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Research paper

Reaction between the Pt(II)-complexes and the amino acids of the β-amyloid peptide

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ABSTRACT

Reaction between [Pt(ophen)Cl_2] and HIS was monitored and the solvolysis (k_1) and Cl/HIS ligand exchange (k_2) rate constants obtained. The k_1 and k_2 were $(6.2 \pm 0.4) \times 10^{-5}\ s^{-1}$ and $52.8 \times 10^{-2}\ M^{-1}\ s^{-1}$, respectively. The corresponding calculated values were $47.5 \times 10^{-5}\ s^{-1}$ and $52.2 \times 10^{-2}\ M^{-1}\ s^{-1}$, in agreement with the experiment. Calculations were used to establish the reactivity order for a set of amino acids: MET ~ LYS ~ HIS(ε) > GLU ~ ASP >> ASN ~ GLN. In spite of the similar reactivity among MET, LYS and HIS, the thermodynamics suggests the reactions with LYS and HIS more favorable than with MET. Therefore, N-containing amino acids should be potential targets of Pt(II)-complexes in β-amyloid.

1. Introduction

The life expectancy increase in the world population raises the demand for studies about diseases directly affecting the neural capacity of people, depending on genetics and lifestyle [1,2]. Thus, the Alzheimer Disease (AD), among other prominent diseases, nowadays calls the interest of the scientific community. This syndrome is featured by different high–complexity manifestation stages [2]. The Amyloid Protein Precursor (APP) segmentation by the β and ϒ-secretase enzymes is the starting point [2]. This proteolysis is more frequent in specific brain regions responsible for the recent memory in AD patients such as the hippocampus and the prefrontal cortex [2]. There is an excess of β-amyloid peptides (Aβ), which are composed of 40–43 amino acid (AA) residues, after the biocycle starts. Some of these residues are potential sites for nucleophilic attack [3–6]. Fig. 1 shows an experimental model of the Aβ(1–42) reported by Tomaselli and co-workers [7], the structure represents a mean arrangement observed in aqueous solution.

The Aβ is predominantly constituted of 40 and 42 AAs, with considerable amounts of Zn(II), Fe(III) and Cu(II) in the advanced AD stage, which are coordinated to 1–16 residues in the hydrophilic motif. Moreover, the bioaccumulation of Aβ in the synaptic clefts triggers different neurotoxic events. According to some *in vitro* studies, the formation of Aβ:Cu and Aβ:Fe adducts in the cerebral environment might lead to the excess of peroxyl and hydroxyl free radicals [2–5]. These free radicals act on the oxidative stress in the cell membrane and induce the formation of neurotoxic species such as the 4-hydroxy-nonenal aldehyde (4HNE), which is responsible for deactivating many cellular proteins [2,3]. On the other hand, the Aβ:Zn adduct leads to the formation of insoluble peptide aggregates, which precipitate between the synaptic clefts and lead to the excessive bioaccumulation of Aβ. This series of events is called "amyloid cascade" [2,5].

There is a series of residues such as HIS, LYS, ASP, GLU, ASN, GLN and MET likely to be targeted by metal-based compounds in the Aβ peptide. The inhibition of Aβ sites by inert centers (such as Pt) has been considered a possible therapeutic route in the search for new compounds with potential anti-AD activity [6,8–12]. Barnham and co-workers [6,13] conducted an intense research involving Pt(II)-complexes and used aromatic ligands such as o-phenanthroline (ophen) and bathophenanthroline (batophen), which provide promising dispersive effect [6,13]. Their results suggest the Pt binding to different residues, mainly HIS. Ma and Collin [9–11] showed that HIS6:HIS14 and GLU11:HIS13 are the main Aβ interaction sites for platinum complexes. Turner and co-workers [14] proposed the coordination at HIS6-HIS13 and HIS6-HIS14 using DFT calculations and molecular dynamics simulation. The HIS was taken as the main coordination site for Pt complexes based

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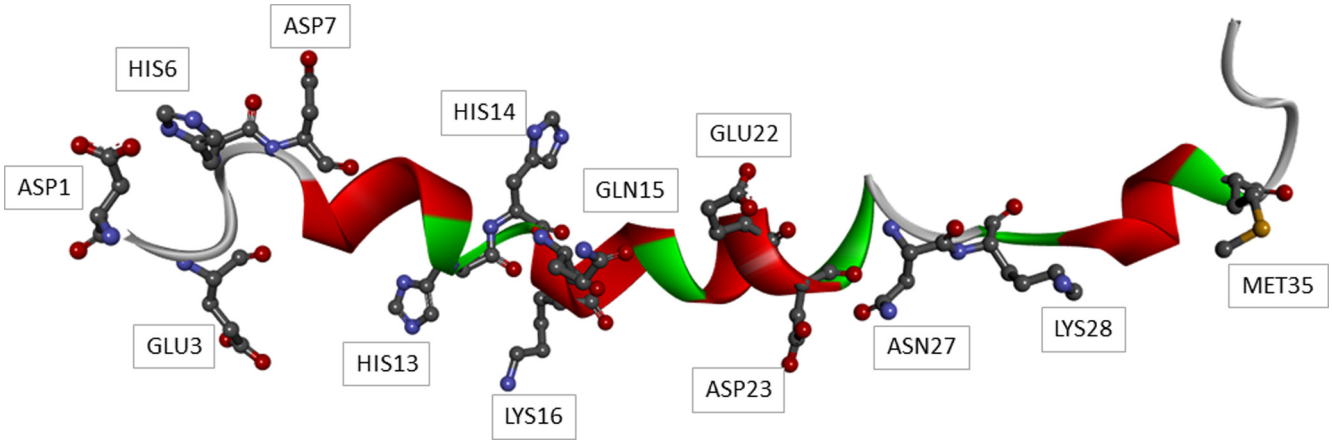

Fig. 1. Experimental structure of Aβ(1–42) obtained from PDB code 1Z0Q [7]. The potential metal-binding sites are represented as ball-sticks.

on these previous studies; however, the need of representing the process on quantitative basis remains.

The reactions between the [Pt(ophen)Cl_2] (pt01) and [Pt(-batophen)Cl_2] (pt02) complexes and the AA found in the Aβ structure were investigated in the present study, providing the structures of the reactive species, as well as the thermodynamic and kinetic parameters. An experimental kinetic analysis of the ligand exchange process involving the pt01 complex and the HIS was conducted in order to validate the used computational protocol.

2. Experimental

2.1. Materials and methods

All reagents and solvents were used without further purification. The UV–Vis spectra were recorded using a Shimadzu PC 1601 spectrometer, in the region 200–400 nm, in quartz cuvettes of 1 cm. The Raman spectra were obtained in a Bruker RFS100 FT-Raman instrument equipped with a germanium detector refrigerated through liquid nitrogen, excitation at 1064 nm from a Nd:YAG laser in the range 4000 to 50 cm^{-1} and spectral resolution 4 cm^{-1}, 256 scans, on average, and power 40 mW. The elemental analyses (C, H and N) were performed in a Perkin-Elmer 2400 elemental analyzer.

2.2. Synthesis of [Pt(ophen)Cl_2] complex (pt01 – Scheme 1)

The complex pt01 was obtained from [Pt(DMSO)$_2Cl_2$] (0.1 mmol) and ophen (0.1 mmol) in 20 mL of methanol, according to Price and co-workers [15]. The reaction mixture was stirred at room temperature for 24 h. The product was filtered and washed in methanol and it generated a yellow solid in 76% yield.

pt01: yellow solid. Raman (ν_{max} in cm^{-1}): 215 δ(ClPtCl); 322 ν_s(PtCl); 337 ν_{as}(PtCl); 443 ν(PtN). Anal. Calc. for [$C_{12}H_8Cl_2N_2Pt$]: C, 32.30%; H, 1.81%; N, 6.28%. Found: C, 31.6%; H, 1.76%; N, 6.04%.

2.3. Kinetic measurements

The reaction between [Pt(ophen)Cl_2] (pt01) and HIS in aqueous solution follows complex multistep reactions where H_2O and HIS act as nucleophiles. Consecutive processes, as represented in Eqs. (1) and (2), can compete with the parallel reaction shown in Eq. (3).

$$[Pt(ophen)Cl_2] + H_2O \xrightarrow{k_1} [Pt(ophen)(H_2O)Cl]^+ + Cl^- \quad (1)$$

$$[Pt(ophen)(H_2O)Cl]^+ + HIS \xrightarrow{k_1'} [Pt(ophen)(HIS)Cl]^+ + H_2O \quad (2)$$

$$[Pt(ophen)Cl_2] + HIS \xrightarrow{k_2} [Pt(ophen)(HIS)Cl]^+ + Cl^- \quad (3)$$

The kinetic scheme represented by Eqs. (1)–(3) is example of complicated rate equations, for which there is no general explicit mathematical treatment. Therefore, in order to simplify the kinetic analysis, processes (1) and (3) was investigated separately avoiding the consecutive step (2). Firstly, only the solvolysis (1) was considered when 2.40 mL of the solution 0.5 mmol/L of pt01 was added to 57.6 mL of ethanol and diluted to the total volume of 80 mL using deionized water (note that [HIS] = 0 and the reaction (2) is avoided). The flask containing the reaction mixture was stirred for 30 min. under reflux temperature 345 K. This temperature was set up instead of normal body temperature (310 K) in order to speed up the process allowing the analysis at affordable time. The rate equation is given in Eq. (4) where the concentration of pt01 complex was monitored by measuring the absorbance (A) at constant wavelength 252 nm.

$$v = k_{obs,1}[Pt(ophen)Cl_2] \therefore k_{obs,1} = k_1 \quad (4)$$

The HIS was added in the ratio [HIS]:[pt01] = 8 in the second experiment, which was supposed to set up the process at pseudo-first-order condition. Moreover, NaCl (5.0 mmol/L) was also added to the reaction mixture to avoid the solvolysis [16], therefore, the consecutive processes (1) and (2) were avoided and the rate law written as in Eq. (5).

$$v = k_{obs,2}[Pt(ophen)Cl_2] \therefore k_{obs,2} = k_2[HIS] \quad (5)$$

The reactant concentrations were [HIS] = 0.14 mmol/L and [pt01] = 0.018 mmol/L. The flask containing the reaction mixture was stirred for 1 h at constant temperature 345 K. As for the solvolysis reaction, the concentration of pt01 complex was monitored through the change in the absorbance at 252 nm. The experiments were conducted in duplicate. The UV–Vis spectra and other details were provided as Supplementary Material.

2.4. DFT calculations

The processes represented in Scheme 2 were theoretically investigated for the pt01 and pt02 complexes. The amino acids (AA) were kept in their zwitterion form, and the aspartic (ASP – pKa = 3.86), glutamic acids (GLU – pKa = 4.07) and histidine (HIS – pKa = 6.10) were deprotonated at side chain. For LYS that is a strongly basic residue (pKa = 10.53), which side chain would be