Drugs Acting on NMDA Receptors

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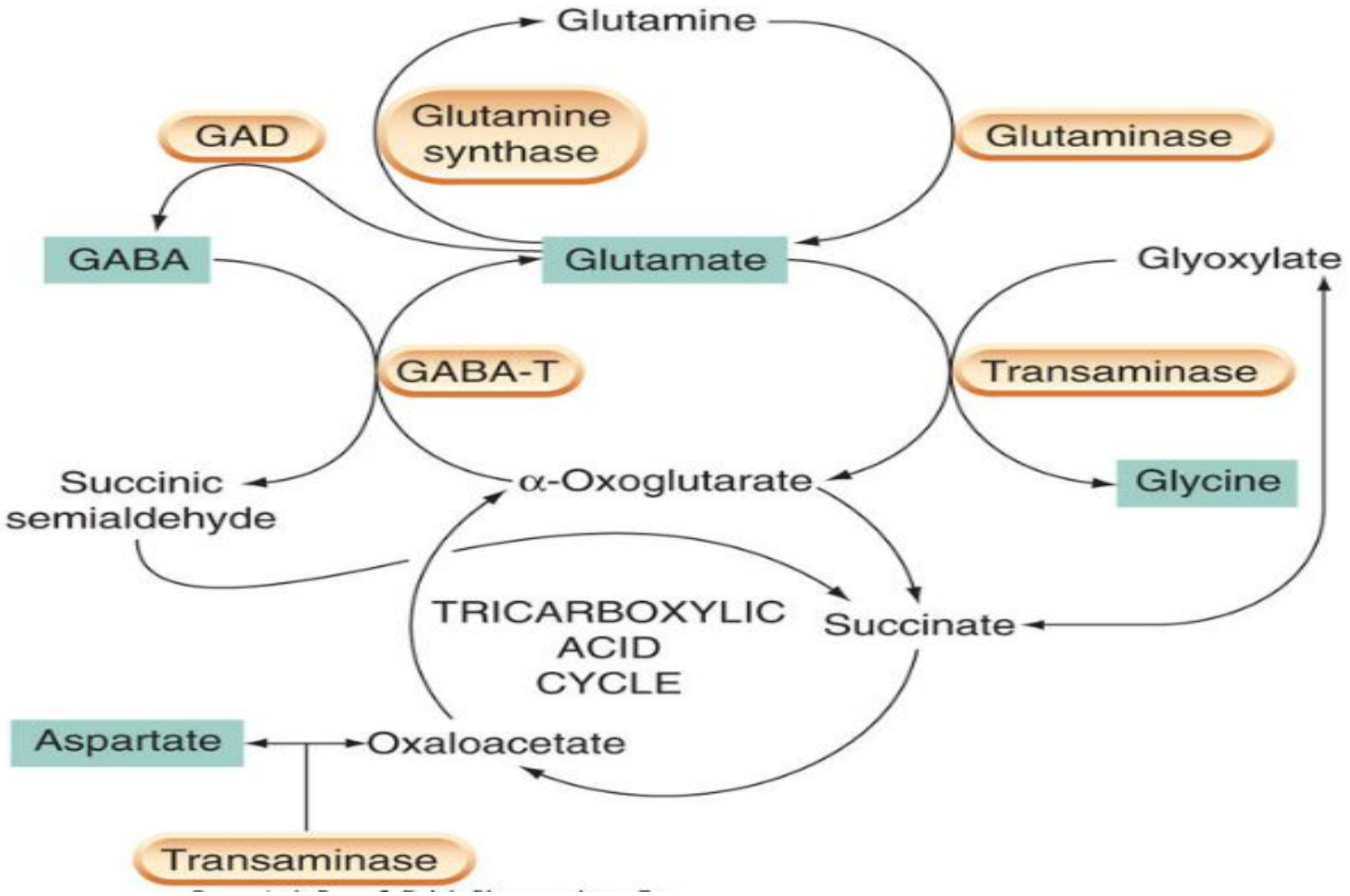
History

- 1970 : Glycine established as an inhibitory transmitter
- A major advance in the aminoacid neurotransmitters was the discovery of EAA antagonists (by Watkins in Bristol)

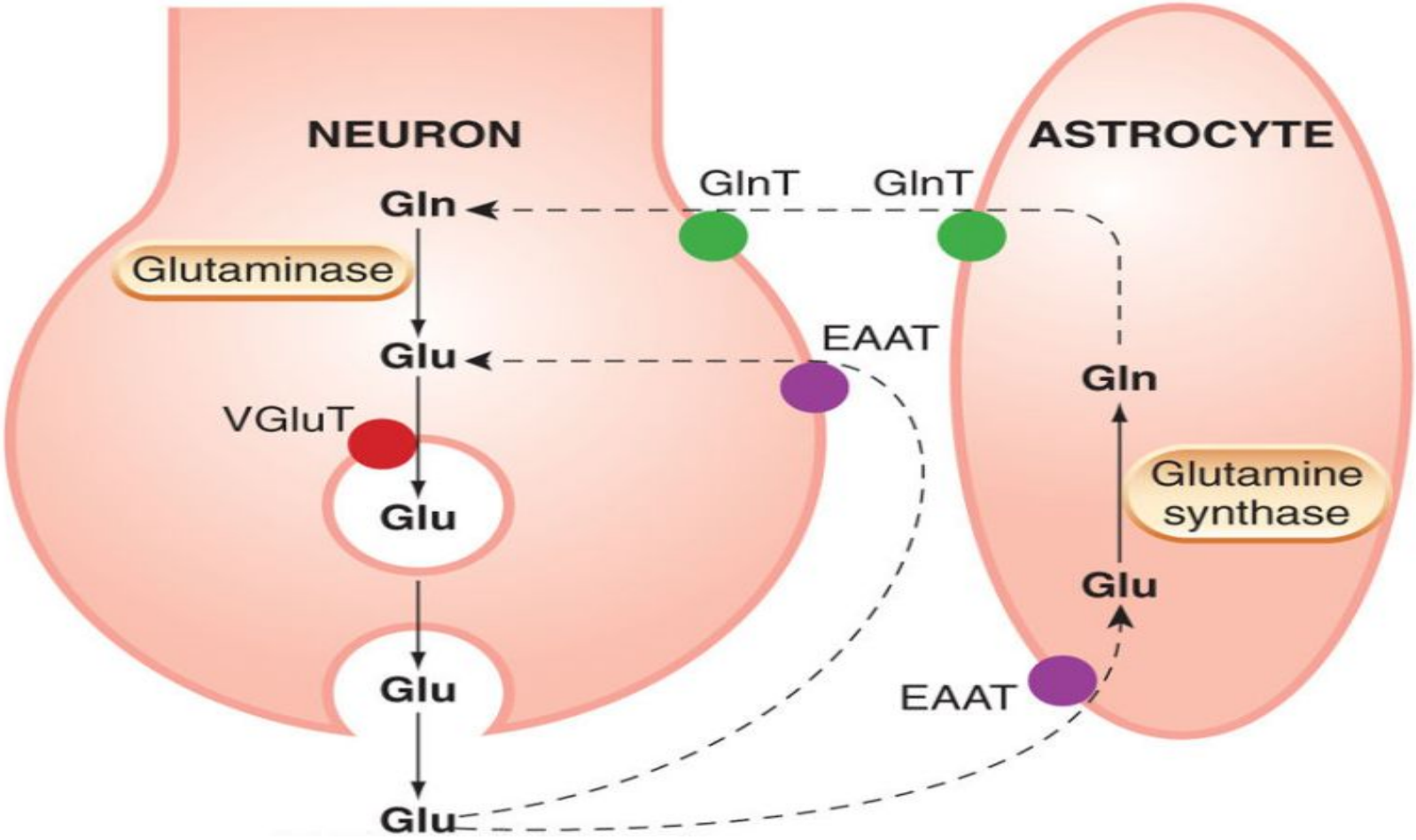
Introduction

- In the CNS amino acids acting as excitatory neurotransmitters (NT) are
  - Excitatory transmitter – Glutamate
    - Aspartate
    - Homocysteate
  - Inhibitory transmitters – GABA, Glycine

Synthesis of amino acid NT

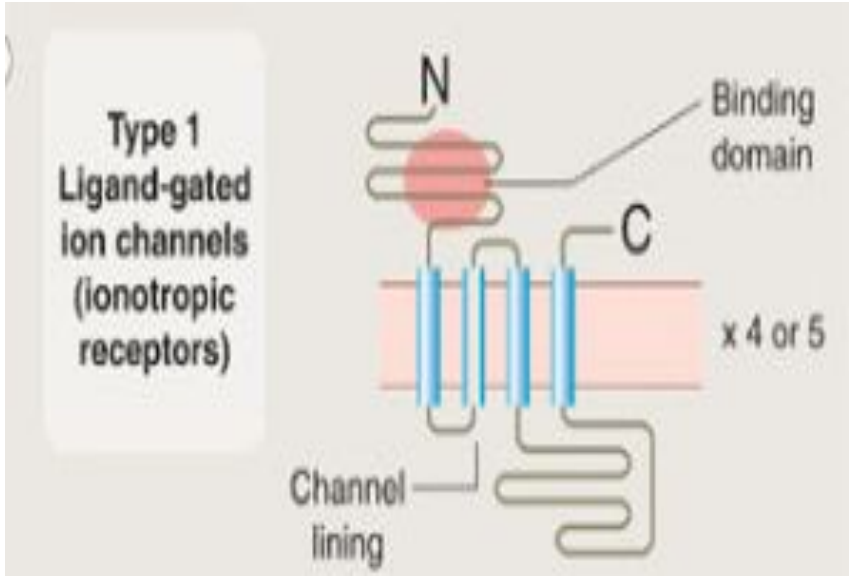


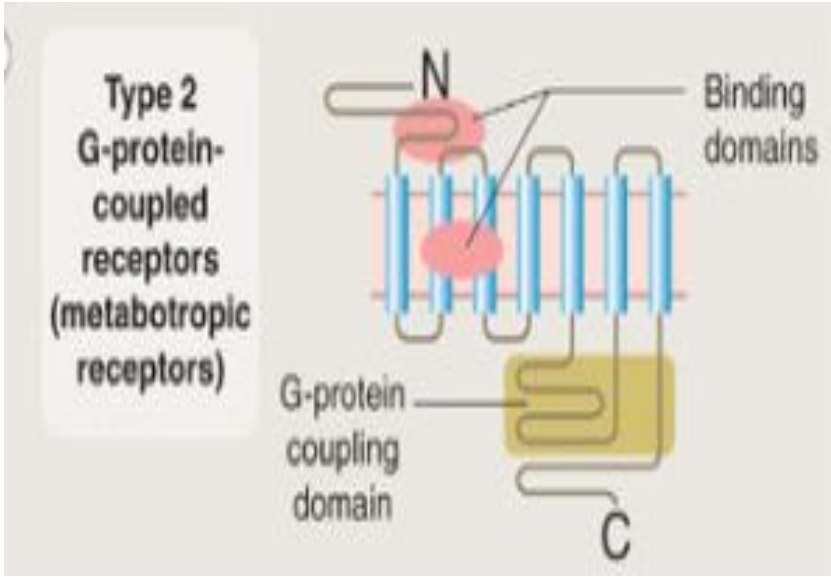
Synthesis, storage and release of EAA



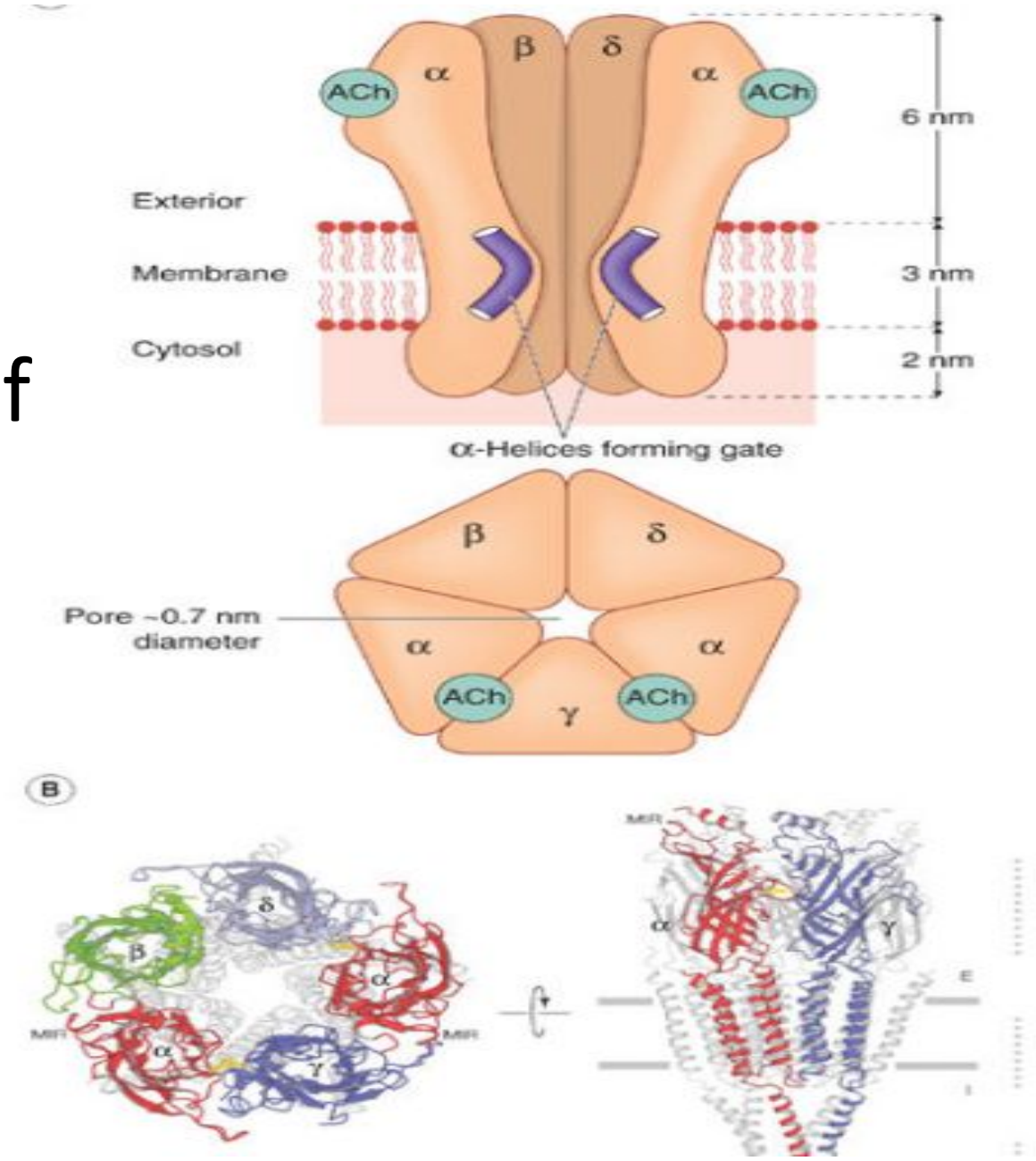
Glutamate receptor subtypes

- Glutamate and related EAA acts through both
  - Ionotropic (Ligand-gated cation channels)
  - Metabotropic receptors





Structure of Ligand gated Ion channel



Metabotropic receptors of EAA

- Also called G- protein coupled receptors
  - Post synaptic - Group1 : mGlu1 & 5, Gq type
  - Presynaptic - Gi/Go type
    - Group 2 - mGlu2 & 3
    - Group 3 - mGlu4, 6, 7 & 8

Ionotropic Receptor subtypes of EAA

- **NMDA receptors :** 7 subunits (GluN1, GluN2A, GluN2B, GluN2C, GluN2D, GluN3A, GluN3B).
- **AMPA receptors :** 4 subunits ($GluA_{1-4}$)
- **Kainate receptors :** 5 subunits ($GluK_{1-5}$)

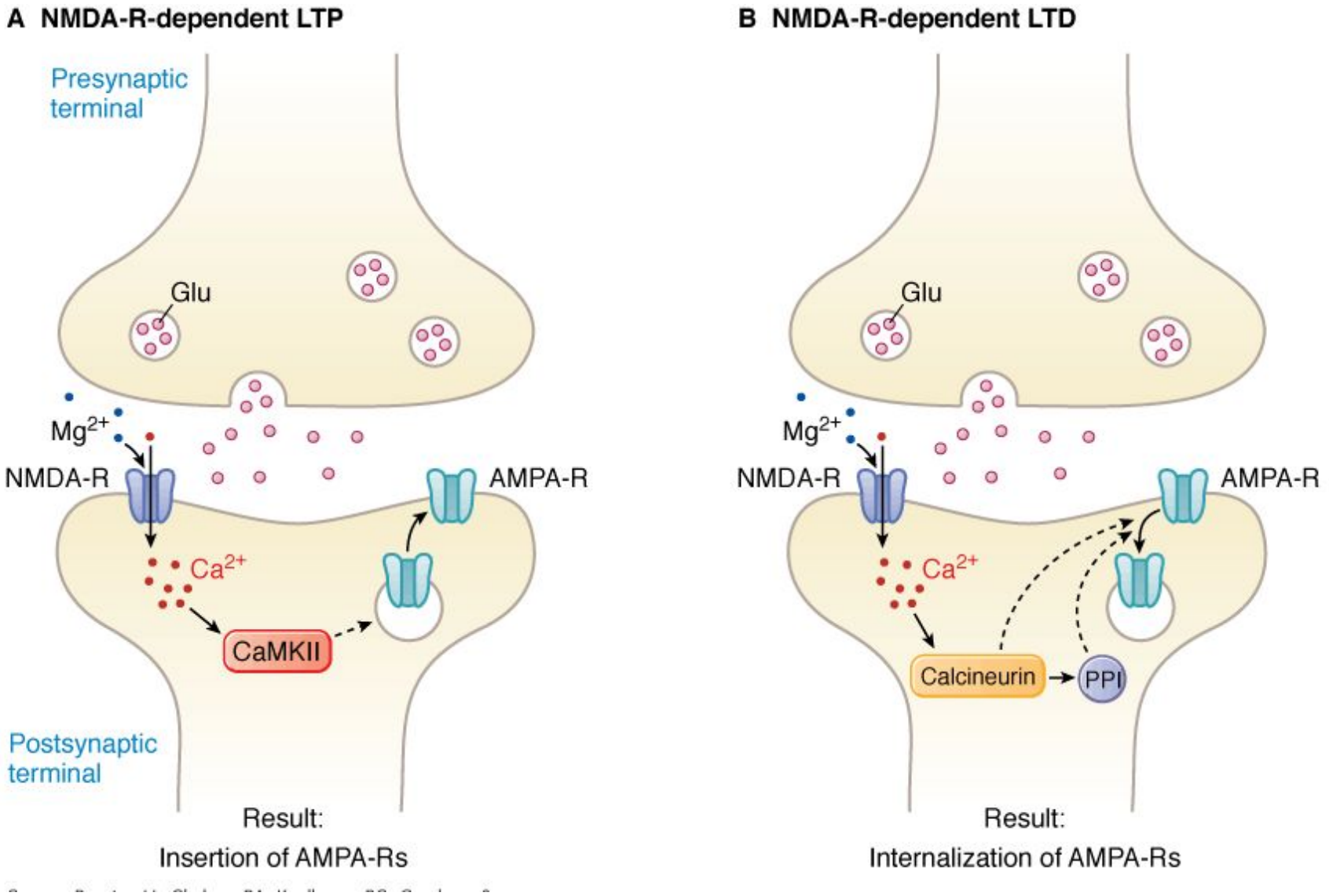
	NMDA		AMPA	Kainate
Subunits	Tetramers consisting of GluN1-3 subunits		Tetramers - GluA1-4	Tetramers - GluK1-5
	Receptor site	**Modulatory site**		
Endogenous agonist	Glutamate Aspartate	Glycine d-Serine	Glutamate	
Other agonist	NMDA	Cycloserine	AMPA, Quisqualate	Kainate, Domoate
Effector mechanism	Ligand-gated cation channel			
	Slow kinetics High Ca^{2+} permeability	Fast kinetics channels with GluR2A subunits show low Ca^{2+} permeability		Fast kinetics Low Ca^{2+} permeability

	NMDA	AMPA	Kainate
Other modulators	Polyamines (e.g. spermine, spermidine), Mg^{2+}, Zn^{2+}	Cyclothiazide, - Piracetam, CX - 516	
Channel blockers	Dizocilpine (MK801), phencyclidine, ketamine, remacemide, memantine, Mg^{+2}	-	-
Location	Postsynaptic, presynaptic, glial Wide distribution	Postsynaptic, glial	Pre & postsynaptic
Function	Slow EPSP	Fast EPSP	
	Synaptic plasticity (long-term potentiation, long-term depression) Excitotoxicity	Wide distribution	Presynaptic inhibition Limited distribution

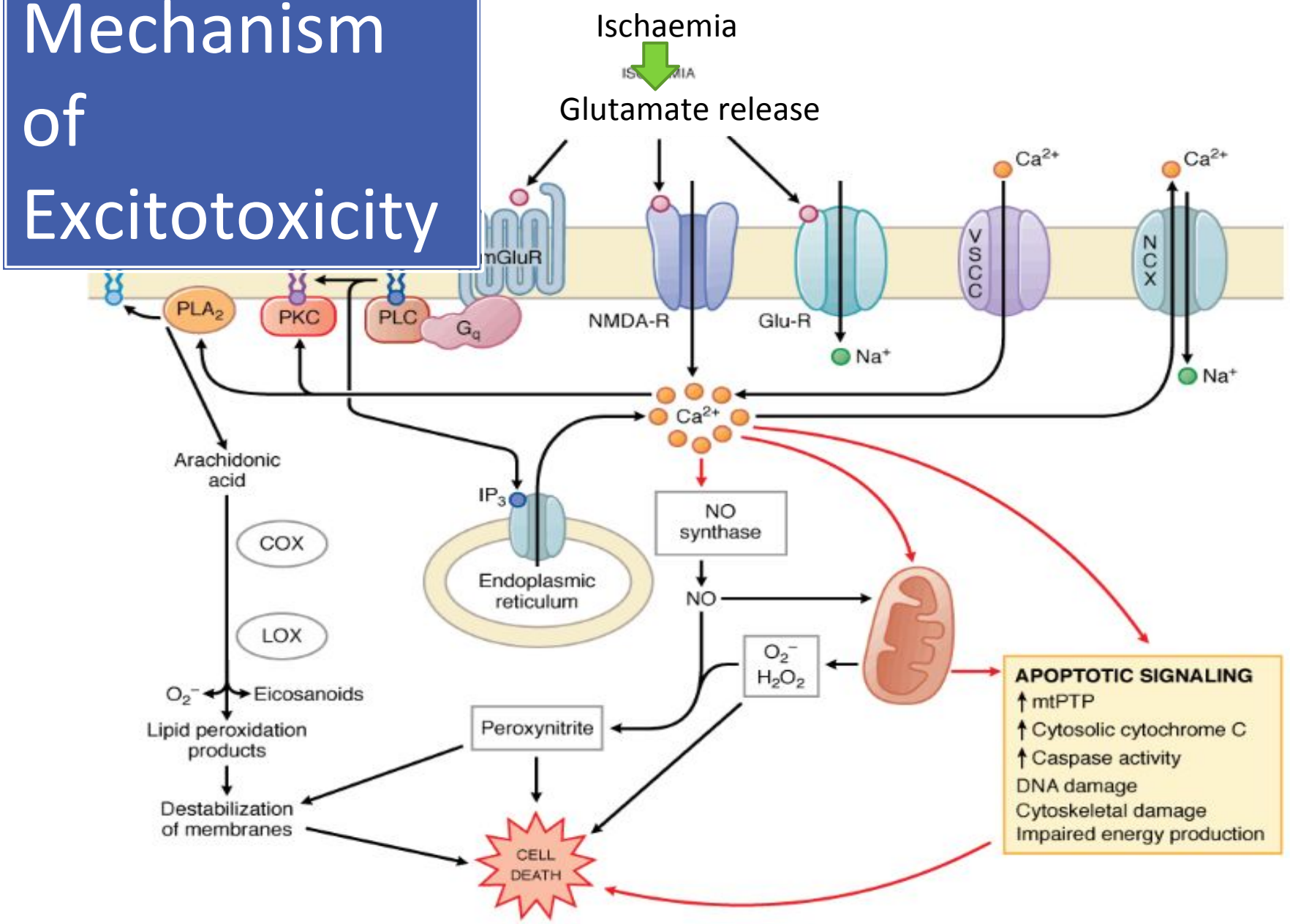
Special features of NMDA receptors

- Highly permeable to Ca^{2+} and other cations
- Readily blocked by Mg^{2+} which is markedly voltage dependent and block disappears in depolarised cell.
- Activation of NMDA receptors requires glycine as well as glutamate. Competitive antagonists at the glycine site indirectly inhibit the action of glutamate.

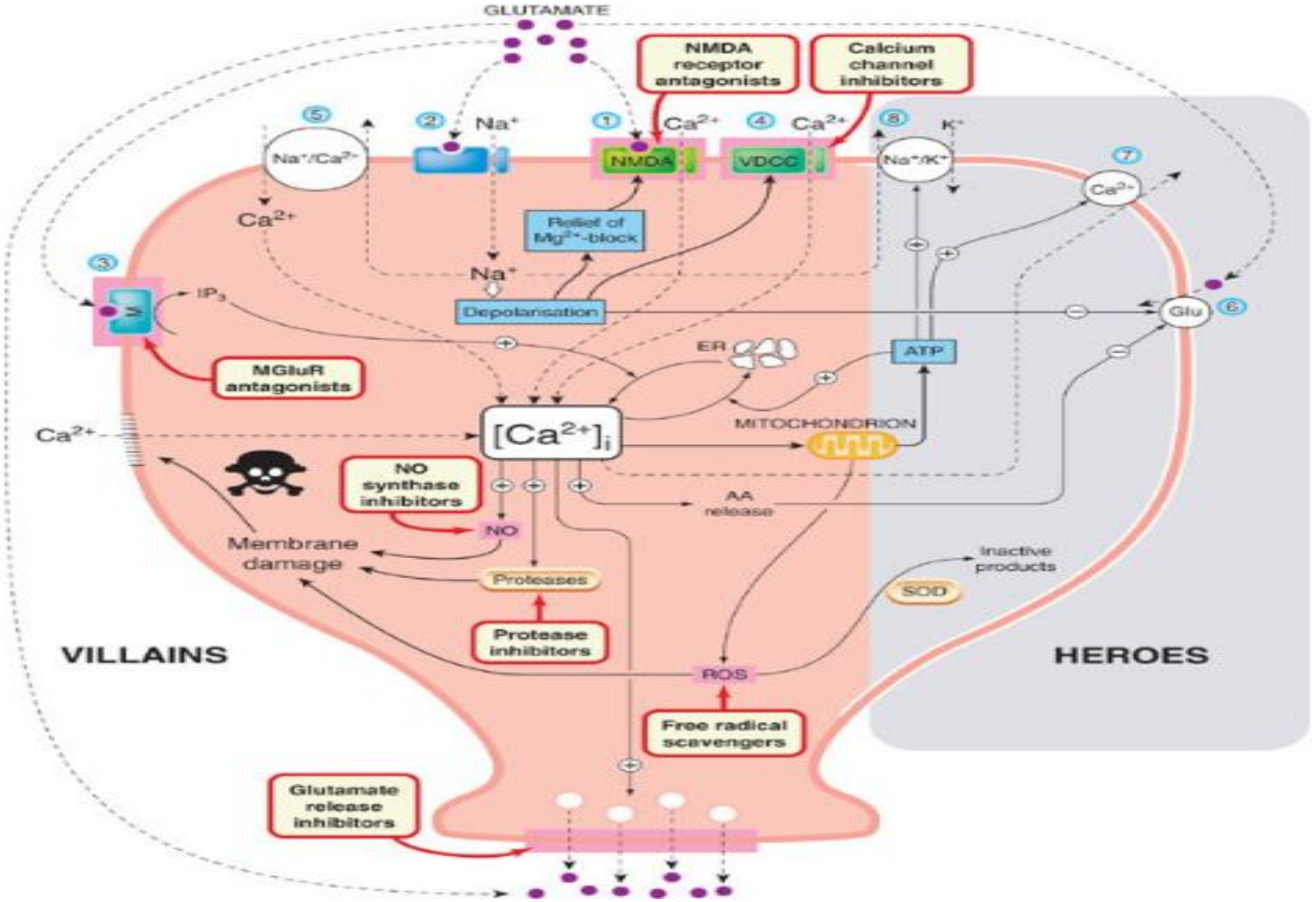
Mechanism of LTP, LTD



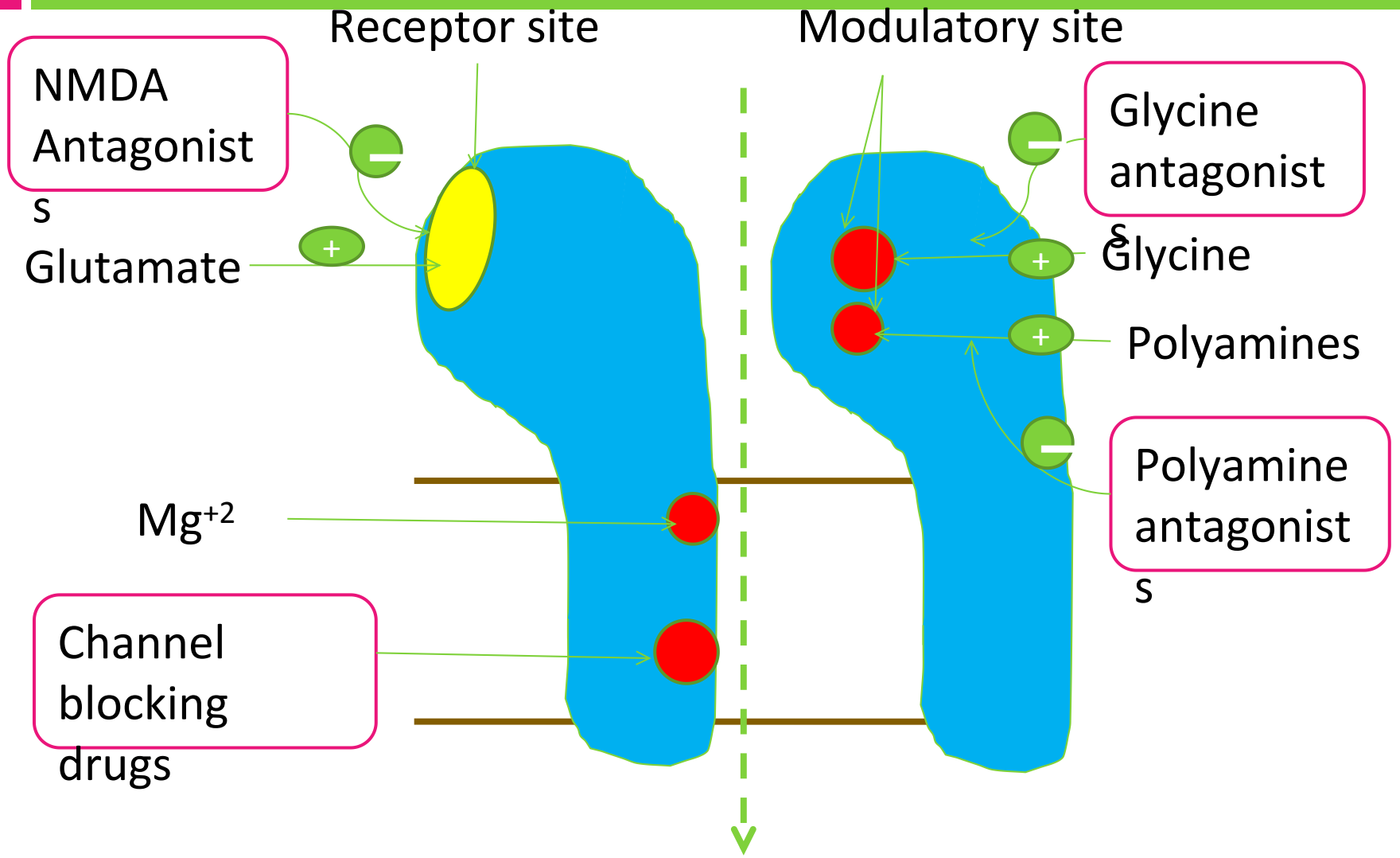
Mechanism of Excitotoxicity



Mechanism of Excitotoxicity



NMDA receptor



Drugs acting on NMDA receptor

- Glycine site blocking drugs – Kynureneic acid
- Channel blocking drugs – Ketamine, phencyclidine, dizocilpine, remacimide, memantine
- NMDA receptor antagonists - selfotel, eliprodil, dextromethorphan, methadone, amantadine
  - Ketamine is a strong blocker and others are weak.
- Adverse effects depends upon the affinity of the drug to the NMDA receptor
  - Hallucinations, lightheadedness, dizziness, fatigue, headache, out of body sensation, nightmares, and sensory changes

NMDA receptor

NMDA receptor modulators ???Potential therapeutic interest

- As general anaesthetic agents
- Neurodegenerative disorders : Alzheimers, Parkinsons disease, ALS, Glaucoma
- Epilepsy
- Drug dependence
- Neuropsychiatric disturbances : Schizophrenia, bipolar disorders
- Pain
- Decreasing the brain damage following stroke / head injury.

NMDA antagonists as general anaesthetic agents

- Ketamine
- Nitrous oxide, Cyclopropane and Xenon are potent and selective inhibitors of NMDA-activated currents apart from their action on two pore K^+ channels in producing the anaesthesia.

Ketamine

- Congener of phencyclidine
- Available as a mixture of the R+ and S- isomers
  - S- isomer is more potent with fewer side effects.
  - Water soluble
  - *It produces dissociative anesthesia with* profound analgesia, unresponsiveness to commands, and amnesia, but have their eyes open, move limbs involuntarily, and breathe spontaneously.
  - Useful for anesthetizing patients at risk for hypotension and bronchospasm and for certain pediatric procedures.

Ketamine contd…

- Adverse effects
  - CVS : indirect sympathomimetic activity - ↑ BP, HR, CO
  - Nystagmus with pupillary dilation, salivation, lacrimation, spontaneous limb movements with ↑muscle tone
  - ↑ Cerebral blood flow and intra cranial pressure

NMDA Antagonists in neurodegenerative disorders

- Parkinsons disease
  - Amantadine
- Alzheimers disease
  - Memantine
- Amyotrophic lateral sclerosis
  - Riluzole
- Glaucoma
  - Memantine

PARKINSON'S DISEASE

- Onset usually gradual, after age 50. (Slowly progressive)
- Mask-Like, Blank Expression
- Stooped Posture
- Pill Rolling Tremors

Bradykinesia
- Loss of normal arm swing while walking
- ↓ Blinking of the eyelids
- Loss of ability to swallow
- Blank expression
- Difficulty initiating movement

- Possible Mental Deterioration
- Depression

Tremor
- Commonly in hands and arm
- Pill rolling motion with the fingers
- Occurs most often at rest
- May involve diaphragm, tongue, lips and jaw
- Increases with stress

Muscle Rigidity
- ↑ Resistance to passive movement
- Cog wheel, jerky slow movement

- Rarely Occurs In Black Population
- Shuffling, Propulsive Gait

Amantadine

- An antiviral agent used for the prophylaxis and treatment of influenza A
- **MOA :** Alter DA release in the striatum
  - Anticholinergic properties
  - Blocks NMDA glutamate receptors
- **Uses :** Initial therapy of mild PD.
  - As an adjunct in patients on levodopa with dose-related fluctuations and dyskinesias.
- **Preparations & Dose :** available as tablets, 100 mg twice a day
- **Adverse effects :** Dizziness, lethargy, anticholinergic effects, and sleep disturbance, as well as nausea and vomiting

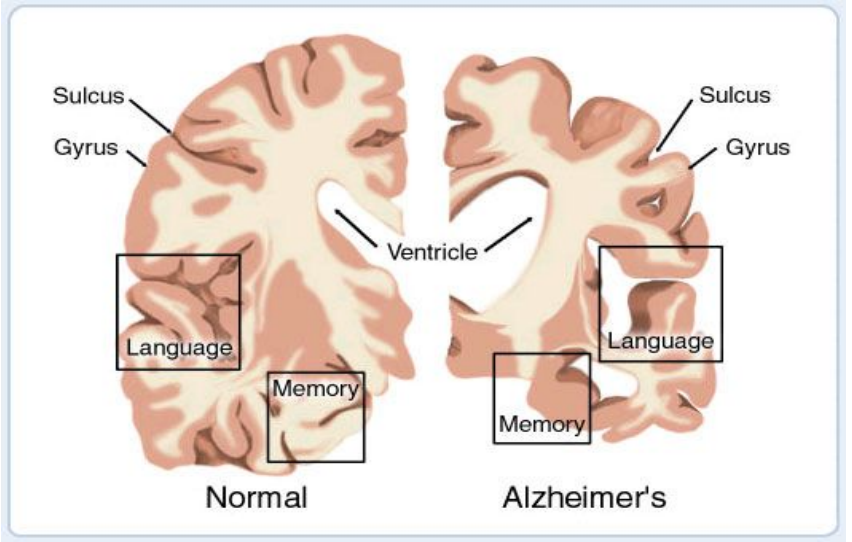
Memantine

- Introduced as an antiviral drug, and resurrected as a potential inhibitor of excitotoxicity.

- MOA : Non competitive NMDA receptor antagonist - interacts with the Mg^{2+} binding site of the channel to prevent excessive activation while sparing normal function

Memantine contd….

- Pk : Oral well absorbed, excreted by kidneys
  - Dose to be reduced in patients with severe renal impairment.
- Uses : As an adjunct / alternative to AChE inhibitors in moderate or severe Alzheimers disease.
  - In glaucoma – in trials
  - Bipolar disorders
  - Huntingtons disease
- ADR : Headache, dizziness



Riluzole

- MOA : presynaptically inhibits glutamate release
  - Post synaptically blocks postsynaptic NMDA- and kainate-type glutamate receptors and inhibits voltage-dependent Na^+ channels.
- Pk : orally absorbed, highly protein bound, metabolised by hydroxylation and glucuronidation.
  - Its $t_{1/2}$ is about 12 hours.
- Use : 1st FDA approved drug for ALS, improved the survival period by2-3 months.
- Dose : 50 mg twice daily, taken 1 hour before or 2 hours after a meal.
- Adverse effects : nausea or diarrhea
  - Rarely, hepatic injury with ↑ serum transaminases

Riluzole

Although the impact of Riluzole is small, it is significant therapeutic milestone in the treatment of a disease refractory to all previous treatments.

NMDA antagonists in Epilepsy

- NMDA receptor antagonists: Felbamate
- Drugs which ↓ the NMDA mediated currents :
  Carbonic anhydrase inhibitors in brain :
  Acetazolamide, Topiramate, Zonisamide

	Felbamate	Topiramate	Zonisamide	Acetazolamide
MOA	Inhibits NMDA receptors Potentiates GABA effect	Inhibits NMDA receptors Weak CA inhibitor + Topiramate - Inactivate Na^+ channels, ↑GABA, opens K+ channels Zonisamide - Inhibits T type Ca+2 channels, inactivate Na channels		
ADR	Aplastic anemia Hepatotoxicity	somnolence, ataxia, anorexia, nervousness, fatigue Renal calculi Metabolic acidosis with zonisamide, acetazolamide		
Uses	Partial seizures GTCS Lennox-Gastaut syndrome		Adjunctive in partial seizures	Absence seizures

Acamprosate : in Rx of Alcohol abuse

- It is an analogue of GABA
- MOA : Weak antagonist of NMDA receptors, activator of $GABA_A$ receptors
  - ↓ drinking frequency & relapse drinking in abstinent alcoholics
- Pk : orally absorbed, minimal metabolism in liver, excreted in urine with elimination $t_{1/2}$ of 18 hours.
- Dose : 666 mg three times daily
- ADR : Diarrhea
- No abuse liability has been noted.
- Concomitant use of disulfiram increase the effectiveness of acamprosate, without any noted adverse drug interactions.

NMDA antagonists in Pain reduction

- Ketamine & Methadone have been shown to improve the neuropathic pain and opioid resistant pain.

- Weak NMDA antagonists like dextromethorphan, memantine, amantidine didn’t show consistent effect in reducing the pain but have lesser adverse event profile.

Dextromethorphan

- D-isomer of the codeine analog methorphan
- MOA : NMDA-receptor antagonist and acts centrally to elevate the threshold for coughing
- Uses : Antitussive agent
  - In the treatment of pain given along with opioids helps in deceasing the development of tolerance and thus requiring low doses of opioid.
- Dose : 10-30 mg 3-6 times daily, not >120 mg/day

Drug & dose used in pain
Ketamine IM: 2–4 mg/kg, IV: 0.2–0.75 mg/kg Continuous IV infusion: 2–7 mcg/kg/min
Methadone : 2.5-10mg q8-12th hrly
Memantine PO: 10–30 mg/day
Amantadine IV: 200 mg infused over 3 h PO: 100–200 mg/day
Dextromethorphan PO: 45–400 mg/day

NMDA agonists in neuropsychiatric disorders

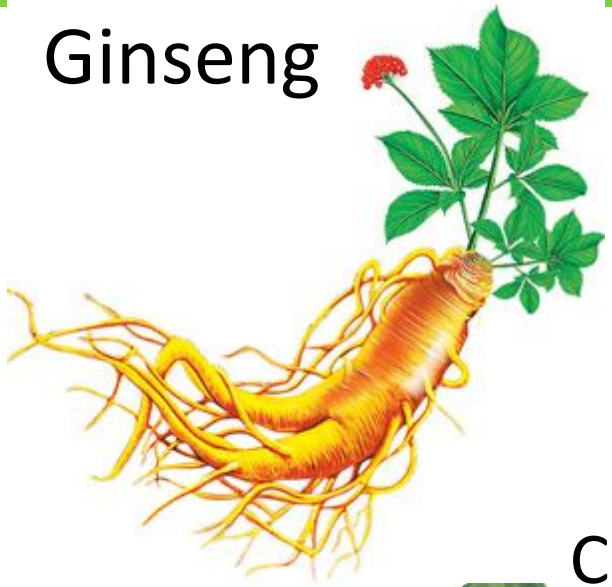
- Glutamate hypofunction hypothesis in schizophrenia led the researchers to focus on NMDA agonists.
- Potential target sites :
  - Glycine agonists : glycine, d-serine, and d-cycloserine (Coyle et al., 2003; Millan, 2005; Long et al., 2006)
  - Inhibitors of Glycine transporter 1(GLY-T_1) (Boulay et al., 2010).
  - Clozapine – also acts as NMDA receptor enhancer

Agonists

- AMPA receptor modulators (ampakines) may improve memory and cognitive performance.
  - Ex: C**yclothiazide**, **Piracetam** and CX-516 (**Ampalex**).
  - Role : Cognition enhancement
    - Treatment of schizophrenia, depression, attention deficit hyperactivity disorder (ADHD) and Parkinson's disease
- Agonists at group 2 and 3 mGlu receptors decrease glutamate release
  - Role : Decrease neuronal cell death in stroke
    - Treatment of epilepsy, anxiety & in controlling the positive symptoms of schizophrenia.

Herbal drugs acting as NMDA modulators

Ginseng



Curcuma longa

Summary

- Excitatory glutamate receptors plays role in synaptic plasticity – learning and memory as well as excitotoxicity leading to neuronal injury/death.
- Hence NMDA modulators are a great venue to explore in the treatment of various CNS disorders.
- NMDA antagonists have shown promising results in treatment of neurodegenerative disorders, epilepsy, pain
- NMDA agonists were in trials in the treatment of neuropsychiatric disorders.

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