Experimental Medicine and Psychiatry Drug Development

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Four problems

- We don’t know the disorders sufficiently
- The biology is complex and heterogeneous
- We have animal models of mechanisms not psychiatric disorders
- We have limited knowledge of the drug (FIH)
The Experimental Medicine Approach

Pathology:
- Disorder
- Genotype
- Mechanism (Pharmacologic Model)

Biomarker:
- Behavior (Symptom, Cognition)
- Electrophysiology (EEG, ERP)
- Activity (fMRI, NIRS, FDG)
- Chemistry (Ligand binding, MRS)
- Structure (MRI, DTI)
- Process (Neuroplasticity)

Putative Therapeutic Intervention (Drug)
Iterative process of testing specific mechanistic hypotheses testing across levels

MODELS

Cellular, Systems & Behavior Animal Studies

Healthy Human Subjects

Patients
Experimental medicine and drug development

• Go/No Go:
  – Common: Does drug get to brain/target (PET)
  – Rare: Putative efficacy readout

• Add/subtract confidence in development program (esp. Phase II)
  – Proof-of-mechanism/principal
Human Laboratory Studies

• Healthy subject studies (Cheaper, Quicker)
• Short-term exposure (Limited toxicology)
• Human pharmacology studies may be more tractable scientific problems:
  – Reduce heterogeneity of patients
  – Reduce “placebo response” problem
  – Probe specific mechanisms
• “Model pathology” often necessary to see therapeutic effect of drug
Case Study: Glutamate synaptic dysfunction in schizophrenia

Genetics

Synapse/Spine Loss

SPECT Ligand Binding

Neuroplasticity (LTP)

NMDA Receptor Dysfunction
Ketamine: Positive and Negative Sx
Amphetamine: Only positive sx
Combination: No significant interaction

Krystal et al. Arch Gen Psychiatry 2005 (n=41)
What has NOT worked?

• Agents:
  – Lorazepam
  – Haloperidol
  – Olanzapine

• Implication:
  – Not an assay for DA hyperactivity or antipsychotics *per se*
Recurrent Excitation Drives the Maintenance of Information in Working Memory
Reduced PFC Activation and PFC Disinhibition as Downstream Consequence of Glutamate Synaptic Dysfunction in Schizophrenia

Alan Anticevic, Ph.D.
NIH Director’s Early Independence Award
PNAS 2012; Schizophrenia Bulletin 2011

Task-based Activation/Deactivation

Schizophrenia

Human Lab Model (Ketamine)

Computational Model
Hypothesis 1:

- Deficits in NMDA-R function might be treated by NMDA-R function-facilitating treatments
  - Example: Glycine Transporter 1 inhibitors
Does glycine (.3 µg/ml) attenuates ketamine effects on PFC activity during WM encoding in healthy subjects (fMRI)?

Glycine: No effects

Reduces ketamine effect?

Drug X Phase, F(6, 336) = 4.56, p = .0002 (4-target task)
Driesen et al., unpublished; n = 4
ORG25935 Effects on Ketamine-Induced Perceptual Alterations

D’Souza et al. Neuropsychopharm 2011

p=0.0039
Cohen’s d = 0.98
GlyT-1 in negative symptoms of schizophrenia

Significant reduction in negative symptom factor score *

Effect Size (Week 8): 10 mg = 0.37, 30 mg = 0.40

*PP nonulation
Mechanisms implicated in animals not yet tested in this human model

- D1 agonist/PAM
- Alpha7 nAChR agonist/PAM
- mGluR5 agonist/PAM
- AMPAkine
- PDE inhibitors
GABA Neuronal Deficits

Gonzalez-Burgos et al. Curr Psychiatry Rep 2010
NMDA receptor deficits disinhibit glutamate release in PFC and hippocampus promoting chaotic cortical activity

(R. Greene, B. Moghaddam)
Ketamine raises glutamate in anterior cingulate cortex: correlated with induction of psychosis (Stone et al. *Mol Psychiatry* 2012:epub)
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A. Anticevic

XJ Wang
Leading to Therapeutics Based on Treating Disinhibition

Neurostimulation: Low Frequency TMS applied to “hallucination regions (fMRI)

Pharmacotherapy: Lamotrigine (ASL)
Does LY354740 Attenuate the Ketamine Psychosis?

LY354740 Effect: $\chi^2 = 3.22$, df = 1, $p = .07$

Ketamine vs. Pla:
*: $p < .05$
**: $p < .01$

Peak Increase in PANSS Psychosis Factor Score (Ketamine - Placebo) ± SEM

Krystal et al. Psychopharmacology 2005
LY2140023: First Non-D2 Receptor Antagonist Treatment for Schizophrenia?
Why didn’t it replicate? Subgroup hypothesis: Elevated Glutamate and Glutamine in Early Course Schizophrenia

Marsman A et al. Schizophr Bull 2011
## Boundaries of the “Model”

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<td>Symptoms</td>
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<tr>
<td>Cognition</td>
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<td>ERPs</td>
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<td>Disinhibition</td>
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<td>WM-FMRI</td>
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<td>DMN Tuning</td>
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<td>GBC</td>
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What we learned about ketamine

- Model of synaptic or neuroplasticity deficit?
  - Risk of ignoring disinhibitory effects (i.e., will it work for AMPAkinases?)

- Model of disinhibition?
  - Risk of ignoring impact of medications on tuning/synchrony

- Model of schizophrenia?
  - Disinhibitory effects most prominent in early course
What we have learned

- Challenge studies are very useful for asking very specific questions that inform drug development.
- Can drive translation from animal to human to patient (or vice versa).
- Are limited as a foundation for go/no-go decisions because they are probes of mechanisms not a model of diagnosis.
- Are not general probes for treatment mechanism but they specifically inform specific mechanisms.
- Iterative process informs models and improves explanatory power.
Functional connectivity hypothesis

SOM inhibits excitability
SOM inhibit PV neurons

PV generate oscillations
PV inhibit SOM

GABA dysfunction: Ketamine versus schizophrenia

Ketamine: SOM-like pattern

Schizophrenia: SOM+PV

 ↑ Excitability
 ↓ Tuning
 ↑ Synchrony*

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 ↓ Tuning
 ↓ Synchrony*