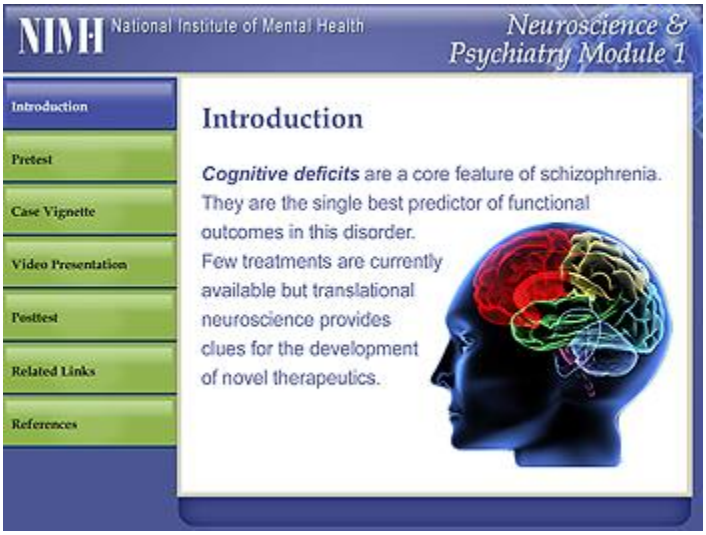
Neuroscience and Psychiatry Module 1: Translating Neural Circuits into Novel Therapeutics



Neuroscience and Psychiatry video

Introduction

Cognitive deficits are a core feature of schizophrenia. They are the single best predictor of functional outcomes in this disorder. Few treatments are currently available but translational neuroscience provides clues for the development of novel therapeutics.

Case Vignette

58 year old single white female with a 40 year history of paranoid schizophrenia. She is an attorney who was able to practice law for a period of time despite hallucinations beginning at age 18.

She has had multiple hospitalizations and symptoms have been variably controlled with medications and supportive therapy/reality testing.

Cognitive decline continued over the years and gradually she was unable to read her law books leading her to retire on disability. She then became unable to read fiction books, then

newspapers and now she is only able to read headlines. She has to hire someone to pay her bills.

Extensive workup revealed neuropsychiatric abnormalities that are consistent with chronic schizophrenia but no other dementing process. Her inability to think or read is very distressing to her.

She retains enough function to live independently but is unable to tolerate being in public, cannot function even at a volunteer job and has become extremely socially isolated.

Video Presentation: Translating Neural Circuits into Novel Therapeutics

Can understanding the disease process free us from a dependence on serendipity in the development of pharmacological treatments of psychiatric disorders and lead us to a rational basis for novel therapeutics?

Dr. David Lewis and his group set out to answer this question in schizophrenia using the following strategy; understanding the pathological entity, linking it to the pathophysiology and the clinical syndrome and using this knowledge as a basis for treatment development. The clinical aspect of schizophrenia that Dr. Lewis and his group focused on is cognitive deficits.

Cognitive deficits are core features of schizophrenia. They are prevalent in patients with schizophrenia, precede the onset of psychosis, persist across the course of the illness and, importantly, predict long term functional outcomes. They are also present in a milder form in unaffected relatives. Treatment of cognitive deficits in schizophrenia remains a challenge.

One cognitive deficit that's been very extensively studied in schizophrenia is working memory. We know that patients with schizophrenia do not perform well on working memory tasks. Normally, working memory tasks lead to the activation of the dorso lateral prefrontal cortex or DLPFC. DLPFC activation is also impaired in schizophrenia.

What types of alterations in DLPFC circuitry contribute to these cognitive deficits in schizophrenia? There are two main groups of neurons in the cerebral cortex, pyramidal neurons and GABA neurons. Pyramidal neurons are the major excitatory cells in the cerebral cortex and most GABA neurons are inhibitory.

Pyramidal neurons are all pyramidal in shape and rather difficult to differentiate from each other. In contrast, GABA neurons are diverse in appearance, neurochemical content and electrophysiological properties and can be differentiated from each other.

Let’s focus on GABA neurons. What is GABA? GABA is an inhibitory neurotransmitter that is synthesized by an enzyme called glutamic acid decarboxylase or GAD_{67}. Once released in the synapse, GABA produces its inhibitory effect.

GABA is then taken back up by the GABA membrane transporter GAT-1.

What does that have to do with cognitive deficits in schizophrenia? One of the most replicated findings in schizophrenia is a reduction in the expression of GAD_{67} and GAT-1 in the dorsolateral prefrontal cortex.

This decrease in the expression seems to be restricted to a subset of GABA neurons. These are the so-called parvalbumin containing neurons including a type of GABA cells called chandelier neurons.

The axon terminals of chandelier neurons synapse on the axon initial segment of pyramidal neurons where action potentials are generated.

Under certain circumstances and because of this critical location, chandelier axons can exhibit a powerful inhibitory effect on pyramidal neurons. In addition, each chandelier neuron synapses on the axon initial segment of ensembles of pyramidal neurons which helps synchronize their firing. Therefore, the reduction of GABA production in chandelier neurons can affect their inhibitory function AND the synchronization of firing of pyramidal cells.

In schizophrenia, because GABA production in chandelier neurons is reduced, the system attempts to compensate. There are findings in the DLPFC in schizophrenia that appear to be compensatory. The first such finding is a decrease in the expression of the GABA transporter GAT-1. GAT-1 removes GABA from the synapse after its release, it is essentially a recycling agent. When there is not enough release, keeping GABA in the synapse longer is one way of compensating. This can be achieved by decreasing the transporter.

Another finding in schizophrenia that can be interpreted as a compensatory change is the increase of a particular type of $GABA_A$ receptors on the postsynaptic side. There are several types of $GABA_A$ receptors, the one containing the alpha 2 subunit protein is particularly enriched at the axon initial segment of pyramidal neurons and is, interestingly, the type of $GABA_A$ receptor that is increased in schizophrenia presumably in order to enhance the postsynaptic effect of GABA in an attempt to compensate.

How can these findings at the level of neural circuits relate to abnormal cognitive function in schizophrenia?

As mentioned earlier, chandelier neurons help synchronize oscillatory activity of cortical pyramidal neurons.

This activity leads to the production of cortical network oscillations in the gamma band (30-80 Hz) range. Gamma band oscillations are an essential mechanism for cortical information processing during cognitive functions.

If a patient with schizophrenia is asked to perform a working memory task, not only is their performance impaired, gamma synchrony in the prefrontal cortex, measured by EEG, is also lower than in normal controls.

These findings are, therefore, consistent with the hypothesis that impaired GABA neurotransmission in chandelier neurons in the DLPFC contributes to deficits in gamma band power and to cognitive impairments in schizophrenia.

Clearly, the compensatory measures that the system produced, namely, decreasing GAT-1 expression and increasing $GABA_A$ receptors that contain the Alpha 2 subunit, are not sufficient. Can we use a pharmacological agent to boost the compensatory response?

One possibility is to use an agonist for $GABA_A$ Alpha 2 subunit receptors.

In a proof of concept clinical trial conducted in 2008, a GABA agonist was administered to patients with schizophrenia for four weeks. Other patients received placebo. Outcome measures included measures of working memory and tasks designed to increase the synchronous Gamma oscillations in the brain.

The investigators showed that patients with schizophrenia who received the agonist had an improved performance on the working memory tasks compared to those who received placebo. Moreover, they showed an increase in frontal Gamma band power during induced activity. The drug was well tolerated. This study is a preliminary study and further clinical testing of this drug is needed.

Nevertheless, the strategy used in developing this promising new drug for the treatment of cognitive dysfunction in schizophrenia can be summarized as follows: Understanding the pathological entity, in this case cell specific deficits in GABA neurotransmission in the DLPFC, linking it to the pathophysiology (reduced gamma band power) and to the clinical syndrome (impaired working memory) in order to develop rational treatment which can then undergo rigorous clinical testing.

If successful, the development of effective treatments for cognitive deficits in schizophrenia can significantly improve quality of life for the patient described in the clinical vignette and that of many patients with this devastating disorder.

References

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