Neurons and Synaptic transmission –Synapses are the site of action for most psychoactive drugs –

Neurons (cells found in the nervous system) are made up of the following:

- **Soma**: cell body
- **Axon**: conducts signal down neuron (output)
- **Dendrites and spines**: receive incoming signals from pre-synaptic neuron
- **Synaptic vesicles**: holds neurotransmitters (inside cell)
- **Synaptic clefts**: space between pre and post-synaptic neurons
- **Pre-synaptic neuron**: sends signal to pre-synaptic neuron
- **Post-synaptic neuron**: receives signal from pre-synaptic neuron

- **Glia**: cells that provide support and protections for neurons –Cell-to-cell junctions:
  - **Tight junctions**: membranes are fused
  - **Gap junctions**: small cleft (2-4nm); electrical synapse
  - **Chemical synapse**: cleft is bigger (20-30nm); polarized (more negative inside)

-Multiple types of connections: axondendritic (axon to dendrite), endrodendritic (dendrite to dendrite), axoaxonic (axon to axon), etc.

Steps in Synaptic Transmission:
- Synthesis of NT –Transport of NT –Storage into vesicles –Release of NT:

  - **Release in detail (excitation–secretion coupling):**
    - Depolarization (voltage of neuron
    - Voltage-gated calcium (Ca++) channels open
      - Ca++ rushes into cell
    - Bind to Ca ++ (calmodulin protein kinase)
    - Phosphorylation of synapsin I
    - Vesicle move to site of release
    - Exocytosis (neurotransmitters are released into the synaptic cleft)

  Diffusion of neurotransmitters –Inactivation -Neurotransmitters are inactivated
  in the following ways:
  - **Reuptake**: neurotransmitters go back into via transporters
  - **Enzymatic degradation**: metabolism, excretion, cycling

Neurotransmitters: Classical vs. Neuropeptides –Classical: small water soluble molecules with amine; formed from dietary precursors.

- **Phenylethylamines**: dopamine (DA), norepinephrine (NE), epinephrine (E), tyramine, etc.
- **Indolamines**: serotonin (5-HT), tryptamine, melatonin, etc.
- **Cholinergics**: acetylcholine, etc.
- **Amino acids**: glutamate, gaba, etc.

-Neuropeptides: produced via protein synthesis; includes enkephalins, substance P, neurotensin

Receptors –Classification by location:

- **Postsynaptic**
- **Autoreceptor**: refers to transmitter receptors, on or near pre-synaptic terminals, which are sensitive to the transmitter(s) released by the terminal itself (inhibitory)
  - Presynaptic, Somatodendritic, Terminal release-modulating, synthesis-modulating, impulse-modulating (detects how much NT to inhibit or to make more)

-Classification by transduction mechanism:
Ligand-gated channels: (ligand = drug, NT, hormone, anything coming to bind)
- Binding site is coupled to the ion channel
- The transmitter or drug gates the channel
- Ionotropic receptors (the ligand binding site is an integral part of the receptor molecule)
  - Ligand opens channel
- Ions flow down concentration gradient
- Rapidly reversible
  - Examples:
    - Nicotinic acetylcholine receptor
    - Coupled to sodium channel
    - Drugs include nicotine and curare
  - GABA receptor
    - Coupled to chloride channel
    - Drugs include sedative hypnotics
  - Example: G protein-coupled: (slower but more pervasive)
    - Receptor is coupled to G-protein
    - G-protein activates the effector
    - Metabotropic receptors (slower than ion-coupled)
      - Two classes of G-proteins:
        - Directly coupled: effector is the ion channel
        - Second messenger system: effector is an enzyme that promotes the formation of intracellular "second messenger"
      - Examples: Cholinergic muscarinic, GABAb, Serotonin (5-HT), Opiod, Dopamine (DA), Norepinephrine (NE)

Psychomotor stimulants: cause increased alertness and motor activity, heightened arousal (ex. amphetamines and related compounds, cocaine)

History & Basic Pharmacology
- β-phenylethylamine derivatives: all have similar structures/effects (ex. amphetamine, ephedrine, pseudoephedrine, phenylalanine)
- Sympathomimetic amines: mimic the effects of the sympathetic nervous system — Naturally-occurring compounds:
  - Cathinone — active ingredient in Khat, chewed (synthetic version: meth-cathinone)
  - Ephedrine — from Ma Huang (ephedra = plant extract), used for asthma (bronchodilator), structurally similar to epinephrine (E), pseudoephedrine (Sudafed) is an isomer of ephedrine

Amphetamine — Synthetic, structurally-related to catecholamines (DA, NE, E) — Widespread adoption since 1932 Benzedrine inhalers — Peak use in early 1970’s, but new west coast popularity — Forms of Amphetamine
  - Racemic:
  - Mixture of d-and l-isomers ex. Benzedrine, Adderall (for ADD), speed
  - d-Amphetamine (dextroamphetamine) — stronger than racemic (ex. Dexedrine) need IV
  - l-Amphetamine (levoamphetamine) — less potent version, not really marketed for anything
  - I-Amphetamine (levoamphetamine) — less potent version, not really marketed for anything
  - Methamphetamine (dl-methylamphetamine) — strongest, most potent (ex. Methedrine, Desoxyn (for ADD), meth, crystal, crank, speed)
    - l-Methamphetamine — “desoxyephedrine”, really weak, not even controlled, in Vick’s inhalers
    - d-Methamphetamine HCl — can be smoked (gets to brain faster = more addictive) or snorted b/c of purity (ex. ice, crank, crystal meth)
      - Synthesis from amalgam method → racemic methamphetamine
      - Synthesis form ephedrine (or Sudafed) → pure dmethylamphetamine HCl
      - Depletes DA and serotonin, causes degeneration of terminals (caudate DA, cortical and hippocampal 5-HT)

Amphetamine Related Drugs: all bad for heart, raises blood pressure and heart rate, anorectic
  - Methylphenidate (Ritalin): treats ADD
  - Fenfluramine (Redux): anorectic (reduces appetite)
• Phenmetrazine (Preludin): anorectic
  • Subiramine (Meridia): anorectic -Medical Uses: (1) Narcolepsy, (2) ADD, (3) no longer used for obesity -Major Effects:
    • Autonomic effects (sympathomimetic effects)
    • increased blood pressure
    • increased body temperature

bronchodilation -Effects on CNS
• analeptic (awakening)
• anorexia
• psychomotor stimulant effects
  • decreased fatigue, increased alertness
  • arousal
  • elevated mood

euphoria -Non-humans
• Low doses: locomotor hyperactivity
• Autonomic responses same as human
• Higher doses: stereotyped behavior (doing same thing over and over again)

○ Reinforcing effects: self-administration and conditioned place preference - Effects of repeated administration:
  ○ Tolerance:
    • most autonomic effects
    • anorectic effect
  ○ Sensitization
    • psychomotor stimulant effects
    • rewarding effects (how reinforcing the drug becomes)
    • psychotomimetic effects (amphetamine psychosis), ability of drug to mimic schizophrenia

Cocaine
-Description:
• Naturally found in coca plant leaves
• Local anaesthetic effects (unique to cocaine, does not occur with amphetamines)
• History of use: been around forever, mostly in S. America, in U.S. mixed with wine, tobacco, Coca-Cola was a response to the temperance movement in the south
• Americans spend the most money on cocaine followed by heroin, marijuana, other, and meth -Forms:
  • Raw leaves – chewed, low alkaloid content, not stable (degrades easily)
  • Coca paste – initial extraction around 80% cocaine, used for smoking, cannot snort
  • Cocaine HCl – crystalline form, purified and converted to HCl salt, snorted or IV use
  • Cocaine free base – extract with volatile solvents, smoked, very strong & expensive
  • Crack – free base made with baking soda & ammonia, crackles when heated, smoked (highly trafficked) -Major Effects: very similar to amphetamine but some major differences...
    • Duration of action – much shorter than amphetamine
    • Cardiovascular effects – danger of heart attack much higher than amphetamine (chance of stroke is much higher; easy to overdose and have a heart attack due to anesthetic properties)
    • Convulsive (vomiting) properties – sensitizes
    • Local anaesthetic effects – totally unique to cocaine (ex. lidocaine, novacaine, benzocaine) -Mechanisms of Action (primary actions on monoamine NT)
      • Monoamine neurotransmission – compounds with one amine group, -NH2)
      • Epinephrine (E), found mostly in periphery (outside brain)
• Norepinephrine (NE), found in brain
• Dopamine (DA), found in brain – mediates psychomotor stimulant & rewarding effects
• Serotonin (5-HT), derived from tryptophan

-Catecholamines (CA; catecholaminergic) – compounds with catechol nucleus and amine group
  • Epinephrine (adrenergic)
  • Norepinephrine (noradrenergic)
  -Dopamine (dopaminergic) –Indolealkylamines – compounds with indole and amine group
  • Serotonin (serotonergic)
  • Melatonin

Catecholamine Synthesis: TYROSINE → E1 → DOPA → E2 → DOPAMINE → E3 → NE → E4 → E (don’t need to know enzymes)
  -Enzymes that catalyze conversions:
    • E1 – tyrosine hydroxylase
    • E2 – amino acid decarboxylase
    • E3 – dopamine β-hydroxylase
    • E4 – phenylethanol amine N-methyl-transferase

MAO (monoamine oxidase) degrades monoamines
  -If you block MAO, less DA breaks down –Cocaine blocks transporters…lots of DA in synapse –Amphetamine dumps DA out of vesicles and pumps in DA
DA synapse (see diagram) NE synapse (see diagram) Distribution of NE: concentrated in LOCUS COERULEUS (where NE is made), diffuses everywhere Distribution of DA: 2 pathways
  1. Nigrostriatal (dorsal striatum) – involved in stereotyped behavior SUBSTANTIA NIGRA → CAUDATE PUTAMEN (STRIATUM)
  2. Mesolimbic (ventral striatum) – the pathway of addiction/reward and locomotor hyperactivity VENTRAL TEGMENTAL AREA (VTA) → NUCLEUS ACCUMBENS
    -Important in addiction, reward, reinforcement

Primary Site of Action:
Cocaine: -blocks monoamine transporter -prevents reuptake -requires calcium
Amphetamine: -calcium independent -release of DA not blocked by reserpine (drug that dissolves MA vesicles) -release blocked by TH (tyrosine hydroxylase) inhibition -requires transporter (blocked by reuptake blockers = cocaine)
Locus of Action: -Autonomic effects: sympathetic nervous system -Psychomotor and rewarding effects: brain monoamine systems, DA critical component
Dopamine Studies: -Pharmacological -Lesion -Neurochemical -Correlational -Molecular Biological
DAT vs. VMAT: The DAT is highly regulated, the VMAT is not. Therefore, the VMAT and not the DAT provides a reliable indicator of DA terminal density.

Methylenedioxymethamphetamine (MDMA) – Extacy
  -Illegal since 1985, 1st schedule I by DEA -Several analogues: DOM, DOB, MDA, MDMA, 2-CB -Synthesis: from Safrole (distilled from sassafras or nutmeg oil) -Typical use is in pill form -Different class of users than traditional drug users (clubbers, college students)
Behavioral and Affective Effects: -Low doses: relaxation, serenity, emotional closeness -Moderate doses: mild hallucinogenic effects, intensification of feelings, notorious memory impairment (unique to this class of drugs) -High doses:
amphetamine-like effects, hyperthermia (heat stroke) *(biggest concern in terms of safety, most seen in ER), “hangover”*

**Neurochemical effects:**

**Monoamine Neurotransmission:**
- increase synaptic DA and 5-HT
- blocks 5-HT transporter
- enters neuron and causes calcium-independent release of 5-HT

**Neurotoxic effects:**
- potent neurotoxin (1-2 times street dose)
- depletes forebrain 5-HT (not DA)
- rapid degeneration of 5-HT terminals (MDMA & MDA)

PMA (paramethoxyamphetamine) is a substitute for MDMA because it is cheaper to make, however it has slower/longer effects and is more hallucinogenic, so the incidence of toxic side effects are much higher than MDMA (narrow safety margin). PMA is responsible for most ER visits instead for heat stokes

**IMPORTANT DISTINCTICTION: AMPHETAMINE NEUROTOXICITY**
- d-Amphetamine: DA only
- Methamphetamine: DA and 5-HT
- MDMA (and MDA): 5-HT only

**Schizophrenia**

Positive symptoms (Type I): excesses, exaggerations, or distortions (+) -disorganized speech - hallucinations -delusion

Negative symptoms (Type II): characterized by behavioral deficits (-) -avolution – lack of energy -alogia – reduction in speech -anhedonia – inability to experience pleasure -asociality – severe impairments in social relationships -flat affect or incongruent affect – lack of or inappropriate emotional expression

**DSM-IV Criteria** -At least 2 Positive or Negative symptoms for 1 month -Marked functional impairment - Continuous signs for 6 months -Not due to drugs (e.g. amphetamine psychosis) – important differentiator

Subtypes: -Paranoid Type (Type I) – most common -Disorganized Type (in between) – lease common -Catatonic Type (Type II)

Causes: Genetic and environmental components Neuroleptic or Antipsychotic refer to drugs used to treat schizophrenia only Neuroleptic Side Effects:
- Parkinsonism
- Dystonia – abnormal face and body movements
- Akathisia – restlessness
- Tardive dyskinesia – severe, irreversible movement disorder, WORST SIDE EFFECT

Dopamine: -Schizophrenia thought to be caused by overactive DA system in brain -Increase in DA transmission exacerbates schizophrenia -Blocking DA only helps positive symptoms, other NT’s involved

DA Antagonist Drugs: -Work through Dopamine D2 receptor blockade -Mostly affect positive symptoms -Prolactin elevation (causes lactation) -Affect all DA pathways -Older drugs have Tardive dyskinesia as side effect
- Chlorpromazine (Thorazine) – very sedating at first but tolerance builds
- Haloperidol (Haldol) – depressant
- Fluphenazine (Permitil & Prolixin) – less sedating

Newer drugs: -Dibenzodiazapine derivatives -Treatment Positive and Negative symptoms (but works better for positive symptoms) -Works through 5-HT2 and D2 receptors, specific to Mesolimbic pathway -Minimal prolactin elevation -Less severe side effects, but some have more potential for liver damage -Expensive
- Clozapine (Clozaril)
Parkinson’s Disease

- Movement disorder (stooped, rigid posture, shuffling gait, akinesia)

Pathology of Parkinson’s:
- Death of DA neurons in the SUBSTANTIA NIGRA
- Loss of DA in the CAUDATE
- Loss of inhibition in the CAUDATE → Overactive output (globus pallidus) to the THALAMUS

    Thalamus OVERINHIBITS the MOTOR CORTEX
- Complex basal ganglia-cortical loops (responsible for fine tuning movement)
- NET EFFECT: Not enough DA and overinhibition of the cortex -Symptoms don’t appear until ~80% loss of DA neurons

Epidemiology:
- Onset: 50s -60s -85% idiopathic (cause unknown) -No cure, just treatment

Etiology:
- Genetic factors
- Environmental Factors: MPTP, MPP+, Paraquat and Maneb, Cyperquat -
    Environmental Insult: kick starts the decrease in DA, rapid loss

Levodopa Therapy (precursor for DA):
- DA will not cross blood-brain barrier but L-DOPA can -Too much L-DOPA → too much NE and E, excess E in periphery → bad side effects

Sinemet = L-DOPA + carbidopa - carbidopa is a peripheral decarboxylase inhibitor (prevents L-DOPA catabolism peripherally)

Problems:
- On/off fluctuation
- Dyskinesias
- Eventually doesn’t work
- Peripheral side effects (NE and E)

Chronic DA treatment can also result in schizophrenic symptoms

Surgical treatments: used after therapeutic window closes
- Stem cell transplantation
- Pallidotomy and thalamotomy