Chapter I

INTRODUCTION

Synaptic plasticity – functional and structural

Brain function is mediated by highly specific circuits that connect widely separate groupings of neurons into functional networks. Such precision in organization is established during development, as connections are made to yield a mature framework for brain function. After development, synaptic connectivity remains functionally dynamic throughout life, allowing new associations appropriate for learning and memory formation, and for repair in case of injury. An important area of neurobiological research focuses on understanding how synapses are formed, maintained, and modified to allow such behavioral flexibility (plasticity).

Synaptic plasticity is the ability of the connections between neurons to change in strength. Plasticity can involve (1) a structural change in synapses (changes in synapse size, formation of new synapses, or elimination of existing ones, or changes in the shape or geometry of spines); (2) changes in the molecular composition of existing synapses (addition of new molecular species or changes in the numbers of the different molecules in the synapse); or (3) changes in the state of the existing molecules of the synapse (changes in phosphorylation state, or other posttranslational modifications).

Adhesion molecules at the synapse

Adhesion molecules are membrane-anchored molecules whose extracellular domains directly interact to help hold the membranes of two cells together. Maintenance of an apposition of the two membranes can be the primary role of the interaction or can result secondarily because of ligand-receptor interactions whose primary purpose is to transmit signals to the cytoplasm.

Adhesion molecules are involved in the regulation of synaptic structure and function. Such involvement is of importance both to synapse maturation, which requires the elaboration of presynaptic boutons and postsynaptic spines, and to synaptic plasticity. Several adhesion molecules are known to regulate spine morphology, as well as electrophysiological measures of the strength of existing synapses which results from nonstructural changes (2) and 3) above). One such example is the cadherins, a group of calcium dependent homophilic adhesion proteins.

In the following chapters, I will first discuss work that has been done describing cadherins, their structure and function, and their role in the nervous system. Second, I will describe my work on developing FRET-based reporters of cadherin adhesive state. Last, I describe my use of these reporters in studying the response of cadherin homophilic interactions to changes in extracellular calcium ion concentration.