INTERACTION BETWEEN NUCLEOSIDE DIPHOSPHATE KINASE AND GRAPHENE OXIDE AND ITS IMPACT ON CARDIOVASCULAR DISEASES

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Abstract

Here we report possibly for the first time the computational understanding of the interactions between the nanomaterial Graphene Oxide (GO) and the enzyme Nuclear Diphosphate Kinase (NDPK) and its implications. Nanoscale Molecular Dynamics (NAMD) and Visual Molecular Dynamics (VMD) were used to run simulations and analyze the interactions between NDPK and GO. The simulations have run for 100 ns, and it is observed that GO is able to block the active site of the enzyme. Graphene oxide is being used because of its excellent biocompatibility, high water dispersibility, and large surface area [3]. NDPK has numerous roles in the body, such as activating G-proteins and transferring a phosphate from ATP to GDP (resulting in ADP and GTP). It also plays a role in cell proliferation, development, signal transduction, endocytosis, etc[2]. Normally, increased activity of NDPK yields the synthesis of the second messenger cyclic adenosine monophosphate (cAMP) . However, during heart failure, NDPK suppresses cAMP formation due to altered signal transduction pathways via G-proteins.[1] In a healthy heart, nitric oxide (NO) is produced by the body in the endothelium that lines the walls of blood vessels so that the veins and arteries can dilate and blood can flow through the body. However, during heart failure, the endothelium lining is damaged, which inhibits the production of NO. cAMP signal transduction pathways have the potential to produce NO after the endothelium lining is in the process of being damaged[4] . Therefore, when NDPK suppresses cAMP during heart failure, it in turn inhibits the production of nitric oxide— which is crucial for a healthy heart. Using NAMD simulations and analysis using VMD, it is observed that graphene oxide is attracted to the active site of NDPK. Strong interactive forces (van der Waals forces) exist between the primary residue of the active site of NDPK (histidine 118) and graphene oxide. Also, throughout the simulation, the structure of the enzyme is preserved. From the 100 ns worth of simulation, it is observed that the graphene oxide blocks the primary residue of the active site of NDPK and can therefore cease the enzyme's function, lower the rate of reaction, and potentially affect heart failure.

1. Methods

Molecular Dynamics

- Interactive forces between graphene oxide and NDPK were setup using VMD and simulations were carried out using NAMD.
- The pdb file for NDPK was obtained from PDB.org.
- An inbuilt graphene oxide builder was used to create six graphene oxide flakes with dimensions of 15.45 Å X 11.68 Å.
- The six graphene oxide flakes surrounded the enzyme on all sides
- All simulations were carried out for a time period of 100 ns.
- All simulations used CHARMM force field and TIP3 water model with a neutralizing salt concentration.
- Periodic boundary conditions were assumed using a constant temperature of 300K and a pressure of 1atm.
- A 10,000 step energy minimization was performed first to stabilize the system.
- RMSD
- Simulations ran for 100 ns.

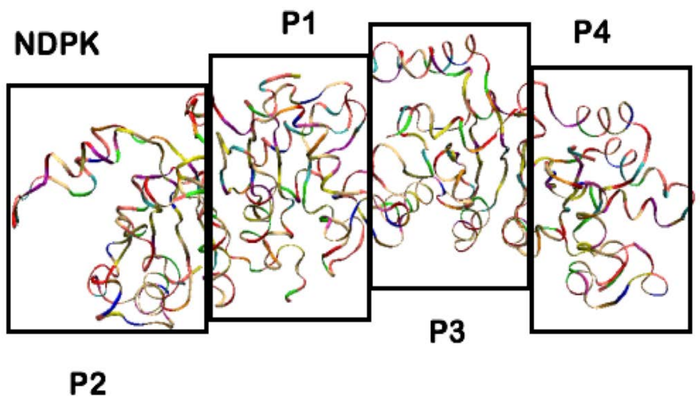

Figure 1: *Segments of the enzyme are displayed in the above picture.*

2. Results

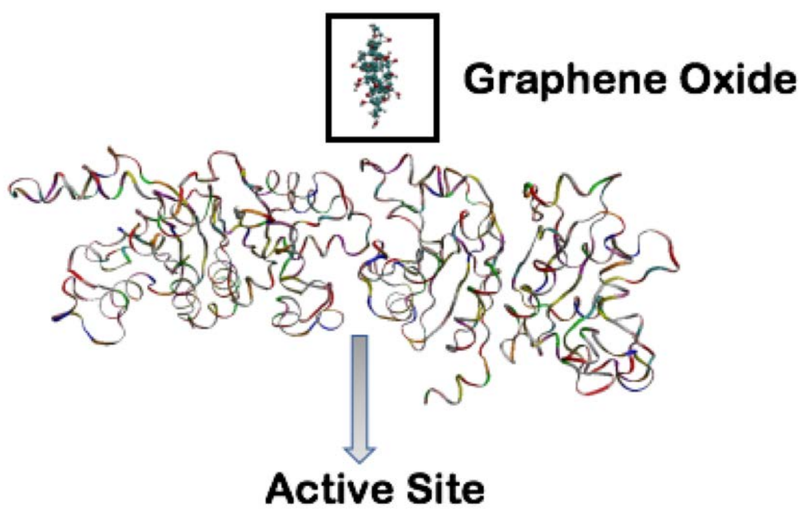

Figure 2: *Initial position of the graphene oxide with respect to the active site*

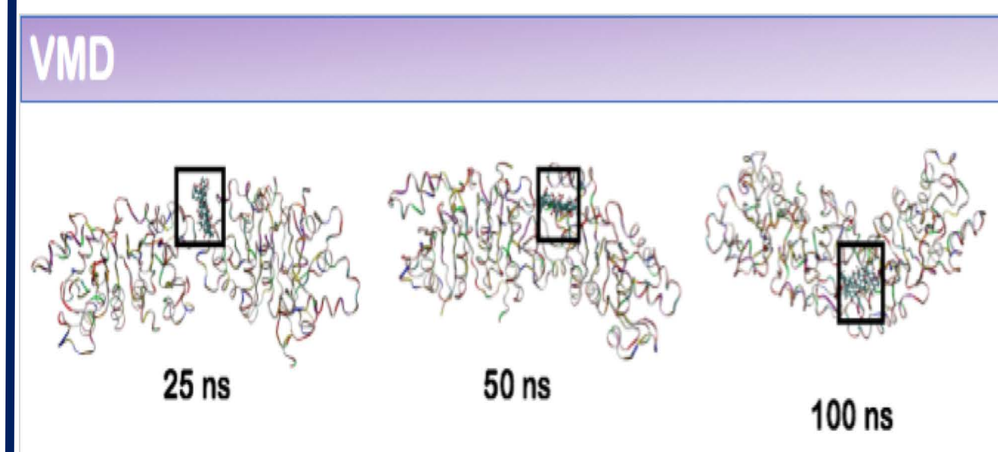

Figure 3*: The progression of the graphene oxide towards the active site of NDPK. All graphene oxide flakes embedded itself in the protein, and one flake was able to block the active site*

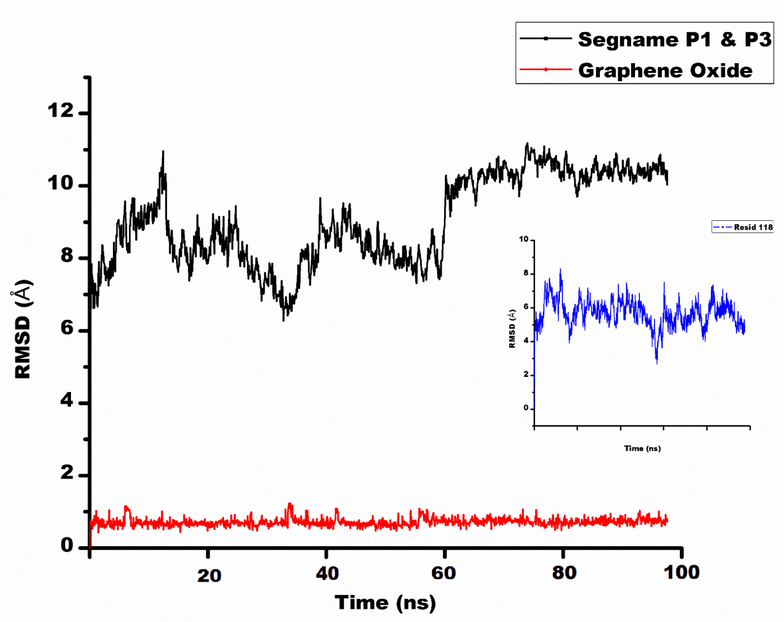

Figure 4*: The larger graph displays the RMSD of segments P1 and P3 (in black), and Graphene Oxide (in red). The smaller graph is the RMSD of the histidine residue.*

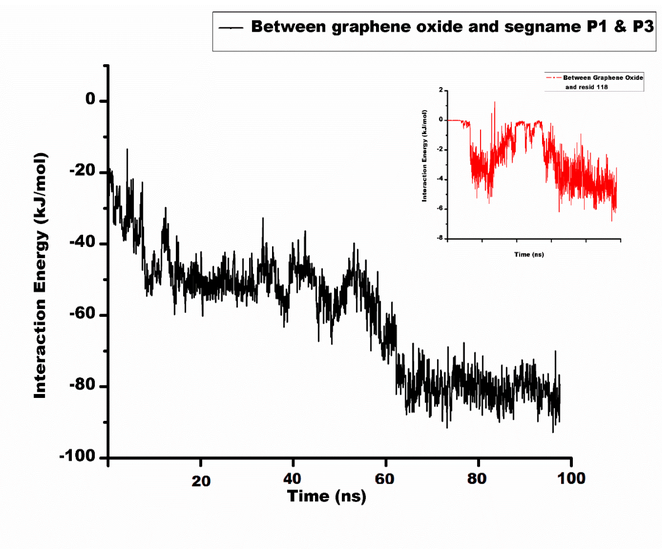

Figure 5*: The larger graph displays the interaction energy between graphene oxide and segments P1 and P3. The smaller graph displays the interaction energy between graphene oxide and the histidine residue*

3. Conclusion

We can see that one of the graphene oxide flakes is able to block the primary residue (histidine 118) of the active site of NDPK. All graphene oxide flakes had an affinity towards the NDPK and embedded themselves in the enzyme. This renders the enzyme inactive. Therefore, cAMP production is not inhibited, and likewise the production of nitric oxide is not suppressed.

4. Acknowledgements

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5. References

[1] Abu-Taha et al., 2016

[2] Berg, JM; Tymoczko, JL; Stryer, L (2002). *Biochemistry - 5th Edition*. WH Freeman and Company. p. 476 ISBN 0-7167-4684-0.

[3] Li, Shanghao. et.al., 2012

[4] Zhang, Xiao-Ping et al., 2002