Review of Neurochemistry

What are neurotransmitters? _________________________________

In molecular terms, neurotransmitters are molecules that _______ _______ (______________) and ___________________________ of neurons by, for example, increasing or decreasing enzymatic activity or altering membrane properties.

Classes of molecules that serve as neurotransmitters:
I. Small molecules:
   A. Acetylcholine (very important at ______________________ in peripheral nervous system and other synapses in the brain - CNS).

   B. Monoamines:
      a) Catecholamines
         1. Dopamine (Substantia Nigra in midbrain);
         2. Norepinephrine (noradrenaline) and Epinephrine (adrenaline)
            - ________________________________, respectively;
      b) Indoleamines
         1. Serotonin
         2. Histamine (found mostly in mammillary nuclei of hypothalamus)

   C. Amino acids:
      a) Excitatory amino acids (ex., glutamate, aspartate, taurine)
         - glutamate most utilized excitatory NT; ex. cortical pyramidal cells.

      b) Gamma-aminobutyric acid (GABA)
         - most widespread inhibitory neurotransmitter throughout the brain.

      c) Glycine
         - inhibitory neurotransmitter, especially in ________________. 1
         - normally inhibits motor neuron activity.
C. Purines
   1. ATP

II. Large Neurotransmitters

Neuropeptides
- there are at least 50 neuropeptides that act as neurotransmitters or neuromodulators (little direct activity by themselves, but modulate action of other neurotransmitters).
- neuropeptides are normally short amino acid chains.
- some examples of neuropeptides:
  - Endorphins (endogenous opioid analgesics of the body).
  - Substance P (involved in pain neurotransmission).
  - Corticotropin-releasing hormone (CRH - stress & anxiety).
  - Neuropeptide Y (NPY - control of feeding).
  - Vasopressin (diuretic hormone - control of drinking).

III. Soluble Gases
   1. Nitric oxide
   2. Carbon monoxide

What’s Dale’s Principle? ____________________________________________
_______________________________________________________________

Is this true? ______

What’s Dale’s Modified Principle? __________________________________
_______________________________________________________________
_______________________________________________________________
SYNTHESIS, PACKAGING, AND TRANSPORT OF NEUROTRANSMITTERS

1. Production controlled by _______ (cell types)
2. Small neurotransmitter molecules; synthesized in ______________
   (ex., acetylcholine, glutamate, GABA)
3. Large neurotransmitter molecules (peptides); synthesized in _____
   ______ (ex., endorphins, Substance P)
7 CRITERIA FOR SMALL NEUROTRANSMITTER STATUS

1. ______________________________
2. ________________________________
3. _______________________________________________________________________
4. _______________________________________________________________________
5. ____________________________
6. ______________________________
7. _______________________________________________________________________

NB. Most neurotransmitters are most accurately called “putative” (supposedly) neurotransmitters because all the above criteria are difficult to obtain.

Neuropeptide status requires a different set of criteria:

1. Includes the development of _______________ to detect the putative neuropeptide (includes extraction and separation of endogenous peptide).
2. Determination of ________________.
3. ________________ of peptide to test for bioactivity.
4. Production of ___________ to endogenous peptide to visualize and localize neuropeptide in the central nervous system.
RELEASE OF NEUROTRANSMITTERS

1. Arrival of _________________
2. Opening of _________________________ channels
3. Ca++ enters into presynaptic button (enters close to vesicles)
4. Ca++ ________________________________
5. Induces the ____________________ of synaptic vesicles to the presynaptic membrane
6. Exocytosis: neurotransmitter released into the ______________

What is quantal release? ____________________________________

_____________________________________________________

Action potential arrives

synaptic vesicle

Vesicle docks to membrane

Ca++ enters cell

Vesicle fuses

NT released
Neurotransmitter vesicle exocytosis

Demonstration of neurotransmitter quantal release
DEACTIVATION OF NEUROTRANSMITTERS

1. ____________________________
   (ex., amino acids and monoamines)

2. ____________________________
   (ex., acetylcholinesterase for ACh, several specific and non-specific
   proteinases for breakdown of neuropeptides - endopeptidases)

3. Recycling (once back inside the presynaptic membrane)
There exist 2 general types of neuronal transmission in the brain:

1. **Wiring transmission**: glutamate and GABA mediate __________ __________ precise excitatory and inhibitory effects of one neuron on relatively few follower (other) neurons.
   - spatially precise: ______________________________________
   - temporally precise: ______________________________________

Wiring transmission is very important for? _____________________
_________________________________________________________________

Thus, wire transmission is nearly entirely mediated by ion channel receptors, which can quickly depolarize or hyperpolarize neurons.

2. **Volume transmission**: monoamines (DA, NE, EPI, 5-HT) and neuropeptides mediate _____________________________ excitatory and inhibitory effects of one neuron on a large number of follower neurons (ex. human substantia nigra of humans contains roughly 10,000 neurons per side, but 1 DA neuron contacts 1000s of neurons)
   - spatially imprecise: ______________________________________
   - temporally imprecise: _____________________________________

Thus, monoamines are believed to play a role more in regulating the general excitatory and inhibitory “tone” of their targets rather than mediating specific transfer of sensory information or motor commands.

Volume transmission important for: _____________________
_________________________________________________________________
1. Receptors are proteins that contain binding sites for ______________________

2. “Lock and Key” arrangement

3. Receptor subtypes: Several receptor proteins can bind __________ ________ (ex., acetylcholine binds both “nicotinic” and “muscarinic” receptors).

4. Effect of a neurotransmitter is determined by the _______________________

The only way that a neurotransmitter can produce an effect on a target neuron is by __________________. 
- every receptor protein has at least 2 important functional domains:
  A. _________________
  B. _________________

Different brain regions

Receptor 1

Receptor 2

ligand

different brain regions
TYPES OF RECEPTORS

There are two general types of receptors based on their type of effector domain:

1. ___________________

2. ___________________

- produces second-messenger molecules which: - _____________________
- _______________________
- ________________________________
PSYCHOPHARMACOLOGY

The study of the effects of drugs on the nervous system and behavior

Drug (pharmacology): __________________________________________
______________________________________________________________
______________________________________________________________

Exogenous: “produced from _______” (ex., aspirin)
Endogenous: “produced from _______” (ex., acetylcholine)

What are Drug effects? _______________________________________
__________________________________________________________

Drug = _______

In neuropharmacology, ligands can have two general effects on synaptic transmission; they can _______ or _____ neurotransmission.

- Drugs that facilitate the effects of a particular neurotransmitter are called ____________.

- Drugs that inhibit the effects of a particular neurotransmitter are called _______________.

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General principles of drug action

**Pharmacodynamics:** __________________________________________________________
- for example, a drug may block or stimulate receptors, or enzymes

**Pharmacokinetics:** __________________________________________________________
- for example, drug solubility, rate of absorption, rate of metabolism.

Although pharmacodynamic factors determine the specific biological effects of a drug, pharmacokinetic factors can be very important in determining how effective a drug is (ex. why not use dopamine to treat Parkinson’s disease?).

I. Important pharmacokinetic considerations

A. How do drugs reach their site of action?
- crossing a variety of biological barriers, for example:

1) The epithelial cell lining of the digestive tract -
   a. epithelial surface area is _____________________________
      than in the stomach, making it an area of choice for absorption.

   b. Food ______ gastric emptying (stays in stomach longer), so it is often recommended that drugs be taken on _______ stomachs to allow drug to reach the small intestines more quickly.

   c. A similar principle works for alcohol. It is absorbed much more efficiently in the small intestines than in the stomach so alcohol’s effects are ________________ when ingested on empty stomachs.
2). The endothelial cell lining of blood vessels -

a. outside the brain, _________________ allow most small molecules to pass through (fat soluble or not). Only large proteins, or protein-bound molecules are excluded.

b. in the brain, _____________ of the endothelial cells, and astrocytes do not allow even small particles to ______________ into the brain (______________). Only fat soluble molecules diffuse into brain.

3). Neuronal membranes -
a. steroids are examples of drugs that act inside cells and must be able to cross the cell membrane. They are able to do so because they are ____________.

B. How do drugs cross biological barriers (issue of permeability)?
1) _________________ – many small and fat-soluble molecules can directly cross (diffuse) all cell membranes without assistance.
- ex. water, some gases {O, CO, CO₂, NO} and some small "uncharged" molecules {such as alcohol and steroids}).
- the net direction of movement = concentration gradient (high to low)

2) _________________ – many molecules cross membranes via *channels* or *transporters*. These are proteins embedded in cell membranes that selectively allow molecules through
- ex. ion channels, neurotransmitter transporters.
- net direction of movement from high to low concentration.

3) _________________ – molecules pumped against concentration **gradient** (from low to high concentration). These special proteins require energy (usually ATP) to carry out their task.
- ex.: the Na+-K+pump (ATPase)
C. How are drugs inactivated and removed from the body (clearance)?

**Biotransformation/metabolism** – many substances are changed chemically (__________) while in the body and in most cases these changes _______ the substance's biological activity and increases its ease of _________ in the urine.

- liver enzymes play a large role in drug metabolism
- blood circulation from digestive tract goes directly to ______
- in order for drugs taken orally to be effective, they need to ______ ________________________________.

So, route of administration of a drug is a very important variable.

**Different routes of administration**

![Graph of plasma cocaine concentration over time for different administration routes.](image)

**Some additional routes:**
- _________ (im);
- _________ (sc);
- _________;
- _________
There exist significant individual differences in pharmacokinetics that lead to substantial differences in sensitivity to pharmacological agents.

Examples of important individual factors:

- **Body weight and size** – smaller and lighter people tend to be more _______ to a particular dose of a drug (simply a _______ effect).

- **Age** – children and old people are usually more sensitive to a particular dose of a drug beyond body size
  - infants may have _______ levels of certain enzymes involved in the metabolism of drugs.
  - older individuals may also have ____________________ and their biological barriers may not be as efficient in _______ drugs from absorption and entry into tissues.

- **Gender** – besides the size component, women have a greater proportion of adipose tissues and a lower proportion of water than men.
  - some fat-soluble drugs are taken up ____________________ ________ in women than men.

- **Genetic** – there are genetic differences in the __________________ ________.
  - ex. individuals (especially of Asian descent) have a deficient form of the enzyme acetaldehyde dehydrogenase. This enzyme is important in the metabolism of alcohol, thus, people with a deficiency in this enzyme are much more sensitive to the "toxic" effects of alcohol, such as "flushing" of the face, sweating and nausea.
II. Important pharmacodynamic considerations:

**Mechanism of action** – invariably, drug actions are produced by interactions with a __________ present in cells.
- for CNS drugs, the functional molecule that the drug interacts with is in many cases a protein (ex. receptor, ion channel, or enzyme).
- drugs often produce more than one physiological effect. However, not all effects will display the same sensitivity (in other words the drug will be more *potent* at producing one vs. another effect).

**Drug Potency vs. Efficacy**

Potency: __________________________
- related to “affinity” of drug for site of action

Efficacy: __________________________

![Graph showing drug potency and efficacy](image)

Drug A more potent than B

Drug B more efficacious than A
A useful drug will be very potent for producing a desired effect and not very potent for producing an unwanted ____________.

**Side-effects:** ____________________________________________
___________ (can be beneficial, but often detrimental)
- ex., barbiturates are effective in reducing anxiety, but they also reduce respiratory rate, which can lead to death (very small therapeutic index).
- death is obviously the ultimate unwanted side-effect. Many drugs when given in a high enough concentration are _______

- the lethality of a drug is often described as the ______ – the lethal dose in 50% of individuals. This can only be determined empirically (by experiment/observation). A "good" drug produces its desired effect at much lower concentrations than the LD50.

- the effective dose of a drug is often described as the ______ – the effective dose in 50% of individuals.

- the therapeutic ratio for a drug is = ________________.

- a very high therapeutic ratio is desired!!!
**Dose-response properties**

- **ED\textsubscript{50}**: Dose of drug at which 50% of maximal effect is achieved
- **LD\textsubscript{50}**: Dose of drug at which 50% lethality is observed

**Therapeutic Index**: Ratio of LD\textsubscript{50}/ED\textsubscript{50} (larger is better)