Biopsychology

Chemical Transmission
Synaptic Transmission, Signal Transduction and Neurotransmitters
Synapses and Neuronal Communication
FACTS ABOUT SYNAPSES

1. A synapse occurs when one neuron wants to talk to another neuron.

2. Types of synapses based on structure:
   (a.) Axo-dendritic
   (b.) Axo-somatic
   (c.) Axo-axonic
   (d.) Dendrodendritic

3. Types of synapses based on neurotransmitter and post-synaptic receptor
   Examples:
   - Excitatory synapses - Glutamate
     - Aspartate
   - Inhibitory synapses - GABA
     - Glycine
   - Modulatory synapses - Monoamines

Post-synaptic excitation/inhibition - form of communication that increasers/reduces a neuron’s responsiveness to all synaptic inputs.

Pre-synaptic excitation/inhibition - form of communication that increases/reduces a neurons responsiveness to specific synaptic input; mediated by axoaxonic synapses

How Do we know that neurons use chemical messengers?
Discovery of neurotransmitters credited to Otto Loewi (1921) using frog hearts only in contact through water bath.

frog hearts

- Both frog hearts isolated and kept in different bath;
- Stimulate nerve (vagus) still attached to heart #1 electrically, which causes it to slow down;
- Take some of the fluid from the bath of heart #1 and add to bath of heart #2;
- Rate of heart #2 also slows down!!!

How does this indicate that neurons communicate with each other with chemical messengers?
Synapses

The junction between two neurons, by which one neuron directly interacts with another neuron

**Anatomy of a synapse**

*Presynaptic neuron* – conducts action potential along its axon toward the synapse

*Synaptic knob* – contains synaptic vesicles

*Synaptic vesicles* – stores neurotransmitter (carries the ‘signal’ across the synaptic cleft)

*Synaptic cleft* – space between the presynaptic and postsynaptic neurons

*Postsynaptic neuron*

‘Receives’ the signal from the presynaptic neuron

Its action potentials are propagated away from the synapse
I. SYNTHESIS, PACKAGING, AND TRANSPORT OF NEUROTRANSMITTERS

1. Microtubules
2. Synaptic vesicles (peptides)
3. Button
4. Synaptic cleft
5. Golgi complex

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Mitochondrion

Dendritic spine

Presynaptic membrane

Postsynaptic membrane

Synthesizing enzymes

Precursor
Figure 5.2 (a) Chemical Synapse

Kolb and Whishaw: An Introduction to Brain and Behavior, Second Edition
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II. RELEASE OF NEUROTRANSMITTERS

1. Action potential arrives
2. Synaptic vesicle
3. Vesicle docks to membrane
4. Vesicle fuses
5. NT released

**EXOCYTOSIS**

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1.) Depolarization ‘wave’ initiated at axon hillock arrives at the axon terminal
2.) Voltage-gated calcium channels open in the synaptic knob
3.) Calcium influx stimulates the fusion or ‘docking’ of synaptic vesicles (containing neurotransmitters) with the plasma membrane
4.) The neurotransmitters (NTs) are released into the synaptic cleft (ECF) via exocytosis
5.) NTs bind specific receptor-gated ion channels that open for Na⁺, K⁺, or Cl⁻
Clearance of Neurotransmitters

Quickly removed from the synaptic cleft by A.) reuptake via presynaptic neuron NOT postsynaptic. B.) reuptake via Glial cells C.) diffusion. Whichever the case the second thing to happens is NT’s are **Recycled or degraded by enzymes** in terminals of postsynaptic neuron, glial cell or extracellular space.
Receptors and Neurotransmitter
Types of Synapses

Signal from the presynaptic neuron either excites or inhibits the postsynaptic neuron,

- **Excitatory synapses**
  - Results in a slight **depolarizing graded potential** in the postsynaptic neuron cell membrane
    - Opens a chemically (NT)-gated **non-specific cation channel**
    - Permits passage of Na+ and K+ across the membrane
    - More Na+ moves in than K+ out, so there is a **net inflow of positive charge**, and, therefore a slight **depolarization**
    - Not enough to bring postsynaptic membrane to threshold

- **Inhibitory synapses**
  - Results in a slight **hyperpolarizing graded** potential
    - Opens a chemically (NT)-gated **K+ or Cl- channel**
    - Lets K+ out or Cl- into the postsynaptic cell
    - Results in slight **hyperpolarization**
    - Necessitates greater depolarizing stimulus to activate an AP (i.e., ‘inhibitory’)

- **Modulatory synapses**

- Neurotransmitters vary from synapse to synapse
- Same neurotransmitter is always released at a particular synapse
RECEPTORS AND RECEPTOR SUBTYPES

1. Receptors are proteins ___________________
   ________________________________

2. “Lock and Key” arrangement

   ![Diagram of "Lock and Key" arrangement]

3. Receptor subtypes: ______________________
   _______________________________________
   _______________________________________
   _______________________________________

4. Effect of a neurotransmitter is determined by
   ________________________________

RECEPTOR LOCATION

1. ________________________________
2. ________________________________
   - ________________________________
3. ________________________________
   - ________________________________

![Diagram of receptor location]

- Neurotransmitter
- Presynaptic terminal button
- Presynaptic heteroreceptor
- Presynaptic inhibition
- Synaptic vesicles
- Presynaptic autoreceptor
- Calcium channels
- Postsynaptic receptor
- Presynaptic facilitation

Receptor 1: different brain regions
Receptor 2: neurotransmitter
1. **Ionotropic receptors**

   *Ionotropic Receptors*
   - Ligand binding opens ion channel rapidly
   - Can cause an EPSP or IPSP
   - Does not involve second messengers and therefore does not affect DNA

2. **Metabotropic receptors**

   *Metabotropic Receptors*
   - Ligand binding opens ion channel more slowly
   - Can cause an EPSP or IPSP
   - Activates second messengers which can act on DNA to alter gene expression
Signal Transduction
Metabotropic Receptors
Signal Transduction: Post-translational activity (not post-translational modification)

Experience dependent alterations of cellular (neuronal) activity, this includes changes in proteins existing proteins and genes.

Link Extracellular signaling activity/events to alterations in intracellular activity and function!

What impact does this have and how does this happen!
Synaptic transmission can produce many more effects on the pre- and post-synaptic neurons than just a change in membrane potential. In most cases these other effects are transduced by metabotropic receptors rather than ionotropic receptors.

Why?

Most ions (e.g. Na+, K+, Cl-) do not bind intracellular proteins and thus can not modify their conformation and subsequent function.

Signal Transduction

1st messenger (NT’s) binds to receptor (extracellular)

*NT’s Activates G-Coupled receptor, which G protein (transducer/primary effector) is activated.*

The effector subunit of the G-coupled protein activates an enzyme which produces a second messenger or other ion channels.

Second messengers can also activate more ion channels, genes and modulates overall overall membrane excitability which leads to NT’s release.

#4 and 5 activate lots of ion channels #6 Results in something different
Synaptic transmission can produce many more effects on the pre- and post-synaptic neurons than just a change in membrane potential. 2nd messengers (or Ca++) typically facilitate the following:

- alter neurotransmitter synthesis
- alter neurotransmitter release
- alter receptor expression
- alter receptor function
- alter ion channel expression
- alter ion channel function
- alter synapse formation
- alter existing synapse “strength”

• Why use the word Alter?
Problem: How to link up conformational change in a metabotropic receptor located on the outer neuronal membrane with a change in an ion channel (at a different site within the membrane) or with gene expression (in the cell nucleus)?

Solution: in all cases there are important intermediate molecules (mostly proteins, but not exclusively proteins) that relay changes from the receptor to other functionally important biochemical changes throughout the neuron. In many cases a sequence of interactions between these intermediate molecules takes place, sometimes referred to as a cascade of biochemical events or signal transduction pathways.
**Problem:** How to link up conformational change in a metabotropic receptor located on the outer neuronal membrane with a change in an ion channel (at a different site within the membrane) or with gene expression (in the cell nucleus)?

Signal Transduction depends on an “astonishing” number of molecular “players” and “pathways”.

cAMP/cGMP is a typical 2\textsuperscript{nd} messenger, Cannabinoids could be a third messenger. (talk about later)

**Other second messengers:** non-gaseous:
- cyclic guanine monophosphate (cGMP)
- arachidonic acid

**gaseous:**
- nitric oxide (NO)
- carbon monoxide (CO)
**Problem:** How to link up conformational change in a metabotropic receptor located on the outer neuronal membrane with a change in an ion channel (at a different site within the membrane) or with gene expression (in the cell nucleus)?
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Signal Transduction depends on an “astonishing” number of molecular “players” and “pathways”.

Signal Transduction
Signal Transduction
Point to Ponder: Why design a system that has so many intermediate steps between activation of a receptor and activation of PKA or PKC?

• Provides multiple points of regulation
• Provides signal amplification
• Provides integration of input from different types of receptors

Signal Transduction depends on an “astonishing” number of molecular “players” and “pathways”.
Neurotransmitter
NEUROTRANSMITTERS: THE MESSENGERS!

7 CRITERIA FOR NEUROTRANSMITTER STATUS:
1. ______________________________________
2. ______________________________________
3. ______________________________________
4. ______________________________________
5. ______________________________________
6. ______________________________________
7. ______________________________________

Note, because most neurotransmitters are unable to meet the above requirements most accurately called “putative” (supposedly) neurotransmitters

- the above 7 criteria have been proven for very few neurotransmitter molecules.

- Several hundred nt identified
- Two main classes: Small- small mics
  - Usually made at the bouton
  - Enzymatic biochemical pathways
- Large- peptides (small proteins-<10 aa)
  - Usually made in the soma and transported (*are a protein and have a gene sequence!*)
- Coexistence: neurons usually contain 1 small nt and often 1 peptide nt., Almost never two different small NT’s
Neurotransmitter Overview

**Monoamines**
- **Altered Amino acids**
  - Acetylcholine
  - Dopamine
  - Norepinephrine/Epinephrine
  - Serotonin

**Amino acids**
- Glutamate
- GABA
- Glycine

**Peptide Hormones**
- CRH
- Opioids
- Vasopressin
- Nitric Oxide

Small molecule NT’s: made by things we eat

Large molecule NT’s: made by DNA transcription and translation

2 or more amino acids linked together with peptide bonds

**Ascending Activating Systems**
- More global modulatory control

**Most abundant neurotransmitters**
- More specific communication

**Used largely in hormonal control and as neuromodulators**

**Used in neuroplasticity (learning)**

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3 MAJOR CLASSES OF NEUROTRANSMITTERS

I. __________________________
A. __________________________
   - contracts skeletal muscles; **neuromuscular junction**
   - autonomic nervous system

B. __________________________
   a) __________________________
      1. Dopamine
         - movement, attention, learning, reward
         - degeneration of Substantia Nigra in midbrain = Parkinson’s disease (loss of DA)
         - schizophrenia (too much DA release)
      2. Norepinephrine and Epinephrine (Adrenaline)
         - released by sympathetic n.s. and adrenals
         - control alertness/wakefulness; alarm
   
   b) __________________________
      **Serotonin**
      - control of eating, sleep, and arousal
      - inhibits dreaming (LSD blocks serotonin)

C. Amino acids:
   a) __________________________ (ex., glutamate, aspartate)
      - excitatory neurotransmitters producing EPSPs
   
   b) __________________________
      1. Gamma-aminobutyric acid (GABA)
         - inhibitory neurotransmitter producing IPSPs
         - degeneration in basal ganglia = Huntington’s chorea
      2. Glycine
         - inhibitory neurotransmitter
         - normally inhibits motor neuron activity in spinal cord

II. **Large transmitter molecules:**
    __________________________: small amino acid peptides
    - very diverse types and functions
      ex., - endorphins (endogenous opiates; pain)
      - cholecystokinin (gut peptide; food intake)
      - vasopressin (fluid regulation)

III. __________
    - small molecules with very different neurotransmitter characteristics
    
    - produced in cytoplasm by enzymes and diffuses freely across lipid bilayers to neighboring neurons

   A. __________
      - regulates vascular relaxation
      - involved in learning and memory
   
   B. __________
      - also regulates vascular relaxation
      - regulates peristaltic relaxation (gut motility)
**EXAMPLE: ACETYLCHOLINE**

Acetyl coenzyme A (acetyl-CoA)  
Coenzyme A (CoA)  

Choline  

ChAT transfers acetate ion from acetyl-CoA to choline  

**INACTIVATION BREAKDOWN REUPTAKE**

Recycled Choline molecules  
Presynaptic membrane  

Choline transporter inside  
out inside 

ACh molecule  

Acetate ion  
Choline molecule  

Action of AChE breaks apart acetylcholine molecule  

**ANOTHER EXAMPLE: CATECHOLAMINES**

**Precursor**

L-Tryptophan  

Tyrosine  

Tyrosine hydroxylase  

L-Tryptophan-5-monooxygenase  

Tryptophan hydroxylase (TPH)  

5-Hydroxy-L-tryptophan (5-HTP)  

5-Hydroxytryptophan decarboxylase  

Aromatic L-amino acid decarboxylase  

Serotonin (5-HT)  

5-Hydroxyindoleacetic acid (5-HIAA)  

**Epinephrine**  

**Precursor**

CH₃  

Phenylethanolamine-N-methyl transferase  

Epinephrine  

**Monday, February 20, 2012**
Basic Psychopharmacology
The study of the effects of drugs on ___________________________ (<G: "Pharmakon" = drug)

**Drug (pharmacology):** ______________________________
________________________________________
________________________________________
________________________________________
________________________________________

**Exogenous**: Produced *outside* the body
(ex. Aspirin, morphine)

**Endogenous**: Produced *inside* the body
(ex. Acetylcholine, dopamine)

**ROUTES OF ADMINISTRATION**

- Intravenous (0.8mg/kg) *(iv)*
- Smoked (100mg base) *(inhalation)*
- Oral (2mg/kg)
- Intranasal (2mg/kg)
DRUG EFFECTS

Drug effects: ____________________________________________
________________________________________________________

Drugs can have two effects on synaptic transmission: _____________________________
________________________________________________________

AGONISTS: Drugs that *facilitate* the effects of a particular neurotransmitter.

ANTAGONISTS: Drugs that *inhibit* the effects of a particular neurotransmitter.

**Drug Efficacy Continuum**

- Full Agonist (agent that activates receptor)
- Partial Agonist
- Antagonist (agent that does not activate a receptor)
- Partial inverse Agonist
- Full inverse Agonist (activate receptor, but produce opposite effects of agonist)
**POTENCY VS. EFFICACY**

**Affinity (Potency):** Related to the strength of binding potential (will a compound bind or not and if so how strong). ________________________________

- related to “affinity” of drug for site of action. Low affinity = low binding ability need more drug to produce effect. High affinity = better binding to receptor!

**Efficacy:** ________________________________

**Drug Efficacy Continuum**

- Full Agonist (agent that activates receptor)
- Partial Agonist
- Antagonist (agent that does not activate a receptor)
- Partial inverse Agonist
- Full inverse Agonist (activate receptor, but produce opposite effects of agonist)

Drug A more affinity than B

Drug B more Efficacy than A
**DOSE-RESPONSE PROPERTIES**

**ED**<sub>50</sub>: **Dose of a drug at which 50% of maximal effect is achieved.**

**LD**<sub>50</sub>: **Dose of a drug at which 50% lethality is observed.**

**Therapeutic Index:** **Ratio of LD<sub>50</sub>/ED<sub>50** (larger number is better!)
**DRUG ACTIONS**

**Agonists:** *facilitate* synaptic transmission or NT’s effects
1. ____________________________
2. ____________________________
3. ____________________________
4. ____________________________
5. ____________________________
6. ____________________________

**Antagonists:** *inhibit* synaptic transmission
1. ____________________________
2. ____________________________
3. ____________________________
4. ____________________________
5. ____________________________
Choline-rich diet increases available acetylcholine (ACh).

Agonist
Black widow spider venom promotes release of ACh.

Agonist
Nicotine stimulates ACh receptors.

Agonist
Botulin toxin blocks release of ACh.

Agonist
Curare blocks ACh receptors.

Agonist
Phystostigmine and organophosphates block inactivation of ACh.

Agonist
Amphetamine promotes the release of dopamine and fosters symptoms of schizophrenia.

Agonist
Both amphetamine and cocaine block reuptake of dopamine and foster symptoms of schizophrenia.

Agonist
Chlorpromazine, a drug that blocks symptoms of schizophrenia, occupies the dopamine site on the D2 receptor, preventing receptor activation by dopamine.

MAO inhibitor
Inhibits breakdown of serotonin...

Agonist
Selective serotonin uptake blockers block transporter protein for serotonin reuptake so serotonin stays in synaptic cleft longer.

MAO inhibitor
...so more serotonin is available for release.

Both these drugs reduce symptoms of depression by increased activation of postsynaptic cells.
Binding of sedative/hypnotic (Barbiturates or alcohol) = acts like a GABA = increase chloride conductance!

Binding of anti-anxiety drugs (benzodiazepines) enhance GABA too!

Because these substance can interact with same receptor but and different locations have additive actions!