Ağrı Tıp Fakültesi Dergisi 2025 3(2):54-61
e-ISSN: 2980-0978

Research Article/ Araştırma Makalesi
DOI: 10.61845/agrimedical.1522158

Investigation of structural suitability of agmatine with glutamatergic ion channels: Molecular docking study

Agmatinin glutamaterjik iyon kanalları ile yapısal uygunluğunun araştırılması: Molecular docking çalışması

Hilal Öztürk[1]*, Nuri Yorulmaz[2]

[1]*Karadeniz Technical University, Faculty of Medicine, Department of Biophysics, Trabzon, Türkiye*
[2]*Harran University, Faculty of Science, Department of Physics, Sanliurfa, Türkiye*

*0000-0003-0079-5184
*0000-0003-4959-2302

**Sorumlu Yazar:*
Hilal Öztürk
Karadeniz Technical University,
Faculty of Medicine,
Department of Biophysics,
Trabzon, Türkiye
e-mail: hilal.ozturk@ktu.edu.tr

Gönderilme Tarihi: 25/7/2024
Kabul Tarihi: 17/02/2025
Yayınlanma Tarihi: 30/06/2025

Cite this article: Öztürk H, Yorulmaz N. Investigation of structural suitability of agmatine with glutamatergic ion channels: Molecular docking study. Ağrı Med J. 2025; 3(2):54-61.

ABSTRACT

Aim: Agmatine is considered a neurotransmitter that is expressed almost everywhere in the brain and is thought to act as a neuromodulator. There is evidence that it interacts with glutamatergic ion channels associated with physiological and pathological states such as excitability and hyperexcitability. In this study, possible relationships of seizure-related ion channels (KARs, AMPARs and NMDARs) with agmatine are discussed using molecular docking method.
Materials and Method: Information on glutamatergic ion channels was obtained from the Protein Data Bank. The 2D structure of agmatine and inhibitors of receptors were retrieved from NCBI PubChem in .sdf format. Simulation studies were carried out using the Auto Dock 4.2.6 software program.
Results: Binding sites were determined. The binding energy of agmatine to these receptors was compared with reference molecules. In this case, the binding energy of agmatine to KAR, AMPAR and NMDARs is -5.73 kcal/mol, -5.41 kcal/mol and -4.01 kcal/mol, respectively. In addition, when compared with the binding energies of the glutamate molecule, approximate energy values were obtained.
Conclusion: In conclusion, it can be said that Agmatine does not have the ability to structurally block the ionotrophic glutamate receptors AMPAR, KAR and NMDAR as a result of its weak bonds. However, it seems to have the ability to bond to the channel with binding energies close to glutamate binding. We think that agmatine binds to the receptor at the glutamate binding site, but instead of activating the receptor, it may have prevented the receptor from being activated by blocking the binding of glutamate.

Keywords: Agmatine, Excitability, Molecular Docking study

ÖZ

Amaç: Agmatin beynin hemen her yerinde eksprese olan ve modülatör olarak görev yaptığı düşünülen bir nörotransmiter olarak kabul görmektedir. Uyarılabilirlik ve aşırı uyarılabilirlik gibi fizyolojik ve patolojik durumlarla alakalı glutamaterjik iyon kanallarıyla etkileştiğine dair kanıtlar vardır. Bu çalışmada, nöbet ile ilişkili iyon kanallarının (KAR'lar, AMPAR'lar ve NMDAR'lar) agmatin ile olası ilişkileri moleküler docking yöntemi kullanılarak tartışılmaktadır.
Gereç ve Yöntem: Glutamaterjik iyon kanallarına ait bilgiler Protein Data Banktan alındı. Kainat reseptörleri için 1YCJ, AMPA reseptörleri için 1FTM ve NMDA reseptörleri için 5EWJ kodlu protein XRD görüntüleri kullanıldı. Agmatin ve iyonotropik glutamat reseptör inhibitörleri olan topiramat, AMPA ve ifenprodilin 2D yapıları NCBI Pubchem'den .sdf formatı olarak alındı. Auto Dock 4.2.6 yazılım programı kullanılarak simülasyon çalışmaları gerçekleştirildi.
Bulgular: KAR, AMPA ve NMDA reseptörlerini sırasıyla bloke ettiği bilinen topiramat, AMPA ve ifenprodil için bağlanma bölgeleri ve bağlanma enerjileri belirlendi. Agmatinin bu reseptörlere bağlanma enerjisi referans moleküllerle kıyaslanarak verildi. Bu durumda agmatininKARlara bağlanma enerjisi -5.73 kkal/mol, AMPAlar için -5.41 kkal/mol ve son olarak NMDAlar için -4.01 kkal/mol olarak hesaplanmıştır. Ayrıca bu reseptörleri aktive ettiği bilinen glutamat molekülünün bağlanma enerjileri ile agmatin bağlanma enerjileri kıyaslandığında yakın enerji değerleri elde edilmiştir.
Sonuç: Tüm bu değerlendirmeler göz önüne alındığında, Agmatinin sahip olduğu zayıf bağlar sonucu iyonotrofik glutamat reseptörleri AMPAR, KAR ve NMDAR'ı yapısal olarak bloke etme kabiliyetine sahip olmadığı söylenebilir. Bununla beraber glutamat bağlanmasına yakın bağlanma enerjileriyle kanala bağ kurma yeteneğine sahip gözükmektedir. Agmatinin reseptöre glutamat bağlama yerinden bağlandığını ancak reseptörü aktive etmek yerine glutamatın bağlanmasını bloke ederek reseptörün aktive olmasını engellemiş olabileceğini düşünüyoruz.

Anahtar Kelimeler: Agmatin, Uyarılabilirlik, Moleküler yerleştirme çalışma

INTRODUCTION

The central nervous system (CNS) can perform the transmission of information in the form of excitation or inhibition. It provides this information network using neurotransmitters. Neurotransmitters such as glutamate and gamma aminobutyric acid (GABA) are the main neurotransmitters of the excitation/inhibition balance. In addition to glutamatergic neurons, which constitute a high percentage of neurons in the cerebral cortex, 95% of the approximately 30.000 synapses of cortical pyramidal neurons are excitatory synapses (1-3). Based on this information, it can be said that glutamate and glutamatergic neurons are the most important parts of the basic excitatory system in the brain. Therefore, the glutamatergic system is important in normal brain activity and an imbalance in this system may cause some pathologies (4). Excessive increase in neuronal excitability (or suppression of the inhibition mechanism) is the most accepted hypothesis in the pathogenesis of epilepsy. The increase in glutamate concentration in the extracellular fluid during a seizure is evidence that it may have a key role in epileptic events (5-7). The glutamate level against possible toxic effects is controlled by the CNS with the contribution of glutamate transporters, autoreceptors and desensitization of postsynaptic receptors (8, 9). Ionotropic glutamate receptors, one of the two subclasses of glutamate receptors, are used both in triggering and arresting seizures, using agonists and antagonists, respectively. Kainate receptors, N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methylisoxazol-4-propionic acid (AMPA) receptors are ionotropic glutamate receptors that are frequently investigated in in vitro and in vivo animal experiments. Activation of these receptors involves binding of the neurotransmitter glutamate, like the molecules from which they are named (such as the kainate for kainate receptor). Kainate receptors, which have a tetrameric structure, are rich in NMDA pathways and contain GluK (1-5) subunits (10). KARs have been associated with a variety of disease states (11). Therefore, to understand the contribution of KARs to neuronal processes, GluK1 has been used to investigate its role in neurological disorders such as epilepsy (12). AMPA receptors, which are involved in fast neurotransmission, can be homo- or hetero-tetrameric. They consist of four subunits, GluR1-4. The GluR2 ligand binding site (S1S2) has been used as a target for drug discovery (13). The GluR2 subunit is the determinant of calcium permeability (14). NMDA receptors, which have much lower channel kinetics compared to AMPA receptors, have two GluN1 subunits together with either two GluN2 subunits or a combination of GluN2 and GluN3 subunits (15). In addition to endogenous agonists/antagonists, it is used as a drug target in different neurological diseases. Depending on the changes in the membrane potential, the Mg ion that blocks the channel at rest is removed. Receptor activity is modulated by protons and Zinc (4, 15).

A dysfunction in these receptors can cause channelopathies such as epilepsy (16). Drug studies are also continued as a series of in vivo and in vitro experiments to reduce the contribution of these receptors to overstimulation. Agmatine, expressed in almost all regions of the brain, is synthesized by decarboxylation to l-arginine (17). Studies have shown that agmatine is a neuromodulator that mimics the functions of other neurotransmitters (18, 19). Among these studies, it was noted that it blocks harmful ion channels (20). Especially in brain studies, it has been stated that endogenous and exogenous agmatine interact with ion channels responsible for different neurological diseases (21). Due to these conflicting results, the role that agmatine plays in the excitability-related pathway has not been fully defined. Here, the possible relations of epilepsy-related ion channels (KARs, AMPARs and NMDARs) with agmatine are discussed using molecular docking method.

MATERIALS AND METHOD

Receptor dataset collection

The first step of the study was the selection of receptor proteins. Protein structures coded 1YCJ for KAR, coded 1FTM for AMPAR and coded 5EWJ for NMDAR were used from the Protein Data Bank. Because these crystal structures are XRD images containing active binding sites and reference molecules. They are also codes frequently used in studies on epilepsy. The molecular structure and properties of 1YCJ, 1FTM and 5EWJ are presented in Table 1. For each protein, the reference molecule in complex with the protein crystal structure was extracted. All heteroatoms were removed and replaced with polar hydrogens.

Table 2. Grid parameters

Receptor ID	Grid Points in xyz	Spacing (Å)	Grid Center Coordinates (x, y, z)
1FTM	40 40 40	0.375	76.001 29.803 41.755
1YCJ	40 40 40	0.375	23.047 28.318 52.362
5EWJ	40 48 40	0.502	83.173 14.255 -37.425

Data source and ligand preparation

The 2D structure of agmatine (Figure 1) and inhibitors of ionotropic glutamate receptors, topiramate, AMPA and ifenprodil were retrieved from NCBI PubChem in .sdf format. The energies of ligands minimized by Avogadro version 1.2 with Force Field type MMFF9, and saved in .mol2 format (22).

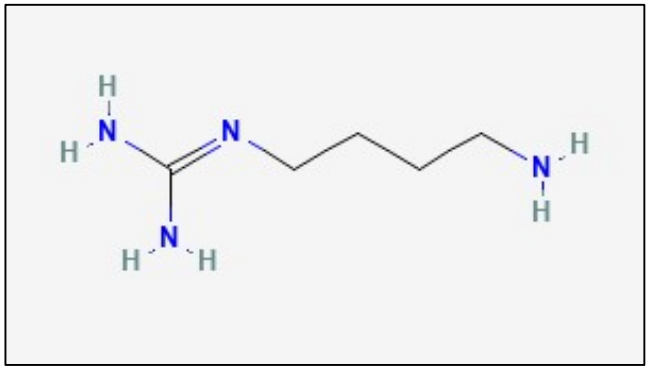

Figure 1. The molecular structure of Agmatine

ADME Studies

The SwissADME website was used to determine the physicochemical, pharmacokinetic and solubility (ADME) properties of the reference molecules and agmatine used in the study (23).

Docking studies

In the study, a computer equipped with Microsoft Windows 10 Education and Intel Core i5-2400CPU 3.10 GHz dual processor and 4 GB RAM was used. Structural binding of Agmatine and reference molecules to receptor proteins was evaluated in the simulation study performed with Auto Dock 4.2.6 software (24). To determine the suitability of the selected grid sizes and central positions, the molecule bound to the protein structure (e.g. topiramate for 1YCJ) was removed and re-docked using the grid values given in the Table 2. Figure 2 shows the redock results for the proteins and its RMSD values. This is data that proves the accuracy of the docking process.

The protein-ligand complexes were visualized and analyzed using AutoDockTools and Discovery Studio version 4.0 (Accelrys Software Inc., San Diego, CA, USA).

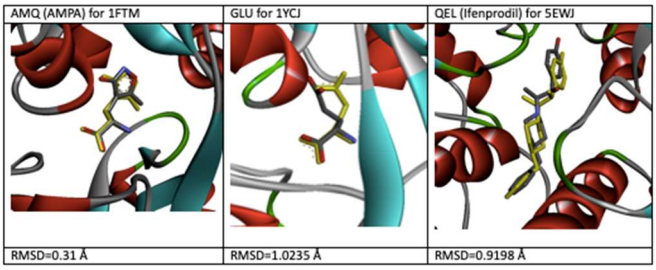

Figure 2. Overlaid re-dock images. Re-dock was performed for molecules bound to AMPAR, KAR and NMDAR, and their RMSD values are 0.31 Å, 1.0235 Å, and 0.9198 Å, respect,vely. The yellow colored molecules represent the original ligand, the others represent the re-docked one.

RESULTS

The physicochemical properties of agmatine with the 3 reference molecules used in our study were compared using SwissADME software. Table 3 shows that all molecules are suitable in terms of molecular weight, number of hydrogen bond acceptors/donors, and number of rotatable bonds. In terms of its dissolution properties in oil-type solvents, it showed soluble properties from all molecules. In addition, agmatine shows very high solubility in water, while the molecules have moderate to good solubility in water. The molecules have high absorption and rapid excretion from the body. The bioavailability score of all molecules was calculated as 0.55 (Figure 3).

Molecular docking results for KAR, NMDAR and AMPAR are presented based on comparison of agmatine with reference molecules. The binding energies of topiramate, AMPA and ifenprodil molecules, which are known to inhibit these receptors, as well as glutamate, an endogenous activator, were calculated. The information including the binding energies and the hydrogen bonds formed between molecules are given in Table 4.

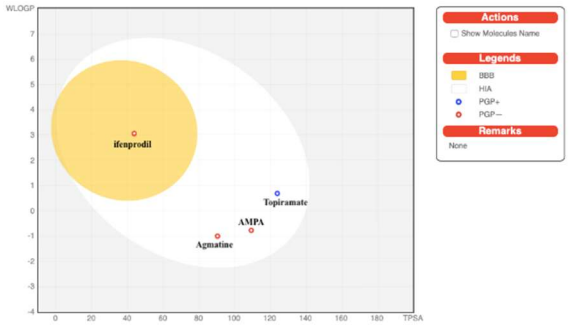

Figure 3. Bioavailability radar plot and The Boiled-Egg model of molecules

The binding energy of the AMPA molecule, which is known to bind AMPARs, which are fast ionotropic channels, to the active site of this receptor was obtained as -8.99 kcal/mol. ARG96, THR91, SER142, THR143, PRO89 and GLU193 amino acids made strong binding with the receptor via hydrogen bonds. And it is also connected with GLY141 by carbon hydrogen bond. It has been determined that agmatine forms hydrogen bonds with same amino acid residues in the same binding site, and also has common van der Waals interactions with AMPA via LEU90 and GLY141. Therefore, the binding energy of agmatine with the GLUR2 ligand binding core is -5.41 kcal/mol. In Figure 4, we see the 2D binding of agmatine and the reference molecule to the AMPA receptor.

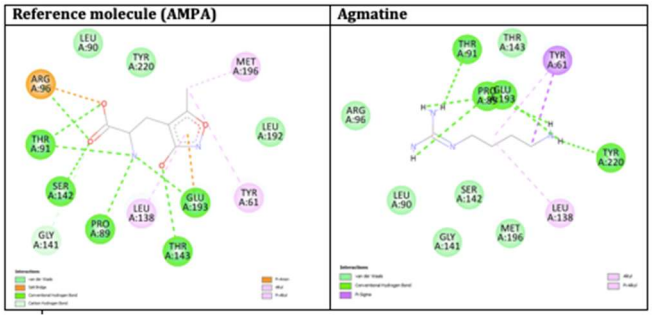

Figure 4. 2D image of the molecular binding between AMPA and 1FTM / Agmatine and 1FTM

In the results obtained for KAR, it is seen that the reference molecule topiramate and agmatine form common hydrogen bonds with the amino acids THR518, GLU738 and double bond with PRO516. SER689 and ARG523 residues, to which topiramate is hydrogen bonded, interacted with agmatine van der Waals bonds. Therefore, the binding energy of topiramate to the active site of the protein was calculated as -8.15 kcal/mol, while the binding energy of agmatine was calculated as -5.73 kcal/mol, which is an approximate but lower value. 2D images of the binding scores of both molecules are given in Figure 5.

According to the results of docking with the amino terminal domains of the NMDA receptor subunit GLUN1 and GLUN2B, it was determined that agmatine made a double hydrogen bond with ILE133, and the reference molecule ifenprodil formed a van der Waals bond. Apart

from this, it is listed as the common interaction between GLN110, where ifenprodil interacts with van der Waals, and agmatine hydrogen bonding. The binding energies of these two molecules, which carry out their other bindings via different amino acids, are -10.71 kcal/mol for ifenprodil and -4.01 kcal/mol for agmatine, respectively. More detailed 2D images of these bindings are given in Figure 6.

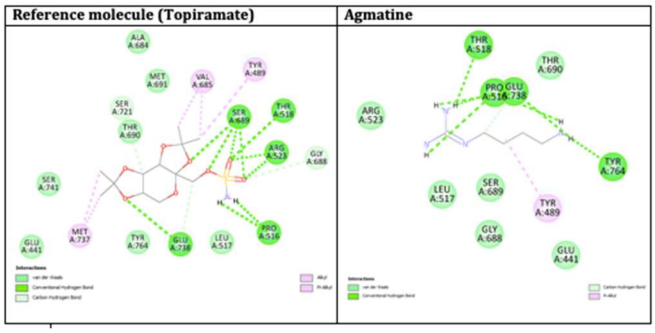

Figure 5. 2D image of the molecular binding between topiramate and 1YCJ / Agmatine and 1YCJ

In our study, the binding energies of glutamate, which is the endogenous agonist of glutamatergic ion channels, to the protein binding sites were calculated. The binding energy of AMPA receptor to GluR2 S1S2J subunit is -6.65 kcal/mol, while agmatine is -5.41 kcal/mol. 3D binding images are shared in Figure 7.

We see the 3D binding images of KAR and NMDAs in Figure 8. Agmatine is located in the same binding site with an energy close to the glutamate binding energy as given in Table 4.

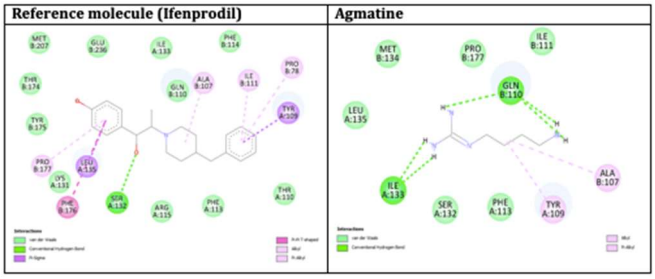

Figure 6. 2D image of the molecular binding between ifenprodil and 5EWJ / Agmatine and 5EWJ

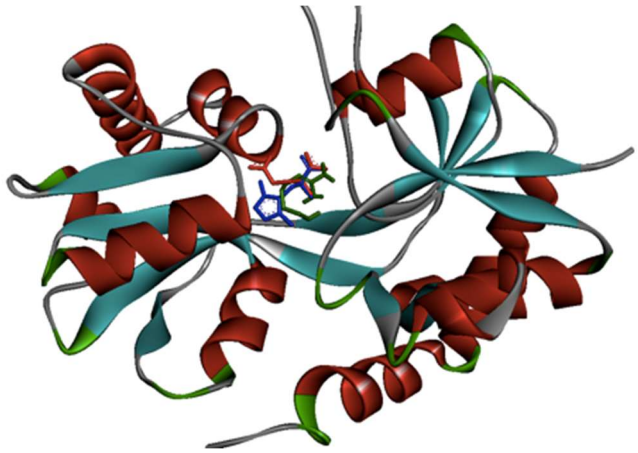

Figure 7. The crystal structure of the GluR2 ligand binding core (S1S2J) in complex with agmatine, glutamate and AMPA. Agmatine is shown as green, antagonist (AMPA) as blue and agonist (glutamate) as red sticks.

Table 1. The structures and properties of receptor proteins

Molecule ID	Molecule Structure	Molecule Binding Core	Organism	Resolution (Å)
1YCJ		Kainate receptor GluR5 ligand binding core	Rattus norvegicus	1.95
1FTM		GLUR2 ligand binding core (S1S2J)	Rattus norvegicus	1.70
5EWJ		Amino terminal domains of the NMDA receptor subunit GLUN1 and GLUN2B	Xenopuslaevis, Homo sapiens	2.77

DISCUSSION

In studies where NMDA antagonists such as ketamine and MK-801 were used, there were findings indicating that agmatine exerts a synergistic antidepressant effect through this channel blockade (25-27). Accordingly, it has been argued that agmatine is an antagonist for NMDA receptors (28). In addition to the thought that agmatine is an NMDA receptor antagonist, it is also thought that the interaction between AMPA and NMDA mediates its antidepressant-like behavior (29, 30).

There are also studies suggesting that it preferentially antagonizes NMDAs, especially those containing the GluN2B subunit (31). It has been reported that ifenprodil, a known NMDA antagonist, reduces neuropathic pain with its blockade on GluN2B, and the same effect is seen with agmatine.In the molecular docking study, it was observed that the binding energy was not sufficient based on the results we obtained in the attachment of agmatine to the ifenprodil binding site in the GluN2B subunit. Accordingly, it can be thought that agmatine binds to a different site than ifenprodil, which inhibits the activation of the NMDA receptor by showing an allosteric effect. In addition, it should be considered that the in silico model only analyzes the structural fit.

Considering all these evaluations, it can be said that Agmatine does not have the ability to structurally block ionotrophic glutamate receptors AMPAR, KAR and NMDAR, as a result of weak bonds it has.

Agmatine may be co-localize with glutamate at synaptic terminals and nerve cell bodies (32). Thus, it is thought that it may regulate glutamatergic neurotransmission. Although studies have focused on inhibition of NMDA receptors, effects on glutamate release may also contribute to this mechanism. In the rat pentylenetetrazole (PTZ)-induced seizure model, it was reported that agmatine regulates the extracellular glutamate level (33).

In the study, the time and amount of exogenously given agmatine to reach the brain were determined, and it was determined that agmatine pretreatment delayed seizures and reduced seizure duration. It has been analyzed that it reduces the increased glutamate level after PTZ injection.

In addition to studies indicating that agmatine blocks glutamatergic ion channels, there are also studies suggesting that it plays an anticonvulsant role against glutamate-induced seizure models (21, 34). In our study, it was theoretically calculated that agmatine binds to the glutamate binding site in glutamatergic ion channels at approximate energies. We think that agmatine binds to the receptor at the glutamate binding site, but instead of activating the receptor, it may have prevented the receptor from being activated by blocking the binding of glutamate.

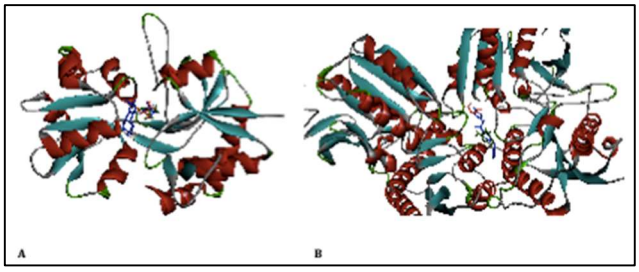

Figure 8. The crystal structure of A) Kainate receptor GluR5 ligand binding core in complex with agmatine, glutamate and Topiramate. Agmatine is shown as green, antagonist (topiramate) as blue and agonist (glutamate) as red sticks. B) Amino terminal domains of the NMDA receptor subunit GLUN1 and GLUN2B in complex with agmatine, glutamate and ifenprodil. Agmatine is shown as green, antagonist (ifenprodil) as blue and agonist (glutamate) as red sticks.

Table 3. In-silico physic-chemical properties of molecules

ADME Properties	Topiramate (Reference)	AMPA (Reference)	Ifenprodil (Reference)	Agmatine
Molecularweight	339.36 g/mol	186.17 g/mol	325.44 g/mol	130.19 g/mol
No. of heavyatoms	22	13	24	9
No. of rotatablebonds	3	3	5	4
No. of H-bondacceptors	9	5	3	2
No. of H-bonddonors	1	3	2	3
Molarrefractivity	71.75	43.35	102.23	37.96
TPSA (Å^2)	123.92	109.32	43.70	90.42
M LOGP	-0.65	-3.07	3.08	-0.43
LogS(ESOL) solubility	-1.22	0.95	-4.35	0.59
Absorption	High	High	High	High
BBB permeant	No	No	Yes	No
CYP1A2 inhibitor	No	No	Yes	No
CYP2C19inhibitor	No	No	No	No
CYP2C9 inhibitor	No	No	No	No
CYP3A4inhibitor	No	No	No	No
Log Kp (skin permeation)	-8.96 cm/s	-9.73 cm/s	-5.52 cm/s	-8.19 cm/s
Lipinskiviolation	Yes	Yes	Yes	Yes
Ghoseviolation	Yes	No	Yes	No
Veberviolation	Yes	Yes	Yes	Yes
Bioavailabilityscore	0.55	0.55	0.55	0.55

Table 4. The binding scores

Macromolecule	Ligand	BindingEnergy (kcal/mol)	InhibitionConstant, Ki	HydrogenBonds	Thedistance of hydrogenbonding (Armstrong)
1FTM (A-Chain)	Agmatine	-5.41	107.89 µM	H – PRO89:O	2.32
				H – PRO89:O	1.84
				H – THR91:OG1	2.04
				H – GLU193:OE1	1.77
				H – GLU193:OE1	1.79
				H – TYR120:OH	2.56
	REF.AMQ	-8.99	256.85 mM	ARG96:NH2 – OT1	3.09
				SER142:N-OT1	3.00
				THR143:OG1-OE1	2.68
				THR91:N-OT2	2.90
				N-PRO89:O	2.72
				THR91:OG1-N	2.83
				N-GLU193:OE1	2.59
	REF. GLU	-6.65	13.34 µM	THR143:N-OE2	2.90
				SER142:N-OE2	2.77
				SER142:N-OXT	2.99
				ARG96:NH1-O	2.87
				THR91:N-O	2.83
				THR91:OG1-N	2.90
				N-PRO89:O	2.80
				N-GLU193:OE1	2.78
1YCJ (A-Chain)	Agmatine	-5.73	63.58 µM	H – GLU738:OE1	1.81
				H – GLU738:OE1	1.89
				H – TYR764:OH	2.75
				H – THR518:OG1	2.19
				H – PRO516:O	2.60
				H – PRO516:O	1.99
				H – PRO516:O	2.32
	REF-TOP	-8.15	1.06 µM	GLU738:N – O	2.94
				H – PRO516:O	2.27
				H – PRO516:O	2.49
				THR518:N – O	2.84
				ARG523:NH1 – O	2.51
				SER689:OG – O	2.74
				SER689:OG – O	2.63
				ARG523:NH2 – O	3.37
				SER689:N – O	3.11
				SER689:N – O	3.26
	REF. GLU	-6.53	16.33 µM	ARG523:NH1 – O	3.02
				THR518:N – O	2.72
				THR518:OG1 – N	2.91
				N – PRO516:O	2.71
				N – GLU738:OE1	2.69
				SER689:N – OE2	2.70
				SER689:OG – OE2	3.10
				THR690:N – OE2	2.72
				THR690:OG1 –OE2	2.90
5EWJ (A-B Chain)	Agmatine	-4.01	1.14 mM	H – A:ILE133:O	2.19
				H – A:ILE133:O	2.34
				H – B:GLN110:OE1	2.03
				H – B:GLN110:OE1	2.16
				H-B:GLN110:OE1	2.15
	REF-Ifen.	-10.71	14.17 nM	O-A:SER132:O	3.08
	REF. GLU	-2.61	12.27 mM	N – B:GLU236:OE2	2.60
				B:TYR175:N-OE2	2.75

CONCLUSION

In conclusion, agmatine is a neurotransmitter whose neurological effect/contribution has been investigated in physiological and pathological conditions. Conflicting opinions about its interaction have been reported in various studies. The molecular docking method provided information about the binding sites and energies of agmatine to the ionotropic glutamate receptor family. Considering all these evaluations, it can be said that agmatine does not have the ability to structurally block the ionotrophic glutamate receptors AMPAR, KAR and NMDAR as a result of its weak bonds. However, it seems to have the ability to bond to the channel with binding energies close to glutamate binding. We think that agmatine binds to the receptor at the glutamate binding site, but instead of activating the receptor, it may have prevented the receptor from being activated by blocking the binding of glutamate.

Conflict of Interest
The authors have no conflict of interest to declare.

Financial Disclosure
The authors declared that this study has received no financial support.

Authors' Contributions: Investigation
Data collection and processing, N.Y.; Data analysis and interpretation, H.Ö., N.Y.; Writing, H.Ö.; Review and editing, H.Ö., N.Y.

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