ESSENTIAL PSYCHOPHARMACOLOGY, 2011: NEUROBIOLOGY OF DEPRESSION

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MONOAMINE THEORY OF DEPRESSION

• Depression: low NE or 5HT
  – Evidence: drugs that increase these neurotransmitters have antidepressant properties; low metabolites of NE and 5HT in depression

• Mania: high NE or 5HT
  – Evidence: drugs that increase these neurotransmitters may cause mania; changes in metabolites 24 hours prior to manic switch

• Monoaminergic transmission is disturbed in depressive states
  – All clinically available antidepressants elicit enhancement of extracellular levels of monoamines
NOREPINEPHRINE AND DEPRESSION

• Presynaptic release controlled by $\alpha_2$ receptors; may be subsensitive in depression
• Postsynaptic $\beta$ receptor upregulated in depression;
  – Sensitivity controlled by thyroid, estrogen, serotonin
• Second messenger (cAMP) and protein kinase A function decreased in depression
• CREB (C reactive element binding) in nucleus activated by antidepressants
Monoamine Neurotransmission (NE)

Tyrosine → Tyrosine hydroxylase → DOPA → DA → NE

Ca

MAO

α₂

COMT

Release

Depolarization

Transporter Protein

Vanillylmandelic acid (VMA)
NOREPINEPHRINE TRANSPORTER POLYMORPHISMS

• There are two genetic variants of the norepinephrine gene
  – GG variant response better than AA variant
Hamilton Rating Scale for Depression Score Changes During 6 Weeks of Treatment With Norepinephrine Reuptake Inhibitor

ROLE OF PRESYNAPTIC MONOAMINE OXIDASE

- Functional promoter polymorphism of MAO-A gene has increased enzymatic degradation of CNS monoamines.
- Low expression of the MAO-A linked promoter region (LPR) variant was more vulnerable to repeated childhood traumas.
- High activity is linked to higher responsivity of amygdala to emotional face viewing and suggests increased risk for psychiatric problems in adolescence.
Post synaptic Neurotransmission (NE)

G → adenylate cyclase → ATP → cAMP → PK_A → Into the nucleus
ROLE OF CREB IN DEPRESSION

• CREB gene-expression is dysregulated in depression
  – Antidepressants upregulate CREB
  – Enhanced CREB increases hippocampal neurogenesis

• Neurogenesis is under control of neurotrophins: BDNF
  – Increased by CREB
  – Increases dendritic arborization (hippocampus)
BDNF

- BDNF is brain derived neurotrophic factor
- Hippocampal protein: Is one of several nerve growth factors
- Specific receptor: TrkB
- Responsible for maintaining neuron health
- Controls terminal branching
- Induces synaptic function
- Induced by antidepressant treatment
PLASMA BDNF IS DECREASED IN DEPRESSION
DEPRESSION INCREASES HEART INFLAMMATION

• Depressive symptoms are associated with higher levels of inflammation in patients with coronary heart disease
  – (Baseline inflammation levels do not predict or cause depressive symptoms in coronary heart disease patients)

• Mechanisms:
  – Inflammation is only a factor in patients with physical inactivity, smoking and higher BMI
DOPAMINE IN DEPRESSION

• May be depleted in anergic depression
• Depletion may be related to anhedonia
• Higher levels in agitated depression (?)
• Higher levels in psychotic depression
• Higher levels of Dopamine Transporter in basal ganglia in depression
  – Results from decreased synaptic DA or diminished DA “tone” in depression
DOPAMINE REWARD SYSTEM IN DEPRESSION

• Two sites for reward:
  – Accumbens (ventral striatum): site for drug reward and natural rewards (food, sex, social interactions)
  – Amygdala: learned associations between negative emotional stimuli, environmental cues, and reward

• These are predominately dopaminergic
  – abnormalities are seen in depression:
    – anhedonia, decreased motivation, anergia
SEROTONIN IN DEPRESSION

• Presynaptic release and firing controlled by 5-HT$_{1A, 1D}$ receptors; both may be subsensitive in depression
• Post synaptic 5-HT$_{2A}$ receptors upregulated
• Second messengers (IP$_3$; DAG) and protein kinase C decreased in depression
• cFos, cJun, AP-1 (activator protein) activated by antidepressants
Serotonin (5HT: 5-Hydroxytryptamine)

- Tryptophan hydroxylase
- 5HT Release
- Ca
- Tryptophan metabolite 5 HIAA (5 Hydroxyindole Acetic Acid)
- 5HT Transporter protein (5HTTP)
- MAO
- 2 autoreceptors
- 5HT₁d
- 5HT₁a
- Release
SEROTONIN $2_A$ RECEPTOR AND DEPRESSION

- $5HT2_A$ receptor polymorphism may interact with parental rejection to increase risk of adult depression
5-HT TRANSPORTER PROTEIN POLYMORPHISMS

• Pre-synaptic 5HT re-uptake from synapse is an active protein transport

• Transporter protein has 2 polymorphisms:
  – Long arm form (L)
  – Short arm form (S)
  – Most individuals are L/L or L/S

• Functional variant of allele: $L_A$, $L_G$
  – $L_G$ and S have comparable levels of 5HT transporter expression; both are lower than $L_A$
SEROTONIN TRANSPORTER GENE AND SSRI EFFICACY

- Functional polymorphism is in the transcriptional control region of the 5-HTT coding sequence
  - 3 forms of 5-HTT based on length of amino acid chain: longest (l/l); shortest (s/s); heterozygote intermediate (l/s)

- Strong association between 5-HTTLPR and response to antidepressants
  l/l and l/s genotypes show more robust response to SSRI antidepressants; s/s variants have lower remission rate

Seretti; Mol Psychiat  2007;12:247
SEROTONIN RECEPTOR POLYMORPHISMS AND ANTIDEPRESSANT RESPONSE

• 5-HTTLPR repeatedly shown to be associated with antidepressant response
  – Metanalyses confirms s/s and s/l association with decreased response

Serretti; 2007; Mol Psychiat 12:247
5HT POLYMORPHISMS INTERACT WITH THE ENVIRONMENT

• “s” allele results in increased synaptic 5HT
  – This may result in “downregulation” of 5HT2 receptors thereby decreasing 5HT transmission

• Decreased 5HT transmission by itself does not affect mood or temperament

• It does increase susceptibility to respond to environmental stress with depressive symptoms:
  – Right amygdala is hyperreactive in those with “s” allele, whether homozygous or heterozygous

Hariri, 2005,2002; Lesch 1998; Caspi 1996
GENES x ENVIRONMENT INTERACTION

Caspi, 2003

![Graph showing the interaction between genes and environment on the probability of major depression episode.](image-url)
GLUTAMATE RECEPTORS AND DEPRESSION

• NMDA antagonists have antidepressant activity:
  – Memantine
  – Amantadine
  – Felbamate

• Drugs that inhibit glutamate release:
  – Lamotrigine

• Drugs that decrease glutamate effect:
  – Lithium, valproate, carbamazepine, topiramate, levetiracetam, riluzole, atypical antipsychotic drugs
  – Ketamine I.V. produced lasting significant relief from depression in a controlled trial
NMDA ANTAGONIST TREATMENT OF RESISTANT DEPRESSION

Zarate; Arch Gen Psychiat 2006;63:856
CRF₁ RECEPTORS

• CRF binds to CRF₁ receptors in amygdala, septum and other limbic structures
• CRF increases anxiety, aversive behavior, and depression via these limbic structures
• CRF₁ directly excite NE cell bodies in locus coeruleus
ANTIDEPRESSANT PROPERTIES OF CRF₁ ANTAGONISTS

• CRF₁ antagonists have antidepressant properties
• SSRI therapeutic effect correlates with reduction of CRF levels
• ECT decreases CRF levels
• Lithium and valproic acid decrease activity of CRF neurons in hypothalamus and corticolimbic structures
MECHANISMS OF ECT

- Noradrenergic mechanisms
  - Increases presynaptic release of NE
  - Increases activity of $\alpha_{1A}$ and $\alpha_{1B}$ receptor subtypes
  - Like other antidepressants, ECT down-regulates $\beta$ receptors
MECHANISM OF ECT -II

- Serotonergic mechanisms
  - Increases 5HT presynaptic release
  - Increases sprouting of 5HT neurons in hippocampus
  - Progressively decreases post synaptic 5HT$_{2c}$ receptor activity
  - Unlike SSRIs, ECT upregulates 5HT$_{2a}$ receptors
  - Enhances hippocampal 5-HT$_{1A}$ and 5-HT$_{3}$ receptors
MECHANISM OF ECT -III

- Increases induction of CREB and BDNF gene expression in hippocampus, frontal cortex and amygdala
- Encourages cellular proliferation in frontal cortex
  - Oligodendrocytes (are reduced in depression)
  - Endothelial cells
MECHANISMS OF AUGMENTATION BY THYROID

• Equivocal data regarding efficacy
• Theoretical mechanisms:
  – Long-term T₃ enhances downregulation of 5-HT₂A
  – Enhances cortical release of 5-HT by rapid desensitization of inhibitory 5-HT₁A autoreceptors
  – T₃₄ is also concentrated at locus coeruleus (NE) and post-synaptic NE receptors
  – T₃/₄ may enhance cAMP in hippocampus
  – T₃/₄ may enhance generation of CREB
NEUROBIOLOGIC MECHANISMS OF ESTROGEN

• Estrogen interacts with monoamine pathways
• Enhances NE and 5HT transmission:
  – Acts directly on nucleus and on membrane located monoamine receptors
  – Inhibits 5-HT and NE transporter proteins
  – Reduces $\alpha_2$ autoreceptors
  – Desensitizes presynaptic 5-HT$_{1A}$ autoreceptors
• Enhances SSRIs and NARIs
NEUROBIOLOGIC MECHANISMS OF ESTROGEN -II

- Possesses neuroprotective properties
- Promotes hippocampal neurogenesis
- Stimulates dendritic spine formation
- Enhances synthesis of BDNF in hippocampus
- Modulates glutamate transmission
- Since testosterone is converted to estradiol in hippocampus, effects are relevant to males as well as females
OTHER NEW ANTIDEPRESSANT TREATMENTS

• Vagus Nerve Stimulation
• Transcranial Magnetic Stimulation
• Deep Brain Stimulation
• Sleep deprivation

• Inadequate data for clinical treatments
  – Best responses are with TMS
MECHANISM OF VAGAL NERVE STIMULATION

- Modifies neural activity in hippocampus, cortex, amygdala, hypothalamus, thalamus
- Enhances locus coeruleus NE activity
- Increases DA turnover (increased HVA)
- Increases 5-HT activity
- Stimulates GABAergic neurons
- Suppresses glutamatergic neurons
MECHANISMS OF VAGAL NERVE STIMULATION-II

- Increases NE activity (like ECT)
- Increases DA turnover (like ECT)
- May stimulate GABA and suppress glutamate
MECHANISMS OF TRANSCRANIAL MAGNETIC STIMULATION

- Like ECT, TMS increases activity at postsynaptic $5$-$HT_{1A}$ cortical receptors;
- Unlike ECT (but like other antidepressants) TMS down-regulates cortical $5$-$HT_{2A}$ receptors;
- Marked increased release of limbic and striatal DA (improves motivation and reward)
MECHANISMS OF TRANSCRANIAL MAGNETIC STIMULATION-II

- Unlike ECT, but like other antidepressants TMS downregulates 5HT\textsubscript{2A} receptors
- Increases presynaptic release of striatal and limbic dopamine
- Increases cortical glutamate release and number of NMDA receptors
- Increases BDNF expression in hippocampus and cortex and elicits cellular proliferation (may increase DA neurons and help Parkinsons)
DEEP BRAIN STIMULATION

• Abnormalities in frontal-basal-ganglia-thalamic circuit in TRD, especially in the anterior cingulate cortex as well as striatum and thalamus

• Deep brain high frequency electrical stimulation

• Approximately 50% relief in symptoms of TRD accompanied by significant improvement in social functioning

Greenberg, 2004
MECHANISM OF SLEEP DEPRIVATION

• Activates 5-HT neurons
  – Increases 5-HT release in hippocampus, frontal cortex, suprachiasmatic nucleus

• Down-regulates 5-HT transporters

• Transient down-regulation of 5-HT$_{1A}$ autoreceptors
MECHANISMS OF SLEEP DEPRIVATION -II

- Increases CRF synthesis
- Increases galanin in L.C. (modulates sleep and mood)
- Increases thyroid hormones in amygdala
- Elevates BDNF gene expression