NEUROBIOLOGY OF MOOD DISORDERS

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Re: the optimal time to study patients with major depressive disorder

-during remission and off medications, observed abnormalities will reflect the vulnerability to depression, i.e. the etiology

-during an episode of depression observed abnormalities may reflect the defenses against depression, i.e. more confusing

Neurotransmitter excess hypotheses of depression: Acetylcholine, Substance P, CRH (Corticotrophin Releasing Hormone)

Neurotransmitter deficiency hypotheses of depression:

SEROTONIN

CSF 5-HIAA (primary breakdown product of serotonin): Disagreement as to whether lower in depression. Lower in suicide attempters. Lower in impulsive aggression. A trait and under genetic control (candidate for genetic cause of depression). Lowered by maternal deprivation; an effect that persists into adulthood in monkeys.

Neuroendocrine challenges:

Serotonin release causes the release of prolactin.
Prolactin responses to fenflurarnine, tryptophan (IV), clomipramine and isapirone are blunted in depression.
Blunting present in remitted patients = trait.
No data in mania.

Depletion of serotonin and depression:

Mild effects on mood and impulsivity in normals.
Does not worsen depressed patients.
Causes a high rate of relapse in remitted depressed patients trait (i.e. same in remitted patients and those with current major depressive episode).
Rapidly reverses the benefit of selective serotonin reuptake inhibitors (SSRIS) indicating that ongoing action is needed for ongoing benefit.

Hypothalamic Pituitary Adrenal (HPA) axis and serotonin in major depression:

HPA overactivity (elevated CRH and cortisol, dexamethasone resistance) is present in many patients with severe depression.

Corticosteroids reduce hippocampal 5-HTIA receptor sites in animal studies and may explain reduced hippocampal 5-HT I A binding in depression.

Platelets:

Model for serotonin neurons
Serotonin content not clearly altered in depression.
Serotonin uptake reduced in depression.
Transporter sites are fewer in depression.
More 5-HT2A sites in association with suicidal acts.
5-HT2A signal transduction is blunted in suicidal cases.
State-trait unresolved.
Possible link to increased risk of death after MI in MDE

Postmortem brain studies:

Fewer transporter sites in prefrontal cortex.
More 5-HT2A receptors in the prefrontal cortex (PFC.)
Perhaps fewer brainstem transportes and 5-HT I A autoreceptors.
Other changes are associated with suicide diathesis and seen in ventral prefrontal cortex and brainstem.

Candidate serotonin genes:

Transporter
Tryptophan hydroxylase
Receptors including 5-HTIA, 5-HTlB.and 5-HT2A
Results are promising but preliminary.
Imply cause and mechanism.

NOREPINEPHRINE

CSF: shows increases in NLHPG (norepinephrine metabolite).
Neuroendocrine challenges: blunted response to alpha-2 adrenergic stimulation
Platelets: altered alpha-2 function
Postmortem brain: stress responses
Depletion with AMPT causes depression in recovered patients, not healthy volunteers.
Imaging: premature
Genes: TH, COMT, and MAO

DOPAMINE

CSF: shows decrease in HVA (dopamine metabolite)
Neuroendocrine challenges: blunted responses to dopamine agonists.
Platelets: N/A
Postmortem brain: no data
Depletion with AMPT causes depression in recovered patients but not normals.
Imaging: reduced dopamine release.
Genes: TH, COMT and MAO

GABA

CSF: shows decrease in GABA
Neuroendocrine challenges: N/A
Platelets: N/A
Postmortem brain: fewer GABA neurons
Depletion: N/A
Imaging: low GABA in cortex.
Genes: N/A

Neurotransmitters and mania: hypotheses:

Deficient serotonergic neurotransmission has been hypothesized as a factor in mania.
Anticonvulsants as mood stabilizers suggest gabaergic deficiency may contribute to mood instability, but low GABA only found in unipolar depression.
Increased NE and DA activity may underlie mania.

Neurotransmitters' differences between unipolar and bipolar depression

Serotonin deficits are more severe in bipolar depression.
Gabaergic deficiency seems to be mostly in unipolar depression.
Noradrenergic indices are high during mania and low during depression in bipolar I disorder.
Doparninergic agonists can produce mania.

Action of antidepressants:

SSRIs cause gradual desensitization of 5-HTIA autoreceptors without change in 5-HTIA postsynaptic terminal field receptors, amplifying the serotonin signal.
Enhance serotonin function by SSRI or MAOI or agonist.
Enhance norepinephrine or dopamine function by reuptake of NIAO antagonists.
Direct receptor increase by ECT or second messenger effects.
Enhance GABA function (anticonvulsants).
Infuse BDNF (serotonin growth).

Second messenger effects:

Noradrenergic signal transduction enhancement by tricyclic antidepressants.
Lithium dampens signal transduction (anti-manic effect).
ECT enhances NE and serotonin signal transduction.

ECT:

Upregulate 5-HT2A and 5-HTIA receptors
Enhance signal transduction.
BDNF increase.

Effect of treatment on HPA function in depression:

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