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An *In Silico* DFT-Approach Towards Carbon Nanotubes Applications as Mito Targeted-Nanoparticles on Neurodegenerative Diseases

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Abstract

Experimental studies have shown that hydrophobic nanoparticles like carbon nanotubes (CNT) could be potentially used for the treatment of several neurological disorders like Alzheimer's disease, brain ischemia, and Parkinson. In this regards, it is of fundamental importance to understand the mitochondrial mechanisms involved in these diseases in order to develop potential treatment-based mitochondrial nanomedicine. In the present study, we evaluate critical interactions based on mitochondrial mechanisms-based *in silico* approaches. Combined molecular docking with *ab initio* computational simulation methodologies, to evaluate the electronic and structural properties of interactions between single wall carbon nanotubes (SWCNT) zigzag (pristine, SWNCT-COOH, SWCNT-OH, SWCNT-monovacancy) with critical mitochondria phenylalanine residue F0-ATPase (Phe-F0-ATPase). Following this idea, the main objective of this work is to theoretically explain if SWCNT can be used to avoid the rapid ATP-hydrolysis from mitochondrial Phe-F0-ATPase towards to alternative of treatment of neurodegenerative disorders. Theoretical evidence, point out that the most significant interaction was SWCNT-COOH interacting with mitochondrial Phe-F0-ATPase, with the binding energy of - 1.79eV and proved to be rationally designed SWCNT-COOH nanoparticle for the treatment of these disorders.

Keywords: *Ab initio*; zigzag-SWCNT; Phenylalanine residues; Phe-F0-ATPase mitochondrial

Introduction

Degenerative disorders are characterized by involving multiple factors like DNA mitochondrial mutation, mitochondrial permeability transition pore (MPTP) characterized by the significant increase of reactive oxygen species (ROS) production and ATP-bioenergetic dysfunction linked to cellular apoptosis. In this regards, mitochondria nanomedicine aroused the interest from the scientific community toward to the rational design of novel mitochondrial-targeted nanoparticles for Precision Medicine of several disease-based mitochondrial dysfunctions such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), Epilepsy and others [1,2].

The mitochondrial ATP synthase is composed of F0 and F1 subunits, which use the rotational energy-derived from H+-protons to form ATP from ADP and phosphate (Pi) that must function synchronously. Nevertheless, under physiopathological conditions like mitochondrial dysfunctions (Increase in intracellular calcium, ischemic conditions), occur the F0F1-ATP-reverse rotation with significant losses of ATP and pathological ATPase-hydrolytic activity [3]. Following this idea, the pharmacological inhibition of ATP-hydrolysis-toxicity induced could be a novel strategy to prevent or minimize acute or chronic event on neurological disorders.

By contrast, single-walled carbon nanotube (SWCNT) has been gaining prominence in therapies of some types of neurological disorders based on its interesting properties such as targeting specific-organelles (like mitochondria). In this regards, Zhou et al (2011) using laser + SWCNTs that shows a treatment for the brain cancer based on the precision of treatment and significant reduction of brain side effects [4]. Other study developed by Yang et al., (2010), used SWCNT as nanocarrier to controlled drug releases into the brain for the treatment of Alzheimer's disease [5].

In addition, oxidized single-walled carbon nanotubes (SWCNT-OH, SWCNT-COOH) are more promising and because they exhibit safe biological behavior, achieve immunological neutrality, and even biodegradation, show great promise for medicinal [6].

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In this circumstances, the present study aims to analyze the SWCNT-interactions with mitochondrial F0-subunit from F0F1-ATP synthase to explore the potential docking mechanisms to inhibit the pathological mitochondrial ATP-hydrolysis similar to oligomycin A (specific F0-ATPase hydrolysis inhibitor). In this regard, we propose an *in silico* methodology based on *ab initio* computational simulation methodology, to evaluate the structural and electronic properties that explain the F0-ATPase-SWCNT interactions with different SWCNT-species like SWCNT-pristine, SWCNT-COOH, SWCNT-OH, SWCNT-vacancy interacting with critical mitochondrial phenylalanine (Phe)-F0ATPase residues and theoretically explore the potential use of single-walled carbon nanotubes to prevent / inhibit the pathological hydrolysis of ATP which has been identified as a common biochemical process of several neurological disorders such as Alzheimer's, Parkinson, epilepsy based mitochondrial dysfunctions.

Materials and Methods

In the first moment we use molecular docking simulation by using Autodock Tools 4.1 in order to identify the best docking position of the zig-zag SWCNT-ligand (pristine-SWCNT, SWCNT-COOH, SWCNT-OH and SWCNT-vacancy) when interaction with critical Phe-F0-ATPase residues (involved in the pathological ATP-hydrolysis) from Protein Data Bank (PDB ID: 5BPS) and using as docking control or reference the oligomycin A (a classical Phe-F0-ATPase inhibitor) to evaluate the biophysical F0-ATPase regions where the SWCNT-interactions take place. It is important to highlight that the zigzag-SWCNT topologies have shown to have significant mitotoxic potential (like channel nanotoxicity).

In this regard, we use the grid box size dimensions of X = 22Å, Y = 22Å, Z = 22Å and the center of the F0-ATPase subunit grid Box X=19.917 Å, Y= 19.654 Å, Z=29.844 Å to identify/evaluate the SWCNT-Phe-F0-ATPase interaction, considering the oligomicin A environment affinity at the Phe-F0-ATPase subunit active site.

Then *ab initio* computational simulation methodology was used after docking analysis in order to better understand the mechanism of interaction of zig-zag single-wall carbon nanotubes, SWCNT-pristine, SWCNT-COOH, SWCNT-OH, SWCNT-vacancy) interacting with the main residues of phenylalanine (Phe-F0-ATPase) and comparing this results with the reference docking control using oligomycin A a specific inhibitor of the dynamic of Phe-F0-ATPase residues. Following this idea, we analyze the electronic, structural properties of the aforementioned-interactions.

The *ab initio* computational simulation methodology, makes use of the Density Functional Theory (DFT) [7], but to find the physical and chemical properties in the DFT, it is necessary to make use of some approximations to enable the simulation of many bodies, such as the Born-Oppenheimer approximation, pseudopotential, supercell and base function [8].

The computational code used was the SIESTA Spanish Initiative for Electronic Simulations with Thousand of Atoms, in which we performed calculations to solve the Kohn-Sham equations [9].

The parameters of calculations that used double-funções base functions plus a polarized function (DZP), the term of exchange and correlation Local Density Approximation (LDA) parameterized by Perdew and Zunger (1981) [10], for the representation of electronic space we used a 200 Ry radius for the real space interaction, the atomic structures were relaxed until the residual forces were less than 0.05 eV/Å for all the atoms of the system. The chosen pseudopotential was the one proposed by Troullier and Martins (1991) [11].

To calculate the binding energy of the pristine and oxidized zigzag carbon nanotube family interacting with Phe-F0-ATPase, and the phenylalanine (Phe-F0-ATPase) and oligomycin A interaction, equation (01) was used:

$$E = - \{[A + B] + E [A] + E [B]\} \quad (01)$$

where [A + B] is the total energy of the system [A] (like: zigzag-SWCNT species or oligomycin A) interacting with [B] (mitochondrial Phe-F0-ATPase residues); and E [A], E [B] are respectively isolated total energy from zigzag-SWCNT species (or oligomycin A) and Phe-F0-ATPase residues.

Results and Discussion

Molecular docking evidence shows that all zigzag-SWCNT interact in the same biophysical environment (mitochondrial ATP-hydrolysis binding site) that the classical F0-ATPase inhibitor (Oligomycin A). Then we hypothesize that theoretically the zig-zag SWCNT species of ligands (SWCNT-pristine, SWCNT-COOH, SWCNT-OH, and SWCNT-vacancy) could be perturbed similar critical residues like mitochondrial Phe-F0-ATPase. Following this idea and in order to refine us *in silico* results we propose the simulation of critical interaction based Density Functional Theory.

The results obtained by means of the *ab initio*-DFT computational simulation, were made three configurations for each system under study, varying the positions of Phe-F0-ATPase residue in relation to the individual SWCNT tested, and the initial distance between the structures is approximately 2.00Å.

The more stable configurations, that is, with a higher value of modulus binding energy, will be presented in this work, in which we analyze the electronic and structural properties of the biophysical interactions.

The most stable configuration from the formed SWCNT-pristine with mitochondrial phenylalanine-F0-ATPase residue showed binding energy of -0.45eV and the intermolecular distance was 1.86Å between the hydrogen atoms from C-atoms of SWCNT-pristine and H-phenylalanine atom, the charge transfer was 0.08 electrons and occurred from the mitochondrial Phe-F0-ATPase residue to the SWCNT-pristine with a difference in the energy between the highest occupied orbital HOMO (Highest Occupied Molecular Orbital) and the lower free-energy molecular orbital LUMO of 0.43eV. The electron density of charges for HOMO and LUMO are concentrated only on the SWCNT-pristine, showing to be a weak interaction with Phe-ATPase residues.

For the SWCNT-OH/Phe-F0-ATPase DFT interaction, the most stable configuration had a bond energy of -0.61eV and the shortest distance between atoms was 1.86Å between the oxygen atoms of the SWCNT and H-bonding of mitochondrial Phe-F0-ATPase residue. The transfer of charges was 0.06 electrons from SWCNT-OH to mitochondrial Phe-F0-ATPase residue, the difference between the HOMO and LUMO orbital calculated is 0.75eV, and the electronic density of charges for HOMO and LUMO were also concentrated only in the hydroxyl groups from SWCNT-OH, and were similarly shown to be a weak interaction mainly based on a physical adsorption regime of interactions.

In the case of SWCNT-COOH/Phe-F0-ATPase DFT interactions, the most stable configuration presented a bonding energy of -1.79eV, modularly higher when compared with the other interacting SWCNT, and the distance between the atoms was 1.52Å between the (H) -atoms from the carboxyl groups of SWCNT-COOH and N-atoms from mitochondrial Phe-F0-ATPase residues. In this value, the charge transfer was 0.23 electrons from the Phe residue to the SWCNT-COOH, the difference between the HOMO or LUMO orbital is 0.11eV. A charge concentration for the HOMO or LUMO orbital was in the C-atoms from SWCNT-COOH and the (OH) from mitochondrial phenylalanine-F0-ATPase residue, describing a chemical absorption regime for this interacting system with a stronger interaction.

Just the same, for the SWCNT-vacancy/Phe-F0-ATPase DFT complex of interactions the most stable configuration has a bonding energy of -0.43eV and the intramolecular distance of 2.62Å between the carbon atoms from SWCNT-vacancy and hydrogen-atoms from Phe, the charge transfer was 0.11 electrons from SWCNT-vacancy to Phe residue, with a difference between the HOMO or LUMO orbital of 0.58eV and the electronic charge density for the HOMO orbital and the LUMO orbital are located in the (C) and (H)-atoms from the SWCNT-vacancy, proving to be a weak interaction based on physical adsorption regime.

In order to simulate the control DFT experiment we use the Oligomycin A/Phe-F0-ATPase DFT complex because oligomycin A acts as a natural inhibitor of reverse rotation of F0-subunit inhibiting the pathological ATP-hydrolysis (ATP--->ADP+Pi) with significant reduction of mitochondrial ATP-levels as a common element to several neurological disorders, as mentioned in the introduction of this work. For this instance, the most stable configuration showed a binding energy of 6.44eV and the shortest distance between atoms was 2.17Å from the oxygen atom from the phenylalanine and the hydrogen-atom from oligomycin A, the charge transfer was 0.16 electrons from the phenylalanine toward oligomycin A, a difference between the HOMO or LUMO orbital is 0.26eV, and that charge is concentrated on the atoms of the oligomycin A molecule and in the vicinity of the phenylalanine molecule. This result characterizes a chemical adsorption, stronger than the interaction between oxidized-SWCNT-Phe-F0-ATPase residues.

Conclusion

In the present work, we address the question about how different SWCNT could potentially be used to prevent the pathological mitochondrial ATP-hydrolysis in the context of neurological disorders by using DFT-*ab initio* computational simulation to study the structural and/or electronic properties of the different SWCNT with critical Phe-residues from mitochondrial ATPase previously-identified with molecular docking simulation. We theoretically concluded that the most promising carbon nanoparticle toward ATP-hydrolysis inhibition is the SWCNT-COOH that shown a binding energy of -1.79eV with a strong interaction-based chemical adsorption regime. Other stable configurations following the order SWCNT-OH (-0.61eV)> SWCNT-pristine (-0.45eV)> SWCNT-vacancy (-0.43) with mitochondrial phenylalanine-F0-ATPase based on the binding energy.Conclusively, we theoretically suggest that interactions based in chemical adsorption regime with oxidized-SWCNT species like SWCNT-OH and SWCNT-COOH with critical mitochondrial Phe-F0-ATPase residues could have a significant impact in the pathological ATP-inhibition hydrolysis toward potential biomedical application in the treatment of neurodegenerative disorders with potential pre-clinical relevance based on rational design and Precision Medicine of new carbon nanomaterials.

References

1. Golpich M, Amini E, Mohamed Z, Azman Ali R, Mohamed Ibrahim N & Ahmadiani A. Mitochondrial dysfunction and biogenesis in neurodegenerative diseases: pathogenesis and treatment. CNS neuroscience & therapeutics. 2017; 23: 5-22.
2. Hroudová J, Singh N & Fišar Z. Mitochondrial dysfunctions in neurodegenerative diseases: relevance to Alzheimer's disease. BioMed research international. 2014; 2014.
3. Spetzler D, Ishmukhametov R, Hornung T, Martin J, York J, Jin-Day L, et al. Energy transduction by the two molecular motors of the F1Fo ATP synthase. In Photosynthesis (pp. 561-590). Springer Netherlands. 2012.
4. Zhou F, Wu S, Wu B, Chen WR & Xing D. Mitochondria-targeting single-walled carbon nanotubes for cancer photothermal therapy. Small. 2011; 7: 2727-2735.
5. Yang Z, Zhang Y, Yang Y, Sun L, Han D, Li H, et al. Pharmacological and toxicological target organelles and safe use of single-walled carbon nanotubes as drug carriers in treating Alzheimer disease. Nanomedicine: Nanotechnology, Biology and medicine. 2010; 6: 427-441.
6. Marchesan S, Kostarelos K, Bianco A & Prato M. The winding road for carbon nanotubes in nanomedicine. Materials today. 2015; 18: 12-19.
7. Kohn W & Sham LJ. Self-consistent equations including exchange and correlation effects. Physical review. 1965; 140: A1133.
8. Bevilaqua RC, Zanella I & Fagan SB. Chlorophyll a and pheophytin a as gas sensors of CO_2 and O_2 molecules. Chemical Physics Letters. 2010; 496: 310-315.
9. Soler JM, Artacho E, Gale JD, García A, Junquera J, Ordejón P, et al. The SIESTA method for ab initio order-N materials simulation. Journal of Physics: Condensed Matter. 2002; 14: 2745.
10. Perdew JP. Density-functional approximation for the correlation energy of the inhomogeneous electron gas. Physical Review B. 1986; 33: 8822.
11. Troullier N & Martins JL. Efficient pseudopotentials for plane-wave calculations. Physical review B. 1981; 43: 1993.