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Potential Role for Astroglial D-amino Acid Oxidase in Extracellular D-Serine Metabolism and Pathogenesis of Schizophrenia

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D-Amino acid oxidase (DAO) is a flavoenzyme that catalyzes oxidative deamination of D-amino acids. Among possible substrates, D-serine is a neuromodulator of *N*-methyl - D-aspartate (NMDA) receptor. Hypofunction of NMDA receptor has been implicated in the pathology of schizophrenia. It is notable that a novel human gene G72 has been implicated in schizophrenia and shown to bind with and up-regulate DAO. In search of pathophysiological role of DAO, we investigated the metabolism of extracellular D-serine in glial cells. We found that after D-serine treatment, rat astrocytes exhibited increased cell death. We then established stable rat C6 glial cells overexpressing mouse DAO (C6/DAO). Treatment with a high dose of D-serine led to the production of hydrogen peroxide (H_2O_2) followed by apoptosis in C6/DAO cells. Among amino acids tested, D-serine specifically exhibited a significant cell death- inducing effect. DAO inhibitors prevented the death of C6/DAO cells, indicating the involvement of DAO activity. We consider that extracellular D-serine can gain access to intracellular DAO, being metabolized to produce H_2O_2, indicating an important role of astroglial DAO in D-serine metabolism. Furthermore, we have purified human DAO and determined its crystal structure in complex with a competitive inhibitor, benzoate. The crystal structure was determined at 2.4 angstrom resolution and showed the overall dimeric structure. These studies will open up new molecular approaches to the understanding of schizophrenia and rational design of effectors specific for human DAO activity.

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Analysis of novel synaptic proteins whose mRNAs are associated with postsynaptic structures.

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The postsynaptic density (PSD) has been a target for massive proteomics analysis during the past 10 years and recent proteomics analyses have suggested the presence of several hundred or even more than 1,000 species of protein localized in the PSD. Most reports have suggested the presence of a relatively large number of still undiscovered protein species. Identification and characterization of these still-uncharacterized proteins will provide basic molecular information and is essential for fully understanding the synapse function and diseases due to dysfunction of synapses. We identified a large number of postsynaptically localized mRNA species, based on the idea that massive identification of them would enable efficient identification of the postsynaptic proteins. We isolated and characterized mRNAs associated with PSD prepared from the rat forebrain. Analyses of these RNAs by gene chip microarray suggested presence of mRNAs highly concentrated in and around PSD and that about half of them (more than a few hundreds) has been functionally uncharacterized. mRNAs related to certain neuronal diseases are also enriched in the PSD fraction. Several novel postsynaptic proteins were identified from the PSD fraction-associated mRNA pool. These include synaptic ubiqutin-specific protease (synUSP), synaptic ArfGEF (synArfGEF), nNOS-interacting DHHC-containing protein with dendritic mRNA (NIDD), and a protein containing a tetratricopeptide repeat (TPR) domain, ankyrin-repeat and coiled-coil region (TANC, a rat homolog of Drosophila rolling pebbles). We have also characterized a protein named as “brain and acute leukemia, cytoplasmic (BAALC) 1-6-8”, and p55 protein in the brain, neither of which had previously been characterized in the brain, particularly in the synapse, before our studies. PSD fraction-associated mRNAs contain large number of still-uncharacterized species, and thus, are intriguing targets for research essential for a full understanding of synaptic function.