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20. NEURAL PLASTICITY AND CELL BIOLOGY OF LEARNING

Summary. Changes in the number, type, and function of nervous system connections, in the morphology and function of glia, and in neuron-glia interactions, are at the center of vertebrate adjustments to changing environmental and physiological conditions. Collected together under the term "neural plasticity", these changes underlie adaptations as apparently different as learning, the physiological response to dehydration, or injury repair. In this chapter, the concepts of synapse renewal and reactive synaptogenesis are revised, as well as the cellular and molecular steps involved in synapsis renewal. A brief review is also made regarding the present understanding of long-term potentiation, and its relationship with synaptic structural changes.

1. INTRODUCTION

The term plasticity was introduced in 1890 by William James to describe the susceptibility of human behavior to modification. It was also used by Marinesco (1907) and Minea (1909), in their work on transplantation of sensory ganglia, to describe the changes in morphology undergone by the transplanted neurons. Cajal was aware of their work, and believed that the behavioral modifiability reported by James must have an anatomical basis, as reported by Marinesco and Minea. However, after Cajal's death, researchers adopted a rigid view of the adult central nervous system (CNS), assuming that once development had finished, CNS anatomy was unchangeable, except for degenerative processes. Against this general view, Liu and Chambers showed in 1958 that axon sprouting occurred in the adult CNS, and overwhelming evidence has accumulated in the last three decades confirming their finding. The nervous system maintains the capacity of functional and anatomical modification throughout life. The neuronal networks that make up the nervous system of mammals remain plastic —modifiable — during their whole life, and plasticity is one of their main adaptations. Plasticity, denominated neural to remind us that it refers to both neurons and glia, is today considered a fact, and the questions now concern its cellular and molecular basis. The stimuli that induce neural plasticity are experiences, environmental pressures, physiological modifications, or lesions of all kinds. I propose that the cellular and molecular processes that underlie neural plasticity are the same, regardless of the precise activity involved. This article presents a general view of plasticity, its origin, function, mechanisms, and possible

clinical manipulation. Assuming that neural plasticity mechanisms apply to the whole CNS, then I propose that we use the information on the physiological principles that apply to learning, an activity mammals are quite good at — to enhance the very limited mammalian CNS lesion repair.

2. NEURONS AND GLIA: A UNIT OF FUNCTION

The main cell types in nervous tissue are neurons and glial cells. Neurons are cells highly specialized for the rapid receipt and transmission of messages. They have a relatively small body and multiple ramifications that cover an extensive surface, allowing them to maximize intercommunication. The human cerebrum contains more than ten thousand million neurons, while the cerebellum, between ten and one hundred thousand million. The synapses, or 'synaptic contacts', are the sites where a neuron transmits its message to another neuron. A typical CNS neuron frequently receives tens of thousands of synaptic contacts, although cerebellar Purkinje cells may receive up to 200,000. Connections between neurons give rise to neuronal circuits and neural plasticity is, to a large extent, synaptic plasticity — that is, the susceptibility to modification of the type, form, number, and function of the synapses, and hence, of the neuronal circuits. Processes as diverse as learning and memory, the response to physiological situations such as pregnancy or thirst, and the response to lesions, have synaptic plasticity and neural plasticity as a common basis.

Today's consensus is that nervous tissue function may be understood only taking into account the other cells characteristic of this tissue: the glial cells. Their number exceeds that of neurons about 10-fold, and they constitute about half the nervous tissue mass (Pope, 1978). The original description of glia by Virchow in 1859 as nervous glue, accorded glia a static image, maintained mainly by neuroanatomists and neuropathologists during the following 100 years. This view has changed notably during the last 25 years, and the neuronal-dominated viewpoint of nervous function has been widened to take in neural development and nervous activity, maintenance, and pathology, based on the neuron-glia as a unit of function. The idea of the neuron-glia as a dynamic unit of function has been proposed independently by various researchers in the last 20 years, but was formulated explicitly in detail by Arenander and de Vellis (1983) and, later by Nieto-Sampedro (1988). The glial types in the CNS are astroglia, oligodendroglia, and microglia, of which astroglia and macroglia are probably most-directly related to neural plasticity.

Astrocytes are intimately associated to both neurons and the whole organism. They envelope central synapses and form the glia limitans, the boundary between the CNS and other tissues, particularly blood vessels, with which their endfeet make intimate contact in high-conductance regions (Newman, 1986). Thereby, astrocytes monitor the blood content of nutrients, oxygen, vitamins, and hormones. They are sensitive to ions, especially potassium, and can bind, transport, and metabolize neurotransmitters. Astrocytes respond to excitatory neurotransmitters by depolarizing, and some may conduct action potentials (refs. in Arenander and de Vellis, 1983, and Nieto-Sampedro, 1988a). In addition, they all intercommunicate directly by "gap-junctions" and similar mixed junctions probably link them with