Experiments and Hypotheses on the Functional Involvement of Secretory Glycoproteins in Neuronal Plasticity

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The anatomical specificity of synaptic connections within neuronal microcircuits of the brain is assumed to code for the contents of acquired information. Biochemical reactions, on the other hand, provide the mechanisms that modify the efficacy of individual synapses. Many synapses become temporarily activated when an animal acquires a new behavioural response. However, no physiological mechanism has yet been elucidated that might provide a means to determine which of many possible new associative pathways should be strengthened, or rather be demolished during long-term memory formation. Teleologically, some additional "factor" might permanently modify all activated synapses if a new behaviour proves to be advantageous. Such a factor should readily be available throughout the CNS. Like, e.g., the cell adhesion molecules, it should have the potential to modify finestructural and/or functional characteristics of synaptic connections, be responsive to the functional state of the neuronal micro-environment (e.g., to changes in ionic concentrations), and it should be regulated by an evaluating function, weighing the importance of the preceding behaviour for the biological fitness of the organism.

Goldfish ependymins are nervous system specific proteins displaying some of the requirements for such a factor. They are acidic, secretory, calcium binding glycoproteins that share immunoreactivity against the HNK-1 antibody and 3-sulfatated glucuronic acid in their carbohydrate moieties with cell adhesion molecules of the N-CAM family. The primary structure of ependymins, as deduced from cDNA cloning, comprises a hydrophobic leading sequence of 21 amino acids, typical of secretory proteins, two N-glycosylation sites, and two clusters of negatively charged amino acids, suitable for calcium binding. Physiologically, the mature proteins occur predominantly in the form of dimeric molecules which respond to decreasing calcium concentrations by polymerization to long fibers. During long-term memory formation following a vestibulo-motoric training task or an active shock-avoidance conditioning, after long-term potentiation of the rat hippocampus, and during regeneration of the retinotectal projection following optic nerve crush, ependymins are preferentially synthesized and secreted into the extracellular matrix. It is inferred that ependymin molecules participate in biochemical reactions of neuronal plasticity from the extracellular fluid, because (1.) radiolabelled ependymins are incorporated into particles of a synaptosomal fraction, and because anti-ependymin antibodies interfere with memory consolidation (2.) after the vestibulo-motoric training, (3.) after the active shock avoidance conditioning, and (4.) with the sharpening of multiunit receptive fields during retinotectal regeneration, i.e. with micro-events in synaptic differentiation involving synchronous and convergent activity of neuronal pathways, both in behavioural and regenerative plasticity. (Supported by the Deutsche Forschungsgemeinschaft.)