Version 2.0

Abstract

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Grant Number:	1R01NS035050-01
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PI Title:	PROFESSOR
Project Title:	MOLECULAR ORGANIZATION OF CNS SYNAPSES

Abstract: DESCRIPTION: (adapted from Applicant's Abstract) Synaptic functions and synaptic plasticity are crucial for information transfer and storage in the brain, but the structure of synapses in the mammalian central nervous system (CNS) is poorly understood, especially at the molecular level. The broad long term objective of this proposal is to understand the molecular basis of postsynaptic organization and diversity in the CNS, with particular reference to protein-protein interactions at the synaptic membrane. The specific aim is to define and characterize the molecules which mediate the clustering and anchoring of two different classes of neurotransmitter receptor (NMDA receptors and GABAA receptors) at excitatory and inhibitory postsynaptic sites, respectively. The experimental approach is to identify intracellular proteins which bind specifically to NMDA and GABAA receptors, by using the major intracellular domain of subunits of these receptors as baits in a yeast two-hybrid screen of a brain cDNA library. In Preliminary studies, a known actin binding protein (a-actinin) and a novel extended coiled-coil protein (termed NIP-1), have been identified as molecules that interact directly with separate domains with the cytoplasmic C-terminal tail of the NMDA receptor subunit NR1. These results demonstrate the feasibility of the two-hybrid approach to detect potential interaction between integral synaptic membrane proteins and components of the postsynaptic cortical cytoskeleton. The authenticity of the protein interactions identified by the two-hybrid system will be confirmed in vitro by binding of recombinant proteins, and in vivo (rat brain) by immunohistochemical co-localization and immunoprecipitation. Protein domains mediating the interaction will be will be defined by deletional mutagenesis, with the hope of identifying novel sequence motifs or modules for protein-protein interactions at the cell membrane. The functional significance of receptor association with its binding protein will be investigated by co-transfection experiments in cultured cells. Developmental and cellular expression patterns of the proteins interaction with NMDA receptor and GABAA receptors will be characterized in rat brain. Determining the molecular organization of receptors in postsynaptic membranes will further our understanding of the mechanisms of synaptogenesis and synaptic structural plasticity, and hence of learning and memory, and developmental and aging processes in the brain. From a clinical point of view, abnormalities in the organization of the postsynaptic membrane and cytoskeleton in the CNS could results

in neurological disease, just as defects in the muscle membrane cytoskeletal protein dystrophin can cause muscular dystrophy. In the context, it is of interest that our preliminary studies have identified a relative of dystrophin (a-actinin) as a putative anchoring protein for the NMDA receptor.

Thesaurus Terms:
GABA receptor, NMDA receptor, neural plasticity, receptor expression, synaptogenesis alpha actinin, cytoskeleton, receptor binding, recombinant protein immunocytochemistry, laboratory rat, site directed mutagenesis

Institution:	MASSACHUSETTS GENERAL HOSPITAL 55 FRUIT ST BOSTON, MA 02114
Fiscal Year:	1996
Department:	
Project Start:	01-MAY-1996
Project End:	30-APR-2001
ICD:	NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE
IRG:	NLS