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The use of ensemble docking to evaluate the inhibition of the dDat enzyme by the sugar compared with cocaine

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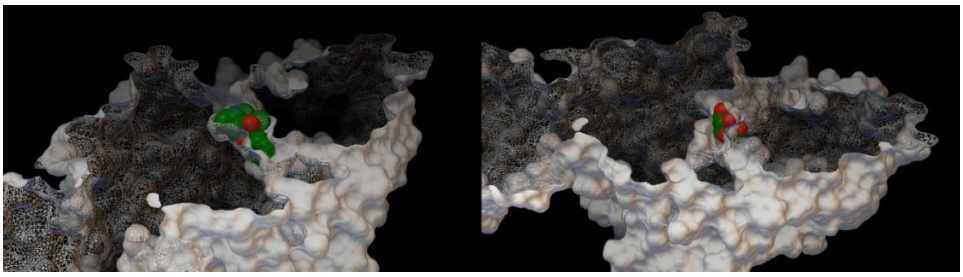
Introduction: The Dopamine is a very important neurotransmitter responsible for the movement control, motivation, and cognition of the human been in order to stimulate the central nervous system by engaging in the sensations of pleasure and motivation. Thus, dopamine is involved in the dependence processes, from the moment its production is inhibited. Consequently, the use of drugs such as cocaine is responsible for blocking the selective monoamine transporters (dopamine, serotonin, etc.) as well as being an inhibitor of monoamines oxidases. With this, cocaine avoid, in a competitive inhibition, the dopamine to be released in the neural synapse and its returns to the cytosol to be reused for a new process of neurotransmission. Thus, the concentration of dopamine rises in the synapse region, causing one of the effects of the drug. In recent years, the indiscriminate use of sugar has been questioned due to the emergence of diseases such as obesity and diabetes[1], because glucose consumed in excess can cause the same effects as illicit drugs, such as cocaine and amphetamines[2,3]; however, in a more lenient way.

Methodology: In this work we use ensemble docking to dock a single ligand against multiple rigid conformations obtained from molecular dynamics simulation (MD) and compare the bind energies of the glucose (hydrolyzed product of sugar) and cocaine in the dDAT active site. For doing this, the MD of the dDAT enzyme (PDB code: 4xp4) was made in explicit water (tip4p model), in NPT ensemble (P = 1 bar e 310K) for 10 ns, using the OPLSAA force-field and the GROMACS 5.06. The ligands (glucose and cocaine) were docked into the dDat active site using the AutoDock 4.2 using Lamarckian Genetic Algorithm (LGA).

Figure 1 – (A) Cocaine into the dDat active site after molecular docking. (B) Glucose docked into the same active site.



(A) (B)

Results and discussion: The structural fluctuation of the dDat in water was evaluated by the RMSD and displayed a mean value of 0.36 nm after 1800 ps.
According to the Table 1, the bind energy and the inhibition constant between the glycose and dDat showed that the sugar is capable of inhibit the dopamine transporter enzyme, which confirm the hypothesis that the saccharide can induce some narcotic effect like cocaine. The Figure 1 shows the interaction between the ligands and enzyme. Moreover, RMSD displayed the water effect on enzyme structure and on the bind energy with the ligands (Table 1). Thus, greater structural fluctuations imply in less favorable interactions, suggesting that the solvent decrease the protein activity, according to these simulation setups. It has been expected because the molecular dynamics simulation did not considered the co-factors: Cholesterol Hemiccinate, Cholesterol, Maltose and 1-ethoxy-2-(2-ethoxyethoxy)ethane.

Table 1 – Molecular Dynamics RMSD and bind energies between dData-cocaine and dDat-glucose resulted from molecular docking made from uncorrelated structures extracted from MD simulation.

Frames (ps)	RMSD	Bind Energy (Kcal) Cocaine	Bind Energy (Kcal) Sugar
0	0	-8.37	-6.18
2000	0.39	-8.49	-7.71
5610	0.27	-8.9	-6.69
7920	0.38	-7.32	-6.89
9780	0.45	-4.16	-2.97

Conclusion: The ensemble docking calculations showed that the glucose is capable of inhibit the dopamine transporter enzyme and reinforces the hypothesis that sugar in excess can cause dependence, as cocaine.

Key-words: Binding energy, inhibition constant, dopamine, cocaine, sugar, ensemble docking, enzymatic activity.
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References:

[1] Bittman, M. “An Inconvenient Truth About Our Food”. *The New York Times. Retrieved Apr 13*, **2014**.
[2] O’Sullivan, M. “Fed Up’ movie review: The sins of sugar”. The *Washington Post*. Retrieved Apr 13, 2014.
[3] Wang, K. H.; Penmatsa, A.; Gouaux, E. Nature. **2015**, *521, 322*.