Neurobiological Perspective of Suicide

Yogesh Dwivedi, Ph.D.
Elisabeth Ridgely Shook Endowed Chair and Professor
Director, Translational Research
Department of Psychiatry and Behavioral Neurobiology
UAB
Magnitude of the Problem

- 30,000 deaths per year due to suicide in the US
- One million suicides per year worldwide
- 10-20 times more suicide attempts
Population at Risk

- Suicide is the 3rd leading cause of death among youth between 15-24 years of age in the US.
- Within the adolescent group, younger adolescents who complete suicide show lower suicidal intent than the older ones.
- 75 years of age and older have the highest suicide rate among all age groups.
Suicidal Behavior

- Stress plays an important role in suicide but suicide is not a normal response to stress.
- But, it is a complication of psychiatric illness in the vulnerable person.
## Relationship to Psychiatric Illnesses

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Co-Morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unipolar Depression</strong></td>
<td>More than half of depressed patients have thought of suicide; mortality rate is about 15%</td>
</tr>
<tr>
<td><strong>Bipolar Disorder</strong></td>
<td>Accounts for 15-20% of all completed suicides</td>
</tr>
<tr>
<td><strong>Schizophrenia</strong></td>
<td>Accounts for 10-15 % of all completed suicides</td>
</tr>
<tr>
<td><strong>Anxiety Disorder</strong></td>
<td>Co-morbid with depression, bipolar or drug abuse</td>
</tr>
<tr>
<td><strong>Panic Disorder</strong></td>
<td>20% of suicide deaths are due to panic attack</td>
</tr>
<tr>
<td><strong>PTSD</strong></td>
<td>Strongest association with suicidality</td>
</tr>
<tr>
<td><strong>Personality Disorder</strong></td>
<td>4-8% suicidal individual have personality disorder</td>
</tr>
<tr>
<td><strong>Alcohol/drug abuse</strong></td>
<td>7-25% of completed suicide are associated with drug abuse</td>
</tr>
</tbody>
</table>
Most patients with psychiatric disorders do not attempt suicide

What determines whether a patient will attempt or commit suicide?

What are the vulnerability factors?
Vulnerability Factors in Suicidal Behavior

- **Impulsivity** is related to probability
- **Hopelessness** or pessimism is related to probability
- **Suicidal intent** is related to lethality
- The best clinical clue to the presence of a vulnerability is a **history of a suicide attempt**
- Vulnerability has biological correlates
Regional Cerebral Metabolic Rates of Glucose Uptake (rCMRglu) in Depressed Suicide attempters vs. Non-Attempters

Hypermetabolism in Ventromedial Prefrontal Cortex
Personal and social decision making, emotion

Hypometabolism in Dorsolateral Prefrontal Cortex
Risky and moral decision making, working memory

Sublette et al., Arch Suicide Res, 17:434-47, 2013
Neurotransmitters in Depression and Suicide

- Normal functioning
- Decrease in neurotransmitters
- Receptor upregulation due to lack of neurotransmitters

Neuron

Synapse

Neuron

Serotonin
Norepinephrine
Receptor
Cerebrospinal Fluid 5-HIAA and Suicide

- Lower 5HIAA in attempters vs. non-attempters
- Lower 5HIAA in violent vs. non-violent attempters
- Only high-planed attempters had lower 5HIAA
- Lower 5HIAA in lethal vs. non-lethal attempters
- Low CSF 5-HIAA group had more attempters

Lower 5HIAA can predict future suicide
### Platelet 5HT$_{2A}$ Receptors in Normal Control, Suicidal and Non-Suicidal Bipolar and Schizoaffective Patients

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Total Bipolar</th>
<th>Suicidal Bipolar</th>
<th>Non-suicidal Bipolar</th>
<th>Total Schizoaffective</th>
<th>Suicidal SA</th>
<th>Non-suicidal SA</th>
<th>Total Suicidal Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>$B_{\text{max}}$ (fmol/mg protein)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>120</td>
<td></td>
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<td></td>
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</tr>
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</table>

*Significant differences compared to control group.*
Serotonin (5-HT)$_{2A}$ Receptors and Suicidal Behavior

TABLE 1. Platelet 5-HT$_{2A}$ Receptors in Suicidal and Nonsuicidal Patients and Normal Comparison Subjects

<table>
<thead>
<tr>
<th>Diagnostic Group</th>
<th>N</th>
<th>Male</th>
<th>Female</th>
<th>Age (years)</th>
<th>$B_{\text{max}}$ (fmol/mg protein)</th>
<th>$K_{D}$ (nmol)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>Mean SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Suicidal patients</td>
<td>42</td>
<td>24</td>
<td>18</td>
<td>35 11.6</td>
<td>71.8 29.2</td>
<td>1.8</td>
</tr>
<tr>
<td>Unipolar depression</td>
<td>23</td>
<td>15</td>
<td>8</td>
<td>36 11.9</td>
<td>69.0 28.7</td>
<td>1.9</td>
</tr>
<tr>
<td>Bipolar illness</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td>41 13.8</td>
<td>78.9 23.9</td>
<td>1.5</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>32 8.7</td>
<td>58.8 15.6</td>
<td>1.9</td>
</tr>
<tr>
<td>Schizoaffective disorder</td>
<td>9</td>
<td>4</td>
<td>5</td>
<td>29 9.9</td>
<td>82.2 37.2</td>
<td>1.9</td>
</tr>
<tr>
<td>Nonsuicidal patients</td>
<td>89</td>
<td>47</td>
<td>42</td>
<td>31 9.4</td>
<td>54.8 21.6</td>
<td>1.7</td>
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<tr>
<td>Normal comparison subjects</td>
<td>40</td>
<td>13</td>
<td>27</td>
<td>34 8.8</td>
<td>44.2 19.6</td>
<td>1.7</td>
</tr>
</tbody>
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*Significantly different from nonsuicidal patients and normal comparison subjects by one-way ANOVA ($F=14.57$, df=$2, 168$, $p<0.001$).

Rate of predictability = 77%
Higher $5$-HT$_{2A}$ Receptor Level in Postmortem Brain of Suicide Victims

A
Molecular Weight (kDa)
- 506
- 396
- 344
- 298
- 220

B
5-HT$_{2A}$ Receptors

$\beta$-Actin

Normal Subjects                 Suicide Victims

56 kDa                         46 kDa
Serotonergic Activity is Related to Aggression, Impulsivity, and Suicidal Behavior

- Low serotonin is proportional to seriousness of aggression and can predict future aggression
- Low serotonin function modulates the intent and impulsive aspects of the suicidal behavior predisposition
• Inescapable restraint in rats depletes norepinephrine and can generate despair and giving up
• Suicide victims have evidence of marked stress responses in the brain norepinephrine system
A Model of Suicidal Behavior

Objective state

- Depression/psychosis + Life events

Subjective state and traits

- Hopelessness
- Suicidal ideation

Low serotonin activity

- Alcoholism, smoking, substance abuse

Impulsivity/restraint

- Suicidal planning

- Low norepinephrine

Suicidal act

Aggression

Adapted from Mann et al., 2011
Adoption studies show a 6- to 15-fold increased risk

Twin studies show that 55% of the variance in suicidal behavior can be explained by genetic factors

Family studies show a 4- to 10-fold increased risk for suicidal behavior in first-degree relatives
Candidate Genes
From the Serotonin System in Suicide

- Serotonin transporter
- Tryptophan hydroxylase

- 5-HT$_{1A}$, 5-HT$_{1B}$ and 5-HT$_{2A}$

Results are promising but preliminary

Adapted from Mann et al., 2011
Childhood Abuse and Suicide

- Parental abuse is associated with suicide attempts in adulthood.
- Childhood abuse may affect suicidal behavior in adulthood due to impulsivity (less serotonin).
- Maternal deprivation in monkeys resets serotonin system function downwards; deficiency persists into adulthood and is associated with more impulsive, aggressive behavior in adulthood.
- Childhood abuse causes epigenetic modifications in brain.
Life Events and Suicide

- Life events are more common in patients with mood disorders compared to healthy individuals.
- Suicide attempters are more hopeless and perceive fewer reasons for living.
Childhood adverse experience

Life events

Excessive NE release

Depression

Pessimism

Serotonin Genetics

Adapted from Mann et al., 2011
Life events
Childhood adverse experience
Serotonin Genetics
Excessive NE release
NE depletion
Lower serotonin
Impulsiveness
Depression
Pessimism
Suicide
Adapted from Mann et al., 2011
Stress Causes Activation of Hypothalamic-Pituitary-Adrenal (HPA) Axis

Stress (Physical, psychological or environmental) activates the Hypothalamus, which releases CRH (Corticotropin-Releasing Hormone). CRH stimulates the Pituitary Gland to produce ACTH (Adrenocorticotropic Hormone), which in turn stimulates the Adrenal Glands to release Cortisol. The hypothalamus responds to levels of cortisol; if cortisol is high and decreases CRH production, if cortisol is low, it increases CRH production.
Strong Relationship Between Hyperactive HPA Axis Attempted and Completed Suicide

- Increased urinary 17-hydroxy corticosterone
- Enlarged adrenal gland
- Increased corticotrophin releasing factor in CSF
- Less CRF binding sites in frontal cortex
- Higher non-suppression of cortisol after dexamethasone administration
Chronic Unpredictable Stress Decreases Brain-Derived Neurotrophic Factor (BDNF) Levels in Rat Brain

- Frontal Cortex
  - Control: Low BDNF Expression
  - Stress: Lower BDNF Expression

- Hippocampus
  - Control: High BDNF Expression
  - Stress: Lower BDNF Expression

- CORT level
  - Graph showing a negative correlation between CORT level and BDNF expression.
Protein Levels of BDNF in PFC and Hippocampus of Suicide Subjects

PFC

Hippocampus

Dwivedi et al., Arch. Gen Psychiatry, 2003
Relationship Between Plasma Paroxetine and BDNF Levels in Depressed Patients

Paroxetine (ng/ml) vs. Change in BDNF (pg/ml)

1 week:
- Paroxetine (ng/ml)
- Change in BDNF (pg/ml)

2 weeks:
- Paroxetine (ng/ml)
- Change in BDNF (pg/ml)

6 weeks:
- Paroxetine (ng/ml)
- Change in BDNF (pg/ml)

Graphs show the correlation between Paroxetine levels and BDNF levels over 1, 2, and 6 weeks. The correlation coefficients and p-values are indicated for each time point.
"The Central Dogma"
Flow of genetic information in a cell

- **Promoter region**
  - binding site before beginning of gene
  - TATA box binding site
  - binding site for RNA polymerase & transcription factors

- **Enhancer region**
  - binding site far upstream of gene
miRNAs play an important role in regulating expression of specific genes post-transcriptionally.

There are about 1300 brain expressed miRNAs.

Only partial sequence complementarity is required for translational repression.

One miRNA can potentially regulate hundreds of genes or one gene can be regulated by multiple miRNAs.

miRNAs can regulate entire gene circuitry and can induce disease phenotype.
Plot of Mean vs. Standard Deviation for Normal Control and MDD Suicide Groups
A Network of microRNAs Showed no Correlation in Healthy Group But Exhibited a Positive Correlation in the Depressed Group

A set of 29 miRNAs formed a very extensive inter-connected network in the depressed group. Several of the miRNAs (let-7b, mir-132, 181b, 338-3p, 486-5p, and 650) were “hubs” correlated with 4 to 9 other miRNAs in the network.

Smalheiser et al., PlosOne, 2012
Suicide Brain Show Changes in a Distinct Set of miRNAs

Suicide-associated miRNAs
- hsa-miR-152, hsa-miR-181a, hsa-miR-330-3p, hsa-miR-34a, hsa-miR-224, hsa-miR-133b, hsa-miR-376a, hsa-miR-625
Can miRNAs be Developed as Biomarker for Disease Pathogenesis?

- Plasma
- Serum
- Saliva
- CSF
- Exosomes
miRNA 134 in Plasma of Bipolar Patients at Base-line and After Treatment

Rong et al., J. Psychiatry Res, 2010
Conclusion

- Altered serotonin/norepinephrine functions are associated with vulnerability factors in suicide
- BDNF is partially responsible for altered brain structure in suicidal patients and can serve as biological marker
- miRNAs participate in the alterations of gene expression networks that underlie the normal response to aberrant suicide phenotype
Prevention

- Prevention starts with recognition of psychiatric illnesses and then recognition of individual patients at higher risk.
- Patients at higher risk have a predisposition (vulnerability factors).
- Biological identification and reduction of the predisposition will reduce risk.
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