Schizophrenia: Uncovering a molecular origin so humanity may better deal with insanity.
What is Schizophrenia?

• Literally “split mind”
• A mental disorder comprising most major psychotic disorders; characterized by disturbances in form and content of thought, sense of self and relationship to the external world.
• A disease of neural connections within the brain that is expressed clinically as a disease of the mind.
DSM-IV Diagnostic Criteria

A. Characteristic symptoms

B. Two (or more) of the following, present for a significant time:

1. Delusions
2. Hallucinations
3. Disorganized speech
4. Grossly disorganized or catatonic behavior
Criteria (continued)

• 5. Negative symptoms
B. Social/occupational dysfunction
C. Duration: Continuous disturbance for at least 6 months; at least one month of active-phase symptoms
D. Exclusions
E. (mood disorders, substance abuse, etc)
Schizophrenia Subtypes

- Paranoid Type
  A. Preoccupation with one or more delusions or frequent auditory hallucinations
  B. None of the following is prominent: disorganized speech, disorganized or catatonic behavior, or flat/inappropriate effect
Subtypes (continued)

- Catatonic Type
  Dominance by at least two of the following:
  1. Motor immobility
  2. Excessive motor activity
  3. Extreme negativism
  4. Peculiar voluntary movements
Subtypes (continued)

- Disorganized
  - Disorganized speech and behavior, flat or inappropriate affect

Undifferentiated

Residual
Development of Schizophrenia

Etiology
- DNA
- Gene expression
- Viruses
- Toxins
- Nutrition
- Birth injury
- Psychological experience

Pathophysiology
- Neuron formation
- Migration
- Synaptogenesis
- Pruning
- Apoptosis
- Activity-dependent changes

Brain development from conception to early adulthood

Anatomical and functional disruption in neuronal connectivity and communication

Impairment in a fundamental cognitive process

Impairment in one or more second-order cognitive processes
- Attention
- Memory
- Language
- Executive functions
- Emotion

Symptoms of schizophrenia
- Hallucinations
- Delusions
- Negative symptoms
- Disorganized speech
- Disorganized behavior
Genetic Linkage to Schizophrenia

Probability of Developing Schizophrenia in Different Groups
(Gottesman 1991)
Etiology of Schizophrenia

Genetic Links
- Tends to run in families, but non-Mendelian inheritance patterns

Schizophrenia Susceptibility Locus (SSL)
-5q11.2-13.3 Glucocorticoid Receptor (?)
Reports of trisomy in some schizophrenics, but many have no abnormalities here
-22q11-q13
22q(Syn3 gene) Synapsin Protein
Genetic Epidemiology (cont)

- 3q13.3 Dopamine receptor subtype 3 (D3)
- Autoreceptor and postsynaptic receptor.
- Localized to limbic areas of the brain, which are associated with cognitive, emotional, and endocrine functions
- Two fold increase of D3 mRNA on lymphocytes in schizophrenics
- Possible diagnostic test (Ilani et al, 2001)
• Dinucleotide polymorphism at 15q13-q14, the site of the CHRNA7 gene
  ➔ Codes for alpha-7 neuronal nicotinic receptor subunit, the major component of brain nicotinic receptors
  ➔ Sensory input filtering deficiency runs in families with schizophrenics—attentional disturbances—diminished inhibition (Freedman et al, 1997)
Empirical evidence of nicotinic receptor dysfunction

- Comorbidity with nicotine dependence
  - 3 fold increase in smoking
  - Medication issues
Chromosomal variances associated with schizophrenia
Is schizophrenia caused by anatomical abnormalities?

- Subtle neuro-anatomical differences often found, but inconsistent
  - smaller limbic parts of temporal lobe
- MRI & PET scans
- Inappropriate connections formed during fetal development; dormancy until puberty
  - role of sex hormones (?)
Pet scans during memory tasks
Neurotransmitter involvement in schizophrenia

- Acetylcholine
- Norepinephrine
- Dopamine
- Serotonin
Dopaminergic Involvement

• Dopamine theory of schizophrenia
  ➔ Certain areas of the brain do not regulate dopamine correctly and this leads to psychosis

Types of Dopamine Receptors

D1: D1A, D1B

D2 like: D2, D3, D4

➔ D1 and D2 like exert opposite intracellular effects
Classical Antipsychotics Drugs

• Antagonism of D2 receptors (and sometimes D2 and D4) results in lessening of positive symptoms

→ Decrease in confusion and disorganization is greatest. Delusions and hallucinations often persist but are more manageable.

Chlorpromazine (Thorazine)  

\[
\begin{align*}
\text{CH}_2-\text{CH}_2-\text{CH}_2-N-(\text{CH}_3)\text{; Cl} \\
\end{align*}
\]

Molindone (Moban)  

\[
\begin{align*}
\text{HO} - \text{N} - \text{CH}_2 - \text{CH}_2 - \text{CO} - \\
\end{align*}
\]


Alternative Mechanisms Besides Dopamine Receptor Antagonism

Lessons learned from psychedelics and dissociative-anesthetic-psychedelics
Serotonin Involvement

- Psychedelic drugs that may lead to symptoms similar to schizophrenia (e.g. LSD, DMT, psilocybin) are 5HT2 agonists.
- Many atypical antipsychotics are 5HT2 antagonists.
- Advantages over classical antipsychotics:
  - Relieves more negative symptoms
  - Fewer side effects (less cognitive inhibition)
  - Can treat psychotic parkinsonian patients

Background: Quetiapine a novel antipsychotic
Glutamine and NMDA Receptor Involvement

- Dissociative/anesthetic psychedelics like ketamine and PCP are non-competitive N-methyl-D-aspartate-glutamate (NMDA) receptor antagonists
- NMDA receptor hypofunction hypothesis:
  - Lack of NMDA receptor activity leads to an increased output of glutamate and acetylcholine. This leads to damage of cortico neurons

Genetically engineered mice with 95% fewer NMDA receptors showed schizophrenic like behavior (Mohn et al, 1999)
# Pharmacology of Antipsychotics

<table>
<thead>
<tr>
<th>DRUG</th>
<th>CHEMICAL CLASS</th>
<th>RECEPTOR TARGET</th>
<th>SEDATION</th>
<th>INVOLUN. MVMT.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine</td>
<td>Phenothiazine</td>
<td>D1-4; alpha-1; H1; mAch</td>
<td>High</td>
<td>Moderate</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Butyrophenone</td>
<td>D2-D4; alpha-1; H1</td>
<td>Low</td>
<td>Very High</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>Phenothiazine</td>
<td>D1-D4, mACh, alpha-1, H1</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Clozapine</td>
<td>NOVEL</td>
<td>D1-2; 5HT2A; alpha 1,2; H1; ACH</td>
<td>Moderate</td>
<td>Low</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>NOVEL</td>
<td>5HT2a, D2, H1, Alpha-1,2</td>
<td>Moderate to Low</td>
<td>Low</td>
</tr>
</tbody>
</table>
Receptor Blockade and Associated Side Effects

- **D$_2$ receptors**
  - Extrapyrimidal movement disorders, prolactin increase (gynecomastia, menstrual changes, sexual dysfunction)

- **mACh receptors**
  - Blurred vision, dry mouth, constipation, urinary retention, memory dysfunction

- **H$_1$ receptors**
  - Sedation, drowsiness, weight gain

- **5-HT$_{2A}$ receptors**
  - Unknown; appears to be mostly beneficial
**Selected Brain Structures Involved in Antipsychotic Activity**

**Limbic System**
- Related structures that control emotion, motivation, and memory. Contains **amygdala** and **hippocampus**.
- Dopaminergic activity here likely responsible for positive symptoms

**Hypothalamus-Pituitary**
- Many of the older antipsychotic’s adverse effects are due to action here.
- Regulation of prolactin, rewards of everyday activities, temperature regulation

**Reticular formation**
- Located in brain stem; acts as sensory reduction filter
Outlook and Summary

- Intermittent symptoms across lifespan is common in most patients, negative symptoms are more persistent, relapses are frequent but...

Early treatment with antipsychotics, especially the new generation agents, combined with rehabilitation allows a high degree of integration into society

- Schizophrenia does not follow a single metabolic pathway. “Schizophrenia” is a broad term and varying forms based on genetic or behavioral differences will likely be further differentiated

- Biological, psychological, and social factors must be addressed for optimal recovery

2. Aghajanian and Marek; “Serotonin-glutamate Interactions: A New Target for Antipsychotic Drugs,” *Neuropsychopharmacology*


References


