An Electrophoretic Coupling Mechanism between Efficiency Modification of Spine Synapses and Their Stimulation*

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Abstract. Changes in efficiency of dendritic excitable spine synapses are interpreted as a result of the electrophoretic movement of particles transferring new membrane material into spines. Restoring membrane particles migrate through cytoplasm along spine axes in endogenous electric field caused by the stimulation of the synapses themselves. During such an electrophoretically controlled spine membrane renewal, the restoring particles are distributed into individual spines proportionally to the stimulation level of the corresponding synapses. Fusion of restoring particles with the spine membrane is facilitated by influx of calcium ions. Degradation of postsynaptic regulatory protein complexes is also supposed to be initiated by an increase of the intracellular calcium concentration. Thus, more stimulated spine synapses than neighbouring ones are restored during calcium influx, whereas those disused are silenced. The proposed short-term memory mechanism is theoretically examined and discussed from the viewpoint of new experimental findings concerning plastic changes in the cerebellar cortex.

1 Introduction and biological background

Recently, Gray [10] and Crick [6] put forward the idea that the change of the dendritic spine geometry could be in a sophisticated manner involved in the neuron memory mechanism. The hypertrophy, branching and elimination of dendritic spines have already been interpreted by Eccles [7] as a morphologically observable manifestation of the stimulation-dependent neuronal plasticity. However, the molecular mechanism underlying such events has not yet been cleared up. In what follows we shall discuss this problem from the viewpoint of the renewal of the dendritic membrane constituents. We intend to show that spine synapses compete for newly synthetized membrane material. The excitable synapses more stimulated than neighbouring ones are supposed to win this competition. The observed growth of the relatively more used spine synapses [8] and the spine size reduction of those disused [25] may be considered as one of the many possible manifestations of the mentioned competition. The spine geometry change itself cannot be taken as an actual memory event because the efficiency of the synapse located on the spine head is not substantially different from that on the parent dendrite [13]. The transient creation of silenced spine synapses and a subsequent function restoration of those relatively more utilized, however, may correlate with a fast neuronal learning process.

The Marr-Albus theory [16, 1] of the cerebellar cortex supposed that a fast change of synaptic efficiency occurs at excitatory spine synapses between granule cells and Purkinje cell dendrites. Recently, Ito et al. [12] have observed that the application of climbing fiber signals to Purkinje cell leads to simultaneous depression of sensitivity of this Purkinje cell to L-glutamic acid (LGA). Under the assumption that LGA is the neurotransmitter liberated from granule cells [12], this finding supports the above mentioned idea that the transient creation of a silenced spine synapse is a partial event involved in modification of the synaptic weight.

A possible way of the synapse activity restoration is the insertion of the newly synthetized membrane constituents into postsynaptic membrane. Much work has been devoted in order to elucidate teh mechanism of the fast axonal and dendritic transport (for the recent reviews see [9, 11, 23]). Since the inhibition of either phospholipids or cholesterol results in a depression of fast transported proteins, it can be concluded that

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membrane constituents are transported as a preassembled membrane [9, 11]. Migration of membrane particles such as vesicles, lysosomes, and mitochondria has been observed in living axons by light microscopy [9, 22]. Electron microscopic study of developing neurons performed by Pfenninger [20] revealed in the growth cone and in the perikaryon the presence of vesicles with an average diameter of about 150 nm. It may be assumed that the growth of neuron processes and the differentiation of synaptic membrane occur via fusion of these particles with neuronal membrane [11, 20]. If the restoring particles had the negative surface charge as the presynaptic vesicles or the plasmatic membrane itself, their movement can be manipulated electrophoretically by the neuron endogenous electric field. Particularly, the spine can act as an electrophoretic trap for the particles which pass over the spine mouth at the time instant when the excitable synapse on the spine head is stimulated. This electrophoretic coupling mechanism between the synapse stimulation and the restoration of its membrane is supposed to be the basis of the neuron short-term memory as well as of the stimulation-dependent competition of neurons for innervation. Such a competition has been observed during the development of neural tissues, after partial denervation and in adult organisms after environmental deprivation (for a review see [5]). The homosynaptic postactivation potentiation and the heterosynaptic postactivation depression observed in hippocampal CA1 pyramidal cells [2, 15] could also be explained by this stimulation-dependent competition for restoring particles.

2 Electrophoretic mechanism for spine membrane renewal

By the assumption that the spine head can be treated as isopotential, the spine stalk as a simple short cable, and the parent dendrite as an infinite cable, the voltage attenuation factor $f_{s\to d}$ from the spine head to the parent dendrite is given by [13]:

$$f_{s\to d} = 2e^{-L}\Big\{1 + 2\Big(\frac{d_1}{d_0}\Big)^{\frac{3}{2}} - \Big[2\Big(\frac{d_1}{d_0}\Big)^{\frac{3}{2}} - 1\Big]e^{-2L}\Big\}^{-1} \ . \qquad (1a)$$

The electrotonic length L of the spine stalk is

$$L = l_0/\lambda_0 = 2\big(R_i/R_m\big)^{\frac{1}{2}} l_0 d_0^{-\frac{1}{2}} \ . \qquad (1b)$$

The symbols $l_0, d_0, d_1, \lambda_0, R_i, R_m$ in Eqs. 1a,b denote the lenghth and the diameter of the spine stalk, the diameter of the parent dendrite, the length constant of spine, the intracellular resistivity, and the membrane resistance, respectively. Taking as an example the same spine parameters as used in computation by Jack et al. [13] (i.e. $l_0 = 2\ \mu m, d_0 = 0.2\ \mu m, d_1 = 5\ \mu m, R_i/R_m = 0.04\ cm^{-1}$), the voltage attenuation factor $f_{s\to d}$ is 0.1827. By the stationary spine head depolarization of 10 mV, the mean electric field along the spine stalk axis would be 40 Vcm^{-1}. The electrophoretic mobility u of a spherical particle is given by the Helmholtz-Smoluchowski equation:

$$u = \zeta\epsilon_r\epsilon_0/\eta \ , \qquad (2)$$

where ζ is the zeta-potential of particles, ϵ_r is the dielectric constant of the cytoplasm, ϵ_0 is the permittivity of free space, and η is the viscosity of the cytoplasm. Assuming (a) that the restoring particle zeta-potential is the same as for presynaptic vesicles under physiological conditions (i.e. $\zeta = -20\ mV$ [18]), (b) viscosity of the cytoplasm is $6 \times 10^{-3}\ Nsm^{-2}$ [4], and (c) $\epsilon_r = 80$, $\epsilon_0 = 8.85 \times 10^{-12}\ Fm^{-1}$, then the velocity $v = uE$ of the electrophoretic movement of restoring particles in the electric field $E = 40\ Vcm^{-1}$ would be of 9 μms^{-1}. If the particle diameter is at least on the order of $10^{-7}m$, the computed electrophoretic movement dominates over Brownian movement. This can be shown by computation of the Einstein equation for Brownian movement in a similar way as it was done by Brewer [4]. In this way we have confirmed the general conclusion of Brewer [4] that the intracellular movement of vesicles towards the plasma membrane could be controlled by cell endogenous electric field. A synapse located on the dendritic spine is extraordinary suitable to perform such a control role. If an excitatory spine synapse attracts restoring particles, then an inhibitory dendritic synapse will reject them. Under appropriately combined stimulation of inhibitory and excitatory synapses, the electrophoretic migration of restoring particles could be powerfully manipulated.

3 Marr's conjunction hypothesis of memory

The depression of chemosensitivity to LGA observed in cerebellar Purkinje cells after the stimulation of climbing fibers is probably initiated by the influx of calcium ions [12]. A transient increase of intradendritic

calcium concentration may also facilitate the fusion of restoring particles with the spine membrane. For this reason, the calcium ions are supposed to play a crucial role in regulation of synaptic plasticity. The influx of calcium ions can be controlled via chemically or electrically gated calcium channels as well as by means of the specific calcium binding proteins. It appears that the surface of Purkinje cell contains calcium channels being opened by the climbing fiber stimulation [14]. If all of the above-mentioned propositions were true, the climbing fibers would control both the silencing of synapses between parallel fibers and Purkinje cell dendrites and the fusion of restoring particles with the postsynaptic membrane of those synapses. However, the membrane renewal of a spine synapse is supposed to occur only in the case when the corresponding spine contains restoring particles, i.e. when the synapse on this spine was stimulated in temporal conjunction with the climbing fiber. This is in agreement with the Marr's conjunction hypothesis of memory [16] which requires the temporal conjunction of both kinds of Purkinje cell inputs for the efficacy increase of a parallel fiber synapse to occur.

4 Concluding remark

The short-term memory state of a neuron might be consolidated by replacing the afferents of silenced synapses by newly sprouted terminal processes of another afferents taking part in the competition of spine synapses for restoring membrane particles. Axonal sprouting may be inhibited by the trophic factors enclosed in the core of restoring particles. After fusion of these particles with the postsynapstuic membrane, the sprouting inhibitor would be released into the region of the extracellular medium with frequently stimulated afferents. In this way, the utilized afferents would be structurally stabilized. Triggering of sprouting by interruption of axonal transport [5] may be taken as a support for this proposal.

The above mentioned consolidation process ought to be interrupted by the stimulation of the disused spine synapses. The amnestic effect of the bilateral electroconvulsive therapy [24] can be explained by this mechanism.

The question whether the basis for the competition for innervation is the electrophoretic competition of spine synapses for restoring membrane particles must be resolved experimentally in future. Especially, the mechanism of fusion of restoring particles with the dendritic membrane and the mechanism of synapse silencing are both unclear. The electrophoretic movement of membrane particles through cytoplasm and the possible electrophoretic movement of proteins within the plane of membrane also require further experimental study. Maybe, investigations carried out in the laboratory of McLaughlin [3, 17] and by Orida and Poo [19, 21] will throw more light on this subject.

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