From Genes to Therapeutics: Nicotinic Receptors and Schizophrenia

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Disclosure

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William Kem has a patent through the University of Florida on the DMXB-A molecule

Robert Freedman, University of Colorado, the sponsor of the FDA IND, has no commercial interest in DMXB-A. Drs. Freedman and Leonard through the VA have a patent on the CHRNA7 promoter.

The clinical use of investigational new drugs is not advocated in this talk and not approved by the FDA.
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Genes to Therapeutics:

A strategy of drug development for schizophrenia

Positive and Negative Symptoms ↓↑ Neurocognitive Dysfunction ↓ Neurobiological Mechanism ↓ Genetic Polymorphism

Clinical Effect Neurocognitive Effect Neurobiological Effect

Molecular Drug Target
Problems in the current treatment of schizophrenia

- Relatively little progress in therapeutic development beyond the dopamine hypothesis

- Partial effects on both positive and negative symptoms and particularly on neurocognitive deficits
Schizophrenics fail to inhibit the neuronal response to repeated sounds.
Inhibitory neurons are the mechanism of sensory gating
Acetylcholine 1 mM
20 μm, 100 msec, 40 pA
Increased hippocampal activity during eye movement in 12 schizophrenics, compared to 12 controls.
$^{125}$I-alpha-bungarotoxin labeling of hippocampal neurons in controls (A,B), reduced in schizophrenics (C,D).
Co-segregation of diminished P50 inhibition (and schizophrenia) with a marker on chromosome 15
The same chromosome 15 locus is linked to sensory gating disturbance, schizophrenia, and *CHRNA7*
A. Figure 1b, from Rare chromosomal deletions and duplications increase risk of schizophrenia, Stone et al., 2008, Nature, July 24, early publication.

B. Figure 1b., from Large recurrent microdeletions associated with schizophrenia, Stefansson et al., 2008, Nature July 24, early publication.

Figure 1. CNV evidence of CHRNA7 deletion in schizophrenia.
Single nucleotide changes in the *CHRNA7* promoter

A. 2602 bp

B. -332 aggccgagag cccgctcggg gtagactggg ggttgaggtg cccggagcgt acccagccg

Pst I

-272 gggatccct cccgctcaca cctcgggtct ggtgcctcttg ggtggcgcgc gcagacgctgg

-212 cccgggtcgg agggatgtgg ggcgggagac gcggaggcgc gcgggtcgcg ttcattaaag gcgcggagc

-152 aggcgcgcgc gggcggggcc gcgggcgcgc tcettaaagg gcgcgcgcgc

-92 gagggcgag gtgcctcttg ggctgagagc gcaggcccgg gcgacatcgc agacgctggag

-32 cgccgctgcct cgcctcagct cccgactca catgcctgtgg ccctggg ttcggg

Exon 1

+29 TGGCGCTGGC CGCGTGCCTC CTGCAGGta aagccac
### Genes to Therapeutics:

**A strategy of drug development for schizophrenia**

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Nicotine mimics the brain’s chemical acetylcholine
Nicotine normalizes P50 inhibitory deficits
Schizophrenics smoke more heavily than any other population
**Acetylcholine** briefly opens the ion channel of the α7 nicotinic receptor and then is removed by acetylcholine esterase.

**Nicotine** also briefly opens the channel, but then remains bound to the receptor and desensitizes it.
Nicotine

3-[(2,4 Dimethoxy) benzylidene]-anabaseine
An initial clinical trial of DMXB-A

- Added to neuroleptic treatment in non-smoking schizophrenics
- Immediate effects expected because of mechanism of action
- Primary outcome is neurocognition, especially attention
- Biological outcome is inhibition of P50 responses
DMXB-A increases P50 inhibition
Effects of DMXB-A on RBANS Performance

![Bar chart showing the effects of DMXB-A on RBANS performance. The chart compares placebo and two dosage levels (75-37.5 mg and 150-75 mg) across different indices: Total, Attention, I-Memory, Visu-Spat, D-Memory, and Language. Significant improvements are indicated by asterisks (*) for the 75-37.5 mg dosage.]
DMXB-A effects on Default mode Activity in Schizophrenia
Next steps

- Sustained release preparation
- Smoking patients
- Alternative agonists
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Caveats

- *CHRNA7* is expressed throughout development
- Other genes are involved in schizophrenia
- Other brain pathways interact with cholinergic inputs to interneurons
Expression of alpha7 nicotinic receptors over the human lifespan

Hippocampus CA1

125I-alpha-bungarotoxin (fmol/mg)
Development of $\alpha7$nAChRs in hippocampus
Acetylcholine 1 mM
20 μm, 100 msec, 40 pA
Effects of perinatal choline in mouse models

DBA/2 mice

Ratio of Test to Conditioning Amplitude

0 0.2 0.4 0.6 0.8 1 1.2 1.4 1.6

Control Choline supplemented

C3H

DBA2/Ibg

Ratio = 0.17

Ratio = 1.14

P20 N40

Conditioning Test

50 msec

-50μV
**Sensory gating in infants.** Top left. Babies in active sleep (REM) have P50 responses to paired stimuli (top middle, positive polarity up). Top right: Test-retest reliability over 10 day intervals is excellent (Hunter 08a).
**Acetylcholine** briefly opens the ion channel of the $\alpha 7$ nicotinic receptor and then is removed by acetylcholine esterase.

**Nicotine** also briefly opens the channel, but then remains bound to the receptor and desensitizes it.
Causes of maternal choline deficiency

- Polymorphism in PEMT, phenylethanolamine transferase—associated with schizophrenia
- Dietary deficiency
- Maternal stress, leading to liver sequestration
- Estimated 25% of women are deficient during pregnancy, an estimated 20% smoke cigarettes
Effects of Perinatal Choline in Mice and Humans

DBA/2 mice

Infants

Ratio of Test to Conditioning Amplitude

0 0.2 0.4 0.6 0.8 1 1.2 1.4 1.6

Control Choline supplemented

0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8

Control Choline supplemented
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