Medicinal Chemistry

Chapter 11

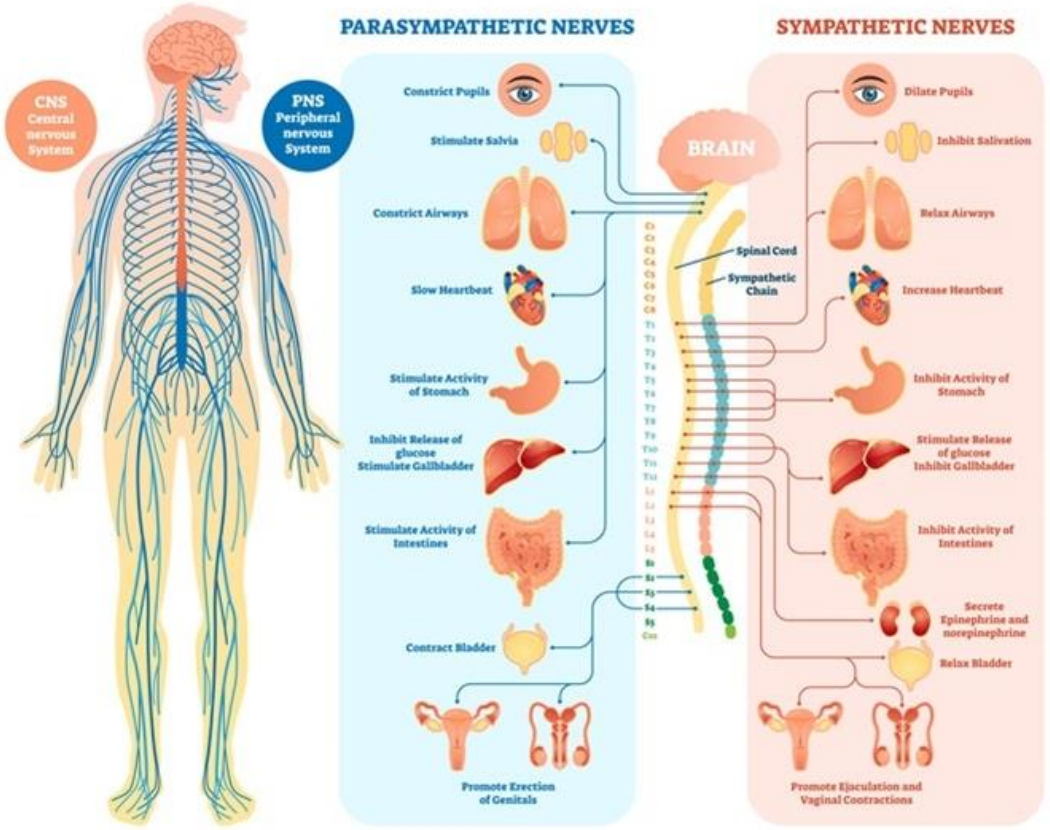
DURGS ACTING ON CENTRAL NERVOUS SYSTEM

Contents

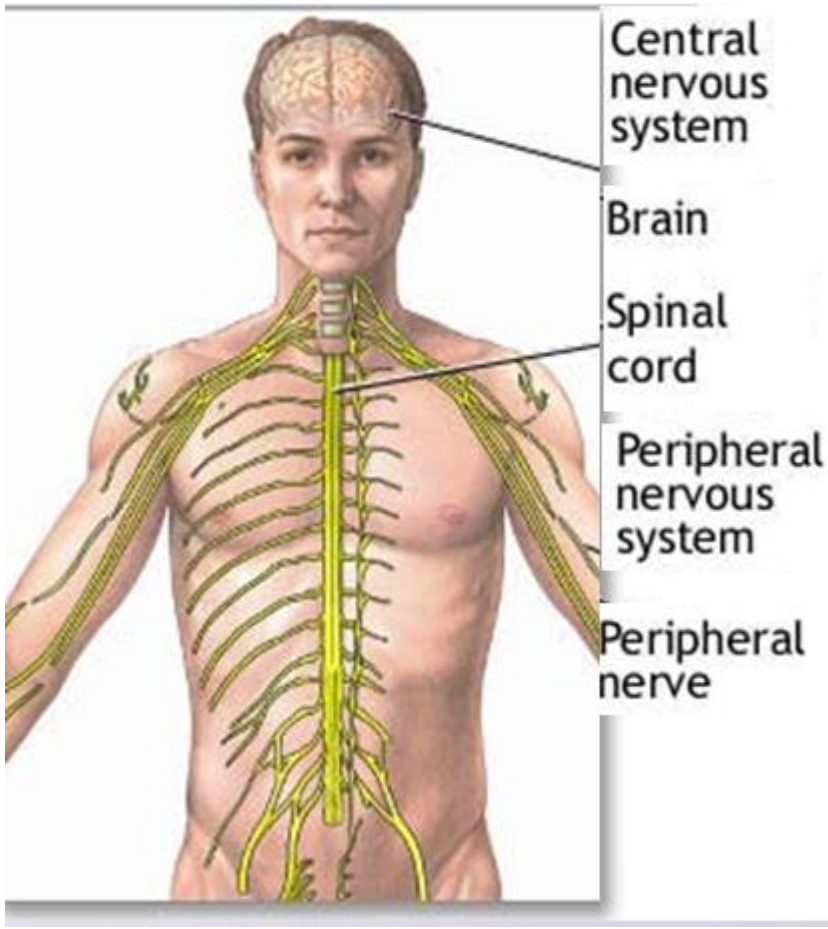
Nervous system

The nervous system is a complex network of nerves and cells that carry messages to and from the brain and spinal cord to various parts of the body.

The nervous system includes both the Central nervous system and Peripheral nervous system. The Central nervous system is made up of the brain and spinal cord and The Peripheral nervous system is made up of the Somatic and the Autonomic nervous systems.



The central nervous system is protected by major physical and chemical barriers. Physically, the brain and spinal cord are surrounded by tough meningeal membranes, and enclosed in the bones of the skull and vertebral column, which combine to form a strong physical shield.



Although nerves tend to lie deep under the skin except in a few places such as the ulnar nerve near the elbow joint, they are still relatively exposed to physical damage

Most neurons collect in one area of the brain. Because of this aggregation partial damage or completely damage to the brain only results in the loss of those functions responsible for that part.

Blood–brain barrier (BBB), one of the barriers that protect CNS,
Circulating drugs must cross BBB in order to gain access to the neurons of the brain

1. Drugs that are cross BBB most readily

a. lipid soluble,

b. small in molecular size,

c. poorly bound to protein,

d. nonionized at the pH of cerebrospinal fluid (CSF)

2. The BBB tends to increase in permeability in the presence of inflammation or at the site of tumors.
3. The BBB is poorly developed in neonates; hence, chemicals can easily gain access to the neonatal brain.

Durgs effect Central Nervous System

It’s the drugs can alter the function of the central nervous system (CNS) to provide:

1. Anticonvulsant effects
2. Tranquilization (sedation)
3. Analgesia

These drugs can selectively relieve pain, reduce fever, suppress disordered movement, induce sleep or arousal, and reduce the desire to eat or ally the tendency to vomit. Selectively, acting drugs can be used to treat anxiety, mania, depression, or schizophrenia and do so without altering consciousness.

Transmission in CNS

- A nerve impulse (electric current) passes along axon to presynaptic membrane.
- Release neurotransmitter into synaptic cleft.
- NT interacts with receptors on effector cells to induce response.
- NT released in response to action potentials is voltage dependent & require calcium influx (Neuroregulators).

Transmission in CNS occurs in 2 ways:

A- Release of Excitatory transmitter by Neuron

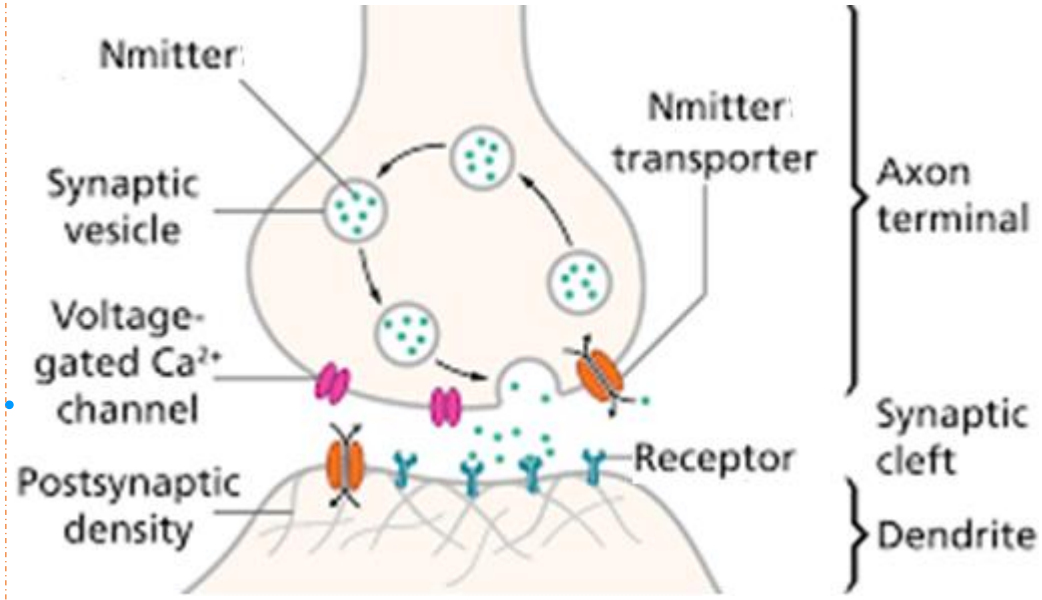
(1) Cause depolarization of postsynaptic membrane of neuron

(2) Cause Conduction of nerve impulse **[postsynaptic excitation].**

B- Release of Inhibitory Transmitter by Neuron

(1) Cause Hyper polarization of postsynaptic membrane .

(2) Block conduction of nerve impulse **[postsynaptic inhibition].**



Major Neurotransmitters

- Cholinergic,
- Dopaminergic,
- GABA-ergic,
- Noradrenergic, and
- Serotonergic networks.

Excitatory

- Aspartate
- Glutamate

Inhibitory

- GABA
- Glycine

Mixed

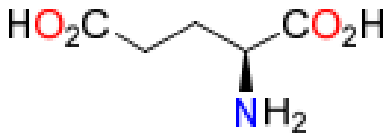
-Acetylcholin

- Norepinephrin

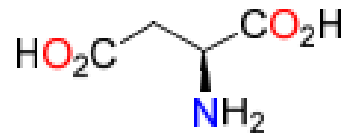
-Epinephrine

- Dopamine

-Serotonin



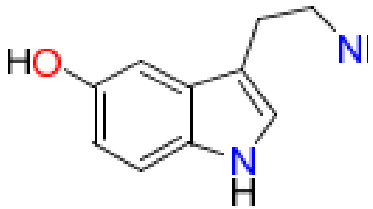
Glu



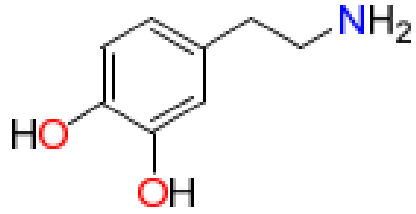
Asp

GABA

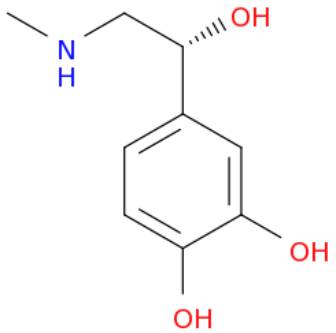
Gly



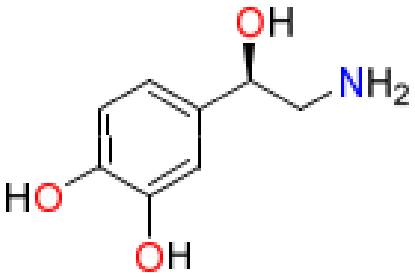
Serotonin



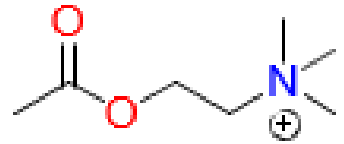
Dopamine



Epinephrine

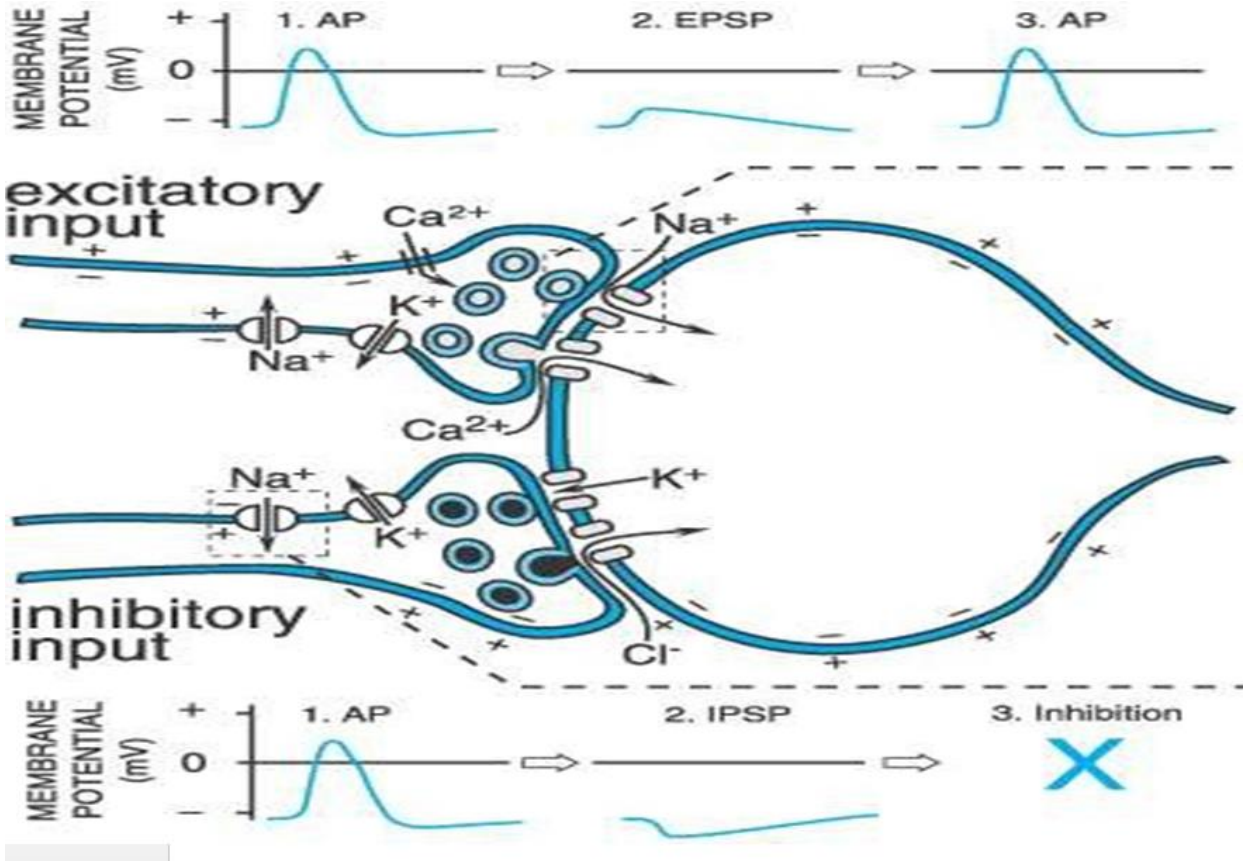


Norepinephrine



Acetylcholine

- **Excitatory:**
  - Create Excitatory postsynaptic potentials: EPSP
  - stimulate or push neuron towards an action potential (*figure*)
- **Inhibitory:**
  - Create Inhibitory postsynaptic potentials: IPSP
  - Reduce probability that neuron will show an action potential (*figure*)
- Some neurotransmitters are both inhibitory and excitatory, depending upon situation and location
  - NE, Ach, Dopamine, 5-HT.



The cholinergic system:

- Uses acetylcholine (Ach) as its NT.
- Ach,
  - the first substance to be designated as a NT in the CNS.
- Located in many areas of the brain,
  - Especially high concentrations in the **motor cortex** and **basal ganglia.**
  - Both types of Cholinergic receptors (nicotinic & muscarinic) occur in CNS
  - Muscarinic receptors are much more abundant than nicotinic & mediate behavioral effects of Ach .

- Exerts excitatory effects at synapses and inhibitory effects at some sites.
- In the CNS, acetylcholine is associated with,
  - **arousal, learning, memory, motor conditioning, and speech**.
- Dementia and Parkinsonism is associated with abnormalities in cholinergic pathways.

The dopaminergic system:

- Uses dopamine as its NT.
- Originate primarily from substantia nigra, ventral tegmental area (VTA) and hypothalamus.
- Projects to different areas of brain including striatum, limbic areas (e.g. amygdala, hippocampus, nucleus accumbens), frontal and prefrontal lobe cortex, pituitary gland.
- Dopamine is important in;
  - motor control (Parkinsonism is due to dopamine deficiency),
  - behavioural effects (excessive dopamine activity is implicated in schizophrenia),
  - hormone release (inhibits prolactin secretion) and
  - chemoreceptor trigger zone causes nausea and vomiting.

Two groups of dopamine receptors have been identified.

- One group includes D1 and D5 receptors, **activate** adenyl cyclase to produce cAMP.

- The other group includes D2, D3, and D4 receptors.
  - **inhibit** activation of adenyl cyclase,
  - suppress calcium ion currents, and
  - activate potassium ion currents.

- Metoclopramide, phenothiazines are antiemetics drugs. (dopaminergic antagonists)

- **The GABA-ergic system**

  - uses GABA as its neurotransmitter.
- GABA
  - **Major inhibitory** NT of CNS
  - Found in virtually every region of the brain.
- GABA receptors- two main types, A and B.
- $GABA_A$ receptor:
  - a chloride ion channel that opens when GABA is released from presynaptic neurons.
  - Activation causes hyperpolarization.
- $GABA_B$ receptor:
  - Leads to increased efflux of K^+ and hyperpolarization
  - Also leads to decreased presynaptic Ca^{2+} influx.

- Benzodiazepines, Barbiturates, Sod. Valporate, Ivermectin → increase binding GABA to nicotinic receptor. (GABA Agonist)

The Noradrenergic system:

- uses norepinephrine as its NT
- Originate primarily in **locus coeruleus** (in the pons).
- Projects diffusely to cortex and brainstem.
- extends to virtually every area of the brain.
- Noradrenergic system is associated with;
  - **mood, wakefulness and alertness, reward, Arousal, Attention,**
- Control mood
  - **Functional deficiency contribute to depression.**
- **Blood pressure regulation.**

- Norepinephrine receptors in the CNS, as in the sympathetic nervous system,
  - divided into alpha- and beta-adrenergic receptors and their subtypes.
- Activation of α1, β1, and β2 receptors:
  - thought to stimulate activity of intracellular adenyl cyclase and the production of cAMP.
- Activation of α2 receptors:
  - associated with inhibition of adenyl cyclase activity and decreased production of cAMP.
- However, the effects of α2 receptor are thought to stem mainly from;
  - activation of receptor-operated potassium ion channels and
  - suppression of voltage-operated calcium ion channels.

The serotonergic system:

- Uses serotonin (5-hydroxytryptamine or 5-HT) as its NT.
- Serotonin-synthesizing neurons
  - widely distributed in the CNS, beginning in the midbrain (**raphe nuclei**) and projecting into the thalamus, hypothalamus, cerebral cortex, and spinal cord.
  - synthesized from the amino acid tryptophan.
- Serotonin in CNS is associated with,
  - **Mood, Arousal** (sleep–wake cycle), **emotional behavior**, **temperature regulation**, **inhibition of pain pathways** in the spinal cord.

Serotonin receptors

- Many types and subtypes – 5-HT1-7
- Mostly metabotropic, Except 5-HT_3, ionotropic
- 5-HT1B/D: Presynaptic autoreceptors and Inhibitory

- **Glutamate**

  - considered the most important excitatory NT in the CNS.
  - It occurs in high concentrations in virtually every area of the CNS, including the cerebral cortex, basal ganglia, limbic structures, and hippocampus.

- NMDA glutamate receptor subtype;
  - plays a role in memory.
  - Overstimulation causes excitotoxicity that may result in cell death.

- Glutamate antagonist (e.g., Ketamine) has therapeutic role in treatment of “epilepsy” & induction of anaesithea

Drugs acting on CNS

There are two types of substances affecting the CNS either as Stimulant or depressant

CNS Stimulants increase alertness, attention, and energy, which are accompanied by increases in blood pressure, heart rate, and respiration.

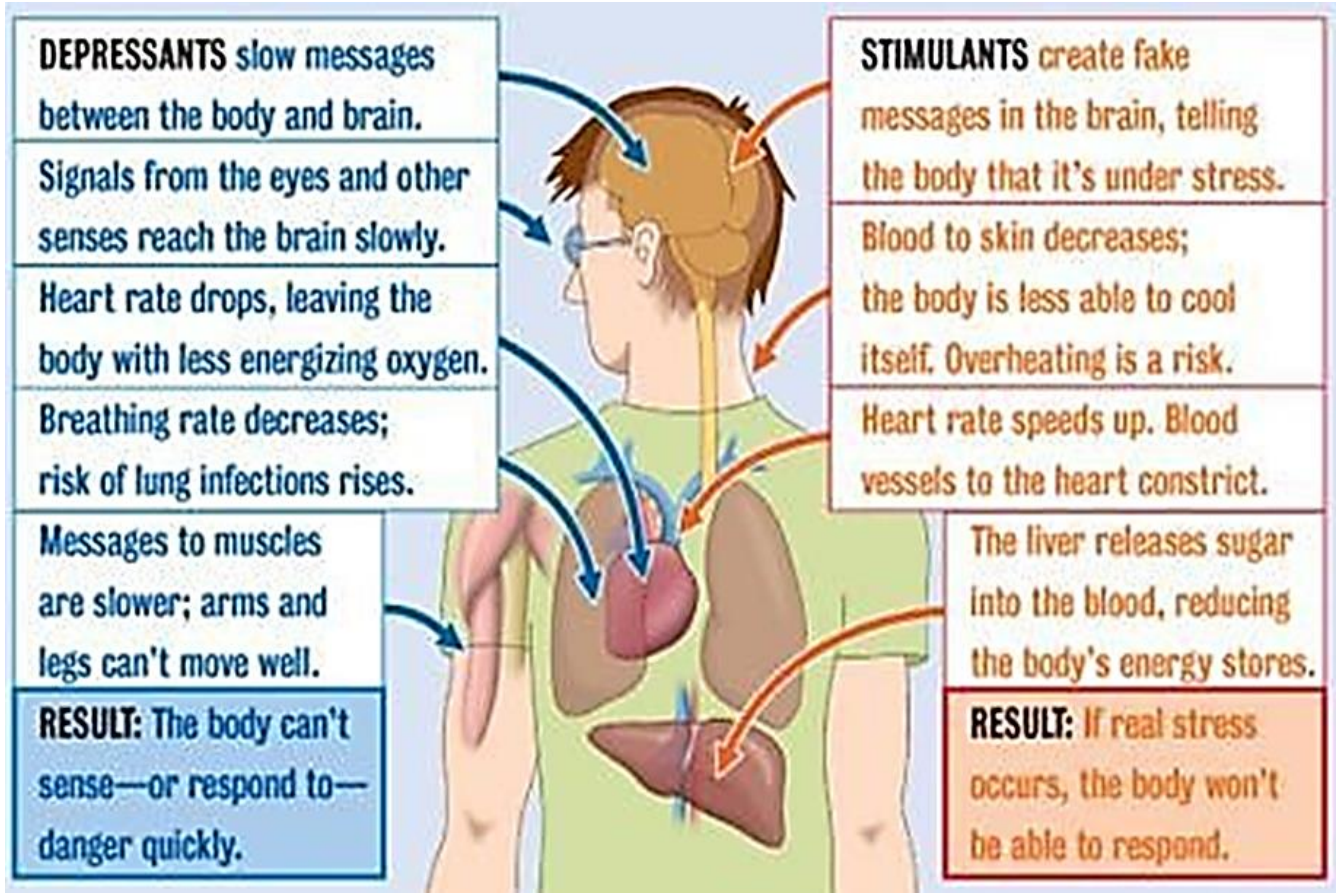
CNS Depressants slow normal brain function. In higher doses, some CNS depressants can become general anesthetics.

CNS Stimulants

- Cerebral stimulants
- Medullary stimulants
- Spinal cord Stimulants

CNS Depressants

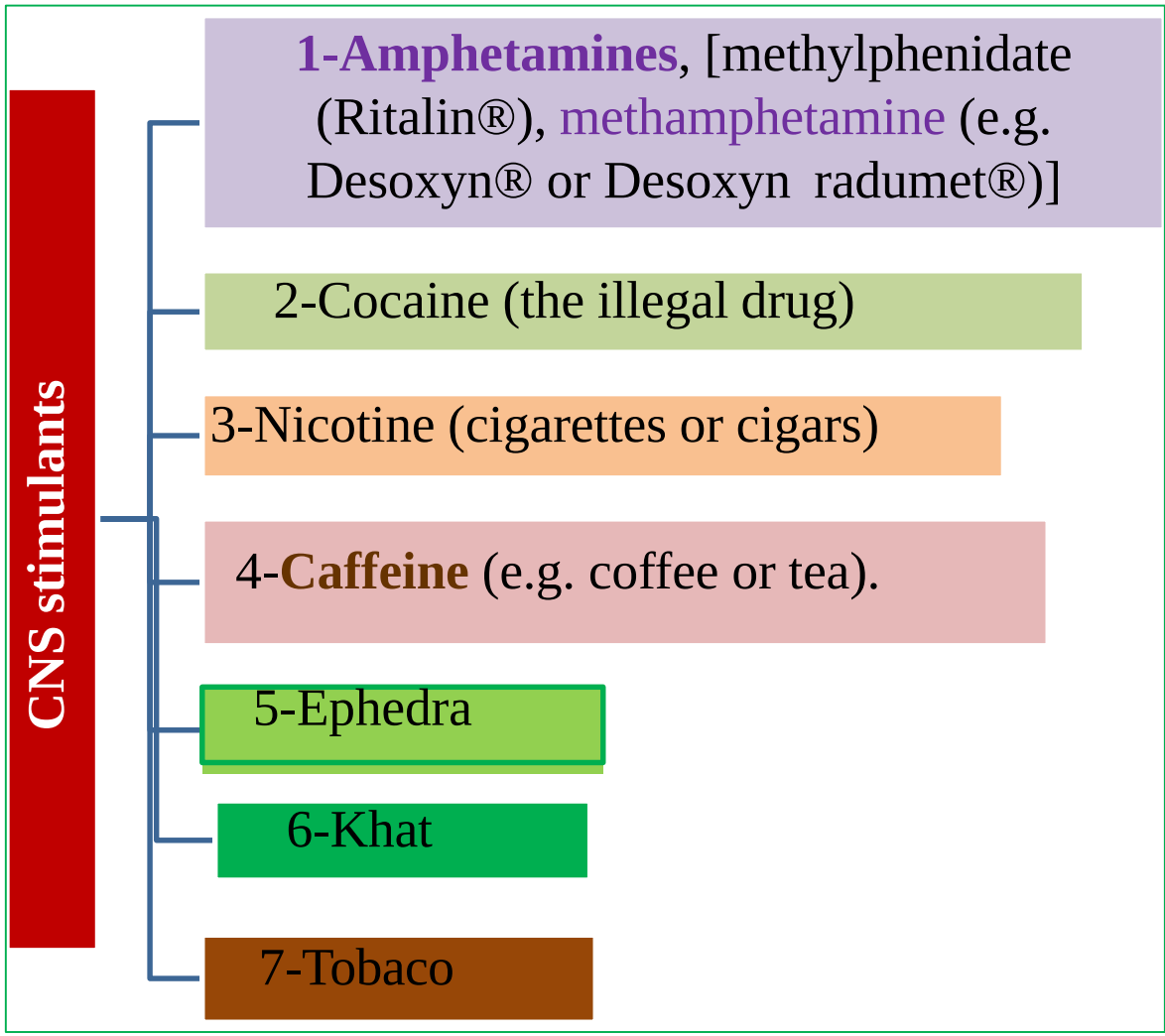
- Nerve Sedatives
- Tranquilizers
- Hypnotics
- Anticonvulsants
- Anaesthetics
- Analgesics


DEPRESSANTS slow messages between the body and brain.
Signals from the eyes and other senses reach the brain slowly.
Heart rate drops, leaving the body with less energizing oxygen.
Breathing rate decreases; risk of lung infections rises.
Messages to muscles are slower; arms and legs can't move well.
RESULT: The body can't sense—or respond to—danger quickly.
STIMULANTS create fake messages in the brain, telling the body that it's under stress.
Blood to skin decreases; the body is less able to cool itself. Overheating is a risk.
Heart rate speeds up. Blood vessels to the heart constrict.
The liver releases sugar into the blood, reducing the body's energy stores.
RESULT: If real stress occurs, the body won't be able to respond.

Central nervous system (CNS) stimulants

Central nervous system (CNS) stimulants, also called **psychomotor stimulants** or **uppers**, are a class of drugs that speed up physical and mental processes. They temporarily make patients feel more alert and improve mood.

Stimulants are typically used to treat medical conditions such as attention-deficit hyperactivity disorder (ADHD), attention-deficit disorder (ADD), fatigue, and narcolepsy. Some stimulants have been used as appetite suppressants, although the safety of this use remains controversial.



CNS Side effects

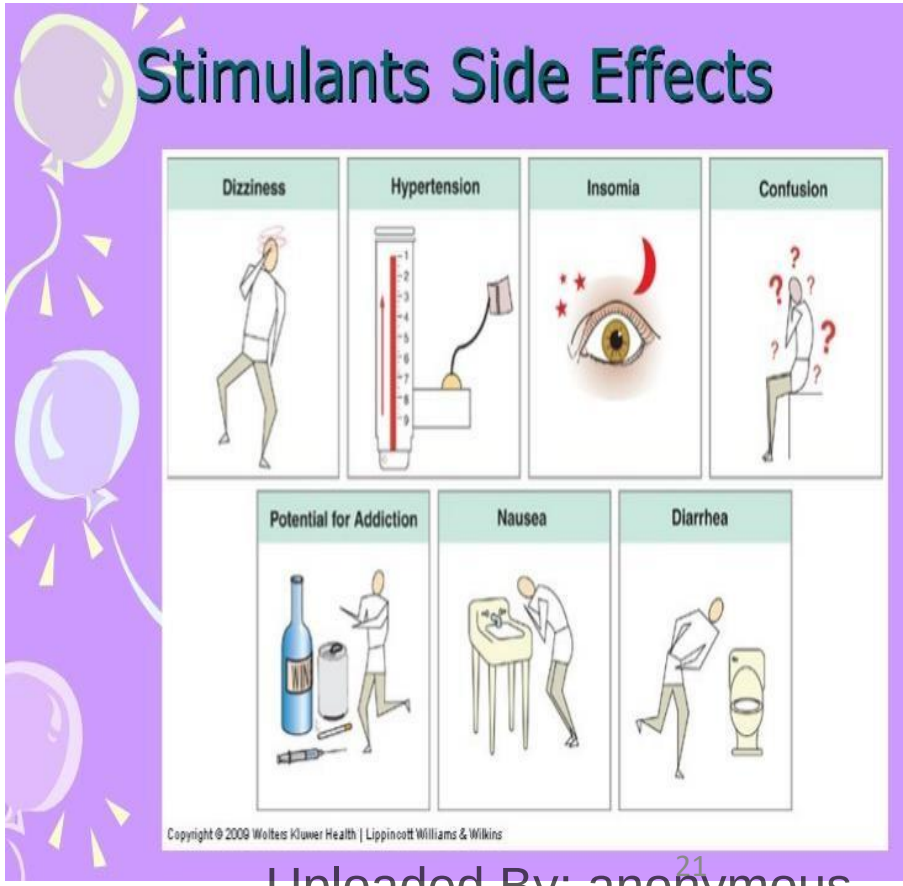
Most CNS stimulants are **highly addictive**. However, some newer drugs, such as modafinil (Provigil®) are less addictive. **Because stimulants are highly addictive** and have euphoric effects on the brain, they are often abused and taken as recreational drugs.



CNS side effects vary depending on the specific dose and type of drug.

1-**Short term** use may include; anxiety, insomnia, dry mouth, depersonalization, feeling of euphoria, increased heart beat, crying, dysphoria, decreased appetite, hyperventilation, irritability, depression, nervousness, paranoia, mood swings, restlessness, and shaking or trembling.

2-Long-term abuse of stimulants can cause changes in the brain and lead to serious health problems, including severe mental illness and memory loss.



Types of (CNS) stimulants

There are two types of CNS stimulants:

Psychomotor Stimulants : are compounds that can produce increases in psychological and physical functioning.

Two primary groups in this drug class:
– Naturally occurring (cocaine Various forms)
–Synthetically produced (amphetamine & analogues).

Side effects: excitement and euphoria and decrease feeling of fatigue and increase motor activity.

Hallucinogens or Psychomimetic drugs it is the stimulants that produce profound changes in thought patterns & moods, with little effect on brain stem & spinal cord

Two primary groups in this drug class:
– Naturally occurring (Psilocybin , Salvia , Mescaline, bufotenin).
–Synthetically produced (LSD, amphetamines (i.e. MDA, MDMA).

Side effects: Incapable of normal decision making because drug interfere with rational thought.

Schedule for Controlled Drugs

There are five schedule for Controlled Drugs

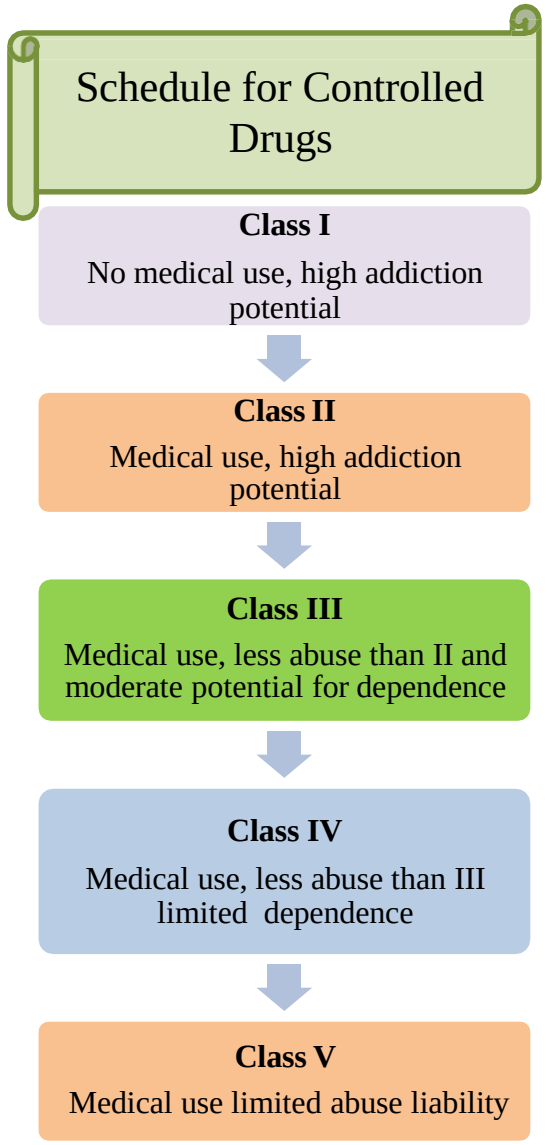
ScheduleI: They have no medicinal value and have a high potential forabuse.

Therefore, these drugs are **not prescribed for medical conditions**.

Including; Diamorphine (heroin), marijuana

Schedule II : have a high abuse potential. Patients are become psychologically and/or physically dependent on these drugs. Unless it is an emergency, prescriptions for schedule II must be made in writing and signed by a healthcare professional. If it is a medical emergency, the healthcare professional must provide written confirmation of the verbal prescription within 72 hours. Prescriptions for this schedule cannot be renewed.

Include; Cocaine, morphine, pentobarbital



Schedule III: less likely to be abused than schedule I and II drugs. Healthcare professionals can give oral or written prescriptions and up to five renewals within six months.

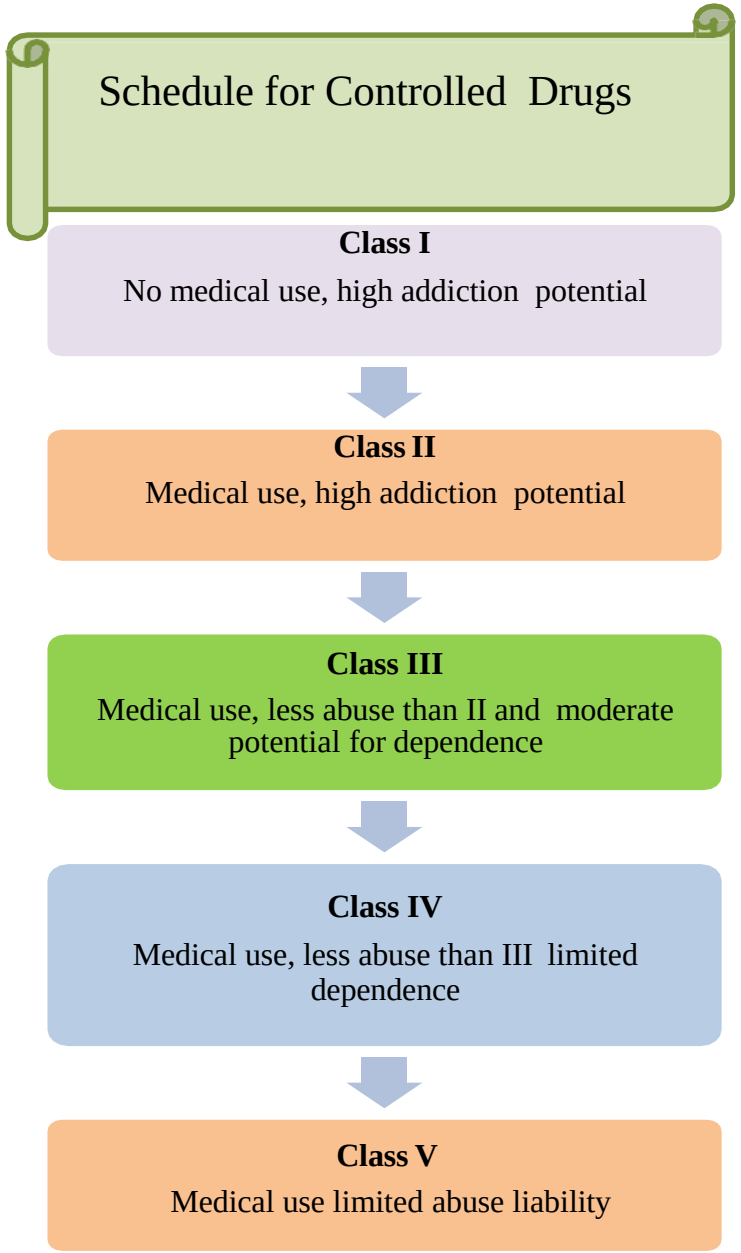
Include; Ketamine, buprenorphine.

Schedule IV : Schedule IV stimulants are less likely to be abused than schedule III stimulants. Healthcare professionals can give oral or written prescriptions and up to five renewals within six months.

Include; Diazepam, barbital ,armodafinil (Nuvigil®).

Schedule V : These drugs are less likely to be abused than class IV stimulants. These drugs are regulated by the state. In some areas, a prescription may not be needed.

Includes; Pregabalin, lacosamide, pyrovalerone.



Uses of (CNS) stimulants Drugs

Appetite suppressant: stimulants cause limited weight loss because patients eventually develop tolerances to long-term treatment.

Include; dexfenfluramine, sibutramine, phentermine.

Attention disorders: are prescription medications that are taken by mouth to treat attention-deficit hyperactivity disorder (ADHD) and attention-deficit disorder (ADD).

Include; Amphetamines, including methylphenidate, dextroamphetamine

Narcolepsy: Patients with narcolepsy, a condition that causes individuals to have sudden attacks of deep sleep or the uncontrollable desire to sleep, also receive stimulants. These drugs help narcoleptic patients stay awake during the day.

Includes : Modafinil (Provigil®), methylphenidate (Ritalin®)

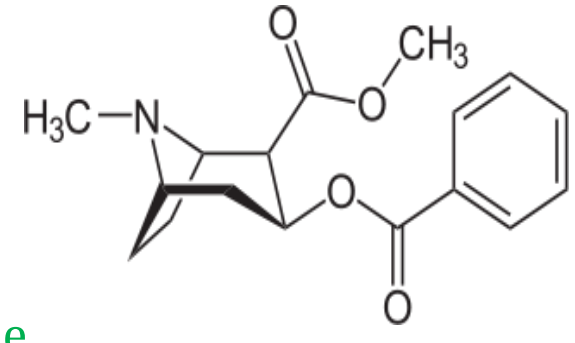
Fatigue: Caffeine is a stimulant that is found in coffee and various teas, soft drinks, and energy drinks.
Include; Methylphenidate (Ritalin® or Concerta®) has also been suggested as a possible treatment for chronic fatigue syndrome (CFS).

Recreational drug use: Many stimulants are used recreationally, for no medical purpose. However, abusing stimulants can lead to serious and potentially life-threatening health conditions.

For instance, nicotine is a stimulant that is found in tobacco products, such as cigarettes or cigars. The nicotine makes patients temporarily feel good or energized after smoking. Although this stimulant is legal, it can cause serious health problems, including cancer and emphysema.

Crack is an unprocessed form of cocaine. Crack is cocaine that has not been neutralized to make the hydrochloride salt. This form of cocaine looks like a rock crystal. Individuals typically heat crack and inhale the vapors.

Cocaine



- **Cocaine** is a powerfully addictive stimulant that directly affects the brain.
- In fact, it is one of the oldest known drugs. The pure chemical, cocaine hydrochloride, has been an **abused substance for more than 100 years**, and coca leaves, the source of cocaine, have been ingested for thousands of years.

- Pure cocaine was first extracted from the leaf of the ***Erythroxylon coca*** bush, which grows primarily in **Peru and Bolivia**. In the early 1900s, it became the main stimulant drug used in most of the tonics/elixirs that were developed to treat a wide variety of illnesses. Today, **cocaine is a Schedule II drug**, meaning that it has high potential for abuse, **but can be administered by a doctor for legitimate medical uses.**

There are basically **two chemical** forms of cocaine: the **hydrochloride salt** and the "**freebase.**“

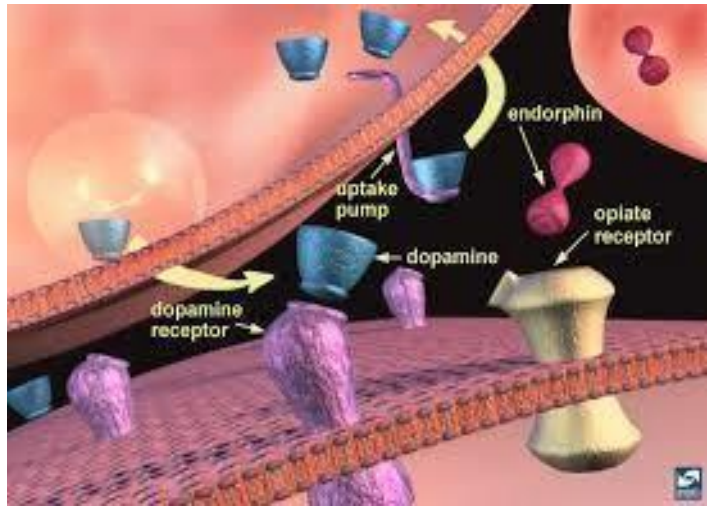
The hydrochloride salt, or powdered form of cocaine, dissolves in water and, when abused, can be taken intravenously (by vein) or intranasally (in the nose).

Freebase refers to a compound that has not been neutralized by an acid to make the hydrochloride salt. The freebase form of cocaine is smokable.

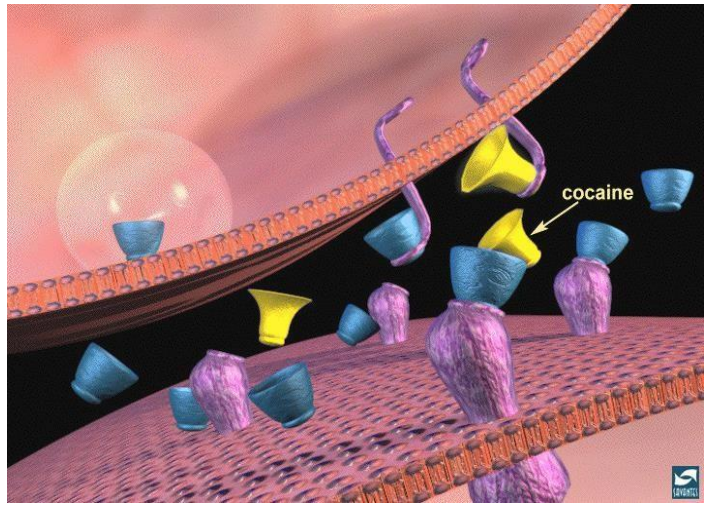
Cocaine is generally sold on the street as a fine, white, crystalline powder, known as "coke," "C," "snow," "flake," or "blow." Street dealers generally dilute it with such inert substances as cornstarch, talcum powder, and/or sugar, or with such active drugs as procaine (a chemically-related local anesthetic) or with such other stimulants as amphetamines.

How does cocaine produce its effects?

Scientists have discovered regions within the brain that, when stimulated, produce feelings of pleasure. **One neural** system that appears to be most affected by cocaine originates in a region, located deep within the brain, called the ventral tegmental area (VTA).



Cocaine in the brain - In the normal communication process, dopamine is released by a neuron into the synapse, where it can bind with dopamine receptors on neighboring neurons. Normally dopamine is then recycled back into the transmitting neuron by a specialized protein called the dopamine transporter. If cocaine is present, it attaches to the dopamine transporter and blocks the normal recycling process, resulting in a build-up of dopamine in the synapse which contributes to the pleasurable effects of cocaine.



Their are tow types of **Cocaine**

A- Natural cocaine - illicit which obtained from The Erythroxylum coca var. coca

B. **Synthetic cocaine** which obtained synthetically.

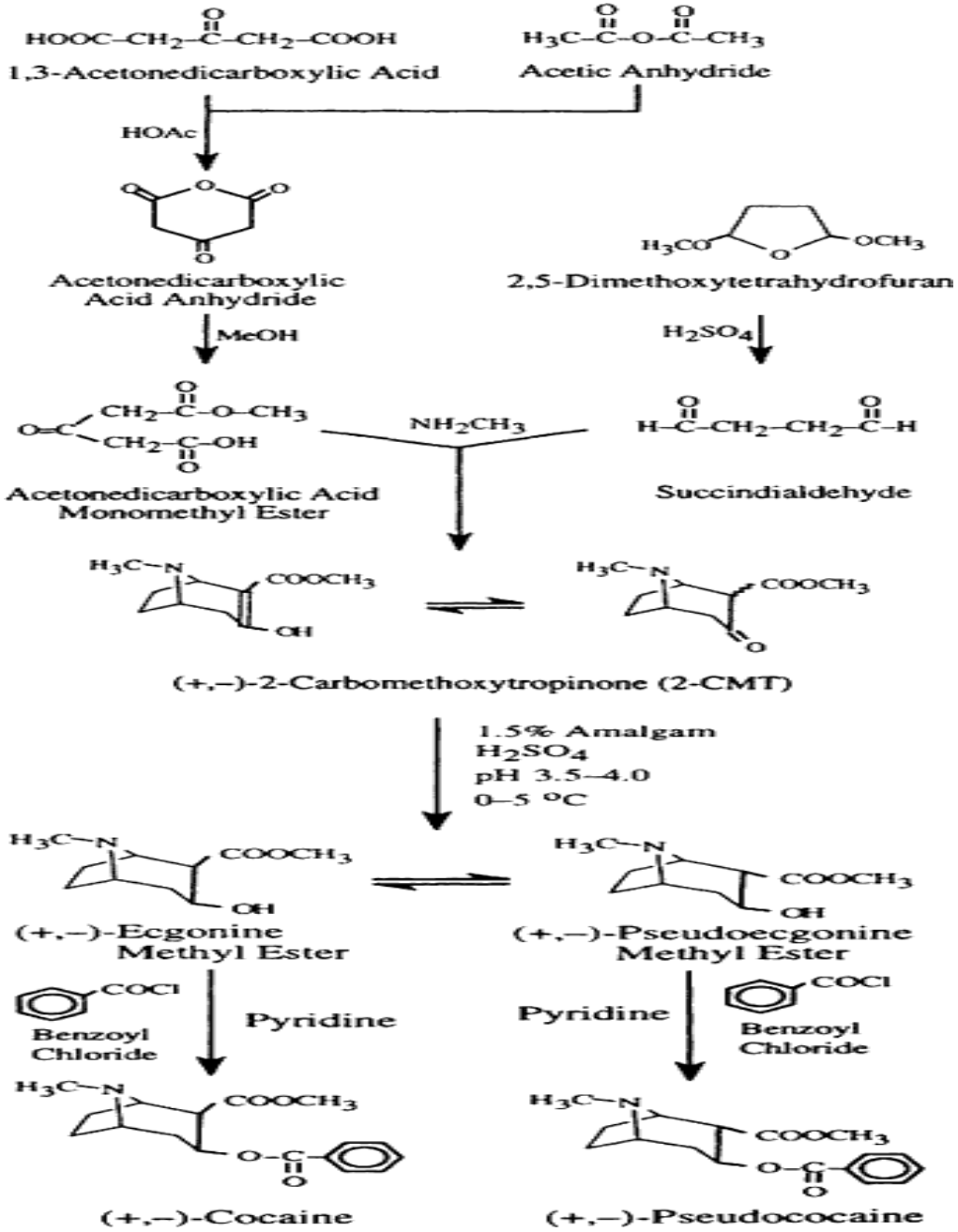
- Production of illicit **natural** cocaine involves three steps:

1) Extraction of crude coca paste from the coca leaf by solvent or acid extraction technique

2) **Purification** of coca paste to coke base

3)Conversion of coke base to cocaine hydrochloride

- The classic total **synthesis** of cocaine involves three synthetic:
  1. Production of 2-carbomethoxytropinone;
  2. Its conversion to Methyl Ecgonine
  3. Benzoylation to Cocaine.



Metabolism

In humans, the principle route of metabolism of **cocaine** is by hydrolysis of the ester linkages. Plasma and liver **cholinesterases** produce the following metabolite,

1- Majour metabolits; ecgonine methyl ester (EME), benzoylecgonine (BE), norcocaine (NC).

2- Minor compounds such as Cocaethylene, Anhydroecogonine methyl ester

The metabolite, benzoylecgonine, is excreted with the urine. It is fairly stable and thus can be detected in wastewater