

ANTIPSYCHOTICS

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LEARNING OUTCOMES

By the end of the lecture, students will be able to...

1. recall the biochemical basis of psychotic illnesses
2. classify the antipsychotic drugs (with examples)
3. describe the mechanism of action, pharmacokinetics, adverse drug effects of antipsychotic drugs
4. list the clinical uses of antipsychotic drugs

OUTLINE....

- A. Definition-Psychosis
- B. Dopamine hypothesis
- C. Classification of Antipsychotics
- D. Pharmacological Profile of Each Category
- E. Clinical Usage

PSYCHOSIS

- A symptom of mental illnesses
- Characterized by a distorted or non-existent sense of reality
 - Hallucinations
 - Delusions
 - Disorganized speech
 - Disorganized or agitated behaviour

PSYCHOSIS

- Mood disorders (major depression or mania) with psychotic features
- Substance-induced psychosis
- Dementia with psychotic features
- Delirium with psychotic features
- Schizophrenia

DOPAMINE HYPOTHESIS

- Put forward by Arvid Carlsson

“The clinical features of schizophrenia (sometimes extended to psychosis in general) is related to over activity of dopaminergic function within the brain.”

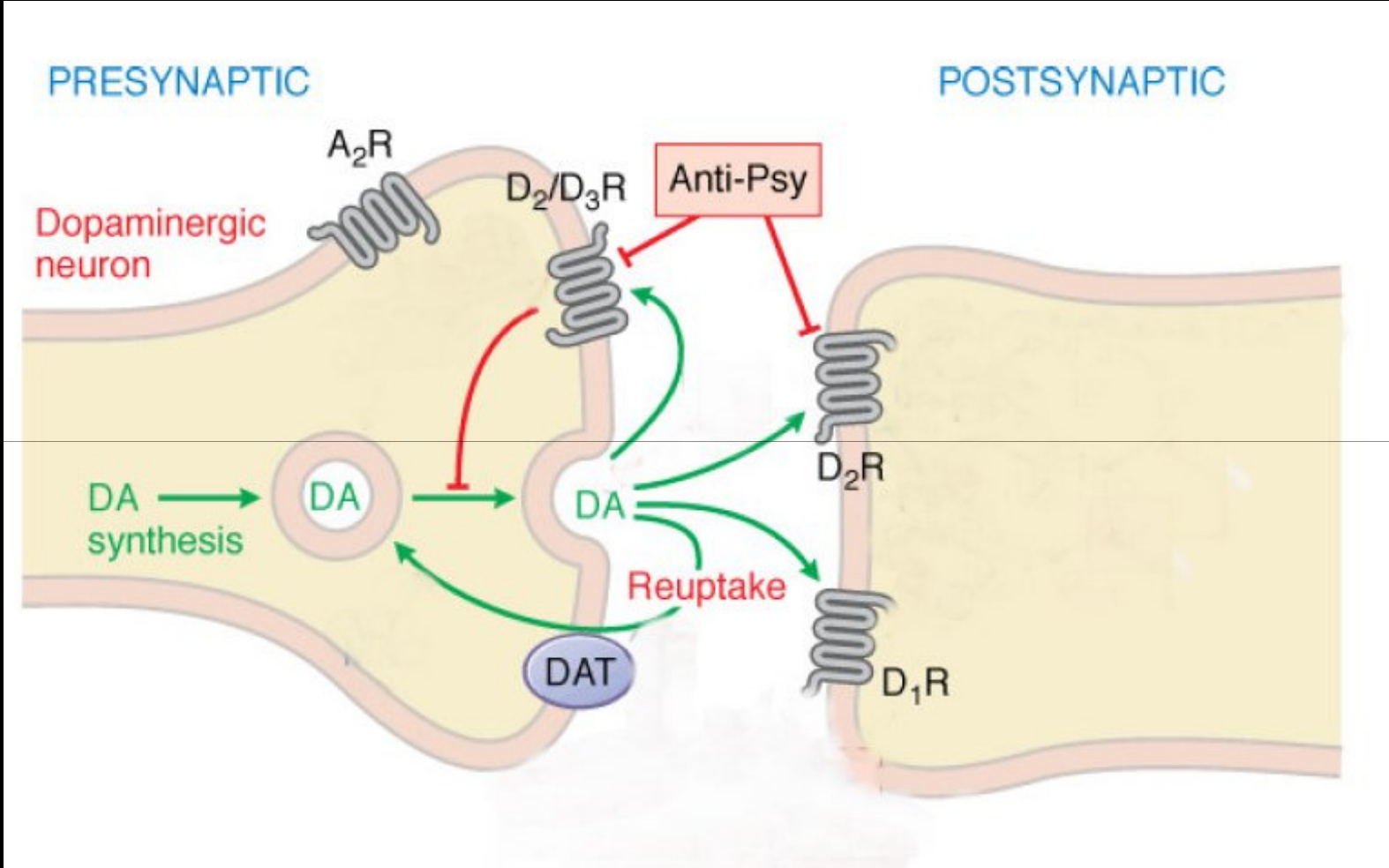
CLASSIFICATION

- A. Typical/First Generation Antipsychotics
 - I. Phenothiazines e.g. **chlorpromazine**
 - II. Butyrphenones e.g. **haloperidol**
 - III. Thioxanthenes e.g. **flupentixol**
- B. Atypical/Second Generation Antipsychotics
e.g. **clozapine, risperidone, olanzapine**
quetiapine, aripiprazole

FIRST GENERATION ANTIPSYCHOTICS

- **Mode of Action:**

- Predominantly act as antagonists at brain dopamine D₂ receptors
- Also blocks
 - Muscarinic acetylcholine receptors
 - Antihistamine receptors
 - α adrenoceptors



PHARMACOKINETICS

- High rapid oral absorption
- Highly lipophilic with high apparent volumes of distribution
- Undergo extensive phase 1 metabolism by CYPs and subsequent phase 2 conjugations
- Excreted in the urine and to some extent in the bile

ADVERSE DRUG REACTIONS

- **Extrapyramidal Motor Effects**

Due to dopamine D₂ receptor blockade in the nigrostriatal pathway (except tardive dyskinesia)

- a) Acute dystonia
- b) Akathisia
- c) Parkinsonism
- d) Tardive Dyskinesia

ACUTE DYSTONIA

- Spasm of muscles of tongue, face, neck, back
- High risk in- first few weeks, young, antipsychotic naive



TARDIVE DYSKINESIA

- Develops after months or years
- In 20-40% of patients treated with first-generation antipsychotic drugs
- Often irreversible, often gets worse when antipsychotic therapy is stopped
- Elderly at 5-fold greater risk

ADVERSE DRUG REACTIONS

- **Endocrine effects**

Due to blockage of dopamine D₂ receptors in tuberohypophyseal pathway → Increased prolactin

- a) Gynaecomastia
- b) Galactorrhoea
- c) amenorrhea in women
- d) sexual dysfunction or infertility in men

ADVERSE DRUG REACTIONS

- Central antagonism of H₁ receptors
 - a) sedation
 - b) weight gain via appetite stimulation
- Muscarinic antagonism -anticholinergic effects
- α_1 Adrenergic antagonism - orthostatic hypotension

ADVERSE DRUG REACTIONS

- **Adverse Cardiac Effects**

Blockage of cardiac K^+ channels



Prolong QT in ECG



Ventricular arrhythmia & sudden cardiac death

ADVERSE DRUG REACTIONS

- Increased risk for cerebrovascular events and all-cause mortality in dementia patients
- Lowers seizure threshold
- Increased triglycerides
- Hyperglycaemia

NEUROLEPTIC MALIGNANT SYNDROME

- A fatal idiosyncratic ADR of antipsychotics
- Characterized by,
 1. Mental status changes
 2. muscle rigidity
 3. Hyperthermia
 4. autonomic dysfunction

CLASSIFICATION

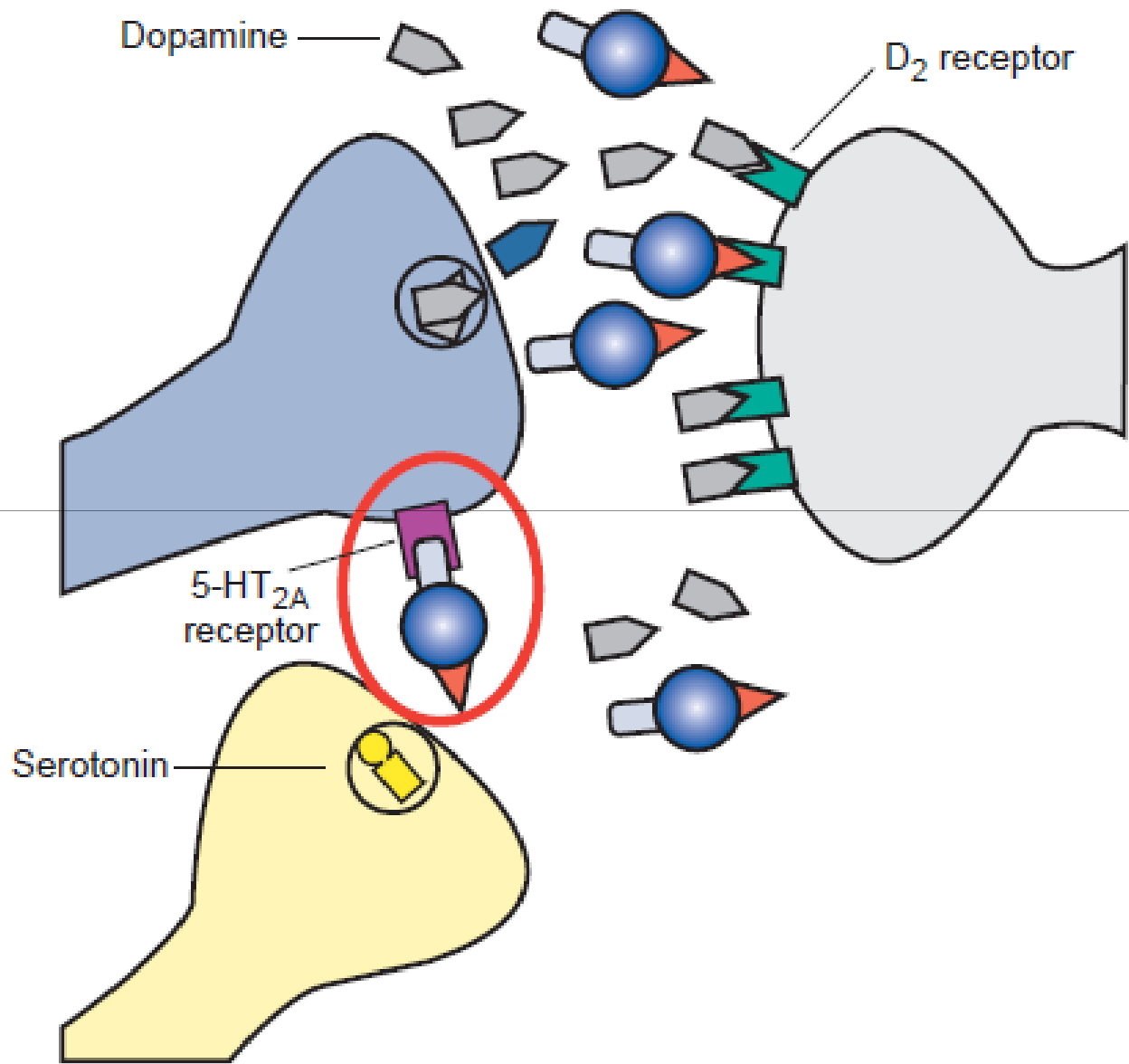
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SECOND GENERATION ANTIPSYCHOTICS

- **Mode of Action:**

Predominant antagonism of 5-HT_{2A} receptors with a lesser degree antagonism of dopamine D₂ receptors

- Has efficacy against negative symptoms esp. clozapine



ADVERSE DRUG REACTIONS

- **Extrapyramidal Motor Effects**

- Considerably less compared to typical antipsychotics
- Blockage of 5-HT_{2A} receptors increase dopamine in striatum preventing extrapyramidal effects

- **Cardiotoxicity**

- Less associated with QT prolongation at therapeutic doses

ADVERSE DRUG REACTIONS

- High risk of new onset diabetes and diabetes ketoacidosis esp. with clozapine and olanzapine
- Agranulocytosis common with clozapine esp. in first 6 months
∴ regular FBC monitoring essential

OTHER CLINICAL USES

- Treatment of Anxiety Disorders
- Treatment of autism
- As an antiemetic
- Treatment of refractory hiccups

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