50 (8.49(d)) [8.49(b)]	4.18 (4.18) [4.21]	2.06, 1.90 (2.06, 1.90) [2.06, 1.90]	2.30 (2.31) [2.31(b)]	
D_{23}	8.33 (8.35) [8.33(b)]	4.57	2.75 (2.80) [2.80(b)]	2.76 (2.82) [2.82(b)]	
d – doublet signal, b – broadened signal, m – multiplet signal, ( ) – spectrum with a molar concentration of 0.191 Mm Gd^{3+} , peptide/ion molar ratio (1:0.127) [ ] – spectrum with a molar concentration of 0.353 Mm Gd^{3+} , peptide/ion molar ratio (1:0.235)					

The chemical shifts proton signals of amyloid peptide $A\beta_{13-23}$ in the borate buffer with and without Gd^{3+} ion were significantly different. In the study of obtained ^{1}H NMR spectra with gadolinium ion Gd^{3+} the following changes in the proton spectrum were observed.

In the amide region (8.7 - 7.4 ppm) in Fig. 6 some signals from amide protons with an increase in the concentration of Gd^{3+} showed a noticeable broadening of signals with subsequent

suppression, a shift of resonance signals and signal splitting. The most important changes in this area were observed for the negatively charged R-groups of amino acid residues of glutamic acid (E_{22}) and aspartic acid (D_{23}) - their signals H_NE_{22}, H_ND_{23} were broadened and suppressed; at the nonpolar R-group of amino acid residue of leucine (L_{17}), the H_NL_{17} signal was broadened and suppressed; at the polar R-group of amino acid residue of glutamine (Q_{15}), the initial signal of H_NQ_{15} split into two lines, and then both H_NQ_{15} lines were suppressed with broadening. The signal from amide protons of the non-polar R-group of amino acid residue alanine (H_NA_{21}) and the positively charged R-group of amino acid residue lysine (H_NK_{16}) first split into two separate signals H_NA_{21}, H_NK_{16}, and then both signals shifted to high-field region and the H_NA_{21} signal broadened. The signal from amide proton of valine (H_NV_{18}) shifted towards strong fields with broadening. The signals from amide protons of two nearby amino acid residues of phenylalanine (H_NF_{19}, H_NF_{20}) slightly broadened and shifted to the region of smaller chemical shifts, and the shift of the signal of amide proton H_NF_{20} turned out to be greater than that of proton H_NF_{19}. The signal of the amide proton H_NH_{14} shifted to the region of strong fields and with suppression, and the proton signal of neighboring amino acid residue H_NH_{13} slightly shifted to the region of weak fields without broadening. The proton signals of amino groups (NH_2) of amino acid residues of lysine (K_{16}) and glutamine (Q_{15}) also shifted to the region of strong fields and then broadened.

In the region 3.0 - 2.2 ppm ^{1}H NMR spectrum in Fig. 7 signals of beta protons (H_β) from amino acid residues F_{19}, F_{20}, D_{23}, signals of gamma protons (H_γ) from amino acid residues Q_{15}, L_{17}, E_{22} and proton signals of amino acid residue K_{16} (H_ε) also noticeably changed with an increase in the concentration of Gd^{3+} ion. The phenylalanine proton signal $F_{19}H_\beta$ shifted to the region of weak fields (positive shift), split into a doublet, and then part of the signal merged with the signal $F_{20}H_\beta$, while the other part of the doublet noticeably broadened. The proton signal from the neighboring amino acid residue of phenylalanine $F_{20}H_\beta$ first split into a doublet, slightly shifted to the region of large chemical shifts, and then part of the doublet broadened. The aspartic acid proton signal $D_{23}H_\beta$ shifted to the region of weak fields and then broadened. The signal of protons of lysine $K_{16}H_\varepsilon$ slightly shifted to the region of weak fields. The gamma protons signal of amino acid residue $Q_{15}H_\gamma$ splits into two signals, in which one part was significantly broadened, and the other part of its signals slightly shifted to the region of weak fields. The proton signal $E_{22}H_\gamma$ significantly broadened with an increase in the Gd^{3+} concentration. The signal of protons $L_{17}H_\gamma$ has slightly shifted to the region of weak fields.

The presence of such changes in the spectrum indicates that in these regions (amide and 3.0 – 2.2 ppm) the protons of the Aβ peptide are influenced by Gd^{3+} ion. The broadening of spectral lines occurs due to an increase in the relaxation rate; This effect is a consequence of spatial proximity to the paramagnetic Gd^{3+} ion. A noticeable broadening of signals H_NE_{22}, H_ND_{23}, H_NQ_{15}, H_NL_{17}, NH_2K_{16}, NH_2Q_{15}, H_NV_{18} allows us to assume that in these regions of the amyloid peptide $A\beta_{13\text{-}23}$ there is a possible localization site of the Gd^{3+} ion.

The shift of resonance signals occurs due to the fact that there is a shift of electrons surrounding the nucleus for which a resonance is observed, as a result, the electron density of the nucleus changes, which leads either to the screening of the nucleus (the inner electrons of atom are located denser to the nucleus), or to the unscreening (inner the electrons of atom move away from the nucleus). If the nucleus is screened by surrounding electrons, then its resonance signal in the NMR spectrum will shift to the region of weak fields (towards large chemical shifts), in the case of screening of nucleus by surrounding electrons, the signal from the nucleus in the NMR spectrum, on the contrary, will shift to the region of strong fields (towards smaller

chemical shifts). Thus, the shift of the H_NA_{21}, H_NK_{16}, H_NV_{18}, H_NF_{19}, H_NF_{20}, H_NH_{14}, NH_2K_{16}, NH_2Q_{15}, $F_{20}H_\beta$ signals to the region of smaller chemical shifts is explained by the fact that in these regions of the peptide the effect of electron shielding of the nuclei of these fragments occurs upon the addition of a positive gadolinium ion. And the shift of signals $D_{23}H_\beta$, $F_{19}H_\beta$, $K_{16}H_\varepsilon$, $Q_{15}H_\gamma$, $L_{17}H_\gamma$ to the region of large chemical shifts is explained by the fact that in these regions of the peptide, on the contrary, the effect of screening of nuclei by electrons occurs when a positive gadolinium ion is added.

The separation of some signals can be explained as follows. Initially, the NMR spectrum is an averaged picture of the nuclei state. The peak of NMR line corresponds to the most probable state of the nucleus with the corresponding resonance frequency. If for the nucleus, we see the splitting of the initial line into two lines with characteristic peaks, then this will correspond to the two most probable states of the nucleus in the molecule. Thus, the signal behavior of polar amino acid residue Q_{15} R-group can be described. The signals H_NQ_{15}, $Q_{15}H_\gamma$ in the course of interaction with the positive Gd^{3+} ion split into two lines, which corresponds to the fact that in the Q_{15} amino acid residue during the spatial approach with the gadolinium ion, two most probable positions of the polar radical appeared, in which at the end there is a positive NH_2 and a negative CO group. Presumably, the lines H_NQ_{15} (8.25 ppm), $Q_{15}H_\gamma$ (2.01 ppm) correspond to such a conformation when the gadolinium ion is localized between N_H and NH_2 fragments of the amino acid residue Q_{15}, and the lines H_NQ_{15} (8.18 ppm), $Q_{15}H_\gamma$ (1.93 ppm) correspond to the location of the gadolinium ion between the NH and CO fragments of the Q_{15} amino acid residue. The splitting of the signal from two protons H_NA_{21} (8.17 ppm), H_NK_{16} (8.16 ppm) into two separate lines can be explained by the fact that, during the Gd^{3+} ion interaction with $A\beta_{13\text{-}23}$, the protons H_NA_{21} and H_NK_{16} were unshielded and their signals shifted to the region smaller chemical shifts. For the H_NK_{16} proton, this effect is more pronounced than for the H_NA_{21} proton, so its resonance signal shifts further into the region of the stronger fields than for the H_NA_{21} proton.

Thus, we assume that Gd^{3+} can be localized to two sites. The first site is at the amino acid residues Gln (Q_{15}), Lys (K_{16}), Leu (L_{17}), Val (V_{18}). The second site is Ala (A_{21}), Glu (E_{22}), Asp (D_{23}) in Figures 8, 9. . The 3D model of $A\beta_{13\text{-}23}$ peptide in Figure 9 was used from the literature data [14].

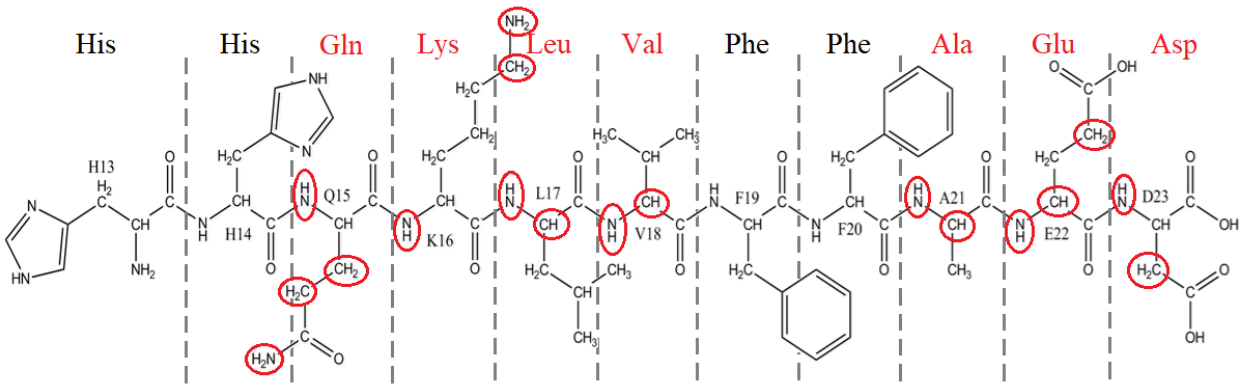


Figure 8 - Chemical structure of beta-amyloid peptide $A\beta_{13\text{-}23}$ (HHQKLVFFAED) and fragments of amino acid residues involved in the interaction with Gd^{3+} ion. Fragments participating in the interaction are circled in red.

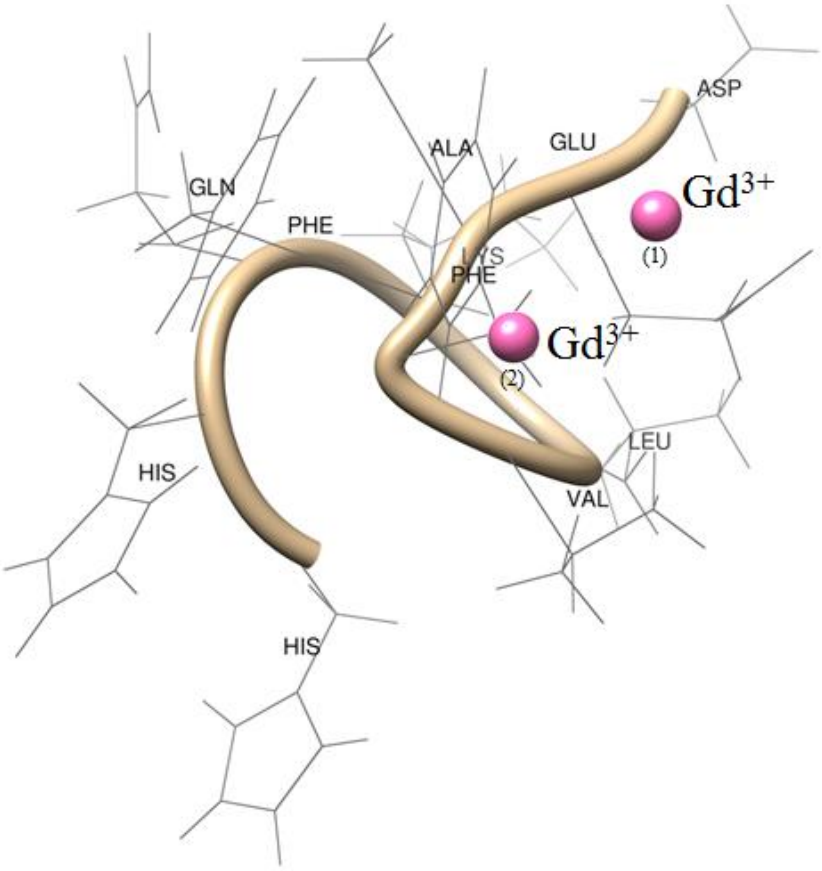


Figure 9 - Model of the interaction of the gadolinium (III) ion with the $A\beta_{13-23}$ peptide. (1), (2) – Possible sites of the gadolinium ion Gd^{3+} with significant effect on $A\beta_{13-23}$ structure.

4. Conclusion

In study, a primary assessment of the influence effect of gadolinium ion Gd^{3+} on the structure of tetrapetide in phosphate buffer and on the structure of beta-amyloid peptide $A\beta_{13-23}$ in borate buffer by NMR spectroscopy methods were carried out. Based on the data obtained from the ^{1}H NMR spectra of the Gd^{3+} complex with the tetrapeptide in the phosphate buffer, it was found that the gadolinium ion is localized mainly in the central part of the tetrapeptide, between the amino acid residues Phe and Val. From the analysis of the ^{1}H NMR spectra of the Gd^{3+} complex with peptide $A\beta_{13-23}$ in a borate buffer, it was noted that the possible sites of the gadolinium ion are positions between Gln (Q_{15}), Lys (K_{16}), Leu (L_{17}), Val (V_{18}) amino acid residues, or the central part between the amino acid residues Ala (A_{21}), Glu (E_{22}) and Asp (D_{23}).

According to previous studies of metal complexes Mn^{2+} – $A\beta_{13-23}$ and Co^{2+} – $A\beta_{13-23}$, the manganese-binding and cobalt-binding centers of the Aβ13-23 peptide are associated with an aspartate residue[13, 14]. A similar behavior was found for one Gd^{3+} binding site of the $A\beta_{13-23}$ peptide associated with an aspartate residue. The second gadolinium ion binding site located near the lysine and leucine residues was observed only for the Gd^{3+} – $A\beta_{13-23}$ complex.

Author contributions section

A.S.: Investigation, Visualization, Writing-Original draft preparation **I.Z.:** Methodology, Investigation, Visualization **D.S.:** Resources, Validation, Writing-Reviewing and Editing **A.V.:** Validation **K.A.:** Funding acquisition **V.V.:** Conceptualization, Writing-Reviewing and Editing, Supervision. All authors discussed the results and contributed to the final manuscript.

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