Biomarkers in Schizophrenia

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Disease Process in Schizophrenia

- Pathogenesis
- Pathophysiology
- Clinical Syndrome
- Prevention
- Treatment
- Etiology
- Pathological Entity
Biomarkers in the Context of Disease Process

- Critical features of a biomarker
  - A direct consequence of the disease pathology
  - A proximal mediator of one or more components of the clinical syndrome
  - Measurable in the clinical setting
  - Detectable in the prodromal state
Schizophrenia Affects Multiple Complex Brain Systems as Evidenced by the Range of Clinical Features

- **Positive symptoms:** Delusions, hallucinations, thought disorder
- **Negative symptoms:** Decreased motivation, diminished emotional expression
- **Cognitive deficits:** Impairments in attention, working memory, verbal fluency
- **Sensory abnormalities:** “Gating” disturbances
- **Sensorimotor abnormalities:** Eye tracking disturbances
- **Motor abnormalities:** Posturing, impaired coordination
P50 Evoked Potential as a Biomarker of Impaired Attention

- Fundamental deficit in schizophrenia is an inability to filter (gate) sensory stimuli, leading to deficits in sustained attention.

- When paired auditory stimuli are presented, the amplitude of the P50 component of the evoked response to the 2nd stimulus is normally reduced compared to the 1st stimulus.

- In schizophrenia, the P50 amplitude in response to the second stimulus is not reduced.
P50 Evoked Potential as a Biomarker of Impaired Attention

• In animals, cholinergic stimulation of alpha\textsubscript{7} nicotinic receptors on hippocampal interneurons is essential for the P50 reduction to the 2\textsuperscript{nd} stimulus.

• Polymorphisms in CHRNA7 are associated with the P50 abnormality in humans.

• Alpha\textsubscript{7} nicotinic receptor expression is reduced in schizophrenia.
Disease Process in Schizophrenia

Pathogenesis

Pathophysicsiology
(Altered P50 Amplitude In Sensory Gating Tasks)

Etiology
(Variants in \textit{CHRNA7})

Pathological Entity
(Deficit In Alpha$_7$ Nicotinic Receptor Neurotransmission)

Clinical Syndrome
(Impaired Sustained Attention)

Prevention

Treatment
(Alpha$_7$ Nicotinic Receptor Agonist)
Proof-of-Concept Trial of an α7 Nicotinic Agonist in Schizophrenia

Ann Oliny, MD; Josette G. Harris, PhD; Lynn L. Johnson, PharmD; Vicki Pender, BS; Susan Kongs, BS; Diana Allensworth, BS; Jamey Ellis, BS; Gary O. Zerbe, PhD; Sherry Leonard, PhD; Karen E. Stevens, PhD; James O. Stevens, DVM, PhD; Laura Martin, MD; Lawrence E. Adler, MD; Ferenc Soti, PhD; William R. Kem, PhD; Robert Freedman, MD

Arch Gen Psychiatry 63:630, 2006
• DMXB-A, partial alpha7 nicotinic agonist

• Assessed response to the acute administration of placebo and two doses of DMXB-A

• P50 inhibition improved consistent with activation of alpha7 nicotinic receptors

• RBANS scores improved consistent with a beneficial effect on attention/cognition

• P50 response may serve as a means for selecting subjects with impaired attention who are likely to benefit from therapy and for monitoring their response
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DLPFC Activation as a Function of Working Memory Load in Schizophrenia

R DLPFC (BA46)

% fMRI Signal Change

0-back 1-back 2-back

WM Load

Controls
Patients

n = 16 per group

Selective Alterations in DLPFC GABA Neurotransmission May Contribute to Working Memory Deficits

Lewis et al., *Nature Rev Neurosci* 6:312, 2005
Provisional Interpretation

- **Pathological entity**
  - Reduced GAD$_{67}$ mRNA expression with decreased GABA synthesis in chandelier neurons

- **Compensatory changes**
  - Decreased PV expression
    - PV reduces the residual intra-terminal Ca$^{2+}$ levels that contribute to the facilitation of GABA release during repetitive firing (*J Neurophys* 89:1414, 2003; *J Neurosci* 25:96, 2005)
  - Reduced GAT1 expression
    - Blockade of GABA re-uptake prolongs the duration of IPSCs when nearby synapses are activated synchronously (*J Neurosci* 23:2618, 2003)
  - Up-regulated post-synaptic receptors
    - Increase the efficacy of released GABA at AIS
Functional Consequences of Reduced Chandelier Neuron Input to Pyramidal Neuron Axon Initial Segments

- PV-positive GABA neurons and pyramidal neurons share common sources (e.g., thalamic afferents) of excitatory input (Melchitzky et al., *J Comp Neurol* 408:11, 1999).
  - The resulting feed-forward, disynaptic inhibition limits the time window for the summation of excitatory inputs required to evoke pyramidal neuron firing (Pouille and Scanziani, *Science* 293:1159, 2001).

- Each chandelier neuron targets multiple axon initial segments (Peters et al., *J Comp Neurol* 206:397, 1982).
  - Thus, a given chandelier neuron can synchronize the activity of local populations of pyramidal neurons (Klausberger et al., *Nature* 421:844, 2003).

- PV-positive, fast-spiking GABA neurons in the middle layers are linked via both chemical and electrical synapses.
  - These networks oscillate in the gamma band (30-80 Hz) range (Tamas et al., *Nat Neurosci* 366, 2000).
DLPFC Gamma Band Power Increases with Working Memory Load in Humans

Howard et. al., *Cereb Cortex* 13:1369, 2003
Prefrontal Gamma Synchrony, Induced in a Cognitive Control Task, is Reduced in Patients with Schizophrenia

Cho et al., *PNAS*, 2006
Disease Process in Schizophrenia

**Pathogenesis**
(NMDA Receptor Hypofunction-
Reduced Signaling via trkB)

**Pathophysiology**
(Reduced Gamma Band Power)

**Etiology**
(Variants in Nrg1 and Other Genes)

**Pathological Entity**
(Deficit in Chandelier Cell-mediated GABA Neurotransmission)

**Clinical Syndrome**
(Impaired Working Memory)

**Prevention**

**Treatment**
(GABA_A Alpha_2 Agonist)
Biomarkers in the Context of Disease Process

• **Critical features of a biomarker**
  – A direct consequence of the disease pathology
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• **Electrophysiological measures that reflect the emergent properties of identified neurobiological mechanisms offer promise as biomarkers**
  – In clinical trials of novel compounds
  – In identifying both prodromal and symptomatic individuals likely to benefit from such compounds
Biomarkers in the Context of Disease Process

• Future promise
  – Ongoing advances in understanding the cell types and local circuits that generate oscillations of specific frequencies
  – More refined and biologically-informed cognitive paradigms to induce oscillations
  – Improved source resolution of scalp potentials
Implications for Improving Working Memory Dysfunction in Schizophrenia

- Goal: Activate selectively $\text{GABA}_A$ receptors containing the alpha$_2$ subunit only when GABA is normally released from chandelier neuron axon terminals.
  - Tonic activation of these receptors or increased firing rate of chandelier neurons would disrupt the synchronization of pyramidal cell activity.

- Agonists with “benzodiazepine-like” properties (i.e., positive allosteric modulators), and selectivity for $\text{GABA}_A$ receptors containing the alpha$_2$ subunit, would preserve the critical timing of inhibition provided by chandelier cell inputs.
  - Available benzodiazepines activate $\text{GABA}_A$ receptors containing alpha$_1$ and alpha$_5$ subunits which mediate sedation and alterations in hippocampal function, respectively.

- The up-regulated state of $\text{GABA}_A$ alpha$_2$ receptors at axon initial segments may improve the specificity of drug targeting.

Lewis et al., *Psychopharmacology* 174:143, 2004