Calcineurin and Schizophrenia: Signal Transduction and Genes-to-Behaviors Pathways in Psychiatric Diseases

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"A mass of evidence -animal and human- shows that genes influence behavior. But the attempt to pin down which genes influence which behaviors has proved frustratingly difficult."
(Mann, CC, Science 1994, 264:1686-9)

At the time I entered the Psychology Department of the University of Tokyo in 1991, the above description was absolutely right and every psychologist knew this fact. However, a revolutionary technology, gene targeting, changed the situation completely. Using this technique, specific gene of interest can be selectively modified. If one can see any specific behavioral changes in animals having a mutation of a gene, it would mean that we pin down a gene which influences a behavior. Since then, my interest has been to reveal behavioral significance of genes expressed in the brain and to know how they affect behaviors.

Our basic method to reveal behavioral significance of a gene is to conduct a systematic and well-defined behavioral test battery with mice which have mutation on the gene of interest. The behavioral test battery covers relatively broad range of various behavioral domains, such as learning and memory, sensory-motor functions, emotions, motivation and drug sensitivity/preference (Miyakawa et al., 1997; Yamada et al., 2001).

Recently, we subjected mice lacking a molecule called calcineurin (=CN) to the comprehensive behavioral test battery. The mutant mice showed severe working memory deficit, increased locomotor activity, decreased social interaction, and impairments in prepulse inhibition and latent inhibition. The abnormalities of CN mutant mice were strikingly similar to those described for schizophrenic patients
(Zeng et al, 2001; Miyakawa et al., 2003). Consistent with these findings, human genetics studies in a large sample of affected families detected significant association of the PPP3CC gene, which encodes the calcineurin gamma catalytic subunit, with the disease (Gerber et al., 2003). The idea that abnormalities in calcineurin signaling pathway is involved in schizophrenia pathogenesis is consistent with traditional theories of schizophrenia and with many facts known about schizophrenia. Calcineurin is a calcium/calmodulin protein phosphatase and tremendous amount of knowledge has been accumulated on this molecule for several reasons. By utilizing such rich information, the studies on the pathogenesis of schizophrenia and its related mental disorders would be potentially accelerated.

References:


MOLECULAR IMAGE OF SCHIZOPHRENIA

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Schizophrenia is a mental disorder characterized by hallucinations, delusions, disorganized thinking, so called positive symptoms and negative symptoms such as affective flattening and avolition. Almost 1% of the population at youthful age suffered from this illness and their social adaptation is often the problem for them and for the society. It typically strikes during the late teens and early twenties. It is a disease with many different faces. Hallucinations and delusions are typical symptoms of schizophrenia. Most common hallucinations are auditory hallucinations, the hearing of voice sometimes from God or devil, sometimes from relatives or neighbors. The voices are threatening or obscene and very disturbing to the patient. Delusions are false ideas that cannot be corrected by reasoning and that are idiosyncratic for the patient. Delusions of persecution are common symptom in schizophrenia. Several neurobehavioral deficits have been reported also in schizophrenia. Antipsychotic drugs are currently being used for the treatment of schizophrenia. The therapeutic effects of antipsychotics are based on synaptic modulation of dopamine neural systems mainly by antagonism of postsynaptic dopamine D2 receptor. On the other hand, dopamine-releasing agents such as amphetamine can produce a paranoid psychosis. Although dopamine is a key transmitter system in the pathophysiology of schizophrenia, recent neurochemical researches suggest the possible abnormality in multiple neural systems including serotonin system and glutamate system and neurodevelopmental abnormalities are hypothesized.

In the last few decades diagnostic and research tools in the medical field have made great advances, yet psychiatry has lacked sufficiently sensitive tools to measure the aberration of brain functions. The development of positron emission tomography (PET) techniques has made it possible to measure changes in biochemical components in living human brain. PET can be used to investigate functional and biochemical regional characteristics of various organs. Biochemical substrates and drugs which can specifically bind to certain protein
such as receptors and transporters or can be a substrate of specific enzyme such as acetylcholine esterase have been labeled with positron emitter. An array of radiation detectors placed around the head to detect the $\gamma$-rays from the tissue distribution of labeled compound. Data provides tomographic images of the cross-sectional distribution of tissue concentration of radioactivity like autoradiography in vitro.

Since the pathophysiology of schizophrenia have been discussed with a functional alteration of dopaminergic transmission in the brain, we have focused the dopaminergic components for the research target of schizophrenia using PET. Dopamine receptors receive signals from presynaptic terminal of dopamine neuron. Those are classified into five subtypes, and selective ligands have been developed for D1 and D2 subtypes. An increasing body of evidence favors a crucial role of extrastriatal regions in the pathophysiology of positive symptoms, and the extrastriatal D2 receptor is expected to be the common site of action of antipsychotics. Using high affinity ligand [C$^{11}$]FLB 457, we found reduced D2 receptor binding in the anterior cingulate cortex of patients with schizophrenia, and a significant negative correlation was observed between D2 receptor binding and the positive symptom score. Subregions of interest were defined on the thalamus using individual magnetic resonance images. D2 receptor binding was also lower in the central medial and posterior subregions of the thalamus in patients with schizophrenia. Alterations in D2 receptor function in the extrastriatal region may underline the positive symptoms of schizophrenia. On the other hand D1 receptor binding was found to be lower in the prefrontal cortex and a significant negative correlation was observed between D1 receptor binding and the negative symptom score. Abnormality of D1 receptor function would be at the bottom of the negative symptoms and cognitive impairment of schizophrenia.

Reference