

The Neurobiology of Suicidal Behavior

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Suicidal Behavior

- Is not a normal response to stress.
- It is a complication of psychiatric illness in the vulnerable person.
- The commonest illness associated with suicide or suicide attempts is recurrent unipolar depression.
- Psychiatric illness can and does lead to social crises.
- Social crises can trigger suicide in the context of psychiatric illness.

Suicidal Behavior

- Prevention starts with recognition of psychiatric illnesses associated with the highest risk of suicidal behavior and then recognition of individual patients at higher risk.
- Patients at higher risk have a predisposition.
- Treatment of psychiatric illness will reduce suicide rates.
- Reduction of the predisposition will reduce risk.

Magnitude of the Problem

- One million suicides per year world wide
- 10-20 times more suicide attempts
- 3rd leading cause of death in 15-34 year olds in the USA
- Leading cause of death in youth in China, Sweden, Australia and New Zealand
- 286,000 suicides per yr in China, leading cause of death in 15-34 year olds.

Demographics

- Women make more attempts than men.
- Men commit suicide at 4 times the rate of women in the USA.
- Young people make more attempts than older folks.
- Older people make more lethal suicide attempts.

Relationship to Psychiatric Illness

- Psychological autopsies in completed suicides confirm that over 90% have a diagnosable psychiatric illness.
- Life-time mortality due to suicide in previously hospitalized patients are high: unipolar depression (15%); bipolar disorder (15-20%); alcoholics (18%); schizophrenics (10-15%); and borderline and antisocial personality disorders (5-10%).
- Comorbidity increases risk.

Vulnerability or Diathesis for Suicidal Behavior

- Most patients with psychiatric disorders including mood disorders do not attempt suicide.
- What determines whether a patient with major depression will attempt or complete suicide?
- At risk patients have a vulnerability or predisposition to suicidal behavior under circumstances of a psychiatric illness.
- What is this vulnerability or diathesis?

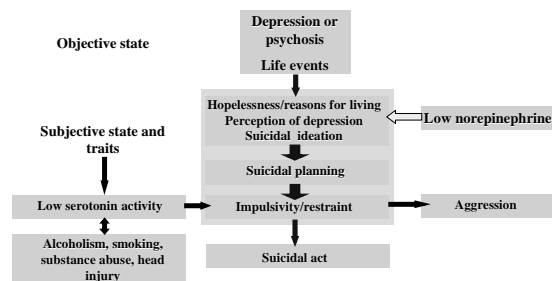
Vulnerability or Diathesis for Suicidal Behavior

- Impulsivity related to probability.
- Hopelessness or pessimism related to probability.
- Suicidal intent related to lethality.
- Diathesis is transmitted in families and has biological correlates.

A Stress Diathesis Model

- Stressors include an acute psychiatric illness such as a major depressive episode or psychosocial crisis.
- The stressor is not enough. There must be a diathesis or predisposition.
- Components of the diathesis include impulsivity, hopelessness or pessimism and intent.
- The best clinical clue to the presence of a diathesis is a history of a suicide attempt.

A Model of Suicidal Behavior



Where Does Neurobiology Fit In?

- Psychiatric illnesses involve brain biology.
- The diathesis or vulnerability to suicidal behavior involves different brain biology.
- Parts of the brain biology related to components of vulnerability such as aggression/impulsivity, suicide intent or hopelessness have been identified.

Serotonergic Activity is Related to Aggression/Impulsivity and Suicidal Behavior

- There is a trait deficiency of serotonin function proportional to seriousness of suicidal acts that predicts future suicide.
- Low serotonin is proportional to seriousness of externally directed aggression and can predict future aggression.
- Low serotonin function modulates the intent and impulsive aspects of the suicidal behavior predisposition.

Norepinephrine Relates to Hopelessness

- Hopelessness predicts future suicide.
- Suicide attempters feel more hopeless and perceive fewer reasons for living than other patients in the face of equivalent psychiatric illness or adverse life events.
- 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.
- Perhaps hopelessness results from NE depletion?

Mapping the Pathobiology of Depression and Suicide

- This approach tells us what parts of the brain is involved in the pathobiology of depression and the predisposition for suicide.
- Postmortem brain receptor maps.
- *In vivo* brain receptor mapping.

Serotonin System Dysfunction: Independent correlations with suicidal behavior and depression

- Deficient serotonergic neurotransmission has been hypothesized as a cause of major depression for 30 years. Depression is a complex disorder and involves many brain regions.
- Deficient serotonergic function is also associated with suicidal behavior. Suicidal behavior involves a basic decision regarding life or death, likely involving a small part of the brain.

Markers of Serotonin Input: Presynaptic markers

- The serotonin transporter is located on serotonin nerve terminals and is an index of serotonin function or input.
- It can be quantified by a radiolabeled SSRI in both post-mortem tissue from deceased patients and more recently in living patients using devices like the PET scanner.

Postmortem Cortical Brain Mapping in Suicide and Depression

- Lower serotonin transporter binding in Major Depression is widespread in PFC.
- Lower serotonin transporter binding in suicide is highly localized to ventro-medial PFC.
- The ventro-medial prefrontal cortex is involved in behavioral and cognitive restraint. Therefore, deficient serotonin input to that brain region could predispose to acting on suicidal or aggressive feelings.

Serotonin Responsivity

Can be assessed by

- Using a PET scanner to study changes in regional brain neuronal activity using glucose uptake to determine the brain regions involved in depression and in suicidal acts.

PET Measures of PFC Activity and Depression or Suicidal Behavior

- Widespread altered activity in the PFC is associated with depression.
- Localized medial PFC hypo-function in suicide attempters is proportional to the medical lethality of the most lethal life-time suicide attempt.
- The activity in this brain region is independent of the objective severity of the depression, but is related to impulsivity and suicidal intent. Thus, it can influence suicidal behavior.

Why are Serotonin Responses Abnormal in that Part of the Brain?

- In depression there are fewer neurons in many areas of the prefrontal cortex, hippocampus and anterior cingulate.
- In suicide there is less serotonin input to each neuron in ventro-medial prefrontal cortex.
- Thus, the function of this area is doubly compromised.

The State of the Serotonin Neurons in the Brainstem

- We counted the serotonin neurons in the brainstem of depressed suicides and controls without a psychiatric illness who did not die by suicide.
- We found no evidence of fewer serotonin neurons, or even smaller average size of the neurons.
- We did find evidence of altered function of serotonin neurons in the depressed suicides.

Less Serotonin Transporter and Gene Expression

- Less SERT binding could be a consequence of less gene expression (cause or regulation).
- Less SERT binding could be a consequence of more SERT internalization due to less intra-synaptic SERT.
- This effect would augment serotonin action.
- Is low SERT and gene expression compensatory or just part of pathogenesis?

Factors Influencing Suicide Diathesis or Predisposition and Serotonin

- Genetics
- Stress
- Sex
- Parenting
- Age

Familial Transmission of Suicidal Behavior

- Genetic factors.
- Non-genetic factors.

Genetics of Suicide

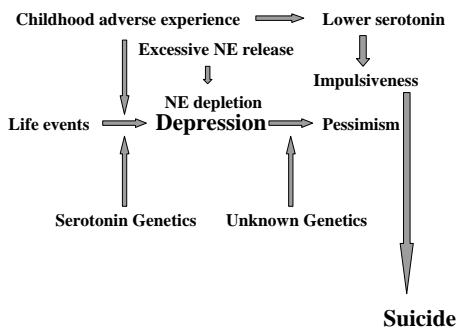
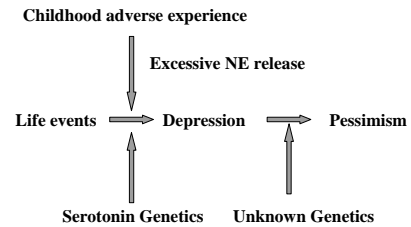
- Adoption studies show a 6- to 15-fold increased risk.
- Twin studies show that 55% of the variance in suicidal behavior can be explained by genetic factors.
- Family studies show a 4- to 10-fold increased risk for suicidal behavior in first-degree relatives.
- Genetic effects on suicide risk are comparable to bipolar disorder and schizophrenia.

Candidate Genes From the Serotonin System in Suicide

- Serotonin transporter.
- Tryptophan hydroxylase.
- Receptors including 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{2A}.
- Results are promising but preliminary.
- Imply cause and mechanism.
- Genome screen to search for more candidate genes.

Life Events or Stress and Suicide

- Life events are more common in patients with mood disorders compared to healthy controls.
- Suicide attempters are more hopeless and perceive fewer reasons for living given an equivalent number of life events compared with psychiatric controls.
- Life events may trigger a suicide attempt in vulnerable individuals. Serotonin transporter gene variant modulates the susceptibility to life events.



Neurobiology of Suicide Looks like a Stress Response

- Stress hormones cortisol and CRF are elevated in blood or CSF of suicide attempters of future suicides.
- Fewer prefrontal CRF receptors in suicide victims suggest excess CRF release.
- Evidence in brain of suicides of more NE release (more tyrosine hydroxylase and beta-adrenergic desensitization).
- Abuse history in childhood associated with excessive adult stress responses in terms of both cortisol and NE.
- Fewer noradrenergic neurons in depressed suicides means lower functional capacity and prone to NE depletion.
- Low norepinephrine may favor more pessimism.

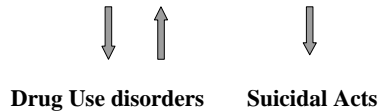
Parenting, Suicide and Psychopathology

- Parental abuse is independently associated with depression, impulsiveness and suicide attempts in adulthood.
- Abuse in childhood may affect suicidal behavior in adulthood due to more trait 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.

Drug Abuse and Suicide

- Alcoholism, drug use disorders and cigarette smoking are all associated with higher suicide rates.
- Low serotonin activity may favor addictive behaviors and independently predispose to suicidal and aggressive acts.
- Some drugs can deplete or lower serotonin further.

Low serotonin function



Summary

- Suicide occurs in the context of depression, stress, hopelessness and suicidal ideation.
- Impaired serotonergic transmission in the ventral prefrontal cortex predisposes some patients to act on suicidal ideation.
- Stress leads to norepinephrine depletion and may explain excessive hopelessness and thereby favor suicidal ideation and suicidal behavior.

The Future

- Better prediction of risk.
- Treat more people with psychiatric illness.
- Develop medication and psychotherapeutic interventions to reduce predisposition to suicidal behavior. Lithium and clozapine are promising anti-suicidal treatments.
- Reduce familial transmission of predisposition to suicidal behavior.