In silico repurposing and side effect studies of first-and second-generation antipsychotic drugs in methamphetamine addiction treatment

16th International Online Mini-Symposium of the Protein Society of Thailand

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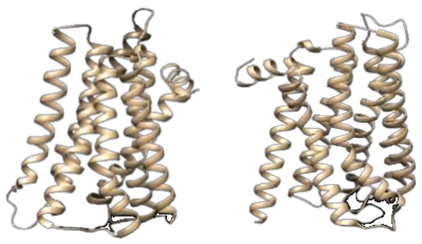
Introduction

METH is a psychostimulant that directly affects the central nervous system (CNS), especially the reward circuitry; METH induces increased dopamine transmission [1].

METH enters neurons via the dopamine transporter (DAT) then affects the vesicular monoamine transporter 2 (VMAT2) on the synaptic vesicle, thus the vesicle releases dopamine higher than that in regular conditions. This mechanism causes an increase of dopamine in the cytoplasm and subsequently in the synaptic cleft [2].



D2 receptor

5-HT2A receptor

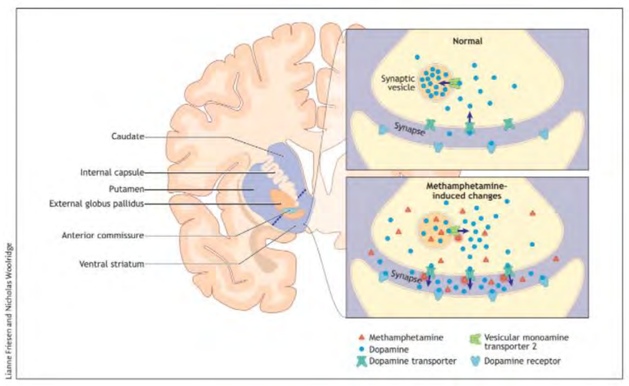


Figure 1 Diagram of methamphetamine mechanism in the human neuron and synaptic cleft [2]

Antipsychotic drugs are divided into two groups: first-generation antipsychotic drugs and second-generation antipsychotic drugs, in which the second-generation type has fewer side effects, known as extrapyramidal symptoms (EPS), than the first-gen drug class [3]. The mechanism of action of the conventional antipsychotic drug is the inhibition of the dopamine receptor subtype D2, which is different from the new one that inhibits both the D2 receptor and serotonin receptor subtype 5-Hydroxytryptamine receptor 2A (5-HT2A) [3]

In this study, we are repurposing five drugs (prochlorperazine, haloperidol, olanzapine, zotepine, and aripiprazole) for METH addiction treatment. Drugs' action via binding D2 receptor may compromise METH-induced overstimulation of dopamine. Molecular docking was performed to predict the interaction energy between antipsychotic drugs/dopamine/serotonin and D2/5-HT2A receptors and their binding energy was analyzed. Their interactions were illustrated using the 2-dimensional (2D) diagram.

Table 2 Analysis of the D2 and 5-HT2A receptor interaction from the 2D diagram.

ligand	H-bonds		Hydrophobic contacts	
	D2	5-HT2A	D2	5-HT2A
control	4	2	6	7
prochlorperazine	0	0	14	12
haloperidol	0	1	17	12
olanzapine	0	0	11	12
zotepine	0	0	15	13
aripiprazole	0	1	14	17

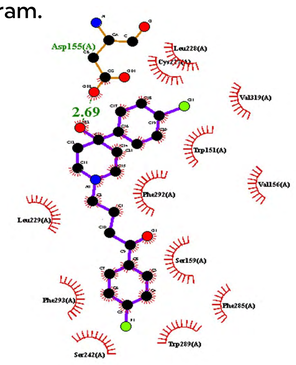


Figure 9 2D diagram from LigPlot+ of haloperidol with serotonin 5-HT2A receptor.

Antipsychotic drugs with high binding affinity with D2 receptor were shown to interact with Asp114 and Cys118 and antipsychotic drugs with a high binding affinity with serotonin 5-HT2A receptor were likely to interact with Asp155 [6]. Our result shows that high affinity drugs interact with the mentioned residues. Haloperidol, which has the highest binding affinity with 5-HT2A, forms an H-bond with Asp155 **(Fig. 8 and 9).**

Conclusion

- Every antipsychotic drug in this study is capable of blocking D2 receptor from dopamine overdose because of the higher binding affinity in comparison to dopamine.
- The most suitable drug determined by binding affinity is prochlorperazine which is the typical antipsychotic drug, followed by olanzapine which is the atypical drug.
- A suitable indicator which used to classify typical and atypical antipsychotic is EPS. Since atypical antipsychotic drugs are defined by their lethal side effects, prochlorperazine clinically displays EPS side effects regardless of its high 5-HT2A/D2 ratio.
- **Olanzapine is the most suitable antipsychotic drug of the five selected drugs used in this study.**

Acknowledgement

In this work, graphic images were produced using the UCSF Chimera package from the Resource for Biocomputing, Visualization, and Informatics at the University of California, San Francisco (supported by NIH P41 RR001081).

Reference

[1] Marshall, J. and O'Dell, S., 2012. Methamphetamine influences on brain and behavior: unsafe at any speed?. Trends in Neurosciences, 35(9), pp.536-545.
[2] Kish, S., 2008. Pharmacologic mechanisms of crystal meth. Canadian Medical Association Journal, 178(13), pp.1679-1682.
[3] Gardner, D., 2005. Modern antipsychotic drugs: a critical overview. Canadian Medical Association Journal, 172(13), pp.1703-1711.
[4] Muench J, M Hamer A. Adverse Effects of Antipsychotic Medications. Am Fam Physician. 2021;81(5):617-22.
[5] Kondo T, Otani K, Ishida M, Tanaka O, Kaneko S, Fukushima Y. Adverse Effects of Zotepine and Their Relationship To Serum Concentrations of the Drug and Prolactin. Therapeutic Drug Monitoring. 1994;16(2):120-124.
[6] Bali A, Sen U, Peshin T. Synthesis, docking and pharmacological evaluation of novel indole based potential atypical antipsychotics. European Journal of Medicinal Chemistry. 2014; 74:477-490.

Methods

Protein Data Bank

NCBI BLASTP

Gaussian (G09)

UCSF Chimera v.1.15

LigPlot+ v.2.2.4

Tools

AVOGADRO v.1.1.2

AutoDock Vina v.1.2.0

Receptor Preparation → Ligand Preparation → Grid Box creation → Docking → 2-Dimentional Interaction

Result and Discussion

- Every antipsychotics has a higher negative binding score than dopamine. Thus, they can prevent dopamine from binding with the D2 receptor. This process decrease the overstimulation caused by METH.
- First-generation antipsychotic drugs are better at binding with D2 and 5-HT2A receptors than second-generation drugs are; however, second-generation antipsychotic drugs are promising for curing patients with METH addiction.
- When only binding affinity is deliberated, two most suitable drugs with the highest 5-HT2A/D2 ratio are prochlorperazine **(Fig. 2,4,6)** and olanzapine **(Fig. 3,5,7),** respectively.
- Olanzapine is the most proper drug to treat patients concerning the side effects of the drugs, since olanzapine affects only dyslipidemia and no other severe adverse effects compared to others [4, 5].

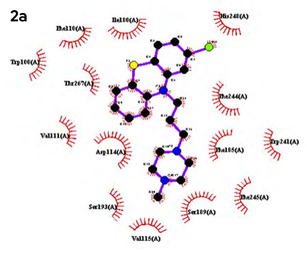
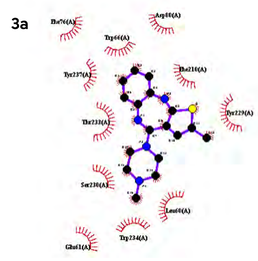


Figure 2 2D diagram from LigPlot+ of prochlorperazine with 2a) dopamine D2 receptor and 2b) serotonin 5-HT2A receptor.



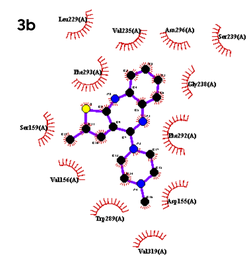


Figure 3 2D diagram from LigPlot+ of olanzapine with 3a) dopamine D2 receptor and 3b) serotonin 5-HT2A receptor.

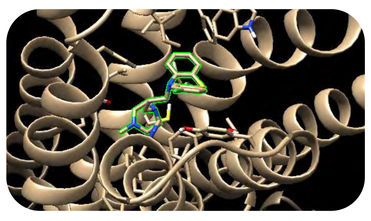


Figure 4 UCSF Chimera visualization shows the best binding conformation of prochlorperazine on the serotonin D2 receptor binding site

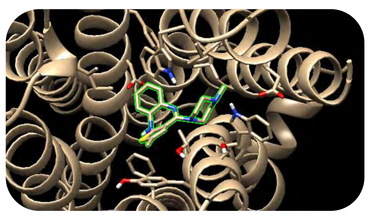


Figure 5 UCSF Chimera visualization shows the best binding conformation of olanzapine on the serotonin D2 receptor binding site

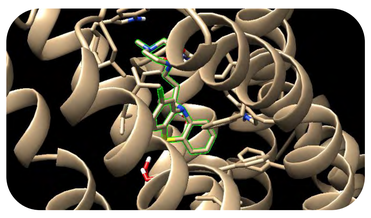


Figure 6 UCSF Chimera visualization shows the best binding conformation of prochlorperazine on the serotonin 5-HT2A receptor binding site

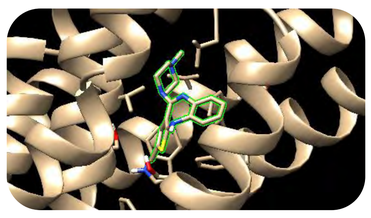


Figure 7 UCSF Chimera visualization shows the best binding conformation of olanzapine on the serotonin 5-HT2A receptor binding site

Table 1 Binding scores and affinity rank of control (dopamine, serotonin) and antipsychotic drugs (prochlorperazine, haloperidol, olanzapine, zotepine and aripiprazole) with D2 receptor and 5-HT2A receptor

ligand	Binding score (kcal/mol)				FDA drug information	Adverse effects [4, 5]
	D2	affinity rank (lowest to highest)	5-HT2A	affinity rank (highest to lowest)		
control	-6.5	1	-6.4	6	neurotransmitters	-
prochlorperazine	-8	4	-9.8	2	typical	extrapyramidal symptoms
haloperidol	-10.8	6	-10.4	1	typical	extrapyramidal symptoms
olanzapine	-7.9	3	-8.7	4	atypical	dyslipidemia, weight gain
zotepine	-7.8	2	-8.1	5	atypical	akathisia
aripiprazole	-10.6	5	-9.6	3	atypical	lower risk side effect

According to the 2D diagram, haloperidol which has the highest affinity with D2 receptor also possesses the most hydrophobic interactions with D2. The H-bond interaction is correlated with high affinity to 5-HT2A receptors as two of the highest affinity drugs, including haloperidol and aripiprazole, possess H-bond interaction in the binding site.

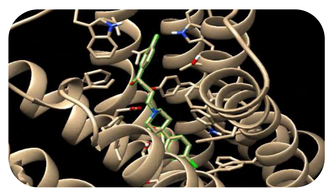


Figure 8 UCSF Chimera visualization shows the best binding conformation of haloperidol on the serotonin 5-HT2A receptor binding site