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The development of the vertebrate brain involves a phase of synaptogenesis during which the activity patterns of young neurons mediate a competition that allows only highly effective synapses to survive. These activity-dependent developmental events are responsible for many of the adaptive changes in brain wiring as children mature and it is also likely to be responsible for some of the devastating and permanent behavioral effects of genetically or environmentally caused disruptions in normal early brain activity. We are investigating the mechanisms involved in this developmental synaptic plasticity. Specifically we are trying to dissect the signaling cascades through which synaptic activity determines which young synapses will be withdrawn and which ones will be retained to mediate adult brain function. Our approach is to work both in vivo and in vitro allowing normal developmental changes in brain structure or function to identify key molecular players that can subsequently be systematically studied in brain slices, dissociated primary neuron cultures and in intact animals with important synaptic molecules either "knocked out" or knocked down with with short inhibitory RNAs. Most of our work concentrates on the glutamatergic and GABAergic neurotransmitter systems in the midbrain optic lobes, (the superior colliculus) and the visual cortex of rodents. Recently we have been focusing on the events that rapidly follow an important event in visual pathway development: namely eye opening. We have shown that the ability to produce long duration increases in synaptic strength develops rapidly in the visual regions of the superior collciulus. Moreover, in layer IV of the visual cortex, these neurons that receive visual axons from the thalamus behave as if their synapses suddenly become fully potentiated: their post-synaptic evoked currents are generally larger than before eye opening and, in response to low frequency long trains of stimulation, the cells show high levels of synaptic depression. Along with these functional changes we have found that the cortical projection to the superior colliculus refines within 2 days of eye opening and the onset of pattern vision. This brings the 2 maps of visual space in the cortex and in the superior colliculus into register allowing the colliculus to initiate visually quided behavior.

By contrast maintaining the eyes closed for 3-4 days beyond normal eye opening causes the corticocollicular axons to lose all branches! However, if eyes are opened on the 4th day after normal eye opening and the pups are examined several days later than the cortical neuron axon terminals in the colliculus start sprouting again. Obviously there is a continued activity-dependent structural (and also a functional plasticity) that is maintained for at least a week after eye opening and we are in the process of dissecting the mechanisms underlying this plasticity.

Molecular Mechanisms of Visual Pathway Plasticity

We use a multidisciplinary approach involving biochemistry and immunoprecipitation, immunocytochemistry and vital imaging in tissue culture to identify and study the signaling molecules that are associated with the glutamate receptors in the "eye opening interval". We have also begun to collaborate with the Broad Institute Proteomics Units headed by Dr. Steven Carr. We are using liquid chromatography and tandem mass spectroscopy (LCMs/MS) to identify the protein changes in visual cortex post-synaptic densities across the eye opening and juvenile to adult intervals and we are using lentiviral vectors to express in vivo in neonate rat visual centers short inhibitory RNA molecules (siRNA) against molecules suspected of involvement in these processes. Other experiments utilize mutant mouse strains to determine whether the trafficking of NMDA receptors and/or the specific NR2A versus NR2B subunits or the receptor scaffolds and signaling modules are requuired for the plasticity observed after eye opening. Finally we are in the middle of two large gene chip experiments with mRNAs from the visual layers of the superior collciulus before, and after, eye opening and from litter mates in which eye are never opened. This has allowed us to factor out changes in gene expression due to eye opening from changes due merely to age. The one completed analysis has suggested several very interesting molecules that are good candidates for siRNA knockdown studies, again in vivo, to test the requirement for these gene products during eye opening induced plasticity. We have an additional ongoing study in which microRNAs that change in the eye opening interval are being compared to transcripts that change in the same interval to determined if any of the synaptic plasticity events are under the control of microRNA.

Translational Research on Neurodegeneration and Psychiatric Disease:

We are also currently involved in two collaborative projects in which we are applying our knowledge of developmental synaptic plasticity. (1) One study involves electrophysiological and molecular experiments designed to identify the cellular basis of motoneuron death in a mouse model of Amyotrophic Lateral Sclerosis (ALS). These studies are undertaken in collaboration with Dr. Robert Brown Jr. at MGH and Harvard Medical a leading ALS Investigator. A second recently begun project involves genes know to be linked to schizophrenia and also known to be involved in NMDA receptor signaling. Currently these experiments use small molecules known to inhibit neuregulin signaling to understand their effect on NMDA receptor activity-dependent regulation. These studies are undertaken in collaboration with Dr. Edward Skolnick's Psychiatric Disease Research Group based in the Broad Institute.

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Additional Publications

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