DRUGS IN DEMENTIA

Dr Ruwan Parakramawansha
MBBS, MD, MRCP(UK),MRCPE, DMT(UK)
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LEARNING OUTCOMES

- By the end of the lecture, students will be able to…
  I. Describe “cholinergic hypothesis” in pathogenesis of Alzheimer's dementia
  II. Describe the mechanisms of action of drugs used to treat AD
  III. List ADRs of drugs used to treat AD
  IV. Compare the pharmacokinetic differences of the different drugs

OUTLINE….

A. Definition of Dementia and Alzheimer's Dementia
B. Pathophysiology of AD
C. Pharmacological Treatment Modalities
D. Individual Drugs Used to Treat Cognitive Decline

DEMENTIA

....a syndrome characterised by progressive deterioration of cognitive functions, most commonly of memory, but other domains such as language, and executive function are also often affected

Alzheimer's Dementia

- Brain shrinkage and localised loss of neurons, mainly in the medial temporal lobe, including entorhinal cortex and hippocampus
- The pathological hallmarks of AD are amyloid plaques- extracellular amyloid plaques, and intraneuronal neurofibrillary tangles
- Amyloid plaque accumulation leads to impaired neuronal function and neuronal death

"Cholinergic Hypothesis"

- A selective deficiency of acetylcholine(Ach) is seen in Alzheimer's Dementia(AD)
- Due to atrophy and degeneration of cholinergic neurons in the basal forebrain nuclei

- **The hypothesis - deficiency of ACh is the main reason for the development of AD symptoms**

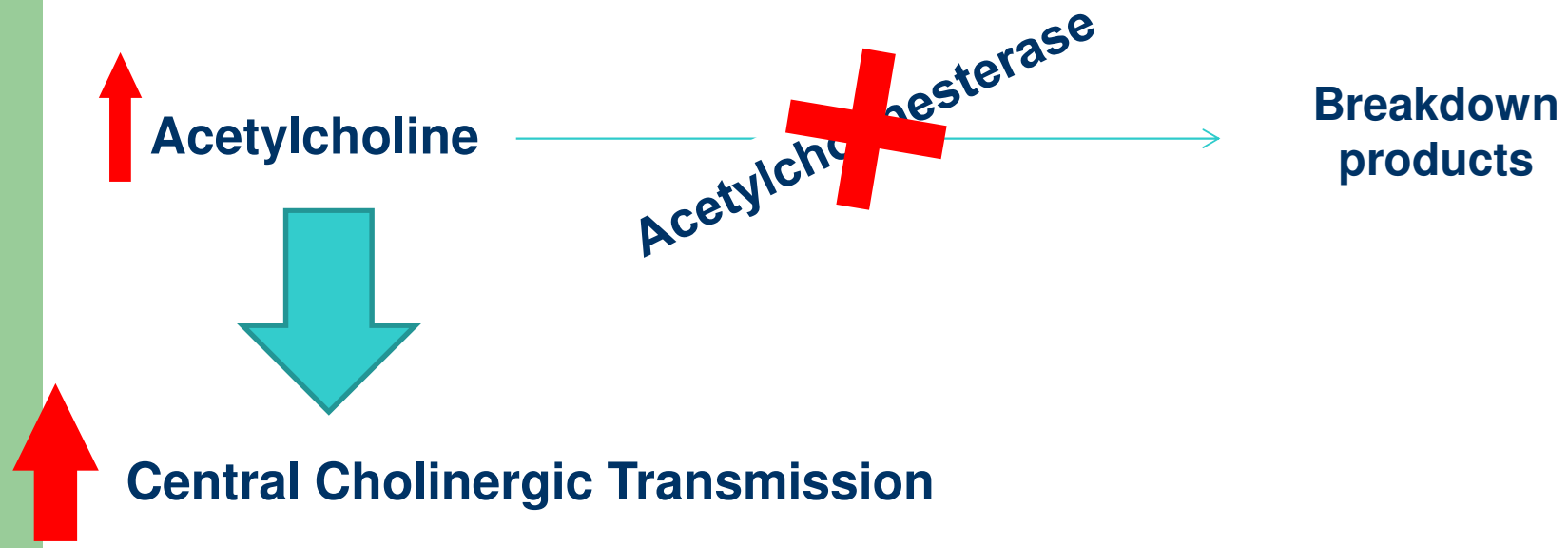
- AD involves multiple neurotransmitter systems
  e.g. glutamate and 5-HT

TREATMENT OF ALZHEIMER'S DISEASE

A. Treatment of Cognitive Symptoms
   I. Cholinesterase inhibitors
   II. Memantine
B. Treatment of Behavioral Symptoms
   I. Atypical antipsychotics
   II. Antidepressants & Mood stabilizers
   III. Benzodiazepines

CHOLINESTERASE INHIBITORS

- Rationale- enhancement of cholinergic transmission might compensate for the cholinergic deficit



CHOLINESTERASE INHIBITORS

E.g. **Tacrine, Donepezil**

Rivastigmine and Galantamine

- Has shown modest improvements in tests of memory and cognition in clinical trials with no effect on disease progression

CHOLINESTERASE INHIBITORS

- **Adverse Drug Reactions:**
  - GI distress(nausea, vomiting, diarrhoea, abdominal pain)
  - Muscle cramps
  - Bradycardia
  - Abnormal dreams

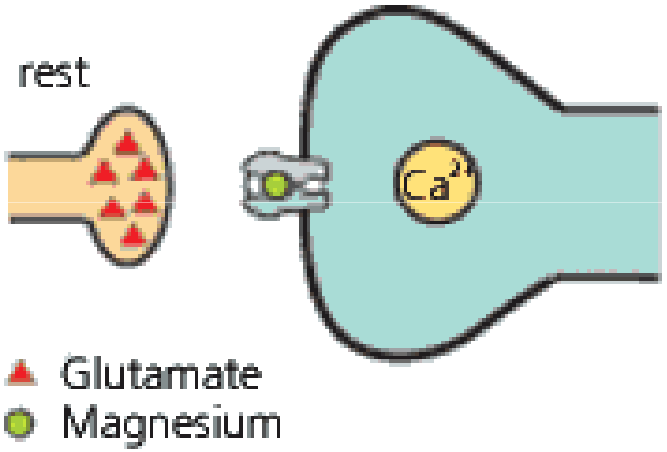
CHOLINESTERASE INHIBITORS

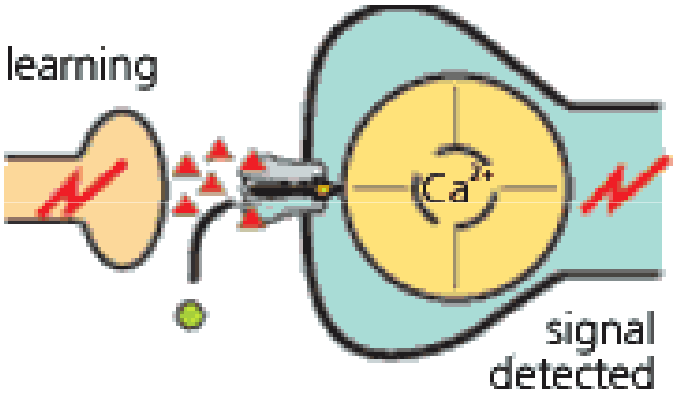
Drug	Type of Inhibition	Duration of Action & Dosage	Metabolism
Donepezil	CNS selective, reversible noncompetitive inhibitor of AChE	~24 h Once-daily	CYP2D6, CYP3A4
Rivastigmine	Pseudo-irreversible inhibitor of AChE and BChE	~8 h Twice-daily orally	Non-hepatic, metabolized by AChE and BChE
Galantamine	Both AChE and BuChE Also enhances nicotinic ACh receptor activation by allosteric action	~8 h Twice-daily	CYP2D6, CYP3A4
Tacrine	Both AChE and BuChE Not CNS selective	~6 h 2-3 times daily	CYP1A2

MEMANTINE

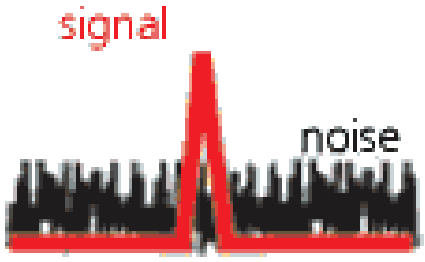
- A non-competitive antagonist of the NMDA-type glutamate receptor
- Chronic, mild activation of NMDA receptors ultimately leads to neurodegeneration – an effect termed chronic ‘excitotoxicity’
- **Reduces excitotoxicity**

MEMANTINE

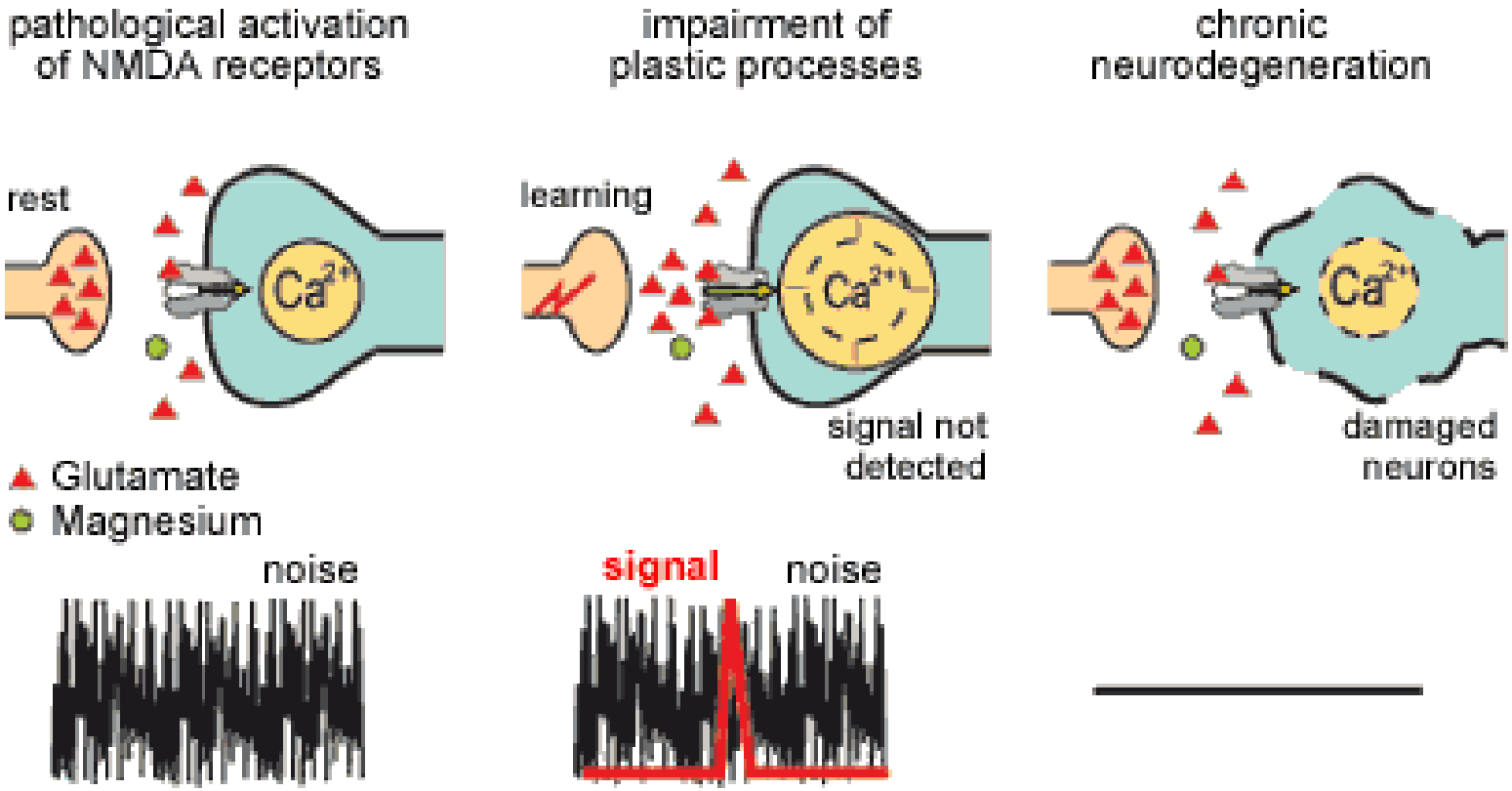

rest
Ca2+
Glutamate
Magnesium


learning
Ca2+
signal
detected

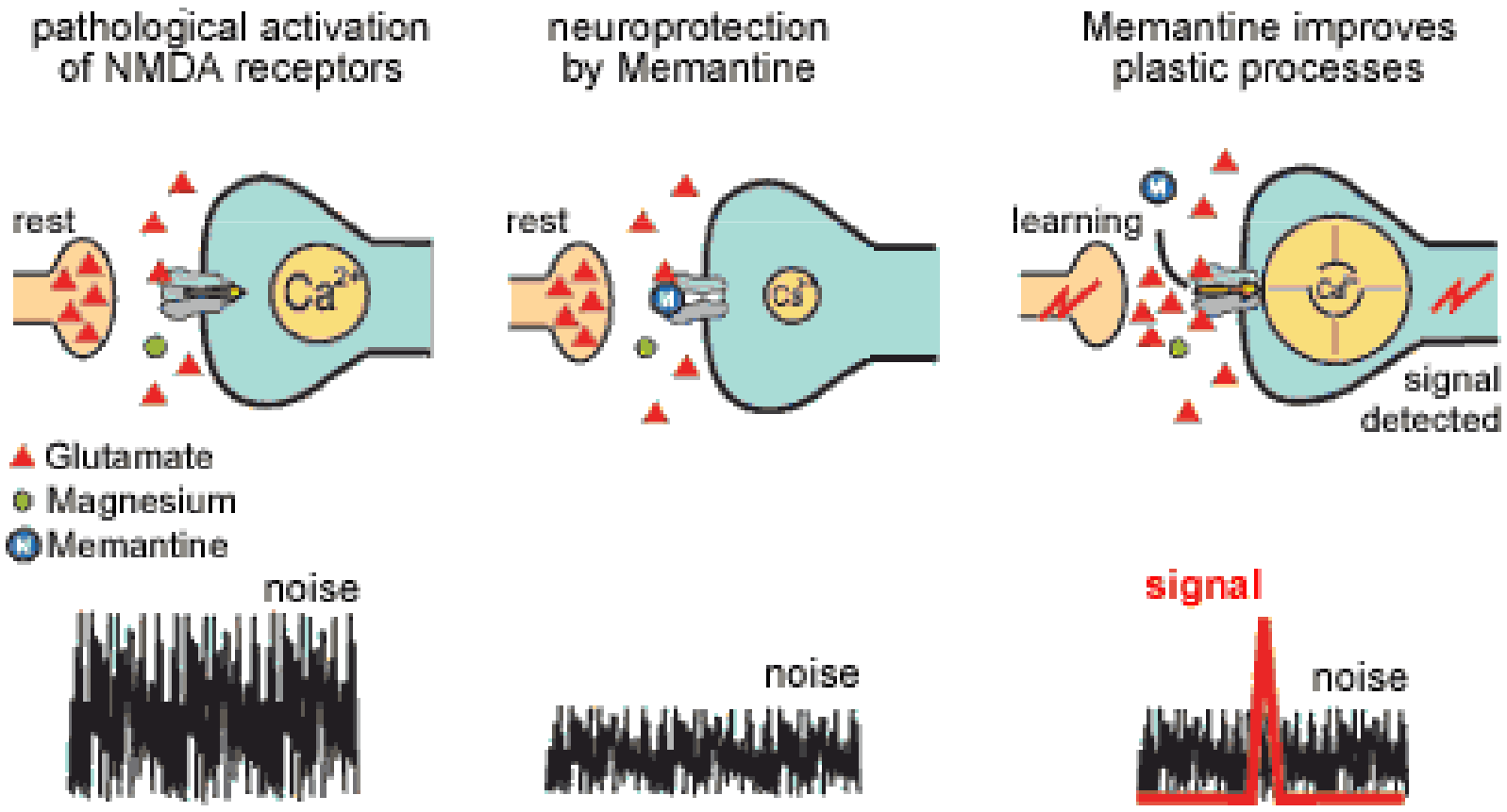

noise


signal
noise

MEMANTINE


pathological activation of NMDA receptors
impairment of plastic processes
chronic neurodegeneration
rest
learning
Ca^{2+}
signal not detected
damaged neurons
Glutamate
Magnesium
noise
signal
noise

MEMANTINE


pathological activation of NMDA receptors
neuroprotection by Memantine
Memantine improves plastic processes
rest
rest
learning
signal detected
Glutamate
Magnesium
Memantine
noise
noise
signal
noise

MEMANTINE

- Reduces the rate of clinical deterioration in patients with moderate to severe AD
- used either as an adjunct or an alternative to cholinesterase inhibitors in AD

- **ADRs-**constipation, dizziness, headache, hypertension, and somnolence

TREATMENT OF ALZHEIMER'S DISEASE

B. Treatment of Behavioral Symptoms

I. Atypical antipsychotics

e.g. risperidone, olanzapine, and quetiapine

II. Antidepressants & Mood stabilizers

e.g. SSRIs

III. Benzodiazepines