A Practical, Clinically Driven Primer on Serotonin Receptors and Targeted Pharmacotherapy

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Outline of Today's Presentation

- History/Discovery of Serotonin
- Role of Serotonin in Brain/Body functioning
- Interplay of Serotonin with other Neurotransmitters
- Serotonin Receptor Pharmacology
- Role of Various Receptors in the Serotonin Family
- Clinical Implications of our Learnings

Discovery of Serotonin:
An “accidental” discovery in search of a hypertension agent ("Sero" = serum; “Tonin” = vascular tone)


Original vial of Serotonin (still displayed at Cleveland Clinic medical museum)

A Timeline of Important Serotonin Events

- 5-HT “low” in depression (1966)
- Discovery of many 5-HT receptors
- Development of 5-HT antagonists
- Identification/isolation of 5-HT (1948–1953)
- Discovery of 5-HT in brain (1954)
- Development of SSRIs
- 5-HT “low” in suicide (1976)
- Identification of 5-HT genetic polymorphisms
- “Low” 5-HT as vulnerability factor for stress-related disorders (stress-diathesis)

SSRI = selective serotonin reuptake inhibitor.

Reason Why Serotonin Matters:
Serotonin is intimately involved in the regulations of a vast number of human behaviors


Serotonin – A Life Story

Serotonin is a neurotransmitter that plays a vital role in various bodily functions, including mood, sleep, pain, and cognitive processes. Its discovery was accidental, and it has since become a target for targeted pharmacotherapy in treating mental health conditions such as depression. Understanding the role of serotonin in the brain and body is crucial for developing effective treatments for various disorders.
Serotonin – Not Just in Humans: 5-HT is a “highly conserved” neurotransmitter and Found in Multiple Places in Nature


Fungus

Plants

Fish species

Nuts / Seeds

Brain–Body distribution in humans

Serotonin in the Human Body, Where Does It Come From?

GI = gastrointestinal.


90% of Human Serotonin, in the GI tract, the Enterochromaffin cells are distributed widely in the epithelium of the stomach, small intestine, and colon

5% of Human Serotonin comes from Myenteric Neurons, which are distributed in the muscle lining of the GI track

5% of Human Serotonin from the Brain – specifically the Dorsal Raphe, which then projects upwards to the cortex, and downwards, to the cerebellum and spinal cord

Serotonin: Its Role in Human Emotion and Behavior

Regulating Sleep-Wake Cycle Regulation

Mood Regulation

Cognition / Memory / Learning

Inflammation / Immune Regulation

Serotonin

Regulating Insulin Secretion and Metabolism

Agrgression / Dominance Modulation


Serotonin: Its Critical Role Even Prior to Birth

The brain of the fetus receives Serotonin also from the placenta of the mother. The contribution of these maternal–placental–fetal interactions appears to be critical for brain circuit wiring and for long-term brain functions


Together with its function as neurotransmitter, 5-HT regulates neurite outgrowth, dendritic spine shape and density, growth cone motility, and synapse formation during development.

5-HT is synthesized early in embryonic development and its receptors are early expressed

Serotonin and Its Receptors are Involved in Neurogenesis in the Hippocampus

BrdU = Bromodeoxyuridine is commonly used in the detection of proliferating cells in living tissues


Serotonin Appears to be Involved at Nearly Every Stage of Neurodevelopment and Neuropathology

HPA = hypothalamic–pituitary–adrenal.


Altered DNA Methylation Patterns

Altered brain development / brain functioning

Altered Response to Stress, via 1. HPA axis 2. Autonomic System 3. Inflammatory system

Development of Psychopathology

Serotonin Receptor Numbers and Functioning are Altered

HPA = hypothalamic–pituitary–adrenal

BrdU = Bromodeoxyuridine is commonly used in the detection of proliferating cells in living tissues.
Serotonin Pathways – Anatomic Connections with Multiple Regions in the Brain

- Major origin in raphe nuclei of brain stem
- Project to forebrain
- Median raphe nucleus innervates:
  - Cingulate cortex
  - Septal nuclei
  - Hippocampus
- Dorsal raphe nucleus innervates:
  - Substantia nigra
  - Striatum
  - Amygdala
  - Nucleus accumbens
- Ascending pathways are implicated in the regulation of mood, feeding, sleep, and sexual behavior
- Descending projections appear to modulate spinal sensory and motor neurons

Serotonin Also Powerfully Modulates Other Neurotransmitter Systems and Inflammation

The Neural Circuitry of Monoamines is Extensively Interconnected

- Serotonin and Immune Interactions in the Body

Serotonin Modulates and Impacts Glia Functioning – Astrocytes, Microglia, and Oligodendrocytes
A Quick Conversation about Receptor Affinity and Receptor Potency

In other words, let's discuss these 2 concepts:

1. \(K_i\) Values
2. \(IC_{50}\) Values

Exploring the Concept of \(IC_{50}\) and \(K_i\) values

**What is \(IC_{50}\)?**
- This quantitative measure indicates how much of a drug is needed to inhibit a given biological process by half.
- According to the FDA, \(IC_{50}\) represents the concentration of a drug that is required for 50% inhibition in vitro.

**What is \(K_i\) value?**
- \(K_i\) is the binding affinity of the inhibitor. It's also called the Equilibrium Constant.
- Calculation is done as follows:

\[
K_i = \frac{(\text{Conc Ligand}) \times (\text{Conc Receptor})}{(\text{Conc of Ligand Receptor Complex})}
\]


Why is an Understanding of Both Affinity and Potency Important?

So, based on \(K_i\) values – the order of affinity is SERT > 3 > 1 > 7 > 1B > 1D

So, based on \(IC_{50}\) values – the order of potency is SERT > 1B > 1A > 1D > 7

Let's illustrate how these 2 can be different in a single molecule – vortioxetine as an example

<table>
<thead>
<tr>
<th>Target</th>
<th>Function</th>
<th>Human</th>
<th>VOR</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT1a</td>
<td>Arg</td>
<td>3.2</td>
<td>3.2-12.2</td>
<td>4.0</td>
</tr>
<tr>
<td>5-HT1a</td>
<td>Arg</td>
<td>1.9</td>
<td>3.0-10.7</td>
<td>3.0</td>
</tr>
<tr>
<td>5-HT1a</td>
<td>Arg</td>
<td>3.0</td>
<td>1.0-10.1</td>
<td>3.0</td>
</tr>
<tr>
<td>5-HT1a</td>
<td>Part agon</td>
<td>3.0</td>
<td>1.0-10.1</td>
<td>3.0</td>
</tr>
<tr>
<td>5-HT1a</td>
<td>Agon</td>
<td>1.0</td>
<td>1.0-10.1</td>
<td>3.0</td>
</tr>
<tr>
<td>Sertraline</td>
<td>5-HT1a</td>
<td>7.0</td>
<td>1.0-10.1</td>
<td>3.0</td>
</tr>
</tbody>
</table>

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Agonism, Partial Agonism, Antagonism and Inverse Agonism – All are Important Concepts for Us Clinicians to Fully Understand

Another Way to Look at Agonism, Antagonism, Inverse Agonism at a Receptor

Serotonin Receptors

A quick primer for the busy, modern clinician
Why We Clinicians Need to Know More about Serotonin and Its Receptor Pharmacology

This enhanced knowledge could diminish side-effect burden

This enhanced knowledge could increase therapeutic benefit

Caution: This is exciting, emerging science where much work still needs to be done

Why We Must be Interested in Receptor Pharmacology of the Serotonin System – Many Tools, Our Medications, Work Through Serotonin Receptors


Serotonin Acts Through Its "Messengers": The 7 Members of Serotonin Receptor Family (5-HT1, 2, 3, 4, 5, 6, 7)

Serotonin Receptors: A Total of 14 Total Family Members

Serotonin Receptors and Their Regional Distribution


LSD = lysergic acid diethylamide; MAOI = monoamine oxidase inhibitor.


5-HT<sub>1A</sub> – Why It Matters and How 5-HT<sub>1A</sub> Agonists / Partial Agonists Can Augment Antidepressant Effect

Normal Serotonergic Neurotransmission

SSRI/SNRI Effects on Serotonergic Neurotransmission

5-HT<sub>1A</sub> upregulation may lead to tachyphylaxis of antidepressant activity

5-HT<sub>1A</sub> agonists/partial agonists can therefore augment antidepressants

SNRI = serotonin-norepinephrine reuptake inhibitor.


How Atypical Antipsychotics May Putatively Work: The Emerging Role of Serotonin 5-HT<sub>2A</sub> and 5-HT<sub>1A</sub> Receptors in Facilitating an Antidepressant Effect

A

5-HT<sub>1A</sub> and 5-HT<sub>2A</sub> have regulatory role in other neurotransmitter release besides Glutamate.

The others include:
- Acetylcholine
- Dopamine
- GABA
- Histamine

SSRI = serotonin-norepinephrine reuptake inhibitor.


B

5-HT<sub>1A</sub> and 5-HT<sub>2A</sub> are regulatory of serotonin functioning. Chronic SSRI treatment was shown to induce desensitization and reduced expression of 5-HT<sub>1A</sub> autoreceptors, likely contributing to increased serotonergic tone during SSRI exposure.

The 5-HT<sub>1A</sub> receptor is another G<sub>i</sub>-coupled receptor, expressed both as an auto- and hetero-receptor. In contrast to the somato-dendritic 5-HT<sub>1A</sub>R autoreceptor, the 5-HT<sub>1B</sub>R is localized in axon terminals of 5-HT neurons thereby controlling 5-HT release in projection regions.


Serotonin 5-HT<sub>1A</sub> and 5-HT<sub>2A</sub> and Glutaminergic Pyramidal Cells – Critical Importance of Serotonin’s Control and Regulatory Properties

PFC = prefrontal cortex.

Serotonin plays a regularly role in other neurotransmitter release besides Glutamate.

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- Dopamine
- GABA
- Histamine

SSRI = serotonin-norepinephrine reuptake inhibitor.


5-HT<sub>1A</sub> and 5-HT<sub>1B</sub> receptors are key players and exert opposite effects on the activity of pyramidal neurons in the medial prefrontal cortex (mPFC).

5-HT<sub>1A</sub> and 5-HT<sub>1B</sub> are regulatory of serotonin functioning. Chronic SSRI treatment was shown to induce desensitization and reduced expression of 5-HT<sub>1B</sub> autoreceptors, likely contributing to increased serotonergic tone during SSRI exposure.

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Another Serotonin Receptor of Interest – 5-HT<sub>7</sub>

Serotonin 5-HT<sub>7</sub> Functions:
- Cloned for 3 independent laboratories in 1993
- Important in normal embryonic brain development
- Expressed centrally and peripherally
- In the CNS, the receptor is expressed in the diencephalon, forebrain, and in the Purkinje neurons of the cerebellum
- Involved with circadian rhythms, sleep-wake cycle, thermoregulation, nociception, cognition such as learning and memory processes
- Thought to be involved in disorders such as anxiety, depression, epilepsy, impulsivity, migraine, etc

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Many Drugs of Abuse / Misuse (and Some Incredible, Potential Clinical Benefits Too!) Exert Their Effects Through the Serotonergic System – Focus on 5-HT<sub>2A</sub>

A

A
typical Anti

psychotics

Psychadelics/
Hallingonens

An Example of How a Side Effect Could be Diminished by Knowing More about Serotonin Receptor Pharmacology

Serotonin Receptors: Weight Gain and Diabetes Risk

The correlation between receptor occupancies and the risks of adverse reactions (weight gain and morbidity rate of type 2 diabetes mellitus)

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Spearman Rank Correlation</th>
<th>Weight gain (Index I)</th>
<th>Morbidity rate of type 2 diabetes mellitus</th>
</tr>
</thead>
<tbody>
<tr>
<td>α1 Adrenergic</td>
<td></td>
<td>0.50</td>
<td>0.60</td>
</tr>
<tr>
<td>α2 Adrenergic</td>
<td></td>
<td>0.41</td>
<td>0.70</td>
</tr>
<tr>
<td>Dopamine D1</td>
<td></td>
<td>0.14</td>
<td>-0.10</td>
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<tr>
<td>Histamine H1</td>
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<td>0.81</td>
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</tr>
<tr>
<td>Muscarinic ACh</td>
<td></td>
<td>0.83</td>
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<tr>
<td>Serotonin 5-HT1A</td>
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</tr>
<tr>
<td>Serotonin 5-HT2A</td>
<td></td>
<td>0.49</td>
<td>0.70</td>
</tr>
<tr>
<td>Serotonin 5-HT2C</td>
<td></td>
<td>0.63</td>
<td>0.90</td>
</tr>
</tbody>
</table>

Therapeutic Potential of Serotonin Receptor Polymorphism Testing Will It be the Wave of the Future?

- Rs6295C/G SNP in the 5-HT2C gene (HTR1A) has been found to affect the expression and function of HTR1A
- Study examined the possible association of a panel of markers in strong linkage disequilibrium of HTR1A with SSRI/SNRI response in 137 Japanese major depression participants followed for 6 weeks
- A significant association of better response to antidepressant in rs10042486C/C (P < .0001), rs6295G/G (P < .0001), and rs1364043T/T (P = .018) genotype carriers, independently from clinical variables

Another Example of Emerging Pharmacogenetics with Serotonin Receptors Focus on 5-HT2A Receptor Polymorphism

- Findings from a 225-patient, decade-long study from the European Group for the study of Resistant Depression
- When 12 SNPs from 5-HT2A, COMT, PPP3CC, and BDNF are combined with 8 clinical variables, this correctly predicted 25% of responders

Summarizing Thoughts on Serotonin Receptor Polymorphism

- This is an emerging, not settled scientific area of investigation
- Individual SNPs have low effect
- But, when using multiple SNPs, and using interactive models, statistically significant predictive models are emerging
- Stay tuned! Cautious optimism is warranted
Serotonin Receptors – Location and Function: Both are Important Elements of Important Clinical Knowledge

Members of the 5-HT family display distinct brain and tissue distributions. The 5-HT2A receptor is enriched in pyramidal neurons in layer V of the cerebral cortex, where it mediates the actions of pimavanserin and other atypical antipsychotic drugs. The 5-HT2B receptor is enriched in interstitial cells of the heart valves, where it mediates the vasoconstrictive actions of certain drugs like fenfluramine. The 5-HT2C receptor is enriched in the hypothalamus, among other areas, particularly in nuclei engaged in regulating feeding behavior, hence it’s a target for lorcaserin.

"Targeted", Selective Serotonin Receptor-Based Drug Development 2 Recent, FDA Approved Examples

1. **Lorcaserin**
   - FDA indication: Weight Loss
   - Mechanism of action: 5-HT2C Agonist

2. **Pimavanserin**
   - FDA indication: Psychosis in Parkinson’s disease
   - Mechanism of action: 5-HT2A antagonist (no dopamine effects)

FDA Labels are Evolving, and Have More Receptor Binding Profile Information

US Food and Drug Administration. www.accessdata.fda.gov/scripts/cder/drugsatfda/

In Conclusion

So, what are we clinicians to take home from our enhanced knowledge base on Serotonin and its receptors?

**Conclusion: Part 1 of 3**

- Serotonin has evolved with us humans over a millennia and play a hugely diverse role in mind–body functioning
- We humans, as early as in utero as fetuses, need optimized Serotonin functioning
- Mental health and mental illnesses are intricately tied with serotonin and its receptors’ functioning (or dysfunction)

**Conclusion: Part 2 of 3**

- Drug development is showing a trend towards selective targeting of serotonin receptors, with the goal to improve efficacy and decrease side effects
- FDA labels increasingly point our serotonin receptor profiles in the package inserts (section 12.2 – "Pharmacodynamics")
Conclusion: Part 3 of 3

- Pharmacogenetics are increasingly (though not yet conclusively) pointing to the importance of serotonin receptor genetic polymorphism as part of a reason for medication response (or lack thereof).

- We clinicians can increasingly use our enhanced knowledge base to offer treatments that are geared towards increasing our clinical output (a balance between safety/tolerability and efficacy).