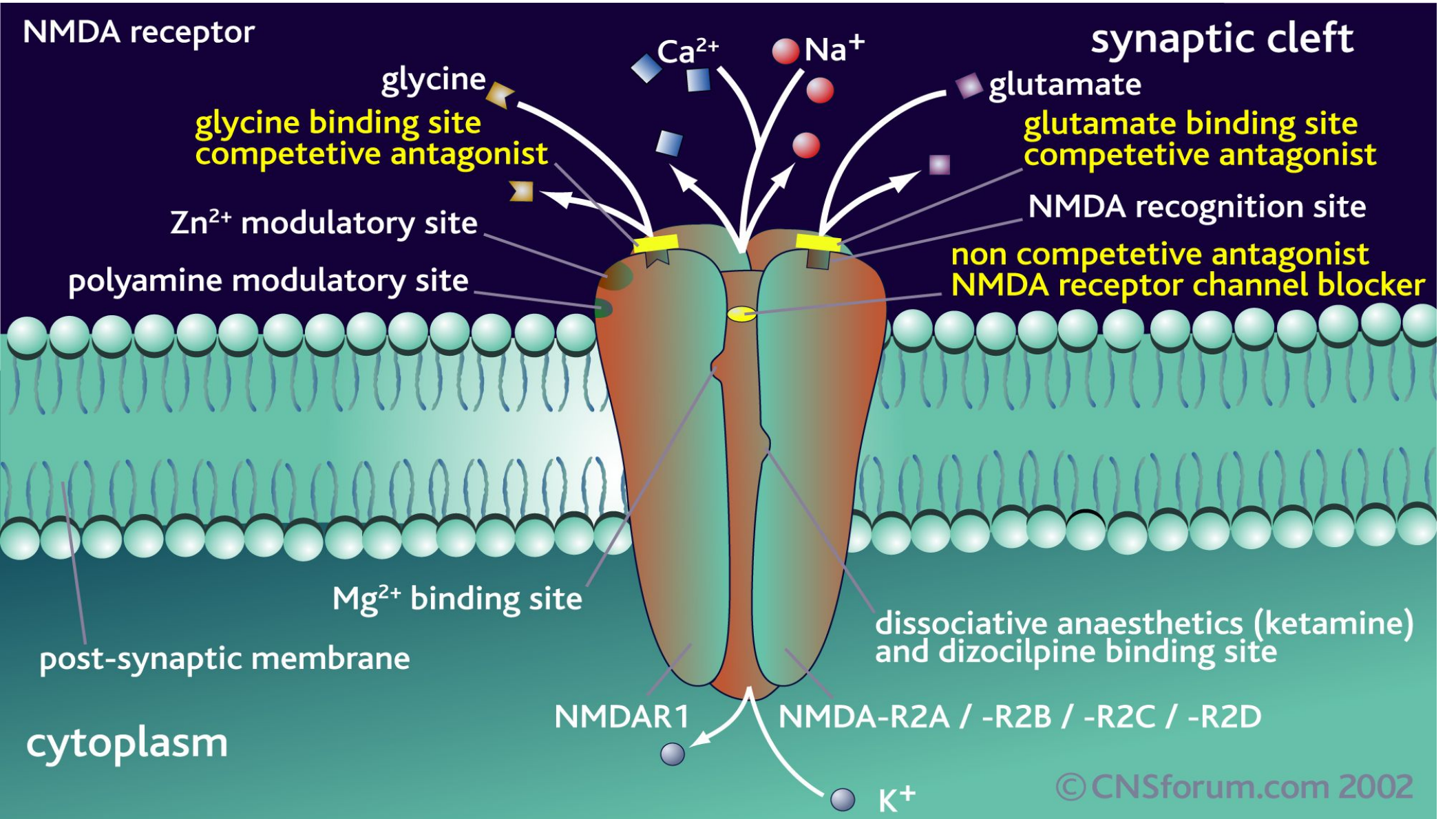
Роль антагонистов NMDA-рецепторов в развитии опухолей

Курсант 5 курса 2 факультета
рядовой Аксенов А.И.

Роль NMDA-рецепторов

- Глутамат-опосредованная передача сигнала в опухолях способствует их росту и пролиферации.
- В клетках опухолей также отмечается повышенный уровень экспрессии генов субъединиц NMDA-рецепторов.


NMDA receptor
synaptic cleft
Ca^{2+}
Na^{+}
glycine
glycine binding site
competetive antagonist
glutamate
glutamate binding site
competetive antagonist
Zn^{2+} modulatory site
NMDA recognition site
polyamine modulatory site
non competetive antagonist
NMDA receptor channel blocker
Mg^{2+} binding site
post-synaptic membrane
dissociative anaesthetics (ketamine)
and dizocilpine binding site
NMDAR1
NMDA-R2A / -R2B / -R2C / -R2D
cytoplasm
K^{+}
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Докинг

- Процедура, позволяющая оценить степень комплементарности молекулярной структуры в соответствующей активной полости молекулярной мишени, отвечающей за те или иные функции.

• Цель докинга

- Найти такое положение лиганда, в котором свободная энергия образования комплекса белок-лиганд будет минимальной.

Оценка результатов

- Скоринг-функция(Score) – рассчитанная энергия связывания белок-лиганд.
- Score < -5 ккал/моль

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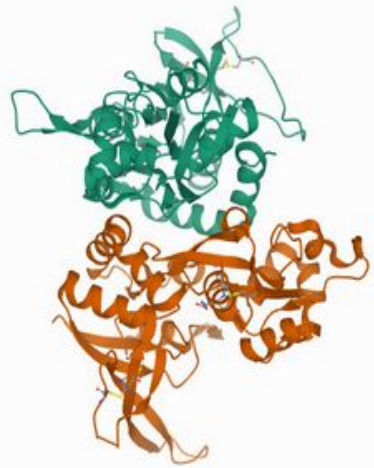
Biological Assembly 1



3D View: Structure | Electron Density | Ligand Interaction

Global Symmetry: Asymmetric - C1
Global Stoichiometry: Hetero 2-mer - A1B1

Pseudo Symmetry: Cyclic - C2 (3D View)
Pseudo Stoichiometry: Homo 2-mer - A2

Find Similar Assemblies

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6OVE

Crystal structure of GluN1/GluN2A NMDA receptor agonist binding domains with glycine and antagonist, 4-propylphenyl-ACEPC

DOI: 10.2210/pdb6OVE/pdb

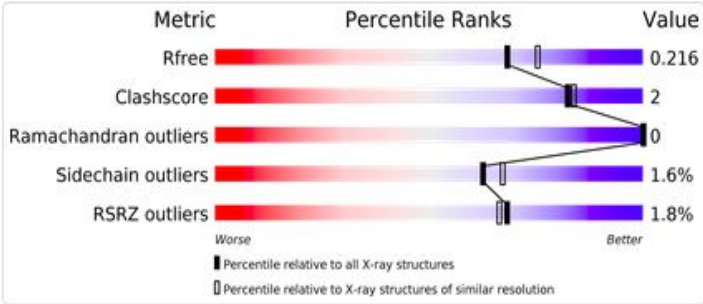
Classification: PROTEIN TRANSPORT
Organism(s): Rattus norvegicus
Expression System: Escherichia coli
Mutation(s): No

Deposited: 2019-05-07 **Released:** 2020-05-13
Deposition Author(s): Syrenne, J.T., Mou, T.C., Tamborini, L., Pinto, A., Sprang, S.R., Hansen, K.B.
Funding Organization(s): National Institutes of Health/National Institute of General Medical Sciences (NIH/NIGMS), National Institutes of Health/National Institute of Neurological Disorders and Stroke (NIH/NINDS)

Experimental Data Snapshot

Method: X-RAY DIFFRACTION
Resolution: 2.00 Å
R-Value Free: 0.216
R-Value Work: 0.182
R-Value Observed: 0.184

wwPDB Validation 3D Report Full Report



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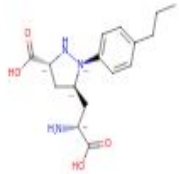
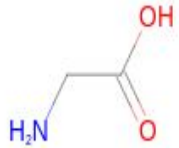
Small Molecules

Ligands 2 Unique

ID	Chains	Name / Formula / InChI Key	2D Diagram	3D Interactions
N9D Query on N9D Download Ideal Coordinates CCD File Download Instance Coordinates	B	**(3R,5S)-5-[(2R)-2-amino-2-carboxyethyl]-1-(4-propylphenyl)pyrazolidine-3-carboxylic acid** $C_{16}H_{23}N_3O_4$ UPNZKJBKYMIUDF-BFHYXJOUSA-N		Ligand Interaction
GLY Query on GLY Download Ideal Coordinates CCD File Download Instance Coordinates	A	**GLYCINE** $C_2H_5NO_2$ DHMQDGOQFOQNFH-UHFFFAOYSA-N		Ligand Interaction

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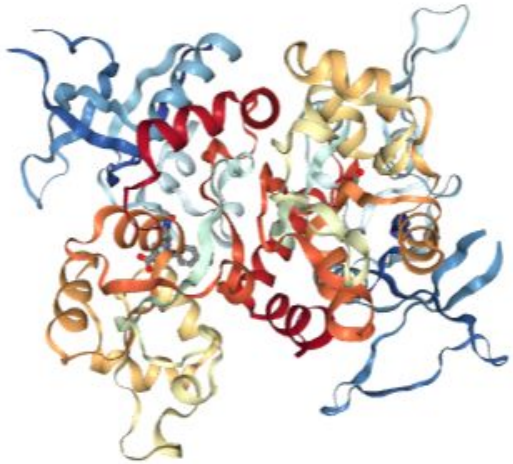
Note: Use your mouse to drag, rotate, and zoom in and out of the structure. Mouse-over to identify atoms and bonds. Mouse controls documentation.



Spin Center Fullscreen Screenshot Perspective Camera White background Focus 0

View Density Maps View

Structure View Documentation

Assembly Bioassembly 1

Model Model 1

Symmetry None

Style Cartoon

Color Rainbow

Ligand Ball & Stick

Quality Automatic

Water Ions

Hydrogens Clashes

Default Structure View

https://www.rcsb.org/3d-view/6ove

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Asm Id 1: Author Defined Asse...

Nothing Focused

Measurements

Structural Motif Search

Components 6OVE

Preset + Add

Polymer Cartoon

Ligand Ball & Stick

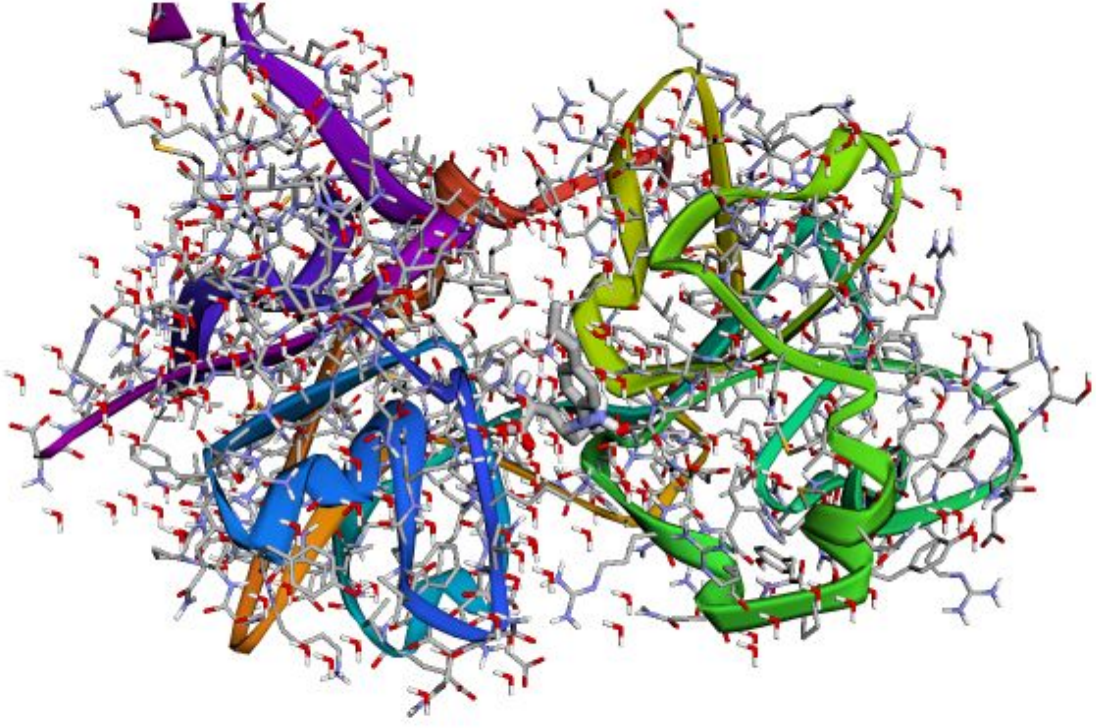
Water Ball & Stick

Unit Cell P 21 21 21

Density

Assembly Symmetry

Visualization



All Atoms Surface

Mode	Affinity (kcal/mol)	Dist From Rmsd L.B.	Dist From Rmsd U.B.
1	1.6	0	0
2	3.5	1.397	2.085

Литература

- Гуреев М.А., Кадочников В.В., Порозов Ю.Б. Молекулярный докинг и его верификация в контекстевиртуального скрининга. – СПб: Университет ИТМО, 2018. – 50с.