The Neurobiology of Mood Disorders

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Mood Disorders are Serious

- Start at early age.
- Hard to diagnose in youth.
- Confused with normal teenage behavior, drug use or other psychiatric illnesses.
- Mostly recurrent episodes or chronic illness.
- High suicide risk.
- Treatment often started late and long-term compliance poor.
- Early treatment and episode prevention is better than responding to each new episode.

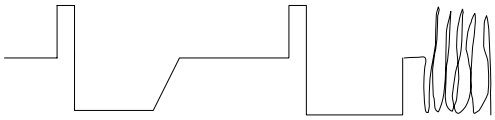
The Course of Unipolar Disorders

Depression **Depression**

School Friends Job Marriage Finances Physical health

The Course of Bipolar Disorders

Mania **Mania**



Depression **Depression** **Mixed state**

School Friends Job Marriage Finances Physical health

Why are Mood Disorders Recurrent?

- Abnormal brain development.
- Why is brain develop not normal? Genetic and developmental effects.

Topics

- Neurotransmitter deficiency hypotheses
- Hyperactive stress systems
- Action of antidepressants

Neurotransmitter Deficiency Hypotheses of Depression

- Serotonin
- Norepinephrine
- Dopamine
- Gamma-aminobutyric acid (GABA)
- Brain-derived neurotrophic factor (BDNF)
- Somatostatin

Neurotransmitter Excess Hypotheses of Depression

- Acetylcholine
- Substance P
- Corticotrophin Releasing Hormone (CRH)

Serotonin in Major Depression

- Cerebrospinal Fluid
- Neuroendocrine challenges
- Platelets
- Postmortem brain
- Depletion
- Imaging
- Genes

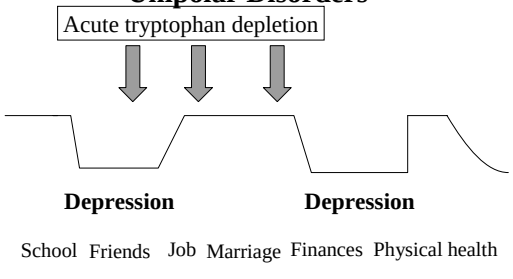
CSF 5-HIAA in DEPRESSION

- An index of serotonin turnover.
- Probably lower in depression.
- A trait and under genetic control (candidate for genetic cause of depression).
- Lowered by maternal deprivation, an effect that persists into adulthood in monkeys.

Serotonin Neuroendocrine Challenges

- Serotonin release causes the release of prolactin
- Prolactin responses to serotonin are blunted in depression
- Blunting present in remitted patients = trait

Effect of Serotonin Depletion in Unipolar Disorders



Serotonin Function is Abnormal Between and During Episodes of Major Depression

- May explain why 80% of patients have recurrences of major depressive episodes.
- May explain why prevention of relapse back into an episode and prevention of future episodes requires ongoing medication.

HPA STRESS AXIS AND SEROTONIN IN MAJOR DEPRESSION

- Hypothalamic Pituitary Adrenal Axis (HPA) overactivity (elevated CRH and cortisol, dexamethasone resistance) is present in many patients with severe depression.
- Corticosteroids reduce hippocampal 5-HT1A receptor sites in animal studies and may explain reduced hippocampal damage in depression.

Platelets Used as a Serotonin Neuron Model In Studies of Major Depression

- Lots of serotonin-related abnormalities.
- Serotonin uptake low.
- Serotonin transporter sites are fewer.
- More 5-HT2A receptors in association with suicidal acts.
- 5-HT2A signal transduction is blunted in suicidal cases.
- Possible link to increased risk of death from myocardial infarction in major depression.

Serotonin 5-HT1A Receptors

- Major part of serotonin communication in brain.
- Both an autoreceptor and a terminal field post-synaptic receptor.
- Role hypothesized in the pathobiology of mood disorders.
- Role hypothesized in the action of antidepressants.
- Can be studied in postmortem brain and in live patients using PET scanning.

Candidate Serotonin Genes in Depression

- Serotonin transporter
- Tryptophan hydroxylase
- Receptors including 5-HT1A, 5-HT1B and 5-HT2A
- Monoamine Oxidase
- Results are promising but preliminary
- Imply cause and mechanism

Norepinephrine System

- Seems hyperactive. But since there are fewer noradrenergic neurons, this can lead to a deficiency.
- Adverse childhood experiences can produce an over-active responsiveness in this system that persists into adulthood.
- In situations that most people may not find too stressful, the vulnerable depressed individual does feels very stressed and may deplete NE. Depletion of NE with AMPT causes depression in recovered patients but not normals.
- Restraint stress in animals causes NE depletion and hopelessness. Hopelessness is part of major depression.

Dopamine Function is Deficient in Major Depression

- Parkinson's Disease associated with depression.
- CSF shows low homovanillic acid (HVA).
- Neuroendocrine challenges: blunted responses to dopamine agonists
- Depletion of dopamine with AMPT causes depression in recovered patients but not normals.
- Imaging: nothing found yet.
- Postmortem brain: no data
- Genes: TH, COM T & MAO

GABA in Major Depression

- CSF levels of GABA are lower in depression.
- Postmortem brain: fewer GABA neurons.
- Imaging: low GABA in cortex.
- Genes: N/A

Fewer GABA Neurons in Anterior Cingulate and Entorhinal Cortex in Bipolar Disorders

- **27% fewer GABA cells in layer II of bipolar group.**
- No statistically significant difference in pyramidal cells or glia.
- No difference in size of pyramidal cells.
- Indicates **deficit in local circuit neurons or GABA cells** in layer II of anterior cingulate in bipolar disorders.
- Benes *et al.*, Biological Psychiatry 2001;50:395-406
- Similar results reported by others in entorhinal cortex.

Neurotransmitters and Mania: Hypotheses

- Deficient serotonergic neurotransmission has been hypothesized as a factor in mania AND depression. Perhaps because it contributes to GABA deficit.
- Anticonvulsants as mood stabilizers and anti-manic agents suggest GABA deficiency may contribute to mood instability.
- Increased NE and DA activity may underlie mania

ANTIDEPRESSANT ACTION

- Enhance serotonin function by SSRI, MAOI, lithium or tricyclic antidepressant medication.
- Enhance norepinephrine or dopamine function by NERI or MAOI.
- Increased receptor number induced by ECT or enhance signal by second messenger effects.
- Enhance GABA function (anticonvulsants).
- Infuse BDNFintrathecally (serotonin growth).

WHY IS THERE A DELAYED ONSET OF ACTION of ANTIDEPRESSANTS

- SSRIs cause gradual desensitization of 5-HT1A autoreceptors without change in 5-HT1A postsynaptic terminal field receptors, gradually amplifying the serotonin signal.
- ECS causes progressive postsynaptic 5-HT1A receptor upregulation, without effect on autoreceptors.

SECOND MESSENGER EFFECTS in ADDITION TO TRANSMITTER EFFECTS

- Noradrenergic signal transduction enhancement by tricyclic antidepressants.
- Lithium dampens signal transduction (anti-manic effect).
- ECT enhances NE and serotonin signal transduction.
- All enhance BDNF and possibly brain growth.

ECT or Convulsive Therapy

- Upregulate 5-HT2A and 5-HT1A receptors
- Enhance signal transduction
- BDNF increase and possible benefit via brain growth.

PEPTIDE ANTAGONISTS

- Corticotrphin Releasing Hormone
- Substance P
- Antagonists are being evaluated as antidepressants.

SUCCESSFUL TREATMENT NORMALIZES HPA STRESS SYSTEM OVER-ACTIVITY IN DEPRESSION

- HPA overactivity may be reduced by successful antidepressant treatment
- Reduced HPA activity may result in more hippocampal 5-HT1A receptors and perhaps hippocampal growth.
- Reduction in CRH may reduce the depression symptoms due to CRH itself.

Consequences of Failure to Diagnose and Treat Depression

- Social and family relationships damaged.
- School failures, job loss and financial dependence.
- Suicide.
- Brain cell loss or process retraction or atrophy.

Finit and good luck.

Contact me if you are interested in research.