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Original Research Article

A novel in-silico based drug discovery of neuroprotective targets for *Monosodium glutamate*

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ABSTRACT

Background: *Monosodium glutamate* (MSG) is a frequently used food additive that enhances flavour and is well-liked worldwide and has a significant interaction on nervous system. It is a ligand based docking study. By using Chem Sketch or Chem Draw, Swiss target prediction tool, Auto Dock Vina 4.2.6, BIOVIA Discovery Studio Visualizer, and neuroprotective targets of MSG with promising interactions with particular brain targets, we harness the computational power of molecular docking.
Objective: The aim of this study is to identify and evaluate the neuroprotective targets for *Monosodium Glutamate* using *In- silico* method.
Result: In silico experiments had been used to screen for monosodium glutamate. Based on the docking interaction score and conventional hydrogen bond interactions, monosodium glutamate demonstrated maximal affinity towards a number of neuroprotective targets, including ionotropic NMDA 2A, metabotropic 4(R), and metabotropic 1(B). These three proteins interact powerfully with MSG. Despite the fact that the US FDA, FSSAI, WHO, and a number of other organizations advise an estimated safe dose of MSG, Certain adverse effects still have an impact on people.
Conclusion: In future the dose reduction study can conduct to reduce the dose range to the particular dose for beneficial and neuroprotective effects by targeting these three proteins based on their docking interactions. For research on neuroprotection, these three targets are better choices. The identification of neuroprotective targets opens the door to more in-vivo and in-vitro research on neuroprotective treatments.

1. Introduction

Monosodium glutamate (MSG) is the sodium salt of the common amino acid glutamic acid.Glutamic acid is naturally present in our bodies, and in many foods and food additives as divisive flavour enhancer. Worldwide, fermentation employing Corynebacterium glutamicum or closely related organisms produces around 1.9 million tons of MSG yearly.[1] The two main active components of flavor enhancers, according to Bera et al., are MSG and salt (NaCl).[2] It is a sodium salt of glutamic acid, as indicated by its IUPAC nomenclature, Sodium 2-aminopentanedioate. It ionizes with water to produce free sodium ions and glutamic acid.Its chemical formula is C5H8NNaO4, and its molecular mass is 169.11 g/mol. It links an alpha carbon atom to both an amino (-NH2) and a carboxylic (COOH) group. MSG is a naturally occurring non-essential amino acid that appears as a crystallized white powder that resembles sugar or salt.[3] Preclinical research links MSG to several possible negative effects. However, most experimental setups used high dosages and/or inappropriate delivery techniques (parenteral, for instance). Therefore, it is difficult to make a definitive decision about the safety of MSG, especially when it comes to long-term, low-dose exposure. The European Food Safety Authority has

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established a safe daily glutamate intake of 30 mg/kg/day. MSG does not appear to be carcinogenic in any organ or tissue when used in vivo, and there are no known drug interactions with MSG. Interaction between MSG and glutamate receptors releases neurotransmitters that are critical to both healthy and pathological processes (Abdallah et al., 2014).[4]

Alpha, beta, delta, and kainite receptors are the four kinds of ionotropic receptors; glutamate receptor-associated metabotropic receptors (mGluR) fall into three families. Each type of receptor is present in the central nervous system. As they control metabolic and autonomic processes, they are especially prevalent in the hypothalamus, hippocampus, and amygdala (Zhu and Gouaux, 2017).[5] Even minute amounts of MSG can have negative effects, according to studies conducted on both humans and animals.According to Solomon et al. (2015), the average person consumes 0.3–1.0g of MSG per day. These concentrations have the potential to damage neurons and have detrimental behavioral effects. Studies conducted on animals have demonstrated that ingesting MSG during infancy sets the stage for the subsequent emergence of obesity.[6]

The word "neuroprotection" refers to a plan or technique for preventing neuronal damage brought on by acute or chronic neurodegenerative diseases (NDs) that affect the central nervous system (CNS).[7] The cause of NDs is the breakdown and degeneration of CNS neurons, which frequently impairs a person's mental as well as intellectual capacities. NDs encompass a broad range of illnesses, including glaucoma, Parkinson's, Alzheimer's, and Huntington's disease. They are distinguished by a gradual loss of neuronal structure and/or function. The majority of short-term memory loss, learning difficulties, poor motor coordination, and several other functional losses are among the signs of non-disruptive dementias (NDs), which often worsen over time.[8] Research has established a clear connection between NDs and aging, a complicated physiological process that includes morphological and biochemical changes that occur gradually as we age.Together with hypertension, genetics, environment, and infections, other ND etiological factors include infection and aging as a key risk factor. Age-related changes in the pathophysiology of NDs include loss of neurotransmitters, oxidative stress, inflammation, and protein aggregation.[9] The goal of neuroprotection is to prevent acute or chronic neurodegenerative disorders from causing harm to the central nervous system (CNS).[10] The ability to postpone or prevent neuronal death and dysfunction is commonly used to characterize neuroprotection. In humans, this should mean a delayed onset of disease or slowed development of existing disease. The search for neuroprotective therapies in movement disorders focuses on neurodegenerative movement disorders, which include corticobasal degeneration, multisystem atrophy, progressive supranuclear palsy (PSP), and Parkinson disease (PD). Huntington disease (HD) and parkinsonian syndromes are also included in this search. Up until now, neuroprotective techniques have been strikingly similar, with an emphasis on stabilizing mitochondrial function and enhancing antioxidant activity, despite the clinical variations.[11]

2. Materials and Methods

2.1. Required software and server

BIOVIA Discovery studio Visualizer – used for visualizing, analyzing protein and modeling data; Chemsketch or ChemDraw - drawing the structure and generating the smiles; Online smile translator - to convert the ligand to a.pdb file; Supporting software – Auto Dock Vina 1.5.7 for docking. BIOVIA Discovery Studio Visualizer is a powerful molecular modelling application that allows you to view, edit, and analyse molecular structures, sequences, and sequence alignments. Whether you're working with proteins or small molecules, this feature-rich tool provides a convenient interface for everyday data analysis tasks. BIOVIA Discovery Studio Visualizer is a versatile tool for analysing protein structures. Drug Bank is a comprehensive, publicly accessible internet database that offers essential information about pharmaceuticals and their targets. It is managed by the University of Alberta and the Metabolomics Innovation Centre in Alberta, Canada.

The Protein Data Bank (PDB) is a globally recognized repository for three-dimensional structural data of large biological molecules, including proteins and nucleic acids. Swiss Target Prediction is a valuable web tool that predicts the most probable protein targets of small molecules. It operates based on the similarity principle, leveraging reverse screening. Auto Dock is a suite of automated docking tools used in molecular modelling simulations. It predicts how small molecules, such as substrates or drug candidates, bind to a receptor with a known 3D structure. Over the years, AutoDock has been modified and improved, resulting in multiple engines. AutoDock Vina is a powerful open-source program used for molecular docking developed by Dr. Oleg Trott at The Scripps Research Institute, it offers several advantages such as accuracy, ease of use, compatibility. It finds applications in protein-ligand docking, virtual screening and lead optimization.

3. Results

Presence of hydrogen bonds Interaction and docking score with various protein (Table 1).

Table 1: Presence of hydrogen bonds Interaction and docking score with various protein

S. No	Targeted Proteins	Class	No. of. Conventional H bonds	Docking Score
1	GABA Transporter 1	Enzyme	-	-4.8
2	GABA Transporter 2	Electrochemical transporter	2	-3.2
3	GABA-A Receptor 1 (A Chain)	Ligand-gated ion channel	-	-3.2
4	GABA-A Receptor -1 (C Chain)	Ligand-gated ion channel	-	-3.0
5	GABA-A Receptor -2	Ligand-gated ion channel	3	-2.9
6	GABA-A Receptor -2	Ligand-gated ion channel	-	-3.1
7	Ionotropic AMPA 1 Receptor	Ligand-gated ion channel	-	-2.1
8	Ionotropic AMPA 2 Receptor	Ligand-gated ion channel	-	-3.6
9	Ionotropic AMPA 3 Receptor	Ligand-gated ion channel	-	-3.3
10	Ionotropic AMPA 4 Receptor	Enzyme	2	-2.7
11	Ionotropic Kainate 1 Receptor	Ligand-gated ion channel	2	-2.1
12	Ionotropic Kainate 2 Receptor	Ligand-gated ion channel	3	-3.9
13	Ionotropic Kainate 3 Receptor	Kinase	1	4.3
14	Ionotropic Kainate 5 Receptor	Protease	2	-3.0
15	Ionotropic NMDA 1 Receptor	Isomerase	2	-4.2
16	Ionotropic NMDA 2A Receptor	Ligand-gated ion channel	5	-6.0
17	Ionotropic NMDA 2B Receptor	Ligand-gated ion channel	2	-3.7
18	Ionotropic NMDA 2C(B) Receptor	Voltage-gated ion channel	-	-3.0
19	Ionotropic NMDA 2C(D) Receptor	Voltage-gated ion channel	-	-3.2
20	Ionotropic NMDA 2D Receptor	Isomerase	-	-3.1
21	Metabotropic Receptor 1(A Chain)	Ligand-gated ion channel	3	-4.0
22	Metabotropic Receptor 1(B Chain)	Ligand-gated ion channel	6	-4.5
23	Metabotropic Receptor 2(A Chain)	Family C GPCR	4	-4.8
24	Metabotropic Receptor 2(B Chain)	Family C GPCR	3	-4.5
25	Metabotropic Receptor 3 (A Chain)	Family C GPCR	1	-3.1
26	Metabotropic Receptor 3 (B Chain)	Family C GPCR	3	-4.6
27	Metabotropic Receptor 4 (R Chain)	Family C GPCR	6	-5.0
28	Metabotropic Receptor 4 (S Chain)	Family C GPCR	-	-5.0
29	Metabotropic Receptor 5	Electrochemical transporter	5	-3.4
30	Metabotropic Receptor 8 (A Chain)	Family A GPCR	-	-3.5
31	Metabotropic Receptor 8 (B Chain)	Family A GPCR	1	-3.2
32	Excitatory amino acid transporter 3(A)	Enzyme	-	-3.3
33	Excitatory amino acid transporter 3 (B)	Enzyme	-	-3.4
34	Excitatory amino acid transporter 3 (C)	Enzyme	1	-3.5
35	Solute carrier family 22 member 6 (A)	Enzyme	4	-4.8
36	Solute carrier family 22 member 6 (B)	Enzyme	-	-4.9

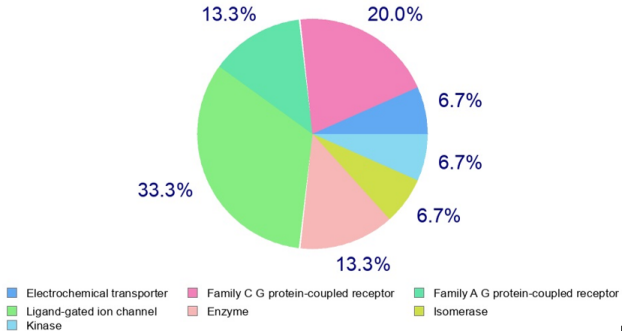
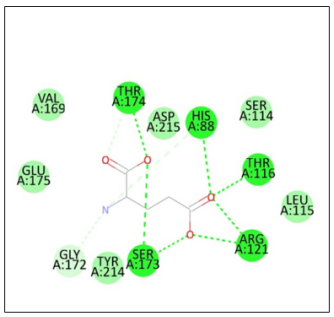
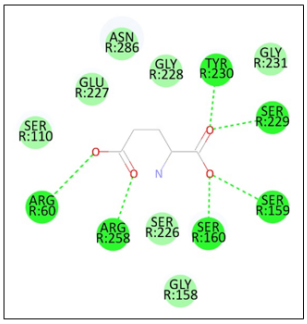


Figure 1: Target class for monosodium glutamate by swiss target prediction tool



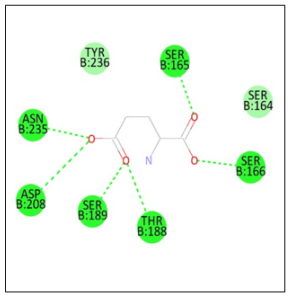
mode	affinity (kcal/mol)	dist from best mode rmsd l.b.	rmsd u.b.
1	-6.0	0.000	0.000
2	-5.6	1.604	4.382
3	-5.3	2.548	4.510
4	-4.7	2.323	3.021
5	-4.7	8.355	8.953
6	-4.6	8.083	9.500
7	-4.5	8.165	8.855
8	-4.1	9.213	10.525
9	-3.9	11.370	12.570

Figure 2: Ionotropic NMDA 2A (UNIPROT ID: Q00959)



mode	affinity (kcal/mol)	dist from best mode rmsd l.b.	rmsd u.b.
1	-5.0	0.000	0.000
2	-5.0	1.325	4.120
3	-4.8	1.640	2.006
4	-4.7	1.905	4.264
5	-4.7	2.483	4.176
6	-4.7	2.323	4.755
7	-4.5	2.579	4.646
8	-4.5	1.806	2.286
9	-4.4	3.355	4.305

Figure 3: Metabotropic 4R (UNIPROT ID: P31423)



mode	affinity (kcal/mol)	dist from best mode rmsd l.b.	rmsd u.b.
1	-4.5	0.000	0.000
2	-4.4	1.647	2.068
3	-4.4	1.236	3.820
4	-4.3	2.169	4.386
5	-4.3	2.117	2.679
6	-4.2	2.531	2.779
7	-4.2	2.096	3.686
8	-4.1	2.488	3.325
9	-3.9	2.094	2.371

Figure 4: Metabotropic 1B (UNIPROT ID: P23385)

4. Discussion

Glutamic acid docked with ionotropic NMDA 2A protein target showed better docking score (-6.0 kcal/mol) with five hydrogen bond interaction with SER A:173, ARG A:121, THR A:116, HIS A:88, THR A:174 amino acid residues in the binding pockets. Study shows that molecular interact with the amino acid residues such as SER A:173, ARG A:121 with more free energy than other residues. Recent studies states that arginine and serine amino acids interaction with ligand molecule showed better neuroprotection.

Glutamic acid docked with Metabotropic 4R protein target showed better docking score (-5.0 kcal/mol) with six hydrogen bond interaction with SER A:160, SER A:159, SER A:229, ARG A:258, ARG A:60, THR A:230 amino acid residues in the binding pockets. Study shows that molecular interact with the amino acid residues such as SER A:160, SER A:159, SER A:229, ARG A:258, ARG A:60 with more free energy than other residues. Recent studies states that arginine and serine amino acids interaction with ligand molecule showed better better neuroprotection

Glutamic acid docked with Metabotropic IB protein target showed better docking score (-4.5 kcal/mol) with six hydrogen bond interaction with SER A:165, SER A:189, SER B:166, ASP B:208, THR B:188, ASN B:235 amino acid residues in the binding pockets. Study shows that molecular interact with the amino acid residues such as SER A:165, SER A:189, SER B:166 with more free energy than other residues. Recent studies states that arginine and serine amino acids interaction with ligand molecule showed better neuroprotection.

5. Conclusion

Based upon the study we conduct, using in-silico method we concluded that MSG can be better neuroprotective molecule for the following proteins like, Ionotropic Glutamate NMDA 2A Receptor, Metabotropic Glutamate 4r Receptor and Metabotropic Glutamate 1b Receptor. These three targets are responsible for some neurological disorders. These three main proteins are taken into the consideration only because of their docking interaction with ligand (MSG) and the number of conventional hydrogen bonding. MSG primarily targets metabotropic glutamate receptors (mGluRs) rather than ionotropic receptors. Metabotropic Glutamate receptor 4(R)(group III) and Metabotropic Glutamate 1(B)(group I) play a crucial role in modulating neurotransmission and are intriguing targets for drug development in various neurological conditions. NMDA receptors play a pivotal role in synaptic plasticity, learning, and memory. Their activation involves both glutamate and glycine binding, contributing

to excitatory neurotransmission. The excitatory effects of glutamate, including neurotoxicity, are mainly mediated by activation of NMDA receptors. Monosodium glutamate, while not directly affecting NMDA receptors, is an interesting compound related to glutamate signalling in the brain. Diseases/Disorders associated with GRM1 are Schizophrenia, Bipolar disorder,Depression and Breast cancer. With GRM4 are Parkinson's disease, Huntington's disease and breast cancer. With GRIN2A are Epilepsy-Aphasia syndrome, Schizophrenia and Children with early onset pyschosis. Consideration of these data used to perform in-vitro study with regulating the synaptic activity and excitatory action of these targets by dose reduction. MSG have strong interaction with these three proteins and Even though WHO, US FDA, FSSAI and several organizations recommended by estimated safe dose of MSG, people are still affected by some side effects. In future, the dose reduction study can conduct to reduce the dose range to the particular dose for beneficial and neuroprotective effects with focussing the by targeting these three proteins based on their docking interactions.

6. Future Perspectives

Monosodium glutamate identified as a better neuroprotective molecule from this study. However, solubility and blood brain barrier penetration capacity is poor for this molecule. Hence identifying and validating the better formulation with minimal dose to target the brain would be a novel approach in this case.

7. Source of Funding

None.

8. Conflict of Interest

None.

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