Antipsychotic Drugs
(Department of Pharmacology Zhang Yan-mei)

General View

The most important types of psychosis are: Schizophrenia Affective disorders (e.g. depression, mania) Organic psychoses (mental disturbances caused by head injury, alcoholism, or other kinds of organic disease).

General View

Classification: anti-schizophrenic drugs (antipsychotic drugs or neuroleptics), antimanic drug, antidepressants or antianxiolytics. Pharmacologically, they are characterised as dopamine receptor antagonists, though many of them also act on other targets, particularly 5-HT receptors, which may contribute to their clinical efficacy.

The Nature of Schizophrenia

Psychotic illness characterised by hallucinations, delusions and thought disorder (positive symptoms), together with social withdrawal and flattening of emotional responses (negative symptoms). Acute episodes (mainly positive symptoms) frequently recur and develop into chronic schizophrenia, with predominantly negative symptoms.

The Nature of Schizophrenia

Incidence is about 1% of population, with a strong, but not invariable, hereditary component. Pharmacological evidence is generally consistent with dopamine overactivity hypothesis, but most neurochemical evidence is negative or equivocal. Increase in dopamine receptors in limbic system (especially in left hemisphere) is consistently found. There is some evidence for involvement of 5-HT, and possibly other mediators, such as glutamate.

Classification of Antipsychotic drugs

Main categories are: Typical antipsychotics Phenothiazines (chlorpromazine, perphenazine, fluphenazine, thioridazine et al) Thioxanthenes (flupenthixol, clopenthixol) Butyrophenones (haloperidol, droperidol) Atypical antipsychotics (e.g. clozapine, risperidone, sulpiride, olanzapine)

Classification of Antipsychotic drugs

Distinction between ↑typical├ and ↑atypical├ groups is not clearly defined, but rests on: Incidence of extrapyramidal side-effects (less in ↑atypical├ group) Efficacy in treatment-resistant group of patients Efficacy against negative symptoms.

Phenothiazines

Chlorpromazine: wintermine

Phenothiazines

Therapeutic uses

(1) treatment of psychotic disorders: schizophrenia, mania, paranoid states, alcoholic hallucinosis. (2) treatment of nausea and vomiting of certain causes. (3) anesthesia in hypothermia and artificial hibernation (used with pethidine and promethazine).

Adverse Effects

Extrapyramidal motor disturbances: (1) Parkinson-like symptoms; (2) akathisia; (3) acute dystonias. Treatment: anticholinergic

Adverse Effects

Pseudodepression and Schizophrenia-like syndrome. Seizures. Cardiac toxicity and

endocrine effects. Adverse Effects

4. Other side-effects (dry mouth, constipation, blurred vision, hypotension, etc.) are due to block of other receptors, particularly adrenoceptors and muscarinic ACh receptors. Contact dermatitis, blood dyscrasias, obstructive jaundice sometimes occurs with phenothiazines.

Thioxanthenes

Chlorprothixene: mild antipsychotic action, and antianxiety and antidepressant action.

Butyrophenones

Haloperidol: control psychomotor excitement. Adverse effects: severe extrapyramidal symptoms.

Others Clozapine: (1) be effective in treating some patients with psychosis unresponsive to standard neuroleptic drug. (2) blocks D4 receptor and have low affinity for D1 and D2 dopamine receptors. (3) lacks extrapyramidal side effects. (4) must monitor the granulocyte counts weekly.

Others Risperidone: be used first episode in and chronic schizophrenia.

Clinical Efficacy of Antipsychotic Drugs

Antipsychotic drugs are effective in controlling symptoms of acute schizophrenia, when large doses may be needed. Long-term antipsychotic treatment is often effective in preventing recurrence of schizophrenic attacks, and is a major factor in allowing schizophrenic patients to lead normal lives.

Clinical Efficacy of Antipsychotic Drugs

Depot preparations are often used for maintenance therapy. Antipsychotic drugs are not generally effective in improving negative schizophrenic symptoms. Approximately 40% of chronic schizophrenic patients are poorly controlled by antipsychotic drugs; clozapine may be effective in some of these ↑ antipsychotic-resistant cases.

Mood altering drug

Mood-stabilizing: lithium carbonate

Adverse effects: Nausea, vomiting and diarrhoea. Tremor. Renal effect: polyuria (with resulting thirst) Various neurological effects, progressing from confusion and motor impairment , to coma, convulsion and death. k& narrow therapeutic limit for the plasma means the monitoring is essential.

antidepressant

Types of antidepressant drug Tricyclic antidepressant (TCA): Selective 5-HT uptake inhibitors: NE uptake inhibitors: Atypical antidepressant: phenelzine

imipramine

Mechanism: block the amines (NE and 5-HT). Pharmacologic effects: (1) CNS: a nondepressed person experiences sleeping. In the depressed patient, an elevation of mood occurs 2-3 weeks after administration begins. (2) autonomic nervous system: anticholinergic effects. (3) cardiovascular effects: orthostatic hypotension and arrhythmias.

Therapeutic uses (1) Treatment of severe endogenous depression (characterized by regression and inactivity). (2) Treatment of enuresis. (3) Treatment of obsessive-compulsive neurosis accompanied by depression, and phobic-anxiety syndromes, chronic pain and neuralgia.

Fluoxetine

Mechanism of action: (1) is a selective inhibitor of serotonin uptake in the CNS. (2) has little effect on central norepinephrine and dopamine function. (3) has less adverse effects because of minimal binding to cholinergic, histaminic, and -adrenergic receptors.

Therapeutic uses: (1) is used for treatment of mild to moderate endogenous depression. (2) be useful in treating obsessive-compulsive disorder, obesity.

Adverse effects: (1) cause anorexia. (2) precipitate mania or hypomania. (3) result in nausea, nervousness, headache, and insomnia. (4) cause 5-HT syndromes (hyperpyrexia, convulsions, and coma) when combinated with and MAO inhibitor.

2. Pharmacologic effects and mechanism: CNS: a. neuroleptic effect--- b. antiemetic effect--- inhibit chemoreceptor trigger zone or directly depress the medullary vomiting center. c. temperature-regulating effect--- produce hypothermia

8D1, D5---D1-like receprtors D2-4------D2-like receptors   9 29

Antipsychotic drugs probably owe their therapeutic effects mainly to blockade of D2-receptors (lies in midbrain-cortex and midbrain-limbic system).

Pharmacologic effects: (2) autonomic nervous system: block -adrenergic and M-Cholinergic receptors and result in hypotension, dry mouth, constipation and blurred vision. (3) Endocrine system: increase the release of prolactin and decrease corticotropin release and secretion of pituitary growth hormone.

@`!. Mood-stabilizing: lithium carbonate
Mechanism (1) effects on electrolyte and ion transport. (2) effects on neurotransmitters---NA, DA. (3) effects on second messengers¶ hormone-sensitive adenylate. Therapeutic uses: prevention of bipolar illness and treatment of acute mania.

!imipramine

amitriptyline

!Fluoxetine, paroxetine, sertraline

desipramine

(Adverse effects: anticholinergic effects

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Department of Pharmacology

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