Lecture XIV.
Brain Diseases - II.
Mental Illness

Bio 3411
Monday
October 15, 2012

[Diagram of brain circuits showing excitatory and inhibitory pathways in normal, Parkinson's Disease, and Huntington's Disease states.]
What this lecture is about:

- Widespread Systems
- Mood Disorders
  - Depression
  - Manic/Depressive Illness
- Schizophrenia
- Drugs
References

†Sheline YI, Gado MH, Price JL 1998 Amygdala core nuclei volumes are decreased in recurrent major depression. NeuroReport 9:2023-2028.


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Neuroscience, p 111

<table>
<thead>
<tr>
<th>NEUROTRANSMITTER</th>
<th>POSTSYNAPTIC EFFECT*</th>
<th>PRECURSOR(S)</th>
<th>RATE-LIMITING STEP IN SYNTHESIS</th>
<th>REMOVAL MECHANISM</th>
<th>TYPE OF VESICLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACh</td>
<td>Excitatory</td>
<td>Choline + acetyl CoA</td>
<td>CAT</td>
<td>AchEase</td>
<td>Small, clear</td>
</tr>
<tr>
<td>Glutamate</td>
<td>Excitatory</td>
<td>Glutamine</td>
<td>Glutaminease</td>
<td>Transporters</td>
<td>Small, clear</td>
</tr>
<tr>
<td>GABA</td>
<td>Inhibitory</td>
<td>GABA</td>
<td>Phosphoesterase</td>
<td>Transporters</td>
<td>Small, clear</td>
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<tr>
<td>Glycine</td>
<td>Inhibitory</td>
<td>Serine</td>
<td>Tyrosine hydroxylase</td>
<td>Transporters, MAO</td>
<td>Small, dense-core</td>
</tr>
<tr>
<td>Catecholamines</td>
<td>Excitatory</td>
<td>Tyrosine</td>
<td>Tryptophan hydroxylase</td>
<td>Transporters, MAO</td>
<td>Large, dense-core</td>
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<tr>
<td>Serotonin (5-HT)</td>
<td>Excitatory</td>
<td>Tryptophan</td>
<td>Tryptophan hydroxylase</td>
<td>Transporters, MAO</td>
<td>Large, dense-core</td>
</tr>
<tr>
<td>Histamine</td>
<td>Excitatory</td>
<td>Histidine</td>
<td>Histidine decarboxylase</td>
<td>Hydrolysis to ADP and amine oxidation</td>
<td>Small, clear</td>
</tr>
<tr>
<td>ATP</td>
<td>Excitatory</td>
<td>ADP</td>
<td>Mitochondrial oxidative</td>
<td>Hydrolysis to ADP and amine oxidation</td>
<td>Small, clear</td>
</tr>
<tr>
<td>Neuropeptides</td>
<td>Excitatory and inhibitory</td>
<td>Amino acids (protein synthesis)</td>
<td>Synthesis and transport</td>
<td>Proteases</td>
<td>Large, dense-core</td>
</tr>
<tr>
<td>Endocannabinoids</td>
<td>Inhibitory</td>
<td>Membrane lipids</td>
<td>Enzymatic modification of lipid</td>
<td>Hydrolysis by FAAH</td>
<td>None</td>
</tr>
<tr>
<td>Nitric oxide</td>
<td>Excitatory and inhibitory</td>
<td>Arginine</td>
<td>Nitric oxide synthase</td>
<td>Spontaneous oxidation</td>
<td>None</td>
</tr>
</tbody>
</table>

*The most common post synaptic effect is indicated; the same transmitter can elicit post synaptic excitation or inhibition, depending on the nature of the receptors and ion channels activated by transmitter binding (see Chapter 3).
Mood Disorder(s): Depressive (Unipolar) and Manic Depressive (Bipolar) Illness

- Sx: (Mood +/-): melancholic (black bile) thoughts, loss of interest in food and sex, sleep disturbances
- Prevalence: 10-15% lifetime
- Predisposition: Strongly genetic but may be multi-factorial
- Prevention: None
- Dx: Interview, suicidal actions.

THE BRAIN ATLAS, 3rd ed p 22

Subgenual cortex
Measurements of activity in persons with different forms of clinical depression demonstrate significant blood flow reductions in a region known as the subgenual (below the knee - genu - of the corpus callosum) cortex as compared to control subjects.

Measurements of activity in persons with different forms of clinical depression demonstrate significant blood flow increases in regions of the frontal lobes, the amygdala, the thalamus (not shown) and the brainstem (not shown) as compared to controls.
Measurements of the volumes of the subgenual cortex in individuals with different forms of clinical depression demonstrate significant reductions in this cortex as compared to control subjects.
Some Connections of the Core Amygdala

Measurements can be made from images of brain structures. The core of the amygdala, outlined here is smaller in persons with recurring depression.
Structural Changes in Patients with Recurrent Major Depression

HAMD (Hamilton Rating Scale for Depression)

<table>
<thead>
<tr>
<th>Table 1. Demographic and volumetric data</th>
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</thead>
<tbody>
<tr>
<td>Control (mean ± s.d.)</td>
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<tr>
<td>-----------------------</td>
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<tr>
<td><strong>Demographics</strong></td>
</tr>
<tr>
<td>Age (years)</td>
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<tr>
<td>Education (years)</td>
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<tr>
<td>Height (cm)</td>
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<tr>
<td>HAMD score</td>
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<tr>
<td><strong>Volumes</strong></td>
</tr>
<tr>
<td>Core</td>
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<tr>
<td>Left amygdala (mm³)</td>
</tr>
<tr>
<td>Right amygdala</td>
</tr>
<tr>
<td><strong>Non-core</strong></td>
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<tr>
<td>Left amygdala (mm³)</td>
</tr>
<tr>
<td>Right amygdala</td>
</tr>
<tr>
<td><strong>Total</strong></td>
</tr>
<tr>
<td>Left amygdala (mm³)</td>
</tr>
<tr>
<td>Right amygdala</td>
</tr>
<tr>
<td>Whole brain (cm³)</td>
</tr>
</tbody>
</table>

- Pathophysiology: reduced activity in subgenual cortex; smaller volume; lower concentration of glia but not neurons; central amygdala
- Treatment: Antidepressants (aka minor tranquilizers). Current best class is selective 5HT re-uptake inhibitors (e.g., Prozac, Zoloft).
- General Strategies refer to the synapse - block breakdown of amines, stimulate receptors, inhibit uptake, increase release, deep brain stimulation.
- Long Term Changes: improvement with drugs and talk
- Brain Science: See schizophrenia.
Schizophrenia (split mind)

- Symptoms: (Schizophrenia +/-): + hallucinations (voices), delusions, schizophrenic thought; - withdrawal, autistic behavior
- Prevalence: ≈ 1% lifetime from early age (dementia praecox)
- Predisposition: Strongly genetic but may be multifactorial
- Prevention: None
There are fewer serotoninergic fibers in the frontal cortex of the brains of schizophrenics.
A bar graph showing the total axon length (μm/10,000 μm²) across different cortical layers for controls and schizophrenics. The graph indicates significant differences between the groups.

\[ F=5.23, \text{df}=3, 10, p=0.02 \text{ (MANOVA).} \]
Activation in an “auditory” verbal imagery task.

- Diagnosis: Interview, family and social history.
- Pathophysiology: enlarged ventricles, smaller hippocampus, possible reduction in cerebral asymmetries
- Treatment: Neuroleptic (aka, major tranquilizers); current best class is DA (D4) blockers
- Long Term Changes: improvement with drugs
Mental illness informs about function and changes are reported with imaging.

The discovery that certain antihistamines (allergy) and antimycotics (tuberculosis) reduced depression and psychosis respectively led to the discovery of central monoaminergic systems and focused discoveries in neurotransmitter pharmacology.

This led to the discovery of NE, 5HT & DA and many receptors involved in central brain pathway function(s).

The side effects of some of the drugs mimic Parkinsonism and suggest common mechanisms and common structures.

THE BRAIN ATLAS, 3rd ed p 235

Dopaminergic Pathways
Widespread Systems Reward & Cocaine

- Self stimulation and reward - the Olds experiment
- History - Incas and jungle conquest, coca leaves, local anesthetics.
- Cocaine shorter term - rush
- Cocaine longer term - craving
- Cocaine reduces DA and 5-HT uptake

Sites of self stimulation in the rat (arrows)
The Brain Atlas, 3rd ed pp 59, 60

Street market in Pisac, Peru.

Coca Leaves
Multiple Correlation of Rush and Craving Ratings to Cocaine fMRI Data (N=10)

Rush:
- NAc/SCC
- BF/GP
- Amygdala (-)
- VT
- Parahipp

Craving:

Reward Circuitry (yellow):
- NAc = Nucleus Accumbens
- BF = Basal Forebrain
- Amy = Amygdala
- VT = Ventral Tegmentum

Other Monoaminergic Sources (blue):
- DR = Dorsal Raphe
- LC = Locust Cerebral

Rush (red):
- BF = Basal Forebrain
- AC = Anterior Cingulate
- PC = Posterior Cingulate
- I = Insula

Craving (green):
- NAc = Nucleus Accumbens
- Amy = Amygdala
- Parahipp = Parahippocampal Gyrus

Specified Regions:

- Caudate
- Putamen
- Thalamus
- Hippocampus
Brain Diseases - Summary

- The brain like any organ has functions; input, output, “thought”, communication. *Brain diseases* interfere with these functions as heart disease interferes with pumping blood.
- Many brain diseases have a *strong genetic component*.
- The prevalence of *brain diseases* is high \( \approx 15-30\% \).
- The impact of *brain diseases* is distributed and often sustained, affecting individuals and their families, friends and co-workers profoundly.
- The cost of brain diseases exceeds $ Trillions annually.
END