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Impact of the Rat R5G, Y10F and H13R Mutations on Tetrameric A β 42 β -barrel in a Lipid Bilayer Membrane Model

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Abstract

Three amino acid substitutions distinguish rat and human A β 42 peptides and contribute to the difference in toxicity properties. Indeed, aged rodents rarely develop the characteristics lesions of Alzheimer's disease in contrast to humans. Both peptides form, however, amyloid fibrils in buffer solution, but their affinities to membrane vary. In particular, there is experimental evidence that the rat A β 42 peptide does not induce Ca²⁺ fluxes in cells. We recently designed a tetrameric β -barrel structure and showed this model is severely destabilized for A β 40 human compared to its A β 42 human counterpart, explaining the absence of ionic currents of A β 40 in planar lipid bilayers. In this study, we asked whether our model is destabilized for the rat A β 42 peptide by using extensive replica exchange molecular dynamics simulation in a dipalmitoylphosphatidylcholine (DPPC) lipid bilayer membrane. Our results show that the much lower propensity of aged rodents to develop Alzheimer's disease symptoms might be correlated to its tetrameric β -barrel stability in the cell membrane.

Introduction

The role of A β amyloid formation and notably of the deleterious effect of small A β oligomers, in the so-called amyloid cascade, is still the leading hypothesis of Alzheimer's disease,¹ despite repetitive failures of drugs and antibodies targeting these oligomers.²⁻⁵ The amyloid precursor protein (APP), from which A β is derived, is well conserved between species, with >96% of the amino acid sequence identical between rat, monkey, and human.^{6,7} Only, three amino acid substitutions distinguish rat and human A β 42 peptides, and these differences are located in the N-terminus of the A β peptide, Arg-5→Gly, Tyr-10→Phe, and His-13→Arg. Soluble A β 40 and A β 42 are produced by rats in neuronal tissues⁸ and both human and rat A β peptides form amyloid fibrils in aqueous buffers^{9,10}; yet, amyloid deposition is not a feature of aged-rat brains.¹¹

Several hypotheses have been proposed to explain why aged-rats do not develop characteristics of Alzheimer's disease. These include the short lifespan of rodents relative to humans,¹² differences in processing of mouse and human APP by β -site APP-cleaving enzyme 1¹³ and differences in solubility and localization of the resulting rat and human aggregates.¹⁴ Cofactors also provide other explanations. The replacement of His13 for Arg disrupts the zinc coordination site, which makes rodent A β much less prone to zinc-induced aggregation than human A β *in vitro* at submicromolar concentrations of Zn²⁺.⁸ Through a combination of several spectroscopic and analytical methods, mutations His13Arg and Arg5Gly were found to induce different coordination sites for Zn(II) ions.¹⁵ Cu²⁺ ions promote limited aggregation of human A β , but not of rat A β .¹⁶ The replacement of three amino acids alters the affinity of A β for heme and prevents the formation of A β -heme complex with peroxidase activity.¹⁷

In addition, to the binding to metal ions, A β interactions with cell membranes are well documented. Membranes containing gangliosides have been shown to play an important role in A β aggregation,¹⁸ and GM1 ganglioside-bound A β has been discovered in the brain of AD patients.¹⁹ There is increasing experimental evidence that human A β 42 peptides can form amyloid channels from tetramers, octamers and larger aggregates,²⁰⁻²³ and this is not the case for human A β 40 peptides.²⁴ Albeit alpha-helical and other topologies cannot be totally excluded,^{20,25,26} several β -sheet structures were proposed in micelles, liposomes and membrane models.²⁷⁻³⁰ Of particular interest is the NMR structure of A β 42 tetramers in a membrane mimicking environment (micelle) at pH 9 which revealed edge conductivity pores.²⁹ The second model is based on size exclusion

chromatography, transmission electron microscopy, electric recording, circular dichroism and NMR information on the structural environment experienced by the Q15, N27 and M35 side chains of A β 42 peptides in micelles,²⁰ as well structural modelling results of A β 40 and A β 42 dimers in bulk solution.³⁰⁻³² Using extensive replica exchange molecular dynamics (REMD) simulations in a DPPC lipid bilayer, we showed that our 3D β -barrel model made of two distinct β -hairpins and an asymmetric of eight antiparallel β -strands is severely destabilized for A β 40 human compared to its A β 42 human counterpart,³³ explaining the absence of ionic currents of A β 40 in planar lipid bilayers.²⁰

Crossing of Ca²⁺ ions through amyloid pores is believed to be among the earliest steps in Alzheimer's disease but also in Parkinson's disease.^{34,35} Interestingly, there is experimental evidence that rat A β 42 peptides does not induce Ca²⁺ fluxes in cells, as assessed by fluorescence microscopy.³⁶ In this study we therefore questioned whether the replacement of the three residues at positions 5, 10 and 13 in the rat sequence destabilizes the propensity of our tetrameric β -barrel structure by computational means. To this end, we performed REMD simulations on the rat A β 42 peptide in a DPPC lipid bilayer membrane and compared to the results of its human sequence counterpart.³³

Materials and Methods

The rat barrel structure, generated from the human barrel³³ by using PyMOL software,³⁷ was centered in a rectangular box of (8.72, 8.72, 8.28 nm), with lipid bilayer dimensions of (8.72, 8.72, 4.00 nm) solvated using the SPC water model.³⁸ As for the human barrel, the peptide was modelled using the GROMOS96 53a6 force field³⁹ and the Berger force field was used for the DPCC lipid bilayer.⁴⁰ The peptides at pH 7 have CO₂⁻ and NH₃⁺ termini, deprotonated Asp and Glu, protonated Lys and Arg, and neutral His with a protonated Ne atom. In total, the transmembrane rat system contains 202 DPPC molecules, 7573 water molecules, and 12 Na⁺ ions (total atoms of 34 427).

The GROMACS version 5.1.3⁴¹ was employed to perform REMD simulations with all parameters regarding time step and force calculations described elsewhere.³³ The system, first minimized by steepest descent, and relaxed by NVT and NPT MD simulations for 1 ns at 300 K, was subsequently sampled with 48 replicas at 310.0, 312.2, 314.3, 316.6, 318.8, 321.0, 323.2,

325.4, 327.7, 329.9, 332.2, 334.5, 336.8, 339.1, 341.4, 343.8, 346.1, 348.5, 350.8, 353.2, 355.6, 358.0, 360.4, 362.9, 365.3, 367.8, 370.3, 372.8, 375.3, 377.8, 380.3, 382.9, 385.4, 388.0, 390.6, 393.2, 395.8, 398.4, 401.0, 403.7, 406.4, 409.0, 411.7, 414.5, 417.2, 419.9, 422.7, and 425.5 K. The rat barrel was explored by 250 ns REMD in the NPT ensemble with the Nosé-Hoover thermostat and the semi-isotropic Parinello-Rahman coupling algorithm,⁴² and the first 50 ns were excluded from analysis. Comparison with the REMD results of the human wild-type (WT)³³ was monitored over the time interval 50-250 ns at 310 K. It is known that the gel-liquid transition temperature of pure DPPC bilayer is 314 K.⁴³ As our REMD sampling of the DPPC bilayer is performed much above the lipid phase transition temperature, our computed results at 310 K are physically relevant.

For analysis, we used the same metrics as described elsewhere, namely the DSSP tool for secondary structure compositions,⁴⁴ the free energy landscape (FEL) projected on the root-mean square deviation (RMSD) using all backbone heavy atoms of residues 9-40 with respect to the MD-refined structure and the mean number of intermolecular side chain contacts per pair (N_{sc}) using residues 9-40.^{33,45} We also determined the number of peptide contacts with water molecules using a cutoff of 0.3 nm, and with the DPPC lipid head groups using a cutoff of 0.6 nm between any heavy atom of all head groups and any non-hydrogen atoms of a residue. A hydrogen bond (H bond) between the residues and head groups was considered formed if the acceptor-donor-H angle is < 30 degrees and the acceptor-donor distance is < 0.35 nm. The FEL was also projected on the first two principal components obtained from the diagonalization of the positional fluctuation covariance matrix of the backbone atoms.⁴⁶

Results and Discussion

The convergence of the REMD simulation at 310 K was assessed by several metrics, including the propagation of the third and forty-three replicas over the temperature index (Figure S1 in the Supporting Information), and the quasi superposition of the turn, coil and β -strand profiles along the sequence as the simulation is extended from 200 ns to 250 ns (data not shown). Using the time intervals 50-150 ns and 50-250 ns, the secondary structure composition deviates by 2% (i.e., within statistical errors) and the FEL is slightly modified (Figure S2). The average of exchange rates between consecutive replicas is 22%.

Upon Arg5Gly, Tyr10Phe and His13Arg mutation, the β -strand content shifts to 42% and the coil content to 56% compared to 48% and 48% for the human sequence. In contrast the turn (2%) content and helix (almost 0%) content remain identical. For both sequences, the β -strand profile (Figure 1A) shows two dominant regions spanning residues 12-22 and 29-42, but upon mutation, the signal is much weaker at positions 37-42 (e.g., 60% vs. 25% for residue 38) and is increased at residues 22-23 and 4-5 (reaching almost 30% for residue 5). This is accompanied by an increase of turn and coil content of residues 37-42 and coil content of the N-terminus (residues 1-10), see Figures 1B-1C.

A better understanding of the impact of the mutations on the conformational ensemble is assessed by the comparison of the FEL of the human and rat tetramers projected on the backbone RMSD with respect to the MD-refined structure and the mean number of intermolecular side-chain contacts per pair (N_{sc}). Whereas the human FEL displays a small conformational space with six free-energy minima characterized by the RMSD varying between 0.42 and 0.67 nm (see Figure 4B in Ref. 33), the rat FEL reveals six free-energy minima, with four minima representing 98% of the total population with RMSD varying between 0.9 and 1.25 nm. The free energy minima on the rat FEL (Figure 2) are denoted by M1, M2, M3, M4, M5, M6 with (RMSD, N_{sc}) values of (1.14, 24.6), (0.96, 28.0), (0.95, 23.3), (0.88, 22.3), (0.75, 25.9) and (0.61, 31.8). Representative structures of M1-M6 are shown in Figure 3. As our RMSD criterion tells us deviation from the reference structure, but does not tell to which direction is the deviation, we also calculated the RMSD between all six free-energy minima. We found the RMSD ranges from a lowest value of 0.72 nm (between the states M4 and M5) to 0.81 nm (M2-M5, M2-M6; M4-M6) and to more than 0.9 nm (between M1-M2, M1-M3, M1-M4, M1-M5, M1-M6; M2-M3, M2-M4; M3-M4, M3-M5, M3-M6).

We previously reported that the dominant free-energy minimum for the human sequence has a population of 48% and is a perfect closed barrel with an inner pore diameter of 0.75 nm and a tilt angle (angle of the β -strands relative to the axis of the barrel) of 37.5 degrees.³³ This topology represents less than 1% for the rat sequence, and the corresponding M6 state has a tilt angle of 37.8 degrees and an inner pore diameter of 0.55 nm.

Rather the rat sequence is dominated by a disordered topology (RMSD of 1.2 nm) characterized by a five stranded β -sheet (made of two chains and the C-terminus of the third chain)

perpendicular to a three stranded β -sheet (made of the fourth chain and the N-terminus of the third chain) with only three chains adopting β -hairpins. This M1 state with a population of 53% is characterized by intermolecular Phe20-Phe20 side-chain contacts between the chains 1 and 3, and between the chains 2 and 4. The M2 state, with a population of 41% and a RMSD of 0.95 nm, is also a highly twisted eight-stranded β -sheet. This tetramer is stabilized by hydrophobic packing interactions between the C-terminus (residues 37-41) of chains 1 and 3, and between the CHC domain of chain 2 and the C-terminus of chain 4.

The three other states for rat, M3 to M5, with a total population of 4% and a RMSD of 0.93, 0.90 and 0.77 nm are also twisted irregular β -sheets with a minimum of 2 to 5 hydrogen bonds between consecutive β -strands. These three non-barrel states differ in their intermolecular side chain contact maps. Looking at the interactions between chains 1 and 3, state M3 shows a high density of contacts between the N-terminus (residues 6-14) and residues 39-41, the two N-termini, and the two C-termini; and states M4 and M5 display contacts between the end of the two N-terminus (residues 14-16) and the C-terminus (residues 32-40) with different probabilities. Altogether, the M2 to M5 states, characterized by changes in the pattern of interactions within the hairpins and their interfaces, are highly disorganized β -sheets.

Altogether there are significant differences in the conformational properties of the rat and human systems and this is also captured by the FELs using principal component analysis based on the residues 9-40 (Figure S3 in Supporting Information).

Next, we analyzed the interactions of rat A β 42 peptides with water molecules and DPPC lipid bilayer. As seen in Figure 4, the three mutations do not change the propensity of the N-terminus and of the loop region to reside in the bulk water, the number of water molecules interacting with the residues 1-9 and 22-28 being similar for the human and rat sequences with the exception of the mutated residue Arg5Gly which deletes water-binding and electrostatic sites. We find very similar profiles in the numbers of amyloid- β contacts considering all side-chain and main chain atoms with the DPPC lipid head groups along the sequence between the two species, the exception being the mutated residue His13Arg with an expected increase of contacts (Figure 5). The three mutations do not alter the distribution of the number of transient H-bonds between the DPPC lipid head groups and each A β 42 amino acid, considering both main-chain and side-chain H bond sites, the exception being at the mutated residues Arg5Gly and Tyr10Phe. We also have calculated the

mean and standard deviation of the electrostatics and Lennard Jones energies between the residues 11-42 of A β and the tail or head group lipid bilayers. We found that each energy component between the rat and human systems varies by about 3%, i.e., within statistical errors. Of note also, the order parameters of the bilayer membrane (tails) are identical between the rat and human systems within our time scales.

Overall, the tetrameric β -barrel conformation is completely destabilized for the rat sequence compared to the human sequence. This destabilization comes from a reduced β -strand and β -hairpin propensity, and change in the intermolecular side-chain interactions, in which the density of contacts between the two CHC's and between the two C-termini is reduced in the rat sequence (Figure 6). Our computational study is therefore fully consistent with experimental data showing that, at nanomolar concentrations, rat A β 42 does not induce Ca²⁺ fluxes in SH-SY5Y cells.³⁶

It is interesting that the replacement of three mutations located in the N-terminus change the ability of the A β 42 peptide to form tetrameric β -barrels in model membranes. Indeed, biophysical studies do not reveal any differences between the rat and human sequences to form amyloid fibrils⁹ and the two species also cross-seed to form mixed A β amyloid fibrils in buffer solution.¹⁰ There are experimental and theoretical evidence reporting that the Ala2Thr mutation⁴⁵ and deletion of residues Asp1 and Ala2 with replacement of Glu3 by a pyroglutamate (A β p3-42 peptide) do not affect pore conductance.⁴⁷

The sequence differences at positions 5, 10 and 13 are not completely without consequence, however, with respect to the interactions with membranes. It has been demonstrated by MD simulations that the Arg5Gly mutation influences A β 42 monomer-membrane interaction and differences in lipid affinity and degree of membrane disruption⁴⁸ and we indeed found a slight difference in the number of H-bonds between the N-terminus and the membrane and the solvation of the N-terminus upon mutation. Experimentally, human A β peptides form toxic, mature amyloid fibrils, whereas rat A β peptides produced less toxic protofibrils on cell membranes, and raftlike membranes with monosialoganglioside GM1 clusters. These results led to the ganglioside cluster-mediated amyloidogenesis hypothesis to explain the immunity of rodents from cerebral A β amyloid deposition.⁴⁹ As the recognition motif between A β 40 and the GM1-glycan cluster involves the segment His13-His14-Gln15,⁵⁰ the His13Arg mutation in rat will impact the recognition motif and the early steps of aggregation.

While the Arg5Gly mutation impacts A β binding to the membrane, the residue 5 is outside of the β -sheet region in our model and the NMR structure in micelles²⁹, we expect that this single mutation will not change the β -barrel population. Similarly, the single Tyr10Phe mutation, which increases the β -strand character, should slightly increase or leave invariant the β -barrel population as our model consists of two distinct β -hairpins with one hairpin spanning residues 9-39 (Hairpin 1). Hairpin 2 spanning residues 15-40 in our model should not be impacted. We emphasize that the NMR tetrameric structure in micelles also shows a β -hairpin with two β -strands spanning residues 9-21 and 28-40.²⁹ It is therefore very likely that the destabilization of the barrel in rat results for the most part of the His13Arg mutation.

Naked mole-rat (the longest-lived rodent) A β , which differs from human A β by the single H13R mutation, and mouse A β have a very similar propensity to aggregate. Like mouse, naked mole-rats do not accumulate amyloid plaques, even if their brains contain high concentrations of A β peptide.⁵¹ Whether naked mole-rat destabilizes the tetrameric A β 42 barrel remains to be determined. Though several protective mechanisms to the development of harmful effects of A β have been proposed for naked mole-rat,⁵¹ it was recently found that the lipodomic profiles in mouse and naked mole-rat are very different and the naked mole-rat should be less sensitive to lipid oxidation than mouse.⁵²

Conclusions

We have investigated the influence of the rat mutations on the stability of tetrameric A β 42 β -barrel embedded in a DPPC lipid bilayer by performing extensive REMD simulation. The simulation shows that rat A β 42 has a very negligible β -barrel populations, consistent with the absence of Ca²⁺ fluxes in cells as measured by fluorescence experiments. This finding provides another plausible explanation for the absence of Alzheimer's disease symptoms in rats, and might be extrapolated to naked mole-rats as the mutation His13Arg play a critical role. To this end, it is important however that simulations go beyond pure DPPC bilayer as real neuronal membranes contain high fraction of unsaturated and polysaturated lipids which create different environment for the incorporated peptides affecting also their conformational and aggregation properties.^{52,53} Including also a physiological concentration of Ca²⁺ and not only Na⁺ ions to neutralize the system would also increase the biological relevance of our simulations.

Supporting Information.

The Supporting information is available free of charge at <https://pub.acs.org/>

Propagation of two replicas over the temperature index; FEL of the transmembrane rat 4A β ₁₋₄₂ system projected on the backbone RMSD (nm) and the mean number of intermolecular side-chain contacts per pair (N_{SC}) at 310 K using the time interval 50-150 ns; FEL of the human (A) and the rat (B) using principal component analysis and the time interval 50-250 ns at 310 K.

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Notes

The authors declare no competing financial interest.

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Figure 1. Secondary structure composition along the sequence of transmembrane rat 4A β ₁₋₄₂ peptide at 310 K over the time interval 50-250 ns of the REMD simulation. Transmembrane rat system is blue and human system is red.

Figure 2. Free-energy landscape of the transmembrane full-length rat 4A β_{1-42} system projected on the backbone RMSD (nm) and the mean number of intermolecular side-chain contacts per pair (N_{SC}) at 310 K using the time interval 50-250 ns.

Figure 3. Representative structures of full-length rat 4A β_{1-42} system over the time interval 50-250 ns at 310 K.^a

N ^o	Minima	Population	X-view	Z-view
1	M1	53%
2	M2	41%
3	M3	2%

4	M4	1%
5	M5	<1%
6	M6	<1%

^a Chain A is blue, chain B is red, chain C is gray, and chain D is orange. The rat mutations Arg5Gly, Tyr10Phe, and His13Arg are in purple, tan, and yellow colors, respectively.

Figure 4. Water molecules interacting with the residues 1-9 and 23-28 using a cutoff distance of 0.3 nm in the rat system (blue) at 310 K averaged over the four peptides and in the wild-type human system (red).

Figure 5. Averaged number of A β 42 contacts and H-bonds with the head groups of the lipid bilayer membrane along the sequence using the rat and WT (human) data at 310 K.

Figure 6. Intermolecular side-chain probability contact maps overlaged over the four interfaces of the wild-type (human) and rat systems at 310 K with the two most populated structures of the human (Minima A and B) and rat (Minima M1 and M2) systems.

TOC Graphic

Rat Tetrameric A β 42 β -Barrel