Neurotransmitter Functioning In Major Depressive Disorder
This program was developed with the support of Otsuka Pharmaceutical Development & Commercialization, Inc. and Lundbeck, LLC. The speakers are either employees or paid contractors of Otsuka Pharmaceutical Development & Commercialization, Inc.
Monoamine Imbalance Theory of Major Depressive Disorder (MDD)

- Imbalance theory describes patients with depression having deficient:\n  - Dopamine (DA),
  - Serotonin (5-HT),
  - Norepinephrine (NE)
- Monoaminergic deficiencies may be caused by depleted or dysregulated:\n  - Monoamine synthesis
  - Monoamine receptor signaling
- The efficacy of SSRIs, SNRIs, and dopamine agonists as antidepressants supports this theory\(^3\)

---


AC, adenylate cyclase; cAMP, cyclic adenosine monophosphate; MAO-A, monoamine oxidase A; PLC, phospholipase-C; PI, phosphoinositide; SNRIs, serotonin norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors.
Monoamine Pathways Overlap in Several Areas of the Brain\textsuperscript{1–8}

A = amygdala
ACC = anterior cingulate cortex
C = cerebellum
H = hippocampus
Hy = hypothalamus
NA = nucleus accumbens
PFC = prefrontal cortex
S = striatum
T = thalamus
VTA = ventral tegmental area

Neural Circuitry of Monoamines and GABAergic Neurons Overlap

- GABAergic interneurons provide a link between several classes of serotonergic receptors and monoaminergic neurons.
- “Long-loop” feedback inhibition is likely mediated by descending glutamatergic neurons which act via stimulation of GABAergic interneurons.

5-HTX, serotonin receptor X; α/βX, noradrenaline receptor X; GABA, gamma-aminobutyric acid; GABAαX, gamma-aminobutyric acid receptor X; Dα, dopamine receptor X; DA, dopamine; FCX, frontal cortex; NA, noradrenaline.

Overlap Between Monoamine Neurotransmitter Systems Plays a Role in Emotional Behavior

5-HT, serotonin; DA, dopamine; NE, norepinephrine.
Serotonin (5-HT)

Findings from research with depressed patients¹:

- Low levels of blood platelet 5-HT
- Low plasma levels of L-tryptophan
- Depletion of dietary tryptophan induces depression
- Tryptophan administration seems to provide beneficial effects


© PsychU. All rights reserved.
5-HT\textsubscript{1A}

**Presynaptic 5-HT\textsubscript{1A}**
- Auto-receptor
- Regulates 5-HT release
- Rapidly desensitize after activation

**Postsynaptic 5-HT\textsubscript{1A}**
- Hetero-receptor
- Regulate inhibition of non-5-HT neurons
- Do not desensitize

5-HT\textsubscript{1A}, serotonin (receptor 1A).


Image adapted from Panesar K, et al.\textsuperscript{2}
5-HT$_{1B}$

- Similar to 5-HT$_{1A}$, 5-HT$_{1B}$ is expressed$^1$:
  - Presynaptically (auto-receptor)
  - Postsynaptically (hetero-receptor)
- Densely expressed in basal ganglia, nucleus accumbens, and substantia nigra$^1$
- Stress upregulates 5-HT$_{1B}$ receptor expression in the dorsal raphe nucleus$^1$
- Antidepressants dramatically effect 5-HT$_{1B}$, possibly underlying their antidepressant and anxiolytic effects$^1$

---

5-HT$_{(1A/1B)}$, serotonin (receptor 1A/1B); GABA, gamma-aminobutyric acid.

5-HT$_{2A}$

- Highly expressed in the frontal cortex, basal ganglia, and parts of the limbic system$^1$
- Depressed patients have greater 5-HT$_{2A}$ receptor density$^2$
- Promotor region of 5-HT$_{2A}$ variant shows increased risk of depression$^2$
- Some SSRIs downregulate 5-HT$_{2A}$$^2$

5-HT$_{2A}$, serotonin (receptor 2A); SSRI, selective serotonin reuptake inhibitor.

Modulating DA Activity via 5-HT Receptors

Proposed Actions:
- 5-HT projections connect with glutamatergic pyramidal neurons in the cortex
- Cortical 5-HT$_{1A}$ receptor stimulation inhibits glutamatergic neurons, increasing DA release in the striatum
- Cortical 5-HT$_{2A}$ receptor activation stimulates glutamatergic neuron, inhibiting DA release in the striatum
- Therefore, it is proposed that blockade of cortical 5-HT$_{2A}$ receptors relieves inhibition of DA release (functionally analogous to 5-HT$_{1A}$ stimulation)

5-HT Transporter (SERT)

- Removes excess 5-HT from extracellular space
- Main target of antidepressants, SSRIs and SNRIs
- Mainly expressed by 5-HT neurons
- Genetic link to SERT: patients with a functional polymorphism tend to have higher probability of depression
- SERT undergo adaptive changes with SSRI treatment

SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin re-uptake inhibitors.

Dopamine (DA)

- Observed dopaminergic dysregulation in patients with depression includes:
  - Functional deficiencies in synaptic DA\(^1\)
  - Reduced homovanillic acid (HVA)\(^1\)
  - Lower DA binding to the DAT\(^1\)
  - Genetic alterations in D\(_4\) receptors, DAT, and COMT\(^2\)
- Neural activation during reward processing tasks differ in patients with depression versus healthy controls:
  - A single major depressive episode, or recurrent MDD, is associated with reduced activation in the caudate and nucleus accumbens\(^3\)

---

3-MT, 3-methoxytyramine; AC, adenyl cyclase; cAMP, cyclic AMP; COMT, catechol O-methyltransferase; DX, dopamine receptor subtype X; DAT, dopamine transporter; G, G protein; MAO-B, monoamine oxidase B; MDD, major depressive disorder; TH, tyrosine hydroxylase; VMAT, vesicular monoamine transporter.

Norepinephrine (NE)

• Post-mortem tissue and functional imaging studies have elaborated on adrenergic modulations in depression¹:
  – Suicide victims with depression have shown an altered α₂ receptor density and sensitivity
  – Patients with MDD demonstrated decreased norepinephrine transporter (NET) binding in the locus coeruleus

• Depleting NE levels during remission in patients with depression resulted in the rapid reappearance of depressive symptoms¹*

* Patients were in remission and no longer taking any antidepressant medication.

α₂, alpha-2 adrenergic receptor; PFC, prefrontal cortex.

α Receptors Appear to Modulate 5-HT Release in MDD\textsuperscript{1,2}

- NE reciprocally regulates 5-HT neurons:
  - $\alpha_1$ receptors (located on 5-HT neurons) promote 5-HT release
  - $\alpha_2$ receptors (located postsynaptically on 5-HT neurons) indirectly attenuate 5-HT release
- Antagonism of $\alpha_2$ receptors indirectly decreases 5-HT inhibition

5-HT, serotonin; α, alpha adrenergic receptor; NE, norepinephrine.

Theorized Involvement of Non-monoamine Neurotransmitters in MDD Pathophysiology

5-HT, serotonin; GABA, GABA, gamma-aminobutyric acid MDD, major depressive disorder; NE, norepinephrine.


Image from: Zhao et al. 2012
Glutamate Hypothesis of Depression

• Glutamatergic dysregulation has been implicated in the pathophysiology of several psychiatric and neurological disorders

• Compared with healthy controls, observed alterations in the glutamate system in patients with MDD include:
  – Neuroanatomically specific modulations in glutamate levels
  – Reduced NMDA receptor-binding affinity
  – Reduced glutamate transporter expression

• Antidepressants and mood stabilizers used in the treatment of mood disorders affect many facets of the glutamate system

• Several agents that affect the glutamate system have been explored as potential treatments in mood disorders. These include:
  – Inhibitors of glutamate release
  – NMDA antagonists
  – NMDA partial antagonists

NMDA, N-methyl-D-aspartate.
Neurotransmitter Functioning In Major Depressive Disorder