An *In Silico* Comparative Study of Interspecies Variability in Neurotransmitter Ligand-Receptor Interactions

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ABSTRACT

Research has shown that epigenetic regulation and spatial distribution of neurotransmitter receptors is linked to the expression of a variety of social behaviors and neurodevelopmental disorders. Studies on relevant receptor neurobiology have focused on signaling patterns as a therapeutic basis and have been successful in modulating behavior in several model organisms. Structure-based approaches may offer insight to molecular mechanisms contributing to observed irregularities in social behavior across species and contribute further investigation of neural circuitry. We examined receptors for dopamine (DRD1 and DRD2), oxytocin (OXTR1), and vasopressin (AVPR1) from a wide array of phylogenies totaling 465 proteins and conducted molecular docking with their respective ligand to compare binding affinity and other interactions. We highlight how this study contributes to our understanding of the role of receptor structure in broader neurobiological mechanisms and possible novel therapies.

INTRODUCTION

The regulation and distribution of select neurotransmitters—dopamine, oxytocin, and vasopressin--has been linked with the expression of polygamy or monogamy in several model organisms. Research has shown a connection between these neurotransmitters and the monogamous nature of prairie voles, a model organism, and the control species for this study [3]. Along with polygamy and monogamy, the regulation and distribution of these neurotransmitters have been linked with the expression of important social behaviors.

Vasopressin and oxytocin have been established to play important role in maternal behaviors along with contributing to the expression of complex social behaviors in mammals [1]. Dopamine is also associated with social behavior, an up-regulation of it associated with more prosocial behavior and a down-regulation with less prosocial behavior [2].

The regulation and distribution of the neurotransmitter receptors contribute to the expression of these important behaviors. In this study, we aim to shed light on the relationship between social behaviors, including polygamy and monogamy, and binding affinity between ligands and their receptors. This study examines the ligand-receptor behavior of dopamine receptors DRD1 and DRD2, oxytocin receptor OXTR1, and vasopressin receptor AVPR1 from 465 protein sequences that encompass multiple phylogenies.

METHODS AND MATERIALS

Used UniProt to collect primary sequences of dopamine D1, dopamine D2, oxytocin, and vasopressin receptors across over 100 species.

Modeled receptors through homology SWISS modeling to create PDB files for each sequence. GMQE and template used was recorded for each receptor.

Binding affinities between each receptor and their canonical ligand was found by molecular docking via Autodock Vina. Protocol was created to ensure consistency between all runs.

The strongest affinity (lowest energy) configuration was recorded as the basis of analysis. Very far outliers and errors in docking (resulting in null or unreasonable data) were found and redocked.

RESULTS

Of 465 receptors identified, 464 were successfully docked. Figure 1 shows the total number of receptors found via UniProt, number of receptors that failed protocol, along with some data characterization. Further visualization of this data is shown in Figure 2, highlighting quartiles via a boxplot and showing some notable outliers in DRD2 and OXTR1.

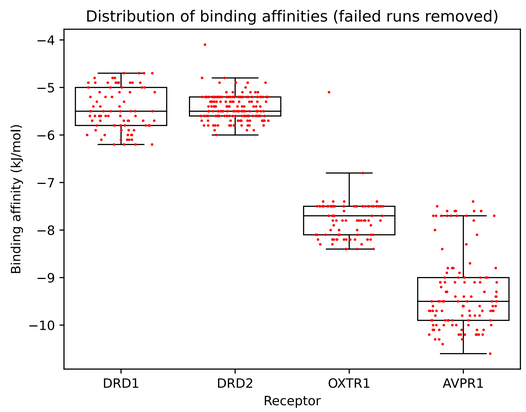
In a t-test with OXTR1 samples 1-39, there was no significant difference between docking run with small versus large boxes at the determined exhaustiveness and CPUs used (df=38, t=1.125, p=0.268). The failed run, OXTR1 sample 59 (taxonomic ID 9598), was inconclusive since the sequence was not long enough to generate a homology model.

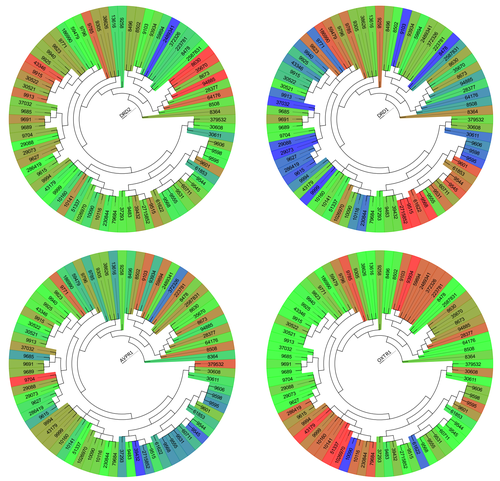
Figures 3a-d show these affinities normalized relative to each receptor and arranged phylogenetically. Blue represents higher affinity with lower kJ/mol binding energy, while red represents the opposite. Basic qualitative conclusions can be derived from the closeness of phylogenies and color.

Figure 1. Data on binding affinities of receptors

	DRD1	DRD2	OXTR1	AVPR1
N (total)	83	174	91	117
N (failed)	0	0	1	0
Mean (kJ/mol)	-5.467	-5.424	-7.753	-9.285
StDev (kJ/mol)	0.453	0.260	0.434	0.834

Figure 2. Distribution of binding affinities of receptors





Figures 3a-d Heat-mapped phylogenetic trees for receptors

DISCUSSION

Neurotransmitter receptor modeling and subsequent analysis with binding affinity has strong potential in predicting social behavior of animals, as significant changes affect those pathways [1,3]. The results show variable distribution in binding affinity between species per receptor. However, the phylogenetic trees show that trends in receptor binding are different between receptors per species.

This project is in progress. We recommend further work in analyzing the qualitative social behavior of animals to create a cross comparison with the data. This could validate binding affinity as a reasonable predictor of social behavior, as well as which receptors are the most important. Furthermore, it will shed light on the strength of the relationship between behaviors and binding affinity, hinting at potential mechanisms.

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