Is schizophrenia a disorder of neurotransmitters?
(If so, why is drug discovery so difficult?)

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Conflicts over the past 3 years

- Consultation: Eli Lilly, Bristol-Meyer-Squibb, Roche, Endo Pharmaceuticals, Genentech, Cypress Bioscience, Dianippon Sumitomo, and Takeda Pharmaceuticals.
- DMC: Otsuka.
- Research funding: Janssen, Pfizer, GSK, PamLab and Novartis.
- Patent applications: Genetic predictors of response to glutamatergic agents and folate.
A brief history

First, there was dopamine

- Excessive activation of D2 (positive symptoms)
- Reciprocal D1 hypofunction (negative symptoms, cognitive impairment)
Evidence: Increased amphetamine-induced dopamine release in schizophrenia subjects predicts antipsychotic response

Laruelle et al, 2003

Abi-Dargham et al, PNACS 2000
Evidence: Reduced prefrontal D1 receptor density in schizophrenia subjects correlates with working memory deficits.
A brief history, continued

• Next, the NMDA hypofunction model

• Ketamine produces positive, negative and cognitive symptoms

• Ketamine also produces characteristic dysregulation of dopamine release
A closed-loop network model implicating D2, NMDA & GABA

Feedback inhibition generates gamma oscillations

Homeostatic loop: reduced GAD and GABA in schizophrenia

Hippocampal disinhibition stimulates dopamine release

Lisman et al, TINS 2008
Are recent failures in drug development due to inadequate models?

- Brain biochemistry is a complex interactive web of neurotransmitters & intracellular pathways
- Redundancy of modulation—“everything is linked to everything else”
- Schizophrenia is a neurodevelopmental illness resulting from a complex interplay between genes and environment.

- How do we construct appropriate models?
Example: A transcriptomic model looking at 1000 post-mortem gene expression connections per module

Roussos et al, Arch Gen Psychiatry 2012
A hierarchical network model based on gene expression modules

Roussos et al, Arch Gen Psychiatry 2012
As network models become increasingly complex:

• Which nodes in these biochemical networks are responsible for the dysregulation observed in an individual patient with schizophrenia?

• Which can be manipulated to improve functioning of networks?
Mathematical models may simplify networks and identify predictors

Barbano et al, PNAS 2007
Can we find points of convergence/divergence between etiologic factors and symptom expression?

Risk Factors
(genomes, environment)

Point of convergence

Biochemical pathways

Point of divergence

Biochemical pathways

Symptoms
(positive, negative, cognitive symptoms)
Schizophrenia risk factors and related treatments

- In utero exposure
  - Infection
  - Starvation (folate?)
- Adolescence/Prodrome
  - Cannabis
  - Stress/cortisol (CBT)
  - Inflammation (fish oil, minocycline)
  - Oxidative stress (NAC)
The neuroinflammation model

Stressful life events (e.g. birth, trauma, infection etc...)

Stimulating agents of microglia (e.g. LPS, IFN-γ etc...)

Resting microglia (ramified type)

Activated microglia

[Cytokines]
- TNF-α
- IL-1β
- IL-6
- etc...

[Free Radicals]
- Nitric Oxide (NO)
- Superoxide (O2·)
- Peroxynitrite (ONOO−)
- etc...

Neuronal cells
Progenitor cells
Oligodendrocytes

Neuronal degeneration, decreased neurogenesis, white matter abnormalities etc...

Pathophysiology of Schizophrenia

Figure 1. Microglia hypothesis of schizophrenia. Immunological/inflammatory activators such as interferon (IFN)–γ and lipopolysaccharide (LPS), which are induced by varieties of stress events and life events, activate microglia in the central nervous system. Activated microglia release pro-inflammatory cytokines and free radicals. These mediators are known to cause neuronal degeneration, white matter abnormalities and decreased neurogenesis. These neuron–microglia interactions may thus be one of the important factors in the pathophysiology of schizophrenia. IL, interleukin; TNF, tumor necrosis factor.
Oxidative stress

Do et al, Current Opinion in Neurobiology 2009
BDNF, IL6 expression & cortisol levels predict left hippocampal volume in first episode schizophrenia

Table 3. Multiple Linear Regression for Left Hippocampal Volume in First-Episode Psychosis Patients

<table>
<thead>
<tr>
<th>Linear Regression Model</th>
<th>Variables Included in Model</th>
<th>Adjusted R²</th>
<th>P Value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>Brain-derived neurotrophic factor expression</td>
<td>0.36</td>
<td>.004</td>
</tr>
<tr>
<td>Second</td>
<td>Brain-derived neurotrophic factor expression, Interleukin-6 expression</td>
<td>0.47</td>
<td>.002</td>
</tr>
<tr>
<td>Third</td>
<td>Brain-derived neurotrophic factor expression, Interleukin-6 expression, Diurnal cortisol levels</td>
<td>0.71</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

<sup>a</sup>Boldface type indicates significance.

Mondelli et al, J Clin Psychiatry 2011
A neurodevelopmental model mimicking *in utero* infection: Postpubertal emergence of enlarged ventricles and reduced hippocampal volume in the offspring of (PolyI:C)-treated dams

Piontkewitz et al, Biol Psychiatry, 2009
A model for preventive drug discovery: Clozapine treatment in adolescence prevents structural brain abnormalities in adult offspring of PolyI:C-treated dams

Piontkewitz et al, Biol Psychiatry, 2009
Stress & inflammatory biomarkers and pathways linked to schizophrenia

Chan et al, Int Rev Neurobiol 2011
Example: Convergence of risk factors; divergence of effects

- Inflammation
- Stress
- BDNF
- AKT
- Cell Survival
- Plasticity
- Neurogenesis
- Dopamine
- Canabinoid
- NMDA NR1 NR2c
- GABA Aβ2
- Dopamine
- NMDA NR1 NR2c
- GABA Aβ2
Summary

- Schizophrenia may reflect a complex neurodevelopmental response to environmental factors
- Biochemical models must reflect complexity of networks
- Ecologically valid animal models which incorporate neurodevelopmental/environmental factors may better predict drug response
Problems ahead:

- How do we determine which biomarkers identify drugable targets that can be used in the clinic (DNA, mRNA, serum, imaging, electrophysiology)?
- Should our strategy differ for prevention in prodrome, halting of progression in first break, & recovery/compensation in chronic illness?
- Are animal models instructive or should they be abandoned (except as assays for toxicity)?