Brain Plasticity: The Effects of Antidepressants on Major Depression

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Scope of Lecture

• Can the neurobiology of major depression explain why certain medications are antidepressants?
• Targets of antidepressants may help identify new faster acting and more effective treatments.
Pharmacotherapy for Major Depressive Episode

- **MDD**: SSRIs, NERIs, SNRIs, NGAs, MAOIs, lithium or ketamine.
- **Bipolar disorders**: lithium, anticonvulsants, NGAs.
- These subtypes of medication are based on their first identified disease target.
- How do their pharmacological targets fit with the known neurobiology of major depressive episodes?

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Neurobiology of Major Depressive Episodes: six pathways

1. High 5-HT$_{1A}$ autoreceptors > low firing > serotonin release > low activity > loss of trophic effect
2. Low CSF MHPG = low noradrenergic activity
3. Low GABA = low GABAergic activity
4. High glutamate > neurotoxicity
5. High HPA axis activity > neurotoxicity
6. Low omega 3/6 PUFA ratio, stress > neuroinflammation and altered brain activity / neurotoxicity

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CSF 5-HIAA: an index of brain serotonin system trait activity

- Low CSF 5-HIAA in mood disorders.
- Low CSF 5-HIAA reflects less serotonin release.
- Low serotonin release can be result of fewer serotonin neurons or less serotonin in each neuron or less serotonin neuron firing and release.

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Serotonin Neurons and Serotonin Content

- Postmortem studies of MDD suicides:
  - More serotonin neurons
  - More tryptophan hydroxylase per neuron
  - More serotonin in neurons.

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Imaging the Serotonin Synapse

Transporter

Less Transporter = less serotonin activity

Serotonin

5-HT₁₅A Autoreceptor

5-HT₂₅A Receptor

5-HT₁₅A Receptor
Mouse Phenotype of High and Low 5-HT$_{1A}$ Autoreceptors

Figure 3. Increased Spontaneous Neuronal Activity in the Dorsal Raphe of 1A-Low Mice

Richardson-Jones et al Neuron, 2009
High (gray) and Low \(5\text{-HT}_{1A}\) Autoreceptors and “Depression” Behavioral Phenotype in Mice

Forced Swim Test

Tail Suspension Repeat Test
Depressed Suicides have more 5-HT$_{1A}$ Autoreceptor Binding in Rostral DRN

![Graph showing binding levels across different DRN rostrocaudal levels.]

5-HT1A Receptor Binding Imaged by PET

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Elevated 5-HT1A Binding in Not-Recently Medicated Depressed MDD

Higher 5-HT$_{1A}$ Binding in Unmedicated Depressed Bipolar Disorder

Sullivan et al. Biol Psychiatry 2009
Summary

• Depressive episodes as part of MDD or Bipolar Disorder are characterized by higher $5$-$HT_{1A}$ autoreceptors binding.
5-HT$_{1A}$ receptor binding is elevated in \textit{remitted} unmedicated Major Depressive Disorder

Stats: remitted vs. controls, $p=0.028$. remitted vs. NRM currently depressed, NS.

Miller \textit{et al} NPP 2005
Summary

- Elevated $5$-$\text{HT}_{1A}$ autoreceptor binding is a biological trait in major depressive disorder that is present during and between episodes.
DiMontigny and Blier on the action of SSRIs in rodents

- Studies in rats and mice identify the $5-HT_{1A}$ autoreceptor as the main target of action of SSRIs.
- In rodents the autoreceptor function and number declines over weeks of SSRI administration, steadily increasing neuronal firing and serotonin release.
- Time frame is consistent with appearance of antidepressant benefit from SSRIs.
5-HT$_{1A}$ autoreceptor binding levels and treatment outcome

- Rationale based on MDD studies
- Preliminary findings: naturalistic treatment
- Prospective study: 24 unmedicated subjects with MDD
- Baseline PET scanning with $[^{11}\text{C}]$WAY-100635 to quantify 5-HT$_{1A}$ receptor
- 8 weeks of standardized pharmacotherapy with escitalopram
- Remission status assessed at 8 weeks
## Study Sample

<table>
<thead>
<tr>
<th>Variable</th>
<th>Remitters (n=11)</th>
<th>Non-remitters (n=13)</th>
<th>R vs N (p-value)</th>
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<tbody>
<tr>
<td>Age</td>
<td>34.7 ± 14.0</td>
<td>35.2 ± 13.3</td>
<td>0.92</td>
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<tr>
<td>HAM Depression</td>
<td>24.6 ± 6.2</td>
<td>24.6 ± 4.7</td>
<td>0.99</td>
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<td>Beck Depression</td>
<td>23.3 ± 10.53</td>
<td>27.1 ± 10.2</td>
<td>0.42</td>
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<td>Lifetime Aggression</td>
<td>14.7 ± 3.1 (n=6)</td>
<td>16.5 ± 3.4 (n=6)</td>
<td>0.36</td>
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<tr>
<td>Suicide Attempters</td>
<td>1 (9.1%)</td>
<td>5 (38.5%)</td>
<td>0.17</td>
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Remission rate = 45.8%

Baseline anxiety severity correlated with treatment outcome at a trend level (p=0.08)
Effect of SSRI Antidepressants on Autoreceptors

19 MDD patients had an 18% decrease in autoreceptors and 52% decrease in HAMD-24 after SSRIs for 7 weeks: Gray et al BP 2013
Dranovsky and Hen, 2006:
Stress in mice > fewer cells and smaller cells in hippocampus
Antidepressants > more and bigger cells
More Time in a Major Depression Produces Smaller Hippocampus

FIG. 3. Correlation between left hippocampal gray matter volumes and total days of major depression.
Why is the Brain Smaller In Major Depression?

- Loss of neurons.
- Fewer synapses.
- Other potential causes include loss of glia and vascular tissue.
Antidepressants Appear to Correct Dentate Gyrus Volume Deficit in Depression

Borldrini et al 2012 BP
Fewer **Mature** Neuronal Granule Cells (NeuN-IR) in Dentate Gyrus in Untreated MDD Suicides.

SSRI-Treated MDD Are Same as Controls

Boldrini *et al* 2012 BP
Serotonin (SSRIs) and More Neuronal Progenitor Cells in Dentate Gyrus in Major Depression

C MDD MDD*SSRI MDD*TCA

<table>
<thead>
<tr>
<th>DG NPC Number</th>
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<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>2000</td>
</tr>
<tr>
<td>4000</td>
</tr>
<tr>
<td>6000</td>
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pes

*p = 0.042

Mid-Body

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*p = 0.036

Boldrini et al 2012 BP
Dentate Gyrus Granule Neurons $5\text{-HT}_{1A}$ Receptors Are Needed For Antidepressant and Neurogenic Effects of Fluoxetine in Mice

Samuels et al
Nature neuroscience 2016

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$5$-HT$_{1A}$ Binding is Proportional to Gray Matter volume
2. GABA and Glutamate Systems
GABA Function Deficit and Major Depression or Suicidal Behavior

• Fewer GABA neurons postmortem in bipolar disorder and possibly MDD
• Less GABA on spectroscopy in occipital cortex in MDD.
• Lower CSF GABA level related to severity of anxiety in MDD.

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Less GABA May Be Due to Fewer GABA Neurons: what causes neuron loss?

- Lack of trophic effects via serotonin and 5-HT$_{1A}$ receptors and BDNF.
- **Glutamate toxic via NMDAR.**
- Glucocorticoid excess is toxic.
- Other factors affecting neurogenesis.

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GABA as a Therapeutic Target in Mood Disorders

- Most antiepileptic drugs (AEDs) raise seizure threshold by increasing GABA transmission.
- ECT raises seizure threshold and is antidepressant.
- AEDs are mood stabilizers and some may be antidepressant.
- Ketamine increases GABA level in anterior cingulate cortex.

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Glutamate in Major Depression

• Brain studies suggest excessive glutamate in MDD.
• Some glutamate is good and cause long term potentiation which is fundamental to memory formation.
• Too much glutamate is potential toxic.
• Ketamine, a fast acting antidepressant enhances glutamate level raising questions about how it works?

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Glutamate Toxicity

- Glial cells remove glutamate from synapses.
- A loss of glial cells is reported in cortex in MDD.
- Impaired uptake of glutamate by glia > toxicity and neuron loss via NMDA receptors in MDD.
- Can glutamate NMDAR signaling be a target of antidepressant action? It can be better thought of as a place to block toxicity.

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Glutamate Levels, Glt1, Ceftriaxone and ABP688 mGluR5 Binding in Rats

Zimmer et al 2015 JCBFM
Lower mGluR5 Binding in MDD Suggests Excessive Glutamate and NMDA toxicity

Figure 1.
Average Volume of Distribution ($V_T$) across healthy control ($n = 13$, black) and depressed ($n = 14$, white) subjects. All individual regional differences were significant in post hoc analysis. Error bars represent standard deviation across subjects.
Patients were scanned while receiving IV ketamine

Pre-ketamine phase:
- T1, T2, anatomical localizers, placement of MRS voxel, pre-ketamine MRS

5 x 13 min MRS acquisition

Psychometrics at 230 min

Post-ketamine psychometrics

Infusion of Ketamine 40 min

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Methods

[A] axial and [B] sagittal images showing ACC voxel size and location.

[C] PRESS $^1$H MR spectra with the editing rf pulse [a] off and [b] on. Note that with the editing pulse off, a standard PRESS spectrum is obtained, which yields high quality spectra for NAA, tCr and tCho in the ACC.

[D] The difference of the spectra in [C] showing (a) the detected GABA and Glx peaks, with (b-d) best-fit model curves and residuals, which yield the areas under the peaks and concentrations. The data were acquired in 13 min from a 2.5 x 2.5 x 3.0 cm$^3$ voxel using TE/TR 68/1500 ms, and 256 interleaved excitations (total 512) with editing pulse on or off.

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Pre-clinical and Clinical Studies of Ketamine’s Antidepressant Mechanism of Action

- Pre-clinical studies have shown that ketamine causes transient increases in glutamate and GABA in mPFC (Moghaddam et al., 1997; Chowdhury et al., 2012).
- We have shown that in humans, ketamine induces rapid increases in Glx and GABA.*

* Milak et al. (2016, *Molecular Psychiatry*)
Kantrowitz et al.* report Glx and GABA increases in mPFC of healthy controls following D-cycloserine administration. Significant group increases relative to pre-ketamine baseline levels for Glx are observed (** $p < 0.01$; * $p < 0.05$).

This effect is not limited to ketamine but may extend to other NMDA receptor antagonists.


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# Demographic and Clinical Characteristics of Study Population

| Dose Group | n  | Sex (F | %) | Age       | Baseline HDRS-24 Total Score | Baseline BDI Total Score |
|------------|----|-------|-----------|-----------------------------|--------------------------|
| 0.0        | 5  | 2     | 40%       | 46.8 ± 12.3                 | 25.6 ± 3.5               | 23.0 ± 6.6               |
| 0.1        | 5  | 4     | 80%       | 37.4 ± 12.3                 | 26.6 ± 7.0               | 25.7 ± 9.5               |
| 0.2        | 6  | 5     | 83%       | 37.8 ± 8.2                  | 24.8 ± 4.4               | 26.6 ± 11.4              |
| 0.3        | 8  | 4     | 50%       | 38.1 ± 7.1                  | 27.5 ± 7.7               | 27.3 ± 7.8               |
| 0.4        | 5  | 3     | 60%       | 30.6 ± 9.4                  | 29.0 ± 5.3               | 27.0 ± 5.5               |
| 0.5        | 9  | 5     | 55%       | 40.2 ± 14.5                 | 28.1 ± 4.9               | 30.1 ± 10.5              |

N = 38
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*Milak et al. (2016, *Molecular Psychiatry*)
FINDINGS

- Ketamine induces a dose-dependent reduction in depression severity in MDD.

- This antidepressant effect is mediated, by a ketamine induced dose dependent increase in glutamate.

- Our data is consistent with the hypothesis that in humans ketamine's antidepressant effect is delivered by an AMPA receptor dependent activation of the neurotrophin and mTOR signaling pathways.
Ketamine Effects Lowers mGluR Binding in Healthy Subjects and MDD Suggesting Glutamate Surge
Ketamine and Depression

- Rapid and robust improvement in depression and SI.
- Benefit does not begin to decline for about a week.
- Partial benefit can persist for weeks.
- Works in medication-resistant depression.

Ketamine → Blocks NMDA receptors

Activates AMPA receptors

Redirects glutamate from toxicity (NMDA) to making more synapses (AMPA)

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Ketamine and Stress-Related Depression in Rats

• Ketamine (20 mg/kg) reversed the chronic unpredictable stress–induced depression-like behaviors in the FST.
• Repeated ketamine exposure resulted in anxiolytic- and antidepressant-like responses 2 months after drug exposure.
• None of the ketamine doses used were capable of inducing drug-seeking behaviors as measured by place preference conditioning.
Summary

• Depression pathogenesis involves impaired serotonin release due to autoreceptor over-expression.
• This chronic lack of serotonin release can lead to brain atrophy.
• Antidepressants can potentially correct autoreceptor over-expression and produce a serotonin-mediated trophic effect on the brain.
• Ketamine switches excessive glutamate transmission from NMDA receptors (toxic) to AMPA receptors (more synapses).
• This trophic effect may be antidepressant.

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