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A computational study of metal ions interaction with amyloid-β 1–42 peptide structure in hyperpyrexia: Implications for Alzheimer disease

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ABSTRACT

Given the current context of the SARS-CoV-19 pandemic, among the interfering risky factors with the Aβ peptide aggregation in the brains of Alzheimer’s disease (AD) patients can be hyperpyrexia and increased intracranial pressure (ICP). According to our hypothesis on the relationship between hyperpyrexia and cognitive decline in AD, two models of Aβ peptides were used in this study: the structure of AD amyloid beta-peptide and near-atomic resolution fibril structures of the Aβ peptide. Therefore, the binding templates were constructed for Aβ peptide regions able to bind 9 different metal ions. The fragment transformation method was used for the structural comparison between Aβ chains. Molecular dynamics simulation (MDS) was applied using the Nose-Poincare-Anderson equation to generate a theoretically correct NPT (isothermal–isobaric ensemble). The smallest dissimilarities were observed in the case of Cu²⁺ binding potential followed by Co²⁺, both with similar variation. Structural changes have also occurred as a result of the dynamic simulation. All these changes suggest an aggravating factor in both hyperpyrexic and AD conditions. Our findings suggest that elevated temperature and increased intracranial pressure rise the effect of peptide aggregation, by converting γ-helix motif to β-sheet and random coil conformation, which are related to the formation of senile plaques in AD brains.

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1. Introduction

Alzheimer’s disease (AD) is a frequent neurodegenerative disease in the elderly and the most common cause of dementia, characterized by progressive cognitive deterioration. Incidence of AD continues to rise worldwide, becoming a major health challenge in the 21st century, expressed in both the medical and financial fields (Fan et al., 2020).

The neuropathological hallmarks of AD include an increase in amyloid plaques and cerebral amyloid formation, neurofibrillary tangles and glial responses, as well as neuronal and synaptic loss (Serrano-Pozo et al., 2011). According to the Chicago Health and Aging Project study, about 700,000 people with age 65 and older in the US will have AD when they die in 2020 (Weuve et al., 2014). A similar report published by Alzheimer Europe shows that the number of people with dementia in Europe is likely to double by 2050, increasing from almost 9 million to more than 18 million in the wider European region (Alzheimer Europe, 2020). Although some older adults with AD die from causes unrelated to the disease, many of them die from Alzheimer’s disease or from conditions where this neurodegeneration was a contributing cause of death, such as pneumonia (Alzheimer’s Association, 2020). Among the numerous hypotheses that describe progression and development of AD, the amyloid one is related to the involvement of various forms of Aβ peptides in damage to neuronal and cognitive functionality (Vijayan and Chandra, 2020). The Aβ peptides (Aβ1–40 and 1–42) are generated as a result of abnormal APP cleavage assisted by β- and γ-secretase (Tambini et al., 2020). These peptides undergo to soluble oligomers that can exist in several conformations, which can aggregate in toxic fibrils and plaques species.
(Guo et al., 2020). Furthermore, in the presence of small molecular catalysts, some species of oligomers and end-products of Aβ peptides have been shown to convert to complete amyloid fibrils (Bieschke et al., 2012).

Besides, the interaction of Aβ peptides with metal ions such as copper, zinc, iron, manganese or nickel has been shown to contribute to neuronal damage (Sciacca et al., 2020). Moreover, copper, zinc, iron, manganese or nickel has been shown to condense structure of Aβ beta monomers and oligomers pose challenges due to the disordered structure of Aβ, its fast aggregation, as well as solvent and paramagnetic effects (Strodel and Coskuner-Weber, 2019; Lupaeascu et al., 2021).

According to our hypothesis in which hyperpyrexia could affect the process of metal- Aβ(1-42) interaction, we resorted to a theoretical comparative in silico analysis with the purpose to investigate the structural changes in the shape of the monomer Aβ(1-42) and fibrils generated by Aβ(1-42) in the presence of various metal ions, such as Cu^+, Cu^{2+}, Fe^{2+}, Fe^{3+}, Mn^{2+}, Mg^{2+}, Ni^{2+} and Zn^{2+}. The analysis was based on the conformational differences between these molecular species, under normal physiological conditions of 37.0 °C and 11 mmHg and specific to hyperpyrexia conditions (up to 41.0 °C and 20 mmHg) (Ghajar, 2000).

These characteristics can provide theoretical valuable information regarding the underlying processes that occur in patients infected with hyperpyrexia under AD. Moreover, this paper highlights the first in silico framework for the analysis of the effect of thermal and osmotic impact on neurodegenerative processes.

2. Materials and methods

The Aβ peptides were constructed using Protein Data Bank (PDB) in Molecular Operating Environment software (MOE) with appropriate residue protonation state at physiological pH (Molecular Operating Environment (MOE), 2017). For this study, two models of Aβ peptides were used, the solution structure of the amyloid-β peptide (1–42) (11YT; denoted Aβ(1-42)) and near-atomic resolution fibril structures of the same peptide by cryo-EM with 9 chains of Aβ(1-42) (5OQV; denoted Aβ(1-42)F) (Crescenzi et al., 2002; Gremer et al., 2017). Binding templates have been constructed for regions that could bind nine selected metal ions (Cu^+, Cu^{2+}, Fe^{2+}, Fe^{3+}, Mn^{2+}, Mg^{2+}, Ni^{2+} and Zn^{2+}). The templates include residues at 3.5 Å from the metal ion according to the fragment transformation method developed by Lin et al. (Lin et al., 2016; Lu et al., 2012), which was used for structural comparison between Aβ chains. Each residue of the query peptide was assigned a binding score, which is composed of the sequence and structure conservation measures. The fragment transformation method was used to align query peptide chain and metal-binding site. By this method, the query peptide was aligned with the metal-binding templates and then each cluster was scored according to its sequence and structure similarity. The BLOSUM62 substitution matrix was used to calculate the sequence similarity, and the root-mean-square deviation of the Cα atoms of the alignments was applied to evaluate the structure similarity (Lin et al., 2016).

The peptide-metal complex was exposed to a MIMF94x Hamiltonian force field potential energy in MOE to configure its parameters and to manage restraint forces applied to the atoms (Halgren, 1996). The energy minimizes application calculates atomic coordinates that are at local minima of a molecular energy function. For this purpose, the gradient was set at 0.05, when the gradient of root mean square falls below that specified value. The root mean square gradient was the norm of the gradient times the square root of the number of unfixed atoms. Water-solvent molecules were also added to the system, positioned in a rectangular arrangement around the peptide-metal complex.

The simulation of molecular dynamics was applied using Nose-Poincare-Anderson equation to generate a theoretically correct NPT ensemble (Bond et al., 1999; Sturgeon and Laird, 2000). The temperature response used to enforce constant temperature was set at 0.2 picoseconds (ps), and the pressure response used to enforce constant pressure at 5 ps. In the first molecular dynamics ensemble, to analyze the conformational and structural changes that occurred to the peptide-metal complex under physiological conditions, a heat time of 200 ps at 310.15 K (37.0 °C) and 1.466 kPa (11 mmHg, the mean value for normal intracranial pressure) was applied. For the second state, the temperature was set to 314.15 K (41.0 °C) and 2.666 kPa (20 mmHg, the mean value for ICP) for 200 ps. The system was monitored at the time step of 0.0005 ps.
3. Results

3.1. The binding potential

First, we studied the binding of the nine metal ions (Cu²⁺, Cu²⁺, Fe²⁺, Fe³⁺, Mn²⁺, Mg²⁺, Ni²⁺ and Zn²⁺) to Aβ (1-42) peptide and 9 chain Aβ(1-42) fibrils (Aβ(1-42)F). Both the Aβ(1-42) monomer and the fibrils were taken from the PDB database as validated structures and analyzed using the fragmentation method described in Section 2 (Fig. 1).

As can be seen from Fig. 1a, in the case of the Aβ(1-42) monomer peptide, the binding potential is predominantly expressed in sequence 1–16, while this index tends to be much lower in the rest of the Aβ structure. This is most likely due to the amino acid residues such as His, Ser or Asp at Aβ N-terminal, which contain nitrogen or oxygen atoms that play an electron donors role in the ligand-receptor interactions.

On the other hand, in the case of Aβ(1-42)F, the binding potential of the metal ions increases even in the region 17–42, which suggests that, compared to the monomer Aβ, metal ions tend to bind to the entire structure of Aβ peptides in fibrils. Hence, these ions tend to bind much easier because Aβ(1-42)F has a much larger binding surface and stability. An alternative explanation involves the inhibition of the α-helix structure in Aβ(1-42)F to the advantage of the β-sheet and random coil pattern, the helix structure prevents the formation of coordinative bonds. Von Bergen and coworkers have demonstrated that the assembly of Tau protein into AD paired helical filaments depends on a local sequence motif (Von Bergen et al., 2000).

Furthermore, by comparing the potential binding plots between Aβ(1-42) and Aβ(1-42)F significant differences regarding metal ions interaction were noticed. These differences can be analyzed by decreasing the binding potential of each metal in Aβ(1-42)F with the binding potential of the same metal for each chain in Aβ(1-42)F.

According to these results (Fig. 2), the smallest dissimilarities can be noticed in the case of Cu²⁺ binding potential followed by Co²⁺, both with similar variation. On the other hand, major differences were observed between the binding of Mn²⁺, Ni²⁺, Mg²⁺ and Fe²⁺, Cu²⁺ and Zn²⁺ ions showed the same deviation from the difference, whereas the most notable variation was observed in the 1–16 Aβ fragment for Fe³⁺.

Therefore, by analyzing these findings, we selected Cu²⁺ ion in our investigation, because it provides the most constant binding potential regarding the structure of Aβ(1-42) or Aβ(1-42)F.

3.2. Conformational and structural analysis

The Aβ(1-42)–Cu²⁺ complex was studied using the molecular dynamics protocol in order to analyze the influence of the metal ion under the imposed dynamic conditions. The conformations resulted regarding the Aβ(1-42)–Cu²⁺ at 37 °C (11 mmHg) and 41 °C (20 mmHg), as well as the Cu²⁺ coordination pattern at the peptide binding site can be observed in Fig. 3.

According to Fig. 2, the smallest dissimilarities can be noticed in the case of Cu²⁺ binding potential followed by Co²⁺, both with similar variation. On the other hand, major differences were observed between the binding of Mn²⁺, Ni²⁺, Mg²⁺ and Fe²⁺, Cu²⁺ and Zn²⁺ ions showed the same deviation from the difference, whereas the most notable variation was observed in the 1–16 Aβ fragment for Fe³⁺.

Therefore, by analyzing these findings, we selected Cu²⁺ ion in our investigation, because it provides the most constant binding potential regarding the structure of Aβ(1-42) or Aβ(1-42)F.

3.3. Ramachandran analysis

A better understanding of Aβ peptides conformations can be achieved by analyzing the Psi and Phi angles, using the Ramachandran plot (Fig. 6).

According to Fig. 6a, Aβ(1-42) monomer displayed a right-handed α-helix conformation with an extension in parallel β-sheet (left quadrant), while the most of the angles values are in anti-parallel β-sheet in the case of Aβ(1-42)F (Fig. 6b), parallel β-sheet and collagen helix area (upper left quadrant), with a few in left-handed α-helix (upper right quadrant) and right-handed α-helix (lower left quadrant). Following the application of dynamic conditions, no significant structural differences were observed in the case of Aβ(1-42) in both physiological and hyperpyrexic conditions. However, a larger dispersion of the angle values to the upper left quadrant specific to the parallel β-sheet (Fig. 6d and Fig. 6e) was observed. These data are well correlated with those obtained by conformational studies presented in Section 3.2.

In the case of Aβ(1-42)F structure, the same buildup characteristics were noticed in the β-sheet area in both circumstances (Fig. 6f and Fig. 6g). However, the difference was observed in the lower left quadrant (the right-handed α-helix area). Following molecular dynamics condition, at higher temperature and pressure, the angle
Fig. 1. The binding potential of the metal ions involved in the Aβ peptide complexation process, where: (a) – Aβ1-42; (b) – Aβ1-42,F Chain 1; (c) – Aβ1-42,F Chain 2; (d) – Aβ1-42,F Chain 3; (e) – Aβ1-42,F Chain 4; (f) – Aβ1-42,F Chain 5; (g) – Aβ1-42,F Chain 6; (h) – Aβ1-42,F Chain 7; (i) – Aβ1-42,F Chain 8 and (j) – Aβ1-42,F Chain 9.
Fig. 2. The binding potential differences $\omega$ of each metal ion from $\text{Al}^{-1}_{(3-42)}$ with the binding potential of the same metal for each chain from $\text{Al}^{-1}_{(3-42)}F$, where: $P$ – the chain of the $\text{Al}^{-1}_{(3-42)}$ and A, B, C, D, E, F, G, H and I represent the 9 fibrillar chains of $\text{Al}^{-1}_{(3-42)}F$: (a) $\text{Cu}^{+}$, (b) $\text{Cu}^{2+}$, (c) $\text{Fe}^{2+}$, (d) $\text{Fe}^{3+}$, (e) $\text{Mg}^{2+}$, (f) $\text{Mn}^{2+}$, (g) $\text{Ni}^{2+}$, (h) $\text{Co}^{2+}$ and (i) $\text{Zn}^{2+}$. 
Fig. 3. The Aβ(1-42)-Cu⁺ complex conformation resulted following the application of molecular dynamics under the conditions imposed (temperature and pressure), where: (a) Aβ(1-42) peptide structure; (b) The structure of Aβ(1-42)-Cu⁺ complex at 37 °C and 11 mmHg; (c) The structure of Aβ(1-42)-Cu⁺ complex at 41 °C and 20 mmHg; (d) Aβ(1-42)-Cu⁺ binding site at 37 °C and 11 mmHg; (e) Aβ(1-42)-Cu⁺ binding site at 41 °C and 20 mmHg; (f) Coordination pattern of the Cu⁺-amino acids at 37 °C (11 mmHg) and (g) Coordination pattern of the Cu⁺-amino acids at 41 °C (20 mmHg). The proximity contour (gray dotted line) denotes the dotted outline that surrounds the ligand, representing the distance to the active site. Ligand solvent exposure is exposed by the blue mark that is drawn behind the ligand atoms. Solvent exposure of the receptor is evidenced by the turquoise discs drawn behind the residues to indicate the difference in solvent exposure due to the presence of the ligand. The yellow circle with no ring color represents polar amino acids, with red ring symbolize acidic amino acid and with blue ring, basic amino acids. The purple line represents metal contact and the cream-colored dotted line, the solvent contact.
values become more disperse suggesting a random coil structure potentiation of Aβ fibers. This confirms the hypothesis that elevated temperature and higher pressure inhibit the α-helix motif, with direct consequences on the Aβ peptide aggregation.

### 4. Discussion

Studies have shown that accumulation of metal ions in the brain is closely related to the progression of AD (Wang et al., 2020). Therefore, it is crucial to comprehend the processes underlying the interaction between metal ions and Aβ peptides.

As other studies have shown, hyperpyrexia can negatively influence the neurodegeneration development (Czepiel et al., 2020; Singhal et al., 2020).

In this study, a theoretical comparative analysis of the structural changes of Aβ(1-42) peptide in complexation with different metal ions was performed. We observed that the addition of trace metals considerably accelerates the Aβ aggregation, which may
Fig. 5. The effect of temperature and pressure on the Aβ(1-42)-F-Cu⁺ complex conformation, highlighted by the use of the molecular dynamics protocol, where: (a) Aβ(1-42)-F structure and (b) Aβ(1-42)-F-Cu⁺ structure. Coordination pattern and binding site of Aβ(1-42)-F-Cu⁺ at (c) 37 °C (11 mmHg) and (d) 41 °C (20 mmHg) for Chain 1; (e) 37 °C (11 mmHg) and (f) 41 °C (20 mmHg) for Chain 2; (g) 37 °C (11 mmHg) and (h) 41 °C (20 mmHg) for Chain 3; (i) 37 °C (11 mmHg) and (j) 41 °C (20 mmHg) for Chain 4; (k) 37 °C (11 mmHg) and (l) 41 °C (20 mmHg) for Chain 5; (m) 37 °C (11 mmHg) and (n) 41 °C (20 mmHg) for Chain 6; (o) 37 °C (11 mmHg) and (p) 41 °C (20 mmHg) for Chain 7; (q) 37 °C (11 mmHg) and (r) 41 °C (20 mmHg) for Chain 8; (s) 37 °C (11 mmHg) and (t) 41 °C (20 mmHg) for Chain 9. The green circle represents the amino acids with no polar or charged side chain.
contribute to neurotoxicity (Hane and Leonenko, 2014). Hence, the in silico experiments were based on the $A\beta$ conformational differences, under normal physiological conditions compared to hyperpyretic pathophysiological effects.

Our data suggest that there are major differences in the structure of amyloid beta peptides under elevated temperature and pressure. The interaction between metal ions and $A\beta$ peptides is maximized at the beginning of the simulations and stabilizes when the temperature becomes constant (Boopathi and Kolandaivel, 2014). Furthermore, the copper ion plays an important role in conformational changes of $A\beta$ peptides by increasing or decreasing the intramolecular distances within the AD fibrils. Moreover, according to the Madisen investigations, Cu is released as well yielding micromolar concentrations in specific synaptic clefts (Madsen and Gitlin, 2007). In addition, these ions have been shown to form an intramolecular complex with amyloid-beta peptides due to substoichiometric levels used in kinetic investigations (Sarell et al., 2010). All these factors lead to serious complications in both hyperpyrexia and Alzheimer’s patients. It has been observed that both elevated temperature and high intracranial pressure accentuate the aggregation process, by transforming the $\alpha$-helix into the $\beta$-sheet conformation and random coil motif. These molecular simulation data suggest that, for amyloid beta monomer, the 1–16 region has a higher binding potential. In the case of amyloid beta fibrils ($A\beta_{1-42}$), the metal ions binding potential increases even in the 17–42C-terminal region. These conformations ($\beta$-sheet and random coil structure) increase the aggregation processes by promoting the formation of new intermolecular hydrogen bonds.
between monomeric forms of Aβ(1–42). Therefore, a higher temperature and ICP can intensify the processes of peptide aggregation at the cortical level, with direct consequences on the morphology of the AD brain. In addition, these results could be explained by the metal-binding kinetics parameters. According to the Pedersen and Noy, the association of Cu ions seems to be very fast and likely close to diffusion controlled (Pedersen et al., 2012; Noy et al., 2008). Copper ion can rapidly exchange with others metal ions and hence, due to the system dynamics and heat friction, the temperature may rise by association and dissociation reactions (Faller et al., 2014). Moreover, according to recent publications, copper ions alter Aβ kinetics, guiding its aggregation from a more stable fibrillar structure, to a pathway that leads to neurotoxic aggregates (Hane and Leonenko, 2014).

In the case of Aβ(1–42), a significant modification occurred in structure conformation due to the decrease of α-helix population to the advantage of β-sheet structure formation, while for β-amyloid fibrils, lack of α-helix structure. These noteworthy changes can be studied in terms of binding sites and interaction between Cu⁺ ions and the corresponding Aβ residues. Moreover, according to these results, tyrosine plays an important role in coordination stabilizations. This feature was also observed by, using DFT calculations which provided a mechanism that included Tyr¹⁰ as a key component in mutagenesis tests (Barnham et al., 2004). Furthermore, the same implications were also noticed which demonstrated that the presence of Tyr in the primary structure of amyloid-beta regulates the formation of toxic β-sheets (Coskuner and Uversky, 2017). In addition, a study from 2019 showed that the structural models obtained with an extended statistical method displays Tys-Tys and Cu-carboxylate interactions are enhanced in dimers (La Penna et al., 2019). Besides, tyrosine oxidation could interfere in metal complexation with copper due to the quinoline generation (Mocanu et al., 2020). Therefore, under these circumstances, the copper ion may form chemical bonds between different beta-amyloid oligomers that could enhance fibril formation.

Fig. 6. The Ramachandran plot of (a) Aβ(1–42) (PDB), (b) Aβ(1–42)F (PDB), (c) Aβ(1–42) at 37 °C and 11 mmHg, (d) Aβ(1–42)F at 37 °C and 11 mmHg, (e) Aβ(1–42) at 41 °C and 20 mmHg and (f) Aβ(1–42)F at 41 °C and 20 mmHg.
Following the application of dynamic conditions, no significant differences were observed regarding \( \text{A}^\beta_{(1-42)} \) structure using physiological AD and hyperpyretic conditions. Regarding \( \text{A}^\beta_{(1-42)} \) structure, the same build-up predisposition is noticed in the \( \beta \)-sheet area in both simulations. These findings support the hypothesis that a higher temperature and elevated pressure impair the \( \alpha \)-helix structure, with direct consequences in peptide aggregation. Furthermore, a recent study proved that the high dynamics of the metal–peptide interaction is incompatible with high control of the metal ions reactivity (Faller et al., 2014). Hence, according to this argument and to our results, the hyperpyretic conditions and the amyloid–beta cascade could enhance the AD pathological symptoms by promoting an extrinsic energy of Cu- \( \text{A}^\beta \) interactions.

Moreover, our results confirmed the molecular pathway in which the copper was involved in amyloid-beta interactions. According to Marino, the DFT computational study showed that copper ion possesses a predisposition to penta-coordination (Marino et al., 2010). In addition, evidence for the involvement of histidine residues of beta-amyloid peptides as N-ligands has been supported by investigations on the complexes formed.

In this study, we demonstrated that the peptide aggregation process may increase due to the promotion of \( \beta \)-sheet and random coil secondary conformations. However, however, for full confirmation of the hypothesis advanced here, further studies should be carried out to determine the structure, interaction and function of the peptide under the action of metal ions.

5. Conclusions

Our findings support the hypothesis that a higher temperature and elevated pressure impair the \( \alpha \)-helix structure, with direct consequences on peptide aggregation. Furthermore, the molecular dynamics data show that these conditions may increase the peptide aggregation process due to the formation of \( \beta \)-sheet and random coil secondary conformations. Moreover, the presence of metal ions in the cortical areas of AD brain caused by abnormal metabolism can have a negative effect over the neurodegeneration rate.

Considering both diseased conditions (AD and hyperpyrexia) further experimental approaches, such as SDS-PAGE with a time and temperature dependent incubation of amyloid-beta 1–42 peptide, AFM, SEM, in vivo investigations of AD model of cells culture, will be applied to extend our current findings to other studies with relevance for developing new efficient treatment strategies.

Author’s contributions

Conceptualization, C.S.M.; methodology, C.S.M. and L.I.; software, C.S.M.; validation, C.S.M. and G.D.; formal analysis, C.S.M. and G.D.; investigation, C.S.M.; resources C.S.M.; data curation, C.S.M. and G.D.; writing—review and editing, C.S.M., L.I., B.A.P., V.R.G. and G.D.; visualization, C.S.M., L.I. and G.D.; supervision, C.S.M., V.R.G. and G.D.; project administration, C.S.M.; resources, C.S.M.; data curation, C.S.M.; writing—original draft preparation, C.S.M.; writing—review & editing, Visualization, Project administration.

Declarations of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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