Neurotransmitters: classical vs. neuropeptides

1. "classical"- small water soluble molecules with amine, formed from dietary precursors
   includes phenylethylamines (DA, NE, E, tyramine, etc),
   indolamines (5-HT, tryptamine, melatonin, etc),
   cholinergics (acetylcholine, etc), and amino acids (glutamate, etc)
2. neuropeptides- via protein synthesis
   enkephalins, substance P, neurotensin

Receptors

•Classification by location

1. Postsynaptic
2. Autoreceptor: refers to transmitter receptors, on or near presynaptic terminals, which are sensitive to the transmitter(s) released by the terminal itself

•Classification by transduction mechanism

1. Ligand-gated channels:
   - either excitatory or inhibitory actions
   - rapid action & rapidly reversible
   - combine receptor & ion channel functions into a single mlc (binding site coupled to ion channel)
   - ionotropic receptors = receptors in which the ligand binding site is an integral part of the receptor molecule
   - ligand opens channel, ions travels down its concentration gradient
   - examples include:
   A) Nicotinic acetylcholine receptor (nAchR)
   -coupled to Na^+ channel, when drug binds, lets Na^+ in; primary actions observed in muscle contraction
   -drugs that bind nAchR include nicotine, curare, and acetylcholine
   -curare competitively blocks nAchR; depolarization cascade blocked ->muscle contraction occurs
   B) $GABA_A$ receptor
   - coupled to Cl^- channel, has an inhibitory effects
   - sedative-hypnotic drugs
2. G-protein-coupled receptors:
   - produces ambiguous/complicated effects
   - characterized by seven transmembrane domains; the binding of these receptors by agonists leads to the activation of intracellular G-proteins.
   - activated G-protein stimulates effector
   - slower in action than ion-coupled receptors, but usually bigger effect
   - two classes:
   A) Directly coupled to ion channel- effector is ion channel; works almost same as ligand - gates channel at a slower rate
   B) G-protein coupled to 2^{nd} messenger system
   - 2^{nd} messenger opens ion channels
   - types of 2^{nd} messenger include: Ca^{++}, cGMP, IP_3, DAG, cAMP
   - cAMP: activates protein kinase which phosphorylates protein, producing a biological response

•Protein phosphorylation alters the conformation of the protein and thus has an effect on protein function.

Ex) Gene regulatory proteins can activate transcription factors such as CREB, (cAMP response element binding protein) leading to enhancement or suppression of transcription. If transcription is enhanced, new gene products are made. Signaling pathways can alter gene transcription via same transcription factor. ("convergence on CREB" is an example)

Gene activation consists of two phases:

Initial phase – Induction of immediate-early genes, protein products initiate 2^{nd} phase of activation

Second phase – Induction of "late-onset genes", products alter cellular function (often permanent changes)

Psychomotor stimulants: cause increased alertness and motor activity,

heightened arousal (ex. amphetamines and related compounds, cocaine) -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:

1 Cathinone – active ingredient in Khat, chewed

2 Ephedrine – from Ma Huang (ephedra = plant extract), used for asthma (bronchiodilator), 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: -Racemic – mixture of d-and l-isomers (ex. Benzedrine, Adderall (for ADD), speed) -d-Amphetamine (dextroamphetamine) – stronger than racemic (ex. Dexedrine)

- o depletes DA, causes degeneration of DA terminals (primarily caudate) -l-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-Methylamphetamine HCl – can be smoked (gets to brain faster = more addictive) or snorted b/c of purity (ex. ice, crank, crystal meth)
- o synthesis from amalgam method → racemic methamphetamine
- o synthesis form ephedrine (or Sudafed) → pure d-methylamphetamine HCl
- o 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 -Subitramine (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

- o decreased fatigue, increased alertness
- o arousal
- o elevated mood
- o euphoria

Effects of repeated administration: Tolerance -most autonomic effects -anorectic effects Sensitization -psychomotor stimulant effects -rewarding effects (how reinforcing the drug becomes) -psychotomimetic effects (amphetamine psychosis), ability of drug to mimic schizophrenia Non-humans -Low doses: locomotor hyperactivity -Higher doses: stereotyped behavior (doing same thing over and over again) -Reinforcing effects: self-administration and conditioned place preference

Cocaine

-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

Forms: -Raw leaves – chewed, low alkaloid content, not stable (degrades easily) -Coca paste – initial extraction around 80% cocaine, used for smoking -Cocaine HCl – crystalline form, purified and converted to HCl salt, snorted or IV use -Cocaine free base – extract with volatile solvents, smoked -Crack – free base made with baking soda & ammonia, crackles when heated, smoked

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 -Convulsive properties – sensitize -Local anaesthetic effects – totally unique to cocaine (ex. lidocaine, novacaine, benzocaine)

Mechanisms of Action

Monoamine neurotransmission – compounds with one amine group, -NH_2) -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 tryprophan (tryptophan → 5-HTP → 5-HT)

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

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

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 **Nigrostriatial (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

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 DISTICTICTION: AMPHETAMINE NEUROTOXICITY

-d-Amphetamine: DA only
-Methamphetaime: 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

-Chorpromazine (Thorazine) – very sedating at first but tolerance builds
-Haloperidol (Haldol) – depressant
-Fluphenazine (Permitil & Prolixin) – less sedating

Newer drugs: -Dibenzodiazapine derivatives -Treat 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)
-Risperidone (Risperdal)
-Olanzapine (Zyprexa)

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

OPIATES: alkaloids found in the opium poppy

Opioids: general term for compounds with opiate-like actions, includes synthetic and endogenous opiates

POLITICS of PAIN MANAGEMENT

Major Effects:

Analgesia: relief of pain in absence of impairment in other sensory modalities

- Specific for blocking PAIN, dulls PERCEPTION of pain
* DIFFERENT than *Anesthesia*: blocks ALL sensory modalities – no sensation

Euphoria: Pleasure – produces sense of well being, reduces anxiety, positive feelings

- Addictive property

Other Effects:

Nausea and Vomiting: especially with initial use

Respiratory Depression: Lethal effect – stop breathing if OD

Miosis: dilated pupils

Gastrointestinal Effects: slows down stomach, large/small intestine→ painful constipation

Cough Suppression: codeine mostly used, least abuse potential

Motor Effects: slows motor movements, discoordination

Types of Opioids:

1. **Naturally Occuring** (sap from opium poppy)
   Morphine (10% opium by weight)
   - High gastrointestinal side effects (constipation)

   Codeine (methylmorphine, ~0.5% opium)
2. **Semi- Synthetics**
   Heroin (diacetylmorphine): Sched 1
   - 10x more potent than morphine
   - Converted to form of morphine (6-acetyl morphine) in brain

   Semi-Synthetic Analgesics:
   Hydormorphone (Dilaudid): Sched 2
   - Stronger than Heroin, surgical pain treatment

   Hydrocodone (Hycodan)
   Oxycodone (Percodan or Percoset)
   - 2x more potent than morphine as pill, ½ potent as IV
   - Long lasting, low gastrointestinal side effects
3. **Synthetics**
   Phenylpiperidines
   Fentanyl ~5000x more potent than heroin
   Meperidine (Demerol, MPPP): surgery

   Methadone and Congeners
   Methadone (Dolophine)
   - Strong narcotic ~3x strong as morphine, but weaker than heroin
   - Initially used as pain killer, than as heroin addict treatment
   - Less gastrointestinal side effects

   Propoxyphene (Darvon) Weak ~ aspirin

   Benzomorphans "non- addictive opiates" but hallucinations at high doses, aversive
   Pentazocine (Talwin)
4. **Opioid Antagonists**: Used for overdose or addiction
   - Immediately stops opiate effects →immediate withdrawal

   Naxolone (Narcan): short acting
   Naltrexone: long acting
   Nalaxonazine: μ1 antagonist
   Suboxone (buprenorphine + naxolone): blocks effects in ~ 35 min, less aversive
   - buprenorphine: long, slow acting opiate (~12-16 hrs) but no "high"
   - opiate minimizes withdrawal, kicks in after naxolone

5. **Endogenous Opioids**: normal neurotransmitters in brain
   Morphine and Codeine in trace amounts
   Peptide transmitters, produced by genes, instead of from diet
   3 Different Gene Families:
   Proopiomelanocortin (POMC) → β-Endorphins: discrete distribution, hypothalamic-endocrine
   Proenkephalin → Enkephalins
   Prodynorphin →Dynorphins
   - enkephalin/dynorphins: wide distribution

Analgesic Potency
Mild→Moderate: codeine, Propoxyphene (Darvon)
Moderate → Severe: Meperidine (Demerol)
Severe: Heroin (outside US), Hydromorphone (Dilaudid)

Tolerance:
- Analgesic effects show rapid tolerance: need more for same amount of pain relief

Withdrawal:
- Stop taking opiates → "Rebound" causing opposite effects of drug
- Detox lasts ~ 72hrs
- Locus Coeruleus: overactivity during withdrawal

Sensitization:
- Psychomotor Stimulant effects
- Rewarding effects: conditioned place preference

Mechanism of Action:
Primary Action: Opioid receptors in CNS (central nervous system) or Periphery (outside brain)
- All are G-protein coupled receptors
- All produce INHIBITION of cells → negative potential

Different Opioid Receptor Subtypes: found in different regions of brain, morphine has affinity for all, but stronger for **μ**

***Mu(μ):** preferentially binds morphine and endorphins → analgesia effects

Delta (δ): enkephalins

Kappa (κ): dynorphins, benzomorphans

Analgesia:
- μ1 sites most important
- Specific μ1 blockade shifts dose-response curve for morphine analgesia → UP and 12x RIGHT

Spinal Actions: many opiate receptors in DORSAL HORN of Spinal cord
- directly inhibits incoming pain signals: keeps cells from firing

Periaqueductal Grey (PAG, midbrain) stimulation here produces analgesia and dorsal horn inhibition
Lesion in Medulla (brain) can block analgesia of morphine

(MOR-1) μ-Opioid Receptor 1 Knockout Experiment
- Morphine, NOT heroin analgesia abolished in MOR-1 knockout mice
  → Analgesic effect of Heroin must act at different receptor

Reinforcing Effects:
- All classical addictive opioids bind to μ-site (morphine, heroin, methadone, fentanyl)
- δ may contribute to small extent
- κ are NOT self-adminstered, psychomimetic and aversive, hallucinations

Opioid/DA Interaction:
- DA ANTAGONIST or 6-OHDA injection into VTA or Accumbens blocks self-administration of opiates
- Opiates do NOT act at DA receptors: Work in same circuit by DISINHIBITION
  - -GABA INHIBITS DA transmission in VTA-accumbens DA system (decreases DA)
  - **OPIATES INHIBIT GABA → INCREASES transmission (increases DA)**
    = Inhibits an inhibitor →disinhibition: big effect

Mechanism:
- μ-compounds:
  - Increase DA cell firing
  - Increase DA release in Accumbens
  - Locomotor activation
- κ- compounds:
  - Decrease DA cell firing
  - Decrease DA release

- Decrease locomotion