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Review article

Talking to the neighbours: The molecular and physiological mechanisms of clustered synaptic plasticity

Bas van Bommel, Marina Mikhaylova (Dr.)*

DFG Emmy Noether Group, Neuronal Protein Transport, Center for Molecular Neurobiology, ZMNH, University Medical Center Hamburg-Eppendorf, Falkenried 94, 20251 Hamburg, Germany

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ABSTRACT

Synaptic connectivity forms the basis for neuronal communication and the storage of information. Experiences and learning of new abilities can drive remodelling of this connectivity and promotes the formation of spine clusters; dendritic segments with a higher spine density. Spines located within these segments are frequently co-activated, undergo different dynamics than synapses located outside of this dendritic compartment and have, in general, a longer lifetime.

Several lines of evidence have shown that chemical synapses located close to each other share or compete for intracellular signalling molecules and structural resources. This sharing and competition directly influences spine dynamics. Spines can grow, shrink, increase or decrease the surface expression of receptors, channels and adhesion molecules or remain stable and unchanged over extended periods of time. Here we summarize recent discoveries and provide a closer look at spine clustering, dendritic segment-specific signalling and potential molecular mechanisms underlying associative and heterosynaptic plasticity.

Contents

* Corresponding author.
E-mail address: marina.mikhaylova@zmnh.uni-hamburg.de (M. Mikhaylova).

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1. Spatial synaptic organization as unit for memory consolidation

1.1. Synaptic organization and signal propagation in neural networks

Neuronal communication via chemical synapses forms the basis for information processing in the brain. Lasting changes in synaptic strength at single synapses are descriptively named Long-Term Potentiation (LTP) and Long-Term Depression (LTD), and provide the brain the opportunity to regulate how signals propagate within neuronal networks (Hebb, 1949; Lüscher and Malenka, 2012). Strengthening of individual synapses likely increases synaptic stability and enhances the efficiency of depolarization at receiving neurons, thereby increasing the probability to generate the action potentials. These features may contribute to a proper linkage of neurons within a memory engram (Govindarajan et al., 2006; Ryan et al., 2015). In addition, the positioning of synaptic connections on the dendritic tree may form an additional 'layer' for information processing (Mel, 1992). Early computational models indicate that a clustered organization of synaptic inputs, including the co-activation, can strongly enhance memory capacity (Poirazi and Mel, 2001). Activation of multiple synapses within a cluster increases the depolarization level by opening of N-methyl-D-aspartate receptors (NMDR) and voltage-gated ion channels. Such events occur when multiple closely located/clustered synapses are activated and will enhance somatic depolarization. As a result, fewer synaptic inputs are required for the initiation of an action potential, which increases the computational power of neurons and its storage capacity given that the total number of synapses remains equal (Poirazi and Mel, 2001). This phenomenon was initially described in the *synaptic clustering hypothesis*, and studied within a computational model named *Clusteron* (Mel, 1992). The first experimental evidence for information processing by synaptic clusters was found in the auditory localization pathway of barn owls, which integrates audio and visual information (McBride and DeBello, 2015; McBride et al., 2008). Incoming axonal projections, carrying visual information, establish a topographic map within the external nucleus of the inferior colliculus and form synaptic clusters on the dendrites of the post-synaptic neurons. To manipulate the system, DeBello and colleagues placed a prism in front of the eye, which shifted the optical field by several degrees. This manoeuvre induced a repositioning of the axonal projections to correct for the shift. Like the former axons, the new axonal projections also formed synaptic clusters on the receiving dendrites. Interestingly, the degree of clustering represented by the mean inter-synaptic distance correlated with the physiological functioning. Highly active brain areas had a lower mean inter-synaptic distance while the total number of contacts was unaffected, indicating stronger synaptic clustering. In the 'former' axonal area, the synaptic contacts became more scattered and activity decreased (McBride et al., 2008). These findings indicated that synaptic mapping according to Mel's hypothesis could be necessary for signal processing within neuronal networks.

1.2. Experience driven morphological clustering

Multiple follow up studies have further associated morphological clustering of synapses with the processing of information (Table 1/Yang et al., 2009; Makino and Malinow, 2011; Fu et al., 2012; Zhang et al., 2015;). For instance, the link between synapse clustering and information processing has been shown in sensory deprivation experiments. *In vivo* labelling of α – Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors positive spines by expression of SEP-GluA1 (super-ecliptic pHluorin), a pH-sensitive AMPA receptor subunit which becomes fluorescent upon insertion within the plasma membrane, revealed that, in the sensory cortex of mice AMPA receptor-rich synapses are often organized in morphological clusters (Makino and Malinow, 2011). This defined organization is lost after sensory deprivation by cutting off the whiskers. On the other hand, training and input of new sensory information can promote the formation of clusters over a period of a few days (Fu et al., 2012). Learning of new motor skills induces growth of new synapses close to strong/larger long-lasting synapses but to a lesser extent near dynamic appearing and disappearing spines (Fu et al., 2012). This process promotes clustered synaptic organisation. The occurrence of synaptic clustering is not limited to studies using experimentally induced stimuli. Labelling of functional synapses within the hippocampus revealed that mice kept in a home cage environment also display synaptic clustering, suggesting that morphological grouping of functional synapses is a process to preserve acquired experiences following spontaneous behaviour (Druckmann et al., 2014).

1.3. Nonlinear integration of synaptic input

Each individual neuron integrates multiple synaptic inputs based on strength and timing and, thereby, forms an integrative unit for information processing. The depolarization of synaptic inputs has an add-on effect, when their timing aligns, which can meet the threshold for the initiation of an action potential at the axon initial segment. How neurons integrate their synaptic inputs is not fully understood. Attempts to model synaptic integration resulted in two different representations, one explaining synaptic integration following a linear model and another using nonlinear integration (Major et al., 2013; Jadi et al., 2014). In the linear model, each synaptic input contributes equally to the initiation of an action potential and their inputs are summed. As a result, the number of synaptic inputs correlates linearly with the level of depolarization. The nonlinear model includes a local integration of synaptic inputs at dendritic branches. In this model the contribution of each synapse to the initiation of an action potential is depending on its local environment at the dendritic segment. When the intercellular environment is depolarized, NMDA receptors lose their Mg^{2+} block and prime additional depolarization by their opening. Further, local voltage-gated ion channels may be opened and contribute to depolarization and molecular signalling. Activation of multiple synapses, as co-activation of synaptic clusters, can lead to a high depolarization in dendritic segments, which does not linearly correlates with the number of synaptic inputs (Polsky et al., 2004; Palmer et al., 2014). Instead, the local membrane potential forms a nonlinear, sigmoid curve and eventually creates a higher depolarization at the soma compared to linear integration. Nonlinear integration has been observed in pyramidal neurons in different brain regions (for review see Major et al., 2013). Synaptic clustering and the initiation of NMDAR spike makes neurons easily excitable by a relative low number of active synapses. A recent study shows that pyramidal neurons within the visual cortex of ferrets make efficient use of clustered input and nonlinear integration to gain a directional specificity for moving objects (Wilson et al., 2016). *In vivo* imaging showed that the number of clustered inputs, activated by a grid