II. BIOLOGICAL THEORIES OF DEPRESSION

A. Biogenic Amine Hypothesis

1. 1950's
   - antihypertensive drug resperine had an antidepressant effect

2. antituberculosis drug iproniazid had an antidepressant effect

3. led to organic cause for depression

4. changes in biogenic amine neurotransmitters in post-mortem brains of suicide victims

5. changes in cerebrospinal fluid (CSF) concentrations of amine metabolites from depressed patients

6. endocrine disturbances and depression onset

7. receptor changes following recovery from depression
B. Research on Amines

1. Suicide Brain
   Increased density of 5HT2 receptors in limbic areas

2. 5HT2 receptors tend to increase in untreated depressed patients in limbic areas

3. Density of muscarinic (Ach) receptors in depression

4. Beta-adrenoreceptors increased density in untreated depression

5. Changes in concentrations of 5-HT and dopamine metabolites (5-H1AA and homovanillic acid (HVA) occur in treated depressed patients)

6. Low levels of 5-H1AA have been associated with violent suicide and impulsivity

7. 5-H1AA normalizes on recovery
C. Catecholamine Hypothesis

1. Low levels of NE in CNS

2. Resperine lowered NE, 5HT and DA and caused depression

3. Depression may be a consequence of decreased NE levels in some individuals

D. Inole Amine Hypothesis

1. Low 5HT associated with depression
2. Reduced 5HT in suicide
3. Tryptophan (precursor of 5HT reduced in depression)
4. 5HT$_2$ receptors are increased in frontal cortex of suicide victims

E. NE and 5HT and DA in neuronal processing

1. NE regulates sensory processing
2. 5HT regulates limbic processing ex: Raphe nuclei activates signaling by inhibiting corticocortical activity that interferes with behaviors
NE facilitates cortical responsiveness

An individual deficient in NE would be less attentive to sensory signals (psychomotor retardation), hypersomnolence, reduced appetite

An individual deficient in 5-HT would process information inadequately
Ex: flat affect, anhedonia

3. Both 5-HT and NE produce melatonin (biological rhythms)
4. Depression is associated with disruption or circadian rhythms

5. mode of action of antidepressants may be to normalize disrupted circadian rhythms

6. most antidepressants delay the circadian phase and lengthen the circadian period

7. 5-HT uptake into the platelets of depressed patents is not reduced between 0600 and 1200 as in normals
8. Serotonin and melatonin share tryptophan as a precursor

9. Prolonged exposure to the dark will decrease 5-HT and increase melatonin

10. NE increase melatonin through beta-adrenergic mechanisms

11. Chronic antidepressant use decreases melatonin

III. BIPOLAR ILLNESS

DMSIV DEFINES CRITERIA

A. Mania

1. Diagnosis of bipolar without history of depression

B. "Double Depression"

1. Dysthymia + major depression
2. Respond well to antidepressants
C. Seasonal Affective Depression (SAD)

1. Most resemble atypical depression
2. Thought to involve 5-HT
3. Light therapy is effective
4. Appetite increase, weight gain, fatigue, hypersomnia

D. Monoaminergic Neurons

NE (Noradrenaline)
DA (Dopamine)
5-HT (Indoleamine Serotonin)

1. Tyrosine is precursor- amino acid that is transported into neuron

2. Once inside neuron - tyrosine is converted to DOPA by tyrosine hydroxylase (rate limiting for synthesis)

3. DOPA (Dihydroxyphenylalanine) is converted into DA by DOPA decarboxylase (DDC)

4. (DBH) Dopamine Beta-Hydroxylase converts DA into NE
5. NE is stored in vesicles and is released by a nerve impulse

E. Enzymes that destroy monoamines

1. MAO - located in mitochondria of the presynaptic neuron

F. Noradrenergic Receptors

1. Postsynaptic
   - 1 (alpha)
   - 1 (beta)

2. Presynaptic alpha_2 receptors
   a. autoreceptors
   b. regulate the release of the neurotransmitter
   c. located both on the axon terminal, soma, and (somatodendritic receptors)
   d. alpha_2 receptors act as "brake" on NE neuron
   e. stimulating the alpha_2 receptor stops the neuron from firing
   f. negative feedback signal in neuron
   g. drugs that activate alpha_2 or antagonize it
   h. antagonists enhance the release of NE
i. **locus coeruleus** - most noradrenergic neurons - brainstem
j. **Reticular Activating System (RAS)**
   attention (internal and external)
   cognition, mood, blood pressure
k. assists with impaired attention, fatigue, psychomotor retardation
l. Pathways:

1. **Locus coeruleus → Limbic Area**
   Emotions, energy, fatigue,
   psychomotor agitation,
   psychomotor retardation

2. **Cerebellum → Motor Movements**
   Tremor

3. **Brainstem NE → Cardiovascular Centers**
   Blood Pressure

4. **NE → Sympathetic Neurons**
   Leave spinal cord - heart rate and bladder
G. Dopaminergic Neurons

1. destroyed by MAO and COMT
2. dopamine receptors are all blocked by antipsychotic drugs D1, D2, D3, D4
3. also have presynaptic autoreceptors

H. Serotoninergic Neurons

1. Tryptophan an amino acid is a precursor
2. Converted by Tryptophan Hydroxylase into 5-Hydroxytryptophan
3. Converted by aromatic amino acid decarboxylase to 5HT
4. Destroyed by MAO
5. Has a presynaptic autoreceptor to regulate 5HT
6. Somatodendritic autoreceptor - on dendrites and cell body 5HT_{1A} receptor
7. Axon terminates 5HT_{1D} receptor - terminal auto receptor
   a. occupancy at these auto-receptors inhibits -5HT release
   b. drugs that block the autoreceptor promote 5HT release
8. Two key presynaptic receptors 5HT$_1$A and 5HT$_1$D

9. Postsynaptic:
   5HT$_1$A
   5HT$_1$D
   5HT$_2$C
   5HT3
   5HT4

10. Some NE presynaptic receptors are located on serotonergic neurons

   a. axon terminal of serotonergic receptors are presynaptic alpha 2 receptors (just like on a 5HT neuron)

   b. NE occupancy on alpha 2 receptors on serotonin neurons will turn off serotonin release

   c. NE receptors on serotonin neurons are called heteroreceptors

   d. Presynaptic NE receptor on serotonin neuron is the alpha 1 receptor (located on the cell body)
11. **5HT Receptors:**

- **basal ganglia**
  - $5HT_2A$ movement control, obsessions, and compulsions

- **limbic**
  - $5HT_2A$ (postsynaptic)
  - $5HT_3C$ anxiety and panic hallucinogens

- **hypothalmic**
  - $5HT_3$ appetite and eating

- **brainstem**
  - $5HT_2A$ (postsynaptic)
    - sleep - slow wave sleep

- **spinal cord**
  - sexual response - dysfunction
  - orgasm and ejaculation

- **brainstem**
  - $5HT3$ chemoreceptors
  - Vomiting - nausea

- **peripheral**
  - $5HT4 - 5HT3$ GI function
12. $5HT_2$ receptor responsiveness is reduced in depression receptors downregulate in recovery

13. $5HT_2$ receptors are increased in density in suicide victims

IV. NEUROENDOCRINE CORRELATES OF DEPRESSION

A. Bioamine influence

1. anterior pituitary hormone releasing factors by the hypothalamus is altered

2. abnormal circadian fluctuations

3. hypersecretion of cortisol

4. not suppressed by the glucocorticoid dexamethasone (biological marker of depression)

5. central glucocorticoid receptors become hypersensitive
6. antidepressants may normalize cortisol secretion and NE and 5HT$_2$

V. Neurotransmitter Receptor Hypothesis

A. Abnormal Receptors

1. upregulation
2. may be normal levels of monoamines
3. deficiency in signal transduction
4. second messenger systems that control gene regulation could be deficient
5. (BDNF) brain derived neurotrophic factor gene may become repressed under stress

   a. may lead to apoptosis of neurons in the hippocampus

6. hippocampal neurons are decreased in size and impaired in depression (PET)
7. antidepressants can activate genes for neurotrophic factors
8. Neurokinins - Peptide NT's
a. antagonist of substance P may be an antidepressant
b. Neurokinin A (binds with NK-2 receptors)
c. Neurokinin B - NK-3 receptors