The study of the effects of drugs on the nervous system and on behavior (<G: "Pharmakon" = drug)

Drug (pharmacology): An exogenous chemical not necessary for normal cellular functioning that significantly alters the functions of cells of the body when taken in relatively low doses (here, in cells of the nervous system).

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

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

How can we use Exogenous and Endogenous substances to learn something about the brain?

Sample and infuse, then measure molecular-cellular-and system levels effects and relate to behavioral outcome.
Drug effects: the changes observed in an organism’s physiological processes and behavior.

Drugs can have two effects on synaptic transmission:
- they can facilitate or ________
- __________Inhibit neurotransmission.

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

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

- Agonists - bind to and activates a receptor
  - (e.g. morphine is opioid receptor agonist)

- Antagonists - bind to receptor, but do not activate it.
  - This blocks ability of agonist to stimulate receptor.
    - (e.g. naloxone is opioid receptor antagonist)

Why would a physician treat with an antagonist?
These processes depend on many factors and are variable between everyone. This is why it is important to know the therapeutic-index.
Rightward and Leftward shift in dose-response curves OF same Drug

Right shift **OR** downward shift of same drug (A) indicates a *reduction* in drug sensitivity (habituation or tolerance). More drug (dose) is need to produce effects.

Leftward shift **OR** upward shift of drug (A) indicates an *increase in sensitivity* to drug. Need less drug is need to produce effects.

**DRUG A is the same drug, but its dose may need to be changed for many reasons, as listed on previous page.**

**Variations effects of different drugs on same receptor**

**Drug A** has great affinity and efficacy.
**Drug B** has good affinity, but poor efficacy.
**Drug C** had great efficacy, but poor affinity.
**Drug D** is What?

Antagonist, has great affinity but almost no efficacy. This means Drug D binds to the receptor, but produces no biological action!

Which Drug is the best A, B, or C? Depends on therapeutic index! Which is the safest.

*Drugs: A,B,C, and D act on the same receptor!*
Three end results of Combining Substances

A. Reduce actions of both, remember that not only will the antagonist influence the agonist but the agonist can influence the antagonist (if competitive!).

**Competitive Antagonist:** Are substances (drugs) that produce inhibitory action on the same exact mechanism that is facilitated by an Agonist. EX: Both Drugs compete for same receptor!
- Agonists - bind to and activates a receptor
  - (e.g. morphine is opioid receptor agonist)
- Antagonists - bind to receptor, but do not activate it.
  - This blocks ability of agonist to stimulate receptor.
  - (e.g. naloxone is opioid receptor antagonist)

**Non-Competitive Antagonist:** Are substances that produce inhibitor actions through indirect mechanism that ultimately influence how an well an Agonist drug will work.

**Why treat a patient with an Competitive substances?**

\[ C = \text{combination of agonist and antagonist!} \]
**Autonomic Nervous System**

Remember many types of receptors exist!

- **Cholinergic Agonists**
  - Examples
    - Bethanechol
    - Carbecol
    - Pilocarpine
  - Physiological Effects
    - Pupillary constriction
    - Salivation
    - Bronchioconstriction
    - Decreased HR
    - Digestion
    - Bladder contraction (elimination)
    - Increased GI motility

- **Anticholinergics**
  - Examples
    - Atropine (muscle relaxant)
    - Scopolamine (motion sick)
  - Physiological Effects
    - Pupillary dilation
    - Dry-mouth
    - Bronchiodilation
    - Increased HR
    - Decreased digestion
    - Decreased urination
    - Constipation

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**Acetylcholine terminal**

- Cholinergic Agonists
  - Examples
    - Bethanechol
    - Carbecol
    - Pilocarpine
  - Physiological Effects
    - Pupillary constriction
    - Salivation
    - Bronchioconstriction
    - Decreased HR
    - Digestion
    - Bladder contraction (elimination)
    - Increased GI motility

- Anticholinergics
  - Examples
    - Atropine (muscle relaxant)
    - Scopolamine (motion sick)
  - Physiological Effects
    - Pupillary dilation
    - Dry-mouth
    - Bronchiodilation
    - Increased HR
    - Decreased digestion
    - Decreased urination
    - Constipation

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**Acetylcholine:** CNS maintains waking state, and neuronal excitability. **Death** of these neurons associated with Alzheimer’s disease. PNS for muscle contraction and ANS Parasympathetic control.
Remember many types of receptors exist!

Dopamine: Active in maintaining and initiating normal motor behavior. Strongly involved in Reward of specific behaviors (Sex, eating etc).
Serotonin: Active in maintaining waking states (inhibit = sleep). Abnormal increases are associated with OCD, tics and Schizophrenia. Decreases are related to major depressive states.

Serotonin syndrome: occurs when you take medications that cause high levels of serotonin to accumulate in your body. OR can occur when you increase the dose of such a drug or add a new drug to your regimen. Certain illicit drugs and dietary supplements are also associated with serotonin syndrome.

- Symptoms
  - Restlessness
  - Hallucinations
  - Loss of coordination
  - Fast heart beat
  - Rapid changes in blood pressure
  - Increased body temperature
  - Overactive reflexes
  - Nausea
  - Vomiting
  - Diarrhea

- Pathophysiology
  - Serotonin overdose

- Cause
  - Self-poisoning
  - Therapeutic drug use
  - Drug reactions.

- Treatment
  - Withdrawal of medicine
  - Fluids by IV
  - Cyproheptadine
  - Benzodiazepines
Characteristics of sedative-hypnotic drugs:

**Tolerance:** decreased susceptibility to a drug that develops as a result of repeated exposure to the drug; compensatory mechanisms opposite to the initial drug effect. [Compensatory = reducing or offsetting]

**Cross-tolerance:** tolerance that develops to one drug carries over to other drugs suggesting that they act through the same target.

**PSYCHOACTIVE DRUGS**

There are several classes of psychoactive drugs:

I. Sedative hypnotics and antianxiety drugs
   - Most common are:
     1. _______ (everything that contains ethyl alcohol).
     2. _______________ (ex., pentobarbital).
     3. ________________ (ex., valium, librium).
   - they are also known as "_________________".

**Behavioral effects:**

- Binding of sedative/hypnotic (Barbiturates or alcohol) = acts like GABA NT’s = increase chloride conductance!
- Binding of anti-anxiety drugs (benzodiazepines) enhance GABA too!
- Because these substance can interact with same receptor but different locations have additive actions!

- Taken individually can = cross tolerance
- Taken together have additive action on efficacy!
PSYCHOACTIVE DRUGS

II. Antipsychotic drugs: used to reduce psychotic symptoms in schizophrenia, paranoia, etc.

Most common are:

1. Phenothiazines (ex., chlorpromazine - Thorazine)
2. Butyrophenones (ex., haloperidol - Haldol)

- they are also known as “major tranquilizers”

One mechanism of action: block dopamine receptors, particularly the D2 subtype.

Activation of D2 receptors by indirect agonist like cocaine and Amphetamines (heavy users or large doses) can lead to psychotic like behaviors

Haloperidol: A D2-receptor blocker that can induce catalepsy (trance or seizure with a loss of sensation and consciousness accompanied by rigidity of the body) in animals when in high doses

Psychotherapeutics
PSYCHOACTIVE DRUGS

III. **Antidepressant drugs**: used to treat depressive illnesses

Most common are:
1. **Monoamine oxidase inhibitors** (MAOI)
2. **Tricyclics** (ex., imipramine - Tofranil)
3. **Serotonin-specific reuptake inhibitors** (SSRIs ex., fluoxetine - Prozac)

Mechanisms of action:
- MAOIs block the breakdown of monoamines (especially serotonin [5-HT] and noradrenaline)
- Tricyclics and SSRIs block the reuptake of monoamines (especially noradrenaline and 5-HT)
1. **Opiates inhibit activity of Inhibitory interneurons in the PAG Mid-brain**. This increases activity of other descending neurons to the Raphe Nucleus neurons.

2. **PAG neurons then excite Raphe neurons.**

3. **Raphe Neurons send projections to appropriate spinal interneuron to inhibit incoming pain signals!**
Marijuana

Cannabinoid (Cannabis) Receptors

• CB1
  – Brain
  – Metabotropic

• CB1
  – How does this receptor work?
  And where are they found!

- THC (exogenous) or endocannabinoid (endogenous, e.g. Anandamide, 2-AG: are lipid soluble compounds or NT’s).
- Stimulate postsynaptic receptors to exert effects by inhibiting Ca++ ion channels!
- Two Cannabinoid Receptors: CB-1: found in brain and CB-2: found in periphery
The hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic-adrenal-medullary (SAM)
Anxiety: All anxiety disorders have something in common!
The areas of the brain affected by **generalised anxiety disorder (GAD)**

The unique aspect about **GAD** is that it does not have what the other Anxiety disorders have:

1.) **PTSD** = Atrophy of the hippocampus (MRI) and whole brain atrophy is exhibited by people with PTSD.

2.) **PD** = Increased activity in the **periaqueductal grey** results in defensive behaviours and postural freezing.

3.) **OCD** = Overactivity of dopaminergic neurones (substantia nigra) may produce excessive excitation in the brain areas implicated in OCD likely produces reward burst for habit behaviors. Which leads to over-excitation of the Basal Ganglia.
Brain area most affected is the Hippocampus
Brain area most affected is the Hippocampus
Depression
MAO-Is

MAOI = Acute increase in Amines (DA, NE and 5HT)

MAOI 2weeks

SSRIs

SSRI block reuptake, thus increase 5HT and NE. However, Auto-receptors decrease NT release and synthesis, resulting in reduced NT activity.

MAOI 2weeks

With repeated treatment (weeks) and changing dose, auto-receptors down regulate Leading to an increase in 5HT. Postsynaptic receptors can down regulate too, so dose is increased.

Second Messenger Signaling (i.e. Signal transduction)

Increase in 5ht and NE (via MAOIs or SSRIs) via chronic treatment produces an increase in signal transduction (second messengers and kinases [signaling proteins]). Which lead to increases in gene activity and production of new proteins i.e. BDNF (and what is BDNF for?)

So what MAOIs and SSRIs increase 5HT and NE! What does this Do on a molecular-neuronal, systems and behavioral level?
**Ketamine: completely novel pathway in how ketamine works to treat depression**

“The story is in the *signal transduction pathway*”

Ketamine activates the mTor pathway. *mTor is a ubiquitous protein kinase* involved in *protein synthesis and synaptic plasticity* in a process called *synaptogenesis*. Synaptogenesis restores the synapse connections in the brain that may deteriorate under stress and depression!
Depression: Ketamine treatment

5HT/NE Model of depression

1.) Increase in 5HT and NE (via MAOIs or SSRIs) via chronic treatment produces an increase in signal transduction (second messengers and kinases [signaling proteins]). Which lead to 3.) increases in gene activity and production of new proteins i.e. BDNF (and what is BDNF for?), for unknown reasons is not the always a good treatment!

Major problem is both SSRIs and MOAs lead to post-synaptic receptor down regulation! Less receptors less activity! (i.e. Back to depressed state, up dose does not work because down regulation!

Ketamine Model of depression

1. Ketamine
2. NMDA (GABA Interneuron) dis-inhibition
3. Ca++ influx via VDCC
4. BDNF Release
5. Synaptogenesis

Ketamine stimulates BDNF, mTOR and synaptogenesis via neurotransmitter and intracellular signaling mechanisms:

1.) Ketamine stimulates glutamate transmission via blocking NMDA (ketamine binds to) receptors activity on GABA inhibitory interneurons. This (2) increases AMPA (glutamate receptor) activity via increased Glutamate NT Binding (2). Resulting in Ca++ influx (via VDCC) leads to BDNF (immediate) release (3), BDNF binds to TrkB (same cell) and stimulates mTOR (4.) (via signal transduction), which (5) stimulates synaptic protein synthesis (more BDNF and other factors important for synaptogenesis, like production and insertion more AMPA receptors) (5). Steps 1-5 contributes to the rapid antidepressant effects of ketamine.
Mutations in the tau gene lead to the abnormal aggregation of tau protein and the onset/progression of frontal lobe and Temporal lobe (what is in the this lobe?) dementia.
**Emotional experience vs expression**

- Must distinguish between: Emotional experiences and expression
  - **Emotional experience** (internal feelings) based on neural states.
  - **Emotional expression** behavioral manifestation of internal feelings, i.e. Actions (both are products of the nervous system).

- In this way can we study emotion in animals. Animals can’t communicate subjective feelings, **but can produce behavioral actions associated with emotions** (i.e. Neurological model: behavior is always related to a neural system, cellular and molecular mechanism).

- **Emotions arise from an interaction between 3 things:**
  - 1.) Sensory stimuli, 2.) brain circuitry (cellular function and molecular interactions) and 3.) Personal experience.

- **Emotions**
  - Love, hate, disgust, grief, envy, shame, fear, anxiety, joy, sadness
  - What defines these feelings?
    - Sensory signals from the body--activity in the cortex---something else?
  - Some emotions have very clear behavioral manifestations, these we know the most about the neurobiology
    - Fear
    - Aggression
Theories of emotion

• **Darwin:**
  – Emotions evolved from behaviors that indicate what an animal would do next in a given situation
  – If advantageous (avoiding a fight), they evolved in a way that enhanced their communicative value!

• **James-Lange Theory:**
  – Emotion inducing stimuli received and interpreted by the brain—triggers visceral changes—visceral changes trigger experience of an ‘emotion’
    • We feel sad because we cry, we do not cry because we are sad
    • Physiological changes are the emotion
    • Requires feedback from autonomic and somatic nervous system

• **Cannon-Bard Theory:**
  – Emotional experience (internal experience) can occur independently of expression (visceral responses).
  – Expression is not independently activated by experience (i.e. Need brain to process stimuli).
The Limbic Circuit (system): Several brain regions are important for emotional expression (overt) and feelings (internal).

1.) Emotional expression is in part produced by the **Hypothalamus**.

2.) Emotional experience (feelings) is the product of the **limbic cortex (cingulate), Amygdala, hippocampus, prefrontal cortex** and **sensory modalities** associated with processing particular environmental cues (stimuli). These areas all converge onto the hypothalamus. Some of these structures seem to support emotions as well as other functions...memory

- If you remove hypothalamus (in animals)--no more rage
- Conclusion: Hypothalamus crucial to expression of aggression and cortex usually inhibits and directs these behaviors
Bilateral anterior temporal lobectomies (destroys the amygdala complex) produces behavioral changes. Flat effect (no expression of emotions), consumption of nearly everything edible, inappropriate/increased sexual behavior (inanimate objects). Tendency to repeatedly investigate objects, lack of fear (tameness).

**Fear:** is consistently accompanied by endocrine activation (increased; heart rate, blood pressure, respiration, arousal, urination, defecation, CORT secretion etc.) and specific behavioral responses (facial expressions, fight or flight behavior [escape, aggression, freezing etc]).

All of these associated characteristics are in part controlled or regulated by the Amygdala (central nucleus), lesion as mention above reduces these behaviors.) Example, in rats, lesion CeNuc-Amygdala (micro-lesion), they become unafraid of predators (cats or ferrets).
Role of the amygdala in fear

Fear Conditioning:
- association between a previously neutral stimulus (like a tone) with a threatening stimulus (shock)--tone comes to predict shock
- Requires the amygdala

Why fear conditioning to study emotion?
- Source of fear is unambiguous (usually footshock)
- Development of fear response can be investigated systematically
- After conditioning produce a variety of defensive behaviors:
  - Freezing (not moving), increased startle
  - Increased HR and BP
- Ability to study learned fear: PTSD, anxiety, phobia

Amygdala and fear

Basis of an emotion neural system

Context Test
- Exposure to context (2 min)
- Independent of Amygdala
- Dependent on Hippocampus

Auditory Cue Test
- Onset of sound (CS: 3 min)
- Dependent on Amygdala
- Independent of Hippocampus
Learned Fear Circuitry

Context info

Tone info

Shock info

Associative convergence

Amygdala and fear

Wednesday, April 11, 2012
Problems with defining/studying psychological stress:

- stimuli do not possess a physical dimension of “stress”.
- we do not have specialized “stress” receptors.
- So then what detects Stress?

What is the biological nature of a psychological stress state?

**Hypothesis:** it is fundamentally a neural circuit state as opposed to a generalized molecular or cellular state.

Features of Psychological Stress that we may agree on:

- It’s a “state”.
- This “state” is easily discriminable from other states.
- Induction and termination are not under voluntary control (Hormone responses)
- It has a conscious aversive/unpleasant component.
The term “stress” and its associated physiological effects were originally defined by Hans Selye (1940’s) in recognition of a “generalized” alarm system in response to Disruption to physiological or psychological homeostasis.

- the current definition of a stress response is a physiological reaction caused by the “perception” or detection of aversive or threatening situations that may jeopardize some functions or goals.

Examples of stressful situations:

1. **Psychological/emotional stressors:**
   - marriage, divorce, job loss, new job
   - entering college, public speech, car crash
   - death of a loved one

2. **Systemic stressors (Physiological)**
   - limb fracture
   - surgical procedure
   - viral or bacterial infection
   - food poisoning
   - illnesses (cancer, heart conditions, etc.)
Control of the Autonomic and Endocrine Responses by Stress

- Sympathetic neurons of the autonomic nervous system activate secretory cells of the adrenal medulla to release epinephrine (adrenaline) and norepinephrine;
- Anterior pituitary releases ACTH, which elicits the release of glucocorticoids (cortisol) from the adrenal cortex.
Physiological Responses to Stressful Situations

1. **Acute stress responses (advantageous):**
   - Activation of autonomic and endocrine responses
   - Release of adrenaline and noradrenaline by the adrenal medulla
   - Release of cortisol by the adrenal cortex
   - Increases in heart rate and blood pressure to bring more blood to muscles
   - Mobilization of energy resources (production and release of glucose for use by muscles)
   - Inhibition of inflammatory/immune responses
   - Inhibits sexual functions and sex steroids production and release

2. **Chronic stress responses (disadvantageous):**
   - Hypertension (high blood pressure)
   - Gastrointestinal ulcers
   - Diabetes
   - Inhibition of growth (particularly important in young children - psychologic dwarfism)
   - Infertility
   - Suppression of the immune system
   - Damage to the brain

Abnormal Stress and CORT Activity are linked to:

**Increased CORT**
- Depressive episode
- Bipolar disorder
- Panic disorder
- Schizophrenia
- Type II diabetes
- Hypertension
- Obesity

**Decreased CORT**
- PTSD
- Chronic fatigue syndrome
- Fibromyalgia (musculoskeletal pain)
- Chronic myogenous facial pain

The adverse effects of stress on health stem from impaired regulation of the HPA axis by abnormal CORT activity, this relationship is a major clinical issue that is not well understood.
STRESS And Learning Memory mechanisms

A

Retrieval failure

Inhibition of transmission
: Retrieval deficits

2-AG / AEA

B

Storage

Facilitation of transmission
: Acquisition and Consolidation

CORT Receptor

Neurobiological approach
Experience

Systems level

Cellular level

Molecular

Behavior

Wednesday, April 11, 2012
Different brain areas are involved in “perceiving” and detecting different stressful situations:

1. **Limbic system** = “Psychological stressors”;
2. **Circumventricular organs** = “Blood born pathogens” - poisons
3. **Somatic sensory system** = “Immune stressors”

Percentage of subjects with colds as a function of an index of psychological stress

**HOW TO CONTROL STRESS?**

There are stressful situations that are unavoidable (ex., cold, infections, etc), and these will produce the same effects in most organisms

However, several situations are “perceived” as stressful by some people, not others

The perceived control over a situation, even if it is an illusion, can prevent some of the negative effects of stress – to have the perception of control is called a **coping response**.

Animals and humans that display coping responses generally have reduced incidence of cardiovascular problems and gastric ulcers.
Model: Inescapable versus Escapable Shock
Groups: 1. Control/baseline: No shock 2. Escapable Shock: Shocks, active wheel/button to terminate shock 3. Inescapable Shock: Shocks, inactive wheel (Spins, but does not turn off shock)

Important: The Inescapable and Escapable animals are YOKED, so they receive exactly the same physical stress, but one has CONTROL, and the other does not. So the stress ENDS at some point.

Test Day: Escape latencies in a shuttle box: Measure how long it takes to escape a mild foot shock by “shuttling” from one side of the box to the other and back again. A short time (small number) is better!

This effect control of stress (Escapable stress) requires PFC activation.
Normal habituation to stress (typically by repeated exposure) is dependent on PFC activation!

Medial Prefrontal Cortex

- receives sufficient multimodal input to discriminate between complex situations
- anatomically well positioned to coordinate a wide range of neural processes
- found to be critical for “top-down” selection between competing responses

We can transiently “turn off” neural activity in the mPFC

Microinfusion of the GABA\textsubscript{A} receptor agonist, \textbf{Muscimol (MX)}

Development of Habituation

Blockade of Habituation

Normal response?

What group is missing?

![Image of brain with highlighted Medial Prefrontal Cortex]

![Graph showing Stress Hormone Levels]

No Stress | Stress | Stress + MX

![Image of experiment setup]

Normal habituation to stress (typically by repeated exposure) is dependent on PFC activation!