Serotonin Receptors and Serotonergic Drugs
Learning Objectives

• Describe the functions of various serotonin receptors and their roles in mental illness

• Optimize treatment strategies by taking into account the serotonin-modulating properties of psychopharmacological agents
Frank is a 38-year-old patient with major depressive disorder who began treatment with an SSRI nearly 1 week ago. So far, he has not shown any improvement in depressive symptoms. You explain to the patient how both 5HT1A and 5HT1B/D receptors are hypothesized to be responsible for the common delay in response to treatment with an SSRI. 5HT1A and 5HT1B/D receptors both:

1. Are located as autoreceptors on the axons of 5HT neurons
2. Inhibit the release of 5HT from serotonergic neurons
3. Both of the above
Susanna is a 48-year-old morbidly obese patient. After numerous unsuccessful attempts by this patient to lose weight and improve her health through diet and exercise, you are considering a trial of lorcaserin. Lorcaserin is hypothesized to suppress appetite through its agonistic actions at which serotonergic receptor?

1. 5HT1A
2. 5HT2A
3. 5HT2C
4. 5HT6
Serotonin Circuits

PFC: prefrontal cortex; BF: basal forebrain; NA: nucleus accumbens; S: striatum; T: thalamus; HY: hypothalamus; A: amygdala; H: hippocampus; C: cerebellum; NT: brainstem neurotransmitter centers; SC: spinal cord.

Serotonin Receptors

7 families and at least 14 subtypes

5HT1A  5HT2A  5HT3  5HT4  5HT5  5HT6  5HT7
5HT1B  5HT2B
5HT1D  5HT2C
5HT1E
5HT1F

Various Actions of 5HT Receptors

5HT1A

• Located in:
  – Hippocampus, septum, amygdala, corticolimbic areas
  – Raphe nuclei (presynaptic autoreceptors)

• Actions include:
  – Regulation of ACh release in the septum
  – Regulation of Glu release in the prefrontal cortex (PFC)
  – Regulation of DA release in the ventral tegmental area (VTA)
  – Autoreceptors in the raphe nuclei inhibit 5HT neurotransmission

5HT1A

- Associated with anxiety, depression, temperature regulation, corticosterone secretion, learning, and memory

- Postsynaptic heteroreceptors
  - Unaltered or reduced in patients with depression

- Presynaptic autoreceptors
  - Increased in patients with depression
  - Located on soma and dendrites of 5HT neurons

5HT1A Somatodendritic Autoreceptors Regulate Serotonergic Neurotransmission

5HT1A Somatodendritic Autoreceptors Regulate Serotonergic Neurotransmission
5HT1A and EPS

- Stimulation of 5HT1A heteroreceptors increases striatal DA activity by inhibiting glutamatergic corticostriatal neurons

- Stimulation of 5HT1A autoreceptors also increases striatal DA activity

Increase in Dopamine Output in PFC by a Selective 5HT1A Agonist


Effect of Systemic 5HT1A Agonist on Dopamine Output in PFC

(R)-8-OH-DPAT = (R)-8-hydroxy-2(di-n-propylamino)tetralin

VTA = ventral tegmental area
Cortical 5HT1A Receptors Increase Dopamine Release

### Psychotropic Agents With 5HT1A Binding Affinity

**Available**
- Aripiprazole
- Clozapine
- Lurasidone
- Quetiapine
- Vilazodone
- Vortioxetine

**In Development**
- Agonists/Partial Agonists
  - Cariprazine
  - Brexpiprazole
  - Adoprazine
  - SSR181507
  - F15063
  - F15599

5HT1B

• 5HT1B postsynaptic heteroreceptors
  – Located on axons of non-serotonergic cells

• 5HT1B presynaptic autoreceptors
  – Located in axons of serotonergic neurons
  – Function similarly to 5HT1A receptors
    • Reduce serotonergic output
    • Must be desensitized for antidepressants to be fully effective

• May be more prominent than 5HT1D in median raphe nuclei

• 5HT1B and 1D have been historically difficult to distinguish
  – Lack of selective agonists/antagonists, rodent vs. human, nomenclature

• Presynaptic autoreceptors
  – Located in axons of 5HT neurons

• Function similarly to 5HT1A receptors
  – Reduce serotonergic output
  – Must be desensitized for antidepressants to be fully effective

• May be more prominent than 5HT1B in dorsal raphe nuclei

Artigas F. Pharmacol Ther 2013;137:119-31;
Serotonin 5HT1B/D Effects on Serotonin Release

5HT1B/D axon terminal autoreceptor
Serotonin 5HT1B/D Effects on Serotonin Release

5HT1B/D antagonists may increase 5HT release

5HT1B/D axon terminal autoreceptor
5HT = GABA

Prefrontal cortex
Stimulate 5HT1B/D autoreceptors

5HT = GABA

Prefrontal cortex
Add 5HT1B/D antagonist

= GABA

5HT

5HT1B/D antagonist

Prefrontal cortex
5HT

Glu

ACh

HA

DA

NE

= GABA

Prefrontal cortex

Basal forebrain

Tuberomammillary nucleus

Ventral tegmental area

Locus coeruleus
Stimulate 5HT1B heteroreceptors

- GABA
- 5HT
- 1B
- Prefrontal cortex
- Basal forebrain
- Tuberomammillary nucleus
- Ventral tegmental area
- Locus coeruleus
Stimulate 5HT1B heteroreceptors

- Prefrontal cortex
- Basal forebrain
- Tuberomammillary nucleus
- Ventral tegmental area
- Locus coeruleus

= GABA

5HT

Glu

ACh

HA

DA

NE

1B
Add 5HT1B antagonist

- Prefrontal cortex
- Basal forebrain
- Tuberomammillary nucleus
- Ventral tegmental area
- Locus coerulescens

5HT = GABA

NE = GABA

5HT1B antagonist

ACh

HA

DA

Glu
### Available
- Aripiprazole
- Asenapine
- Clozapine
- Iloperidone
- Quetiapine
- Ziprasidone
- Vortioxetine

### In Development
- **Agonists**
  - Anpirtoline
  - CP94253
- **Antagonists**
  - GR127935
  - SB 216641

5HT2A

• Located in:
  – Cerebral, piriform, and entorhinal cortices, claustrum, olfactory bulb, anterior olfactory nucleus, brainstem nuclei, and limbic regions

• 5HT2A receptors are found on GABAergic interneurons and glutamatergic neurons in cortex

• 5HT2A receptor density is increased in depressed patients

• 5HT2A receptors have been implicated in depression, anxiety, and negative symptoms of schizophrenia

5HT2A Antagonism

• Chronic administration of 5HT2A antagonists results in:
  – Down-regulation of 5HT2A receptors
  – Antidepressant effects
  – Improvement in EPS
    • Via disinhibition of DA release in the striatum

Cortical 5HT2A Receptors Decrease Dopamine Release

Cortical 5HT2A Receptors Decrease Dopamine Release

5HT neurons

GABA release from GABA neuron

inhibited DA neuron

glutamate release from glutamate neuron

5HT2A receptor

5HT neurons

activated glutamatergic pyramidal neuron

5HT1A receptor

Blocking Cortical 5HT2A Receptors Increases Dopamine Release

5HT neurons

inactivated GABA neuron

activated DA neuron

glutamate release from glutamate neuron

5HT neurons

5HT2A receptor

2A antagonist

5HT1A receptor

inactive glutamatergic pyramidal neuron

increased DA release

Nigrostriatal Pathway

Nigrostriatal Pathway: Blocking D2 Receptors

Nigrostriatal Pathway: Blocking 5HT2A Receptor Disinhibits DA Release and Reduces D2 Blockade

Psychotropic Agents With 5HT2A Binding Affinity

Available

• Aripiprazole
• Asenapine
• Clozapine
• Iloperidone
• Lurasidone

• Olanzapine
• Paliperidone
• Risperidone
• Quetiapine
• Ziprasidone

• Mirtazapine
• Trazodone
• Pimavanserin

Pimavanserin

- **5HT2A inverse agonist**
  - Blocks intrinsic activity when no agonist is present and blocks the agonist when present
- Recently received FDA Breakthrough Therapy Designation for Parkinson’s disease psychosis
  - Reduction in psychotic symptoms
  - Unlike antipsychotics, pimavanserin does not impair motor function or reduce the efficacy of L-DOPA

Pimavanserin Mechanism of Action

- Primarily visual hallucinations in PD
- Loss of nigrostriatal DA neurons causes compensatory increase in 5HT signaling
- 5HT2A receptors are increased in visual processing and limbic circuits in PD patients with psychosis

5HT2C

• Located in:
  – Hippocampus, amygdala, anterior olfactory and endopiriform nuclei, cingulate and piriform cortices, thalamic nuclei, and substantia nigra

• Preferentially located on GABAergic interneurons
  – Also on DA neurons in the mesolimbic pathway

5HT2C

- Both 5HT2C agonists and antagonists may have antidepressant effects
  - Increase release of DA and NE in terminal regions

- 5HT2C agonism
  - Suppresses DA release more from the mesolimbic pathway than from the nigrostriatal pathway
    - An antipsychotic without EPS?
  - May be useful for treating obesity

Serotonin 2C Agonist Lorcaserin Suppresses Appetite

Lorcaserin Actions: Enhance POMC

- **NPY**
- **AgRP**
- **MSH**
- **MC4R**

**αMSH**: α-melanocyt stimulating hormone
**AgRP**: agouti-related protein
**MCR4**: melanocortin 4 receptor
**NYP**: neuropeptide Y
**POMC**: proopiomelanocortin

Psychotropic Agents With 5HT2C Binding Affinity

Available

- Asenapine
- Clozapine
- Olanzapine
- Quetiapine
- Agomelatine
- Fluoxetine
- Mirtazapine
- Mianserin
- Nefazodone
- Trazodone
- Lorcaserin

5HT3

• Located in:
  – Spinal cord, brainstem, hippocampus, amygdala, and entorhinal, frontal, and cingulate cortices
  – Regulate DA, NE, 5HT, ACh, GABA, and histamine release

• 5HT3 antagonists may
  – Enhance cognition
  – Be anxiolytic
  – Reduce EPS

Serotonin 5HT3

5HT3 receptors are localized in:

- The chemoreceptor trigger zone of the brainstem
  - Mediate nausea and vomiting

- The gastrointestinal tract
  - Mediate nausea, vomiting, and diarrhea/bowel motility

Blocking 5HT3 may protect against the serotonin-induced gastrointestinal side effects that often accompany agents that increase 5HT release

Systemic 5HT3 Antagonist Reverses 5HT-Induced Decrease of Cortical Acetylcholine

Serotonin 5HT3 Effects on Norepinephrine and Acetylcholine Release

NE neuron

Baseline NE release

Reduced NE release

GABA neuron

5HT3R

5HT release

5HT3R

Baseline ACh release

Reduced ACh release

ACh neuron

NE: norepinephrine
ACh: acetylcholine

Serotonin 5HT3 Effects on Norepinephrine and Acetylcholine Release

5HT3 Modulates Cortical Pyramidal Neuron Activity

5HT3 Agonist Inhibits Pyramidal Neurons in Cortical Slices

- Time: 100μM mCPBG
- Layer I neuron: Greater inhibition
- Pyramidal neuron: 5 sec
- Inhibitory Postsynaptic Current
- mCPBG = 1-(m-chlorophenyl)biguanide

5HT3 Antagonist Increases Excitability of Pyramidal Neurons
- Orthodromically-Evoked Field Potentials
- Control
- 100 μM Zacopride
- 2nd spike
- 1 mV
- 10 ms

mCPBG = 1-(m-chlorophenyl)biguanide

Serotonin 5HT3 Effects on Glutamate Release

**Baseline**

- 5HT3 receptor
- GABA neuron
- PFC
- Pyramidal neuron

**Baseline glutamate release**

- 5HT neuron
- Raphe

Stimulation of 5HT3 receptors in the prefrontal cortex reduces glutamate release from pyramidal neurons.

Blockade of 5HT3 receptors in the prefrontal cortex enhances glutamate release from pyramidal neurons.

Overactivation

Psychotropic Agents With 5HT3 Binding Affinity

Available
- Clozapine
- Fluoxetine
- Mirtazapine
- Vortioxetine

In Development for Psychotropic Effects
- Tropisetron
- Ondansetron
- Granisetron

5HT4

• Located in:
  – Putamen, caudate nucleus, hippocampus, nucleus accumbens, globus pallidus, substantia nigra, neocortex, raphe and pontine nuclei, and thalamus

• Involved in the expression of genes for synaptic plasticity
  – 5HT4 agonists may enhance cognition
  – 5HT4 antagonists cause impairments in learning and memory

• Increase release of ACh and reduce amyloid β

Psychotropic Agents With 5HT4 Binding Affinity

In Development

• Tropisetron
• RS67333
• PRX-3140
• PF-04995274
• RQ-9

5HT6

• Located in:
  – Striatum, nucleus accumbens, olfactory tubercles, cortex, hippocampus, amygdala, hypothalamus, thalamus, and cerebellum

• Implicated in schizophrenia, depression, eating disorders, and cognition

• Regulate release of ACh, NE, GABA, and DA

• Both 5HT6 agonists and antagonists may have antidepressant and pro-cognitive effects

### Psychotropic Agents With 5HT6 Binding Affinity

#### Available
- Asenapine
- Clozapine
- Olanzapine
- Quetiapine

#### In Development
- **Antagonists**
  - SB-399885
  - SB-742457
  - Lu-AE-58054
  - P7C3
  - SUVN-502
- **Agonists**
  - LY-586713
  - WAY-181187
  - WAY-208466

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5HT7

• Located in:
  – Thalamus, hypothalamus, hippocampus, and cortex

• Implicated in thermoregulation, circadian rhythms, sleep, and mood disorders

• 5HT7 antagonism has antidepressant effects

5HT7 Antagonist SB-269970 Increases Cortical 5HT

5HT7 Antagonist Augments SSRI-Induced Cortical 5HT Release

Extracellular 5HT in Frontal Cortex (% of basal level)

SB-269970, 10 mg/kg + Citalopram, 3 mg/kg (n=4)
Citalopram, 3 mg/kg (n=3)
Vehicle (n=3)

Subcutaneous injection
Time (min)

DR = dorsal raphe

5HT7: Serotonin Release in the Prefrontal Cortex

Baseline

Baseline 5HT release

PFC

5HT7 receptor

GABA neuron

Raphe

5HT neuron

Stimulation of 5HT7 receptors in the raphe reduces serotonin release in the PFC.

Blockade of 5HT7 receptors in the raphe increases serotonin release
Psychotropic Agents With 5HT7 Binding Affinity

Available

- Aripiprazole
- Asenapine
- Clozapine
- Lurasidone
- Paliperidone
- Risperidone
- Quetiapine
- Ziprasidone
- Amisulpride
- Amoxapine
- Desipramine
- Imipramine
- Mianserin
- Fluoxetine
- Vortioxetine

Multimodal Agents

• Combine multiple modes of monoaminergic action

• Example: vortioxetine (LuAA21004)
  – Transporter mode: SERT inhibitor
  – Ion channel mode: 5HT3 antagonist
  – G protein receptor mode:
    • 5HT1A agonist
    • 5HT1B partial agonist
    • 5HT1D antagonist
    • 5HT7 antagonist
  – Raises neurotransmitters in preclinical models
    • 5HT, NE, DA
    • Plus histamine, acetylcholine, and glutamate
Vortioxetine: 3 Modes, 6 Pharmacological Actions

- SERT inhibition
- 5HT1A agonism
- 5HT1B partial agonism
- 5HT1D antagonism
- 5HT7 antagonism
- 5HT3 antagonism

5HT, NE, DA, ACh, HA, GABA, Glu

**Vortioxetine**

<table>
<thead>
<tr>
<th>Transporter</th>
<th>G protein-linked receptor</th>
<th>Ion channel-linked receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>SERT inhibition</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5HT1A agonism</th>
<th>5HT1B partial agonism</th>
<th>5HT1D antagonism</th>
<th>5HT7 antagonism</th>
<th>5HT3 antagonism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressant</td>
<td>Antidepressant</td>
<td>Antidepressant?</td>
<td>Antidepressant</td>
<td>Pro-cognitive?</td>
</tr>
<tr>
<td>Reduce sexual dysfunction?</td>
<td></td>
<td></td>
<td>Pro-cognitive</td>
<td></td>
</tr>
</tbody>
</table>


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Summary

• Neurotransmission through the various serotonin receptors may have a wide range of molecular and behavioral effects.

• Antidepressant effects may be mediated by agonism of 5HT1A, 5HT2C, 5HT4, and 5HT6 receptors or by antagonism at 5HT1B/D, 5HT2A, 5HT2C, 5HT3, 5HT6, and 5HT7 receptors.

• Pro-cognitive effects may be mediated by agonism of 5HT2C, 5HT4, and 5HT6 receptors or by antagonism at 5HT1A, 5HT1B/D, 5HT3, and 5HT6 receptors.

• Anti-drug-induced EPS may be mediated by agonism of 5HT1A receptors or antagonism at 5HT2A, 5HT2C, 5HT3, and 5HT6 receptors.

• Employing treatment strategies that target a variety of serotonin receptors as well as increasing 5HT levels through the inhibition of SERT may provide for optimal clinical outcomes.