Zaporozhye State Medical University
Pharmacology and Medical Formulation Department

Lecture № 7

PSYCHOSTIMULANTS, ADAPTOGENS, ANALEPTICS, ANTIDEPRESSANTS, and NOOTROPIC DRUGS

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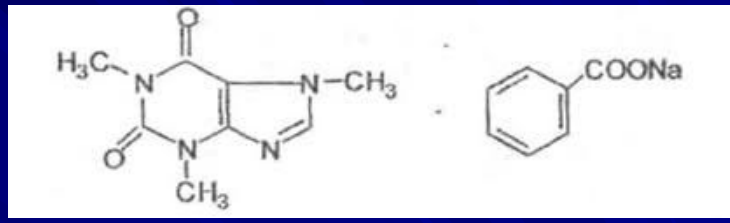
Psychostimulants
(*Psychomotor Stimulants*)

1. Methylxanthines:

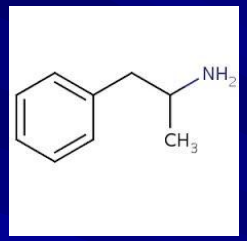
   Caffeine (*Coffeinum-natrii benzoas)*

   tab. 0.1 g; amp. 10% and 20% - 1 ml)



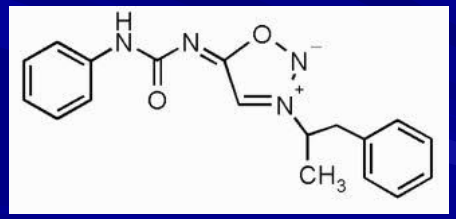
2. Phenylalkyl amines:

   Phenamine (*Amphetamine*)



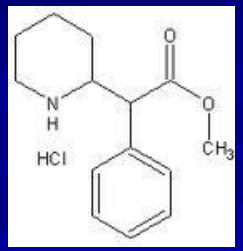
3. Phenylalkyl sydnonimines:

   Sydnocarb (*tab. 0.005 and 0.01 g*)



4. Piperidine compounds:

   Meridil (*tab. 10 mg*)



Mechanisms of Action of Caffeine

1). Blockade of *Phosphodiesterase* => and ⇑*cGMP*

2) Blockade of *Adenosine Receptors*

Adenosine –

- an Inhibitory Transmitter of the CNS
- inhibits Adenyl Cyclase activity, causing Contraction of Airway Smooth Muscle

ATP or GTP —*Adenyl Cyclase* / *Guanyl Cyclase*→ cAMP or cGMP

cAMP or cGMP —*Phosphodiesterase*→ 5-AMP or 5-GMP

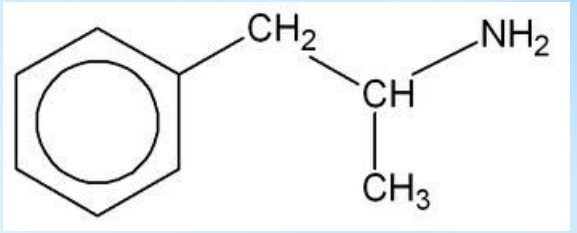
Inhibited by Methylxanthines

Pharmacological Effects of Caffeine :

- Stimulation of Medullary, Vagal,
  Respiratory and Vasomotor centers
- ↑ Cardiac Output and ↓ Cardiac Work
- (+) Inotropic and (+) Chronotropic Effects
- Improvement of :
  - Coronary, Cerebral and Renal Circulation,
  - Eye Ground Blood Circulation
  - Acuity of Vision and Color Vision
- Smooth muscles relaxation, most prominent effect –
  on Bronchi, esp. in asthmatics
- Clinical Uses: CNS depression,
  Neonatal Apnea, Hypotension.

Phenamine (***Amphetamine***)-

a central sympathomimetic.



It was synthesized in the late 1920s and has a large number of analogs including Dex amphetamine, Meth amphetamine, Methylene-dioxy -meth-amphetamine (MDMA, or "**Ecstasy**").

Phenamine is chemically a phenylalkylamine, i.e.

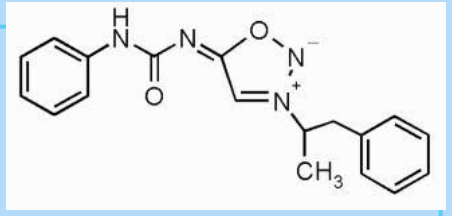
its structure is similar to *Noradrenaline* and *Adrenaline*.

It has the same pharmacological profile as *Ephedrine*; orally active with long duration (4-6 hours).

Mechanism of action. *Phenamine* acts primarily by releasing noradrenaline and dopamine in the brain, inhibits catecholamines reuptake, MAO activity and increases receptors sensitivity to catecholamines.

Clinical uses: attention deficit disorder,

narcolepsy (an uncontrollable desire for sleep).



Sydnocarb (*Mesocarb*) –

chemically and pharmacologically similar to *phenamine* but does not cause drug dependence, hypnosis, less influences on peripheral adrenoreceptors.

Sympathomimetic and cardiovascular actions are insignificant.

Mechanism of action:

- Catecholamines Reuptake
- MAO activity
- Receptors Sensitivity to Catecholamines

Clinical uses: Neurotic disorders, Narcolepsy, Asthenia, Apathy, Attention deficit hyperkinetic disorder, Excessive day time sleepiness, Decreased working capacity.

Adverse effects: anorexia, insomnia, abdominal discomfort and bowel upset, AP increase.

ADAPTOGENS

1. **Plant origin** –

Powders, T-res and Extracts from roots or fruit of:

Ginseng, Eleutherococcus,

Rhodiola, Schizandra, Aralia

2. **Animal origin** – Extracts from

the young Siberian male deer's antlers: Pantocrin, Rantatrin

Mechanism of Action:

1). Activation of *RNA* and *Protein* synthesis

2). Biochemical Disorders in Stress Reactions

3). Normalization of Pituitary-Adrenal and Immune System functions

Pharmacodynamics of Adaptogens:

- ↑ Physical and Mental Capacity
- ↓ Fatigue, ↓ Appetite Disorders
- ↑ Tolerance to Harmful Influences,
  High t°, Cooling, Intoxications;
  Ionizing Radiation
- ↑ Specific and Non- Specific Immunity
- Improvement: Blood Circulation,
  Breathing, Vision and Hearing,
- Cardio-Protector and Hepato-Protector effect

Ginseng

Eleutherococcus

Clinical Uses:

- Physical Overwork
- Physical and Mental Overfatigue
- Asthenic Syndrome
- State after Infection and Somatic Diseases
- Ionizing Radiation Influence

Adverse effect:

Overexcitement of Nervous and Cardio-Vascular Systems, Arterial Hypertension, Hyperglycemia

Rhodiola

Schizandra

Aralia

Classification of ANALEPTICS

1. With prevalent action upon the BRAIN CORTEX

Caffeine

Caffeine-Natrium Benzoate

2. With prevalent action upon the MEDULLA OBLONGATA:

Bemegride– *amp. 0.5%-10 ml*

Etimizol – *amp. 1.5%-3 ml*

Cordiamin – *amp. 1 ml, vial 15 and 30 ml*

Sulfocamphocaine – *amp. 10%-2 ml*

3. With prevalent action on the SPINAL CORD:

Strychnine Nitrate

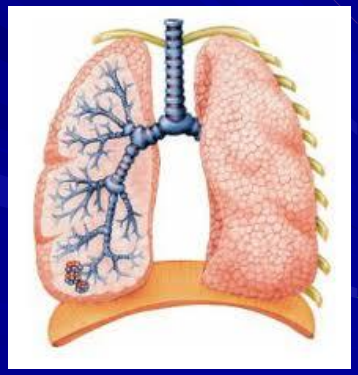
- Strength According to *Analeptic Activity:*

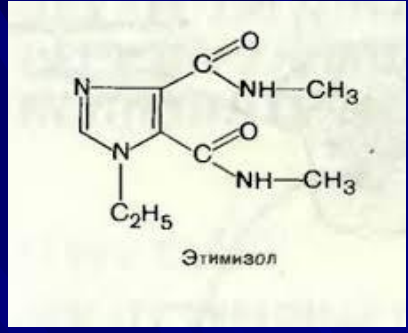
Bemegride – Cordiamin - Sulfocamphocaine - Etimizol

Clinical Uses of Analeptics

Acute Respiratory Failure:

- Aggravation of COPD [*Chronic Obstructive Pulmonary Diseases*] with sleepiness, inability to cough out
- Respiratory depression during Infectious Diseases, Shock, Syncopal conditions
- Asphyxia (Respiratory Arrest) of Newborns and during surgical operations
- Poisons with Hypnotic drugs, Opioid Analgesics, General Anesthetics





Etimizol amp. 1.5% - 3 ml, tab. 0.1 g –

an analeptic of ***direct* action**

1. Direct excitement of the Respiratory Center
2. □ ACTH production => Glucocorticoids' level in blood

- is used as Anti-inflammatory and Antiallergic agent

to treat Arthritis, Polyarthritis, Asthma

3. ***A***cceleration and Deepening of Respiration
4. □ HR, □ BP.

Clinical uses:

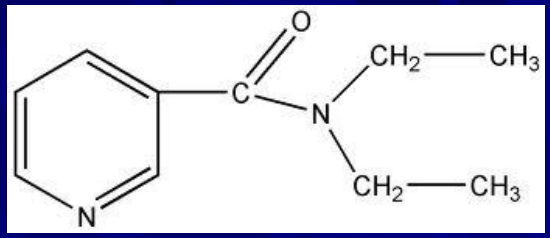
Respiratory failure in Shock; Collapse, Asphyxia; Respiratory Depression in Infectious Diseases; Prophylaxis of Lung Atelectasis and Pneumonia,

Arthritis, Polyarthritis, Asthma

Cordiamin (*Niketamide*) –

amp. 1 ml, vial 30 ml –

an analeptic of *mixed* action



- direct exciting influence on Respiratory Center
- Stimulates N-Receptors of Carotid Sinus

Acceleration and Deepening of Respiration

↑HR, ↑BP

Clinical uses:

Respiratory failure in Shock, Collapse, Asphyxia; Respiratory depression in Infectious diseases; Prophylaxis of lung atelectasis and pneumonia

- Adverse effects:

clonic seizures, face hyperemia

Depression

is the most common of affective disorders, which includes disorders of mood, thought and cognition:

➡ **Emotional symptoms:**

- Grief, pessimism, hopelessness.
- Low self-esteem: feeling of guilt, inferiority and spite.
- Indecisiveness, loss of motivation, apathy.

➡ **Biological symptoms:**

- Retardation of thought and action.
- Loss of libido.
- Sleep disturbance and loss of appetite.

Monoamine theory - insufficiency of noradrenaline and serotonine (5-hydroxytriptamine) or their receptors in some brain structures.

Classification of antidepressants

- **Monoamine uptake inhibitors:**
  - **Non-selective monoamine reuptake inhibitors (noradrenaline and serotonine) - IMIZINUM *[Imipramine]*, AMITRIPTYLINE**

Sedative, M-cholinoblocking, α-adrenoblocking and H_1-histaminoblocking effects, postural hypotension, seizures, impotence

  - **Selective serotonine reuptake inhibitors - FLUOXETINE, FLUVOXAMINE, PAROXETINE, SETRALINE,**

Small psychostimulating effect, nausea, diarrhoea, agitation, insomnia, anorgasmia, inhibition of other drugs' metabolism.

  - **Selective noradrenaline reuptake inhibitors - MAPROTILINE, DESIPRAMINE**

Dizziness, insomnia, M-cholinoblocking effects.

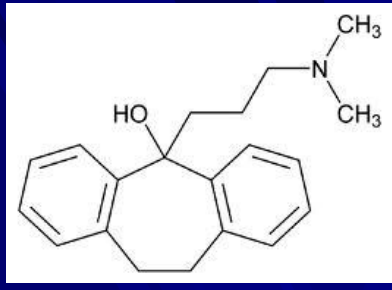
- **Monoamine oxidase (MAO) inhibitors:**
  - **Non-selective MAO inhibitors (MAO_A and MAO_B) - NIALAMIDE, TRANSAMINUM**

Significant psychostimulating effect, "cheese reaction" (hypertensive crisis, cerbrovascular accidents after tyramine-containing food - cheese, beer, wines, pickled meat and fish) M-cholinoblocking effect, hypertension, insomnia, weight gain, liver damage.

  - **Selective MAO_A inhibitors in CNS - MOCLOBEMIDE, PYRAZIDOLE**

MAO A – NORADRENALINE and SEROTONIN,

MAO B – **DOPAMINE, PHENYLETHYLAMINE, TYRAMINE**



Amitriptyline (*tab. 0.01 and 0.025 g*) –

a Tricyclic Antidepressant.

- Inhibits reuptake of

  Noradrenaline and Serotonin

  in Nerve Terminals (Presynaptic Neurons) =>

  => ↓ their Level in the synaptic cleft.
- More actively inhibits reuptake of

  Serotonin than Noradrenaline => SEDATION.
- Anxiolytic, Sedative and

  Psychomotor Dampening effects.

Clinical uses:

Depression, Anorexia, Bulimia.

Adverse Effects of Tricyclic Antidepressants

Antagonism at *M-cholinoceptors* □

Atropine-like effects:

- Tachycardia
- Inhibition of Exocrine Glands
- Xerostomia (dry mouth)
- Urinary retention
- Constipation
- Blurred vision
- Aggravation of Glaucoma and Epilepsy

Fluoxetine (Prozak – tab. 0.02 g)

- a Selective Serotonin-Reuptake Inhibitor (SSRI) – specifically inhibits *SEROTONIN* reuptake

Advantages include:

- Absence of cardiotoxicity
- Free of Anti-Cholinergic Effects, orthostatic hypotension
- Loss of appetite and Weight Reduction
- the ease of once-a-day dosing

Clinical Uses:

Depression, Bulimia nervosa, Obsessive-Compulsive disorder, Anorexia nervosa, Panic disorder, Premenstrual Syndrome

Adverse Effects: Over arousal, Insomnia, Tremor, Anxiety, Akathisia (a state of Agitation, Distress, Restlessness and the Inability to sit still), sexual dysfunction, hot flashes, cough, flu-like syndrome

MAO Inhibitors: *Nialamide, Moclobemide* and

SSRI : *Fluoxetine* et al.

should not be co-administered due to the risk of Life Threatening "*Serotonin Syndrome*"

as a result of excess *SEROTONIN* (5-HT):

- □ t^o, Muscle Rigidity, Myoclonus,
- Rapid Changes in Mental Status and Vital Signs
- Cardiovascular collapse

Drugs require WASHOUT PERIODS of *6 weeks* before administering the other.

Nootrop Drugs – activate learning,
improve memory and intellectual activity

I. ACTOPROTECTORS:

1. Activators of Brain Metabolism:
   - Methyl Xanthines:
     - Instenon
     - Caffeine
     - Aminophylline (*Euphylline*)
   - Protein Hydrolyzates:
     - Actovegin
     - Cerebrolysin
     - Solcoseryl
2. Cerebral Vasodilators:
   - Nicergoline (*Sermion*)
   - Vinpocetine

3. Ca^{2+}- Antagonists: Nimodipine, Cinnarizine
4. Antioxidants: Tocopherole acetatate (*Vitamin E*)
5. GABA and its derivatives:
   - Aminalon (GABA)
   - Oxybutyrate Sodium (GOBA)
   - Pantogam, Phenibut, Picamilon

II. Affecting Advantageously MEMORY:

1. Racetams - cyclic GABA derivatives:
   - Piracetam (*Nootropil*)
   - Aniracetam
   - Oxiracetam
2. Pyridoxine (Vitamin B_6) derivatives:
   - Encephabol

Actovegin - amp. 4% 2 and 5 ml, vial 20%-250 ml, Dr. 0.2 g, is proved to be the Most Effective Nootrop.

contains Deproteinized Hemoderivate from plasma of the Calf blood with Low-molecular Peptides, Amino Acids, Nucleosides, Lipids, Electrolytes and Microelements.

After 60-90 min IV infusion of 20% 250 ml:

- Cardiac Index by 25%
- Stroke Index by 30%
- O_2 Content in Arterial Blood by 13%

• HR does not change

- Intensity and Efficiency of Aerobic Processes
- Energy and Contractibility of Muscles
- Prevents accumulation of LACTATE

Instenon – 1 ampoule 2 ml contains:

Methylxantine Ethophylline - 100 mg

Analeptic Etamivan - 50 mg

Vasodilator Hexobendin- 10 mg

- Cardiac Output
- Perfusion Pressure in the Vessels of the Edge Zone of Ischemia

STIMULATES:

- the *Respiratory* and *Vasomotor centers*
- Centers of vegetative regulation
- Nuclei of the cranial nerves.

Clinical uses:

brain diseases of vascular and age-dependent nature, stroke, sequences of cerebrovascular insufficiency.

Cerebrolysin amp. 21.5% 1, 5 and 10 ml

a peptidergic nootrop with neurotrophic action.

1 ml ∈ 215 mg of NEUROPEPTIDES

from the Swine's Cerebrum.

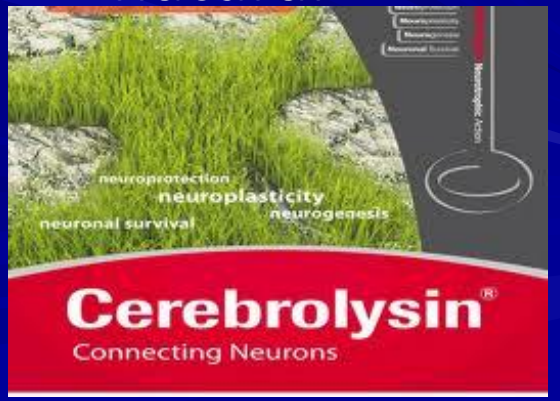
Pharmacological action: *nootrop,*

Metabolic regulation

Neuroprotection

Functional Neuromodulation

Neurotrophic activity - analogous to natural Neuron Growth Factors



Mechanisms of action of GABA derivatives - 1

➡ **Mediator mechanisms:**

► **In exited state of CNS - inhibiting effect due to:**

- **Exitation of postsynaptic ionotropic $GABA_A$-receptors** and opening of Cl^- channels.
- **Exitation of presynaptic metabotropic $GABA_B$-receptors**, opening of G-protein-coupled K^+ channels, inhibition of adenylatcyclase, closing of G-protein-coupled N, P and Q Ca^{++} channels.

► **In inhibited state of CNS - activating effect due to:**

- **Exitation of glutamatergic NMDA and AMPA receptors** (receptors for exitatory aminoacids).
- **Exitation of adrenoceptors**.
- **Exitation of cholinoceptors**.
- **Exitation of 5-HT-receptors**.

Mechanisms of action of GABA derivatives - 2

→ **Metabolic mechanisms:**

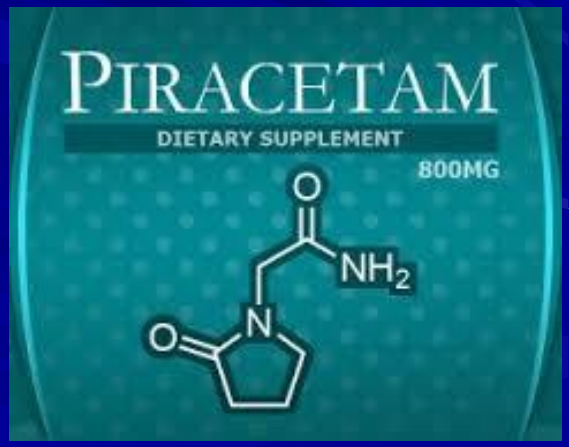
- In normal or increased blood supply - stimulation of aerobic glycolysis:
- In decreased blood supply - stimulation of anaerobic glycolysis due to:
  - Activation of GABA-shunt.
  - Activation of glyconeogenesis.
- Normalization of function of membranes after:
  - Normalization of Na^+-K^+-pump function.
  - Stabilization of phospholipid layer, increase of fluidity of membranes.

Piracetam (*amp.* 20%-5 ml, tab. 0.4 g) -
a derivative of **GABA**

Mechanism of action: Improvement of *metabolic* and *bioenergetic processes* in neuron:

- Activation of *synthesis* of ***proteins*** and ***RNA***
- Improvement of utilization of *glucose*
- Intensification of *ATP synthesis*
- Membrane-stabilizing action

In large doses and at repeated introduction it is capable to strengthen GABA-ergic *inhibitory processes* in brain




Thank You for Attention!