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RESEARCH ARTICLE

Modeling Astrocyte Influence on Risperidone Response in Neuropsychiatric Treatment - Using COPASI

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ABSTRACT: Bipolar disorder and schizophrenia are prevalent neuropsychiatric disorders. Risperidone is an antipsychotic drug that has variability among patient responses to it. Astrocytes play a critical role in regulating neurotransmitter levels, particularly glutamate. Glutamate is the primary excitatory neurotransmitter; elevated glutamate concentrations in the synapse can lead to excitotoxicity, potentially influencing the efficacy of risperidone. This research aims to find how astrocytic glutamate uptake influences risperidone's efficacy. A computational simulation was developed using COPASI, a biochemical pathway modeling tool, to explore the dynamics of dopamine and risperidone binding to the D2 under a high glutamate concentration of 5 μmol/L. Two trials were conducted: a normal astrocyte model with active glutamate uptake, and a defective astrocyte model, where glutamate uptake was absent (V_{max} set to 0). Other values were held constant. The results showed that despite simulating excitotoxic conditions with high glutamate levels in both models, there was no significant change in risperidone's binding efficacy to the D2 receptor compared to the normal astrocyte model. These observations suggest that, under the utilized experimental conditions, glutamate uptake by astrocytes does not directly influence the rate of risperidone binding to the D2 receptor. This suggests that there may be other mechanisms influencing risperidone response.

KEYWORDS: Behavioral and Social Sciences, Neuroscience, Cellular and Molecular Biology, Neurobiology, Computational Biology and Bioinformatics, Computational Pharmacology.

Introduction

Schizophrenia and bipolar disorder are two of the most prevalent and severe neuropsychiatric disorders, each characterized by significant disruptions in mood, cognition, and behavior. Schizophrenia is expressed through symptoms such as hallucinations, delusions, disorganized thinking, and cognitive deficits, while bipolar disorder involves episodes of mania and/or depression, often accompanied by impairments in executive function, emotional regulation, and memory.[1] Despite their differences, both disorders share certain neurochemical variances that contribute to the dysregulation in dopamine and glutamate signaling.

Risperidone, a commonly used atypical antipsychotic drug, is prescribed to ease the symptoms of neuropsychiatric conditions like schizophrenia and bipolar disorder. Its primary mechanism of action involves antagonism of dopamine D2 receptors (D2Rs), reducing excess dopamine activity in key brain regions such as the striatum and prefrontal cortex.[2] However, patient response and outcomes with risperidone vary significantly between individuals. Some patients experience effective symptom relief, while others suffer from severe side effects such as cognitive impairment, metabolic dysfunction, or psychomotor agitation. In some cases, risperidone fails to produce a meaningful therapeutic response at all.[3] The variability in treatment response suggests that additional neurochemical factors play a role in risperidone's neurotransmitter interactions.

Recent evidence suggests that astrocytes, a specialized type of glial cell, may play a crucial but unrecognized role in maintaining antipsychotic drug efficacy. Traditionally thought to be passive support cells, astrocytes are now recognized as active regulators of neurotransmission, maintaining homeostasis within the central nervous system (CNS).[4] One of their most critical functions is the regulation of glutamate, the brain's primary excitatory neurotransmitter. Astrocytes accomplish this by expressing excitatory amino acid transporters (EAATs), which actively remove excess glutamate from the synapse and recycle it for reuse (Figure 1).[5] This process is vital for preventing glutamate excitotoxicity, a condition that results in overactivation of glutamate receptors and eventual neuronal damage or death.[6]

Maintaining homeostasis of glutamate levels is particularly relevant to behavioral health because glutamatergic dysregulation has been related to schizophrenia and bipolar disorder.[7] Excessive glutamate levels have been associated with cortical thinning, synaptic destabilization, and disruptions in neural connectivity, all of which contribute to cognitive and emotional impairments observed in these disorders.[8] Astrocytic dysfunction, whether due to reduced rates of glutamate uptake or imbalanced transporter activity, may lead to an accumulation of extracellular glutamate, which in turn can interfere with drug-to-neurotransmitter interactions and alter the efficacy of antipsychotic drugs.[9]

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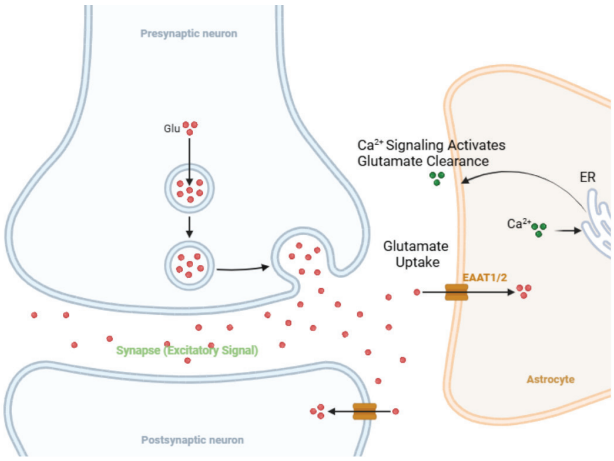

Figure 1: Model depicts Calcium Signaling and Glutamate Uptake between Neurons and Astrocyte cells. This also shows activation of Glutamate Clearance through Calcium Signaling. (Student Produced)

Glutamate, the primary excitatory neurotransmitter, is transported to neurons via the synapses. During this process, astrocytes initiate glutamate uptake to maintain stable levels of glutamate being transported. Excess levels of glutamate in the synapse may lead to excitotoxicity, resulting in neuronal damage or cell death.

The relationship between astrocytic glutamate regulation and risperidone efficacy is not fully understood, yet it may hold the key to explaining why treatment outcomes vary among individuals. If astrocytic glutamate uptake is compromised, excess extracellular glutamate may alter dopamine receptor availability and efficacy. This disruption could lead to lower risperidone binding affinity for D2Rs, thereby reducing its intended effects on dopamine regulation. Conversely, enhancing astrocytic glutamate uptake may improve drug efficacy by creating neurotransmitter balance, possibly reducing the need for higher doses and minimizing adverse symptoms of risperidone use.[10]

This study aims to investigate the role of astrocytes in influencing risperidone's pharmacological effects through glutamate regulation. By utilizing computational modeling, risperidone's interaction with dopamine D2 receptors will be simulated under two conditions: one representing normal astrocytic function with active glutamate uptake, and another representing a defective astrocyte where glutamate uptake is impaired (V_{max} = 0). This approach allows for an analysis of how astrocytic function influences drug binding kinetics, dopamine-glutamate interactions, and overall treatment efficacy.

Understanding how astrocytes contribute to the variability in risperidone response has great implications for behavioral health. It competes with the longstanding neuron-focused view of psychiatric disorders and introduces astrocytes as key regulators of drug activity. If astrocytes are found to play a significant role in risperidone's effectiveness, future pharmacological interventions could more efficiently utilize astrocyte-targeted treatments to enhance drug efficacy and develop more personalized therapeutic strategies for schizophrenia and bipolar disorder. By bridging the gap between dopamine and glutamate-based models of mental illness, this study contributes to a more holistic understanding of psychiatric disorders and their treatment, aiming to eventually improve overall patient responses and quality of life for affected individuals.

Methods

Hypothesis: If astrocyte-mediated signaling inhibits dopamine receptors, then astrocytes influence the efficacy of risperidone.

This research study was conducted in three phases: information gathering, computational model development, and simulation. The first phase involved an extensive review of existing literature to establish a foundation for modeling risperidone's interaction with astrocytic glutamate uptake. The goal was to identify relevant biochemical pathways, kinetic parameters, and reaction mechanisms necessary for developing an accurate computational model. Data sources included peer-reviewed journals, pharmacokinetic studies, and neurobiological research on dopamine-glutamate interactions, astrocytic glutamate transport, and risperidone's pharmacodynamics. Various experimental studies were used to find specific parameters, such as the binding affinities of risperidone to dopamine D2 receptors and the kinetics of glutamate uptake. These values allowed for defining the initial conditions, rate laws, and reaction equations used in the computational model.

Once the necessary data were collected, a computational model was developed to simulate the biochemical interactions between risperidone, dopamine, astrocytes, and glutamate uptake. Biochemical simulation software COPASI (v4.36) was used to depict specific drug-to-neurotransmitter interactions. The model was designed to capture the role of astrocytic glutamate clearance in maintaining a balance in neurotransmitter activity and its potential influence on risperidone's pharmacodynamics. Ligand-receptor interactions were incorporated by modeling the binding of risperidone and dopamine to dopamine D2 receptors using Michaelis-Menten irreversible kinetics, with K_{on} and K_{off} rates pulled from literature sources (Table 2). Glutamate uptake by astrocytes was modeled using Michaelis-Menten rate laws to represent EAAT-mediated glutamate clearance. Two conditions were created: one where astrocytes actively removed extracellular glutamate and another where glutamate uptake was impaired (V_{max} = 0) to simulate astrocytic dysfunction. The model also tracked changes in extracellular glutamate and dopamine levels over time, allowing for an analysis of how astrocytic function affects risperidone-D2 receptor interactions. The initial concentrations for dopamine, risperidone, D2 receptors, and glutamate were set based on past experimental data (Table 1). Each reaction was parameterized with literature-derived rate constants, K_m, and V_{max} values to ensure accuracy. After constructing the model, preliminary simulations were conducted to confirm that the system behaved as expected before experimental simulations were run.

The final phase involved running simulations in COPASI to examine the effects of astrocytic glutamate uptake on risperidone's binding efficacy to dopamine D2 receptors. The model was simulated for 600 seconds under two conditions: one representing normal astrocyte function, where glutamate uptake

remained active, and another where glutamate uptake was absent (V_{max} = 0) to simulate impaired astrocyte function. Key variables, such as glutamate clearance rates, dopamine fluctuations, and risperidone receptor binding levels, were recorded for analysis. Data were exported from COPASI and visualized using Microsoft Excel to generate graphs comparing neurotransmitter levels and receptor occupancy across different astrocytic conditions. The results were then analyzed to determine whether glutamate uptake influences risperidone's ability to decrease dopamine signaling, providing insight into how astrocytic function may contribute to treatment variability in schizophrenia and bipolar disorder.

Table 1: Shows the key molecular components and initial conditions utilized in the COPASI simulation of the effects of glutamate uptake on risperidone's binding efficacy to D2 receptors.

Molecule	Initial Concentration	Role
D2-DA Complex	0 M	DA-bound receptor
D2 Receptor (D2)	1.0 e^{-8} M	Dopamine Receptor
Risperidone (RISP)	2.51e^{-9} M	Antipsychotic drug
D2-RISP Complex	0 M	RISP-bound receptor
Glutamate (Glu_ext)	5.0e^{-8}M	Excitatory neurotransmitter

Table 2: Shows the kinetic values utilized to replicate the movement during the various biochemical interactions. The biochemical interactions modeled include dopamine to D2 receptor binding, risperidone to D2 receptor binding in competition with dopamine, and astrocytic glutamate uptake.

Reaction	K_{on}	K_{off}	V_{max}	K_m
DA + D2 →D2-DA	2.75 x 10^4 $M^{-1}s^{-1}$	0.197 s^{-1}	–	–
RISP + D2 → D2-RISP	1.65 x 10^6 $M^{-1}s^{-1}$	1.86 x 10^{-4} s^{-1}	–	–
Glu_ext → Glu_astrocyte	–	–	6.367 x 10^{-12} M/s	6.1 x 10^{-5} M

Result and Discussion

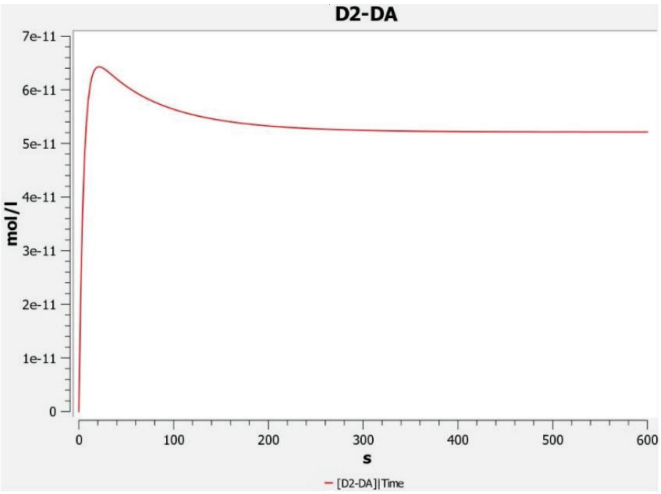

Figure 2: Graph of Trial 1 concentration of DA bound to D2 receptor over 600 seconds. This trial depicts the concentration of dopamine binding affinity with the simulated "normal" astrocyte.

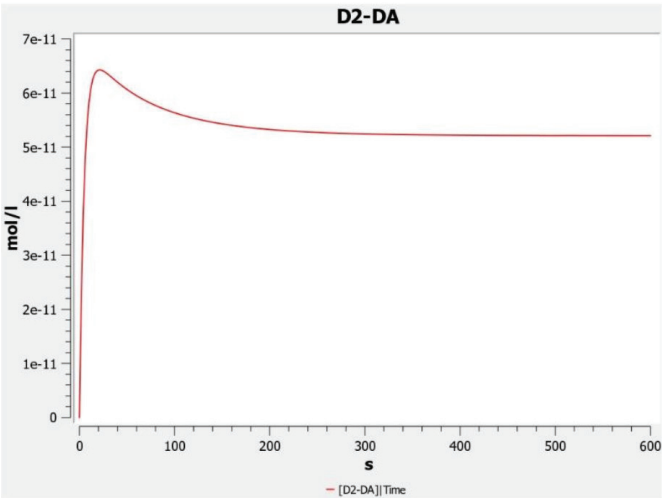

Figure 3: Graph of Trial 2 concentration of DA bound to D2 receptor over 600 seconds. This trial depicts the concentration of dopamine binding affinity to the dopamine receptor with the simulated "defective" astrocyte.

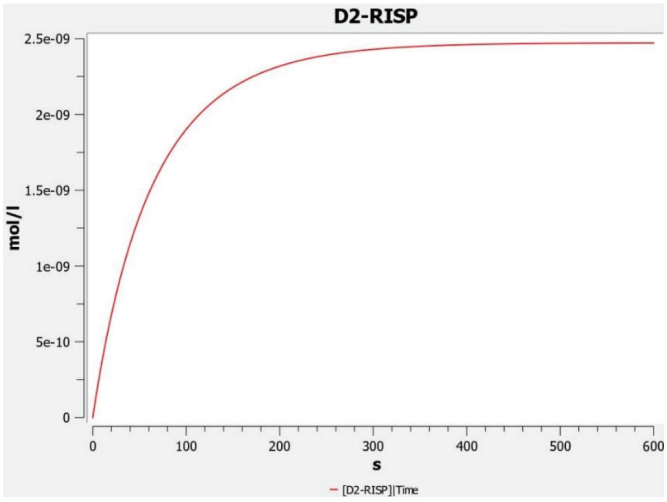

Figure 4: Trial 1 concentration of Risperidone bound to D2 receptor over 600 seconds. This trial depicts the concentration of risperidone binding affinity to the dopamine receptor with the simulated "normal" astrocyte.

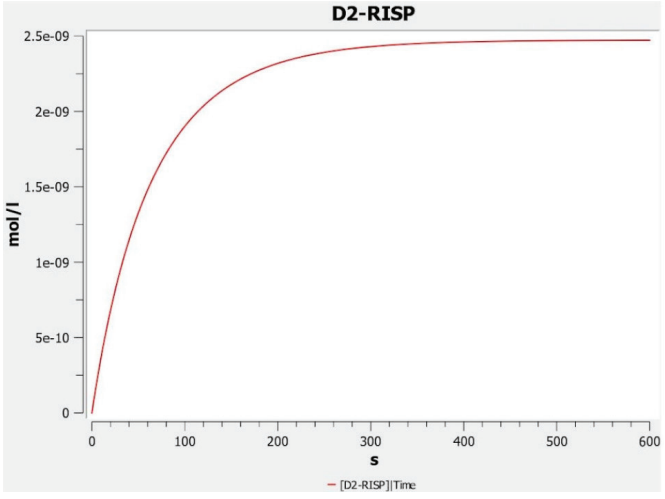

Figure 5: Trial 2 concentration of Risperidone bound to D2 receptor over 600 seconds. This trial depicts the concentration of risperidone binding affinity to the dopamine receptor with the simulated "defective" astrocyte.

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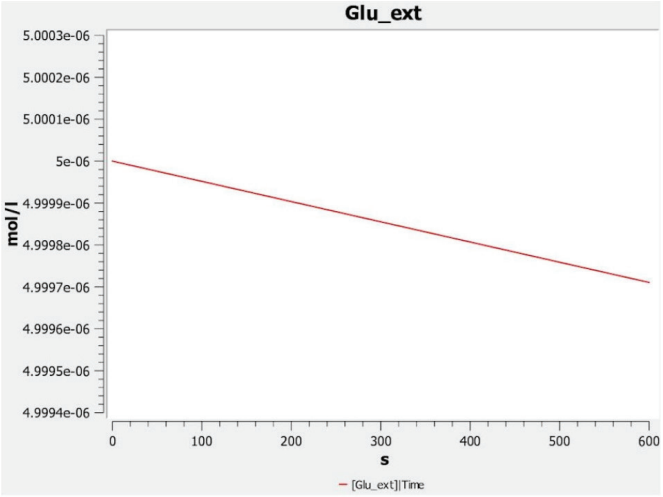

Figure 6: Trial 1 concentration of extracellular glutamate. The decrease in concentration over time of extracellular glutamate implies that the simulation of the "normal" astrocyte is accurate.

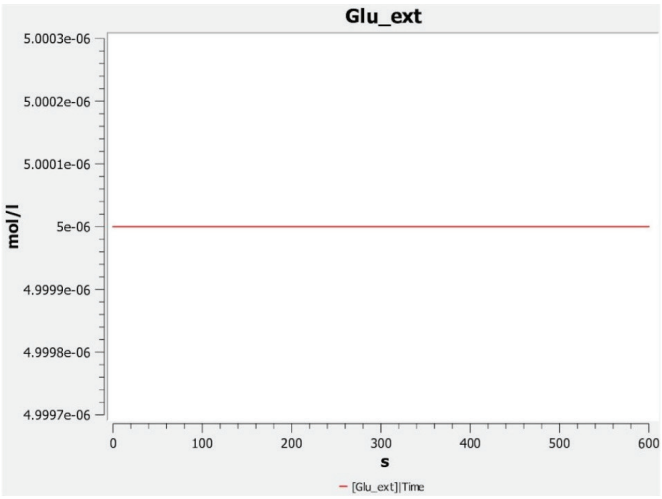

Figure 7: Trial 2 concentration of extracellular glutamate. The constant concentration of glutamate over time indicates that there is no astrocytic glutamate uptake, as intended with the simulated "defective" astrocyte.

Analysis:

The experiment aimed to evaluate the efficacy of risperidone treatment under two conditions: one with a normal Vmax for glutamate and another with Vmax set to zero. Data was collected over a period of 600 seconds for both trials, and key variables such as risperidone binding (RISP), dopamine receptor activation (D2-DA), and glutamate concentrations were analyzed. Graphs depicting these variables over time were generated to compare the trends observed in each trial. A visual inspection of the graphs for D2-DA suggests that there was no significant difference between the two trials, indicating that modifying the rate of glutamate uptake did not significantly impact dopamine receptor activation (Figures 2-3). Similarly, the trends show that the RISP values appear consistent between the two trials (Figures 4-7). To confirm whether there was a statistically significant difference in risperidone efficacy, a statistical analysis was conducted. A Welch's t-test was conducted comparing risperidone-D2 receptor binding levels (RISP) between two simulation conditions:

Condition A: Normal astrocytic glutamate uptake (V_{max} = 6.367 x 10^{-12} M/s)

Condition B: Impaired astrocytic glutamate uptake (V_{max} = 0 M/s)

Hypotheses:

• Null Hypothesis (H_0): There is no significant difference in risperidone-D2 receptor binding (RISP) between the normal and impaired astrocyte models.

• Alternative Hypothesis (H_1): There is a significant difference in risperidone-D2 receptor binding (RISP) between the normal and impaired astrocyte models.

The sample size was equal to the number of time-point measurements for each condition. The α level is 0.05 (5% significance level). It was found that the p-value was 1.0 and exceeded the alpha level. As such, the null hypothesis is not rejected. This means that there is no statistically significant difference in risperidone binding with the D2 receptor in either condition, despite the changes in glutamate uptake.

Discussion:

The results indicate that altering the Vmax of glutamate did not significantly affect risperidone binding or dopamine receptor activation over a 600-second timescale. This suggests that glutamate uptake in astrocytes does not play a major role in risperidone's mechanism of action, or it may be working in conjunction with other mechanisms. Risperidone primarily functions as a dopamine D2 and serotonin 5-HT2A receptor antagonist, and these findings support the idea that its efficacy is likely not associated with glutamate transport.

One explanation for the lack of difference between trials is that the timescale may not be sufficient to observe downstream effects of glutamate modulation. While receptor binding occurs rapidly, changes in neurotransmitter dynamics may take longer to be apparent. Additionally, the experimental model may not fully capture the complexity of glutamatergic signaling in a biological system. If glutamate uptake influences risperidone efficacy, it may be through mechanisms that were not reflected in this study.

■ Conclusion

The findings show that risperidone's efficacy remains unaffected by alterations in glutamate uptake. The statistical analysis revealed no significant variation in dopamine receptor activation or risperidone binding between trials (t = 0.0, p = 1.0), suggesting that its primary mechanism of action is not related to glutamate transport. These results contribute to a better understanding of risperidone's pharmacological effects and provide evidence that glutamate uptake does not significantly impact its therapeutic function.

Future studies should investigate whether sustained alterations in glutamate uptake over longer periods influence risperidone's effects. Additionally, utilizing in vivo experiments could better depict the nuances in brain chemistry that contribute to changes in glutamate homeostasis and play a role in risperidone's long-term efficacy.

Another area for further investigation is the interaction between glutamate uptake and other neurotransmitter systems. Since schizophrenia involves disruptions in dopamine, serotonin, and GABA pathways, studying how risperidone's effects change under different neurochemical conditions may help in developing more patient-specific treatment. Computational models could be expanded with additional receptor interactions, and additional experimentation may determine whether alternative pathways influence risperidone's clinical outcomes.

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