Neurobiology of Learning and Memory 138 (2017) 3–9

Contents lists available at ScienceDirect

Neurobiology of Learning and Memory

journal homepage: www.elsevier.com/locate/ynlme

Dendritic spines: Morphological building blocks of memory

Menahem Segal

Department of Neurobiology, The Weizmann Institute, Rehovot 76100, Israel

ARTICLE INFO

Article history:
Received 6 April 2016
Revised 22 May 2016
Accepted 12 June 2016
Available online 14 June 2016

Keywords:
Dendritic spine
Memory
LTP
Calcium

ABSTRACT

The introduction of novel technologies, including high resolution time lapse imaging in behaving animals, molecular modification of the genome and optogenetic control of neuronal excitability have revolutionized the ability to detect subcellular changes in the brain, associated with learning and memory. The sequence of molecular cascades leading to formation, longevity and erasure of memories are being addressed in growing number of studies. Still, major issues concerning the relationship between the morphology and physiology of dendritic spines and memory mechanisms and the functional, neuronal network relevance of such parameters remain unsettled. The present review will summarize recent studies related to the immediate and long lasting changes in density, morphology and function of dendritic spines and their parent neurons following exposure to plasticity-producing stimulation in vivo and in vitro. Standing issues such as the relations between volume/shape and longevity, with respect to different classes of memories in different brain regions will be addressed. These studies indicate that the rules governing the structure/function relations of dendritic spines and memory in the brain are still not conclusive.

1. Introduction

Long term memory has always been intuitively associated with morphological changes in the brain. Ever since their first description by Ramon Y Cajal, dendritic spines have been demonstrated to undergo significant changes in size, density and shape, relative to other organelles, and consequently they have been postulated to underlie the anatomical locus of plasticity. Thus, short term dynamic alterations in synaptic strength are assumed to be converted to long lasting stable morphological changes which underlie the '*memory trace*'.

The diversity of morphological changes following exposure to plasticity-producing stimulation has been summarized before (Sala & Segal, 2014). While the initial morphometric studies which compared populations of spines in fixed tissue have yielded important information, showing that dendritic spines can undergo distinct brain region-specific changes following an intense experience, they were not informative with respect to the exact nature of the changes that a given spine undergoes following such an intense experience.

The ability to visualize individual dendritic spines over extended periods of time, using in vivo time-lapse imaging, was introduced over two decades ago (Guthrie, Segal, & Kater, 1991; Müller & Connor, 1991). It allows an analysis of changes that take place in specific dendritic spines in response to plasticity-producing stimulation. The advantages of the time lapse imaging over the more traditional counting and measuring of different populations of spines are obvious. Consequently, there was a tremendous increase in the amount of information accumulated in the past decade about the molecular mechanisms acting on dendritic spines during the process of neuronal plasticity, as evidenced by the large number of review articles (over 100) published in the past few years (e.g. DeFelipe, 2015; Maiti, Manna, Ilavazhagan, Rossignol, & Dunbar, 2015; Nishiyama & Yasuda, 2015; Okabe, 2012; Segal & Korkotian, 2015; Villalba, Mathai, & Smith, 2015; Vose & Stanton, 2016).

Once a spine is formed, how long does it take to become functional, and to react to presynaptic stimulation? There are reports of different time scales, from minutes to days and weeks but the verdict is not out yet. These issues are dealt with herein only as they are relevant specifically to learning and memory mechanisms. In this context, the critical issue concerns the time at which a spine change can be correlated with 'memory'. Likewise, once a spine is formed, how stable it is, and what might cause it to disappear/shrink; does spine disappearance underlies extinction of a memory? Also, given the large number of different families of molecules assumed to be necessary for the formation of spines, are all spines equipped with the same molecular cascades, or are spines in different brain structures endowed with different molecules, which may cause different morphologies and perhaps functions? One of the

E-mail address: Menahem.segal@weizmann.ac.il

http://dx.doi.org/10.1016/j.nlm.2016.06.007
1074-7427/

issues that complicates the analysis of spine changes in association with plasticity is the preparation and the wide variety of methods to induce plastic changes; The dissociated tissue culture has the advantage of ability to produce high resolution time lapse images of spines, but the unclear cell type and the natural environment of the cell are very different from those of the real brain. The slice culture combines advantages of the culture, with the organization of the tissue in vivo. On the other extreme, the brain of the freely moving animal is highly challenging technically, and the reaction of the tissue to the damage produced by the imaging system in the brain is often under-estimated.

Finally, current studies on spines and 'learning' are mostly correlative, in that changes in spines are correlated with formation of memory, or its erasure, but no clear causality is presented, with some recent exceptions (below).

2. What are the functional demands on 'plastic' spines?

A key issue in spine research is the functional correlates of the heterogeneity of spine morphologies. Why are there short and long, stubby and mushroom spines, do they serve different functions, or are only the 'mature' mushrooms functional, and the other types are 'silent' contacts, to be used in the future upon demand? On the functional end, the attempt to narrow down the wealth of memory processes, including working, procedural, declarative, semantic and perceptual, into a minimal number of electrophysiological and molecular 'building blocks' within dendritic spines is at best only a crude approximation. Also, memories are embedded in different brain areas, for different lengths of time and may utilize different molecular cascades (Milner, Squire, & Kandel, 1998). In fact, despite extensive studies utilizing pharmacological and genetic manipulation of specific genes related to plasticity, there is still no clear link between different plasticity processes and spine morphologies. It is plausible that different types of memories obey different electrophysiological rules, and may leave different morphological fingerprints in the brain. This is yet to be explored.

The traditional classification of spines to different shapes, mushroom, thin and stubby assigned different roles to these shapes. However, a recent revolutionary time lapse imaging study, using super resolution STED microscopy (Tønnesen, Katona, Rózsa, & Nägerl, 2014) suggested that 'stubby' spines are in fact 'mushroom' spines, and that the classification of spines to categories is obsolete. The reason for the demarcation of 'stubby spines' is that earlier studies employing lower resolution microscopy could not resolve the neck of these spines, and thus they were considered a different category. Interestingly, in their study Tønnesen et al. (2014) assigned an important plastic role to the neck width, not clearly measureable with the more conventional confocal microscope. While the proportion of stubby spines may have been overestimated in the earlier studies, 3D electron microscopic studies (e.g. Medvedev et al., 2010) show that stubby spines do exist in on central neurons and their physiological and biochemical identity is still unclear.

At the cellular level, there are different plasticity-producing stimulation patterns which may use different molecular cascades to form morphological plasticity. For example, while the dominant mode of producing LTP in brain areas such as the hippocampus involves tetanic activation of the NMDA receptor (Harris, Ganong, & Cotman, 1984; Herron, Lester, Coan, & Collingridge, 1986), there is a distinct non-NMDA mediated LTP, which is assumed to activate release of calcium from stores (Grover & Teyler, 1990; Raymond & Redman, 2006). Is it possible that these two ways to generate LTP are funneled into the same morphological changes in the spine? Also, spike timing dependent plasticity (STDP), metaplasticity and chemical LTP (Goldin, Segal, & Avignone, 2001), are assumed to involve changes in distributions of glutamate receptor subtypes following a change in intracellular calcium concentration and affect synaptic responses for extended periods of time. Are all these plastic processes sharing the same morphological change?

2.1. Longevity of memories

Different types of memories have different time course; motor memory (e.g. speech, bicycle ride, piano playing) is persistent, while working memory is highly labile. Can we assume that all types of memories are 'stored' in dendritic spine morphology? Recent studies on motor learning in vivo addressed these issues, and will be discussed below.

2.2. Direct vs indirect effects on spine morphology

There are several ways to generate changes in spine morphology. One can activate individual spines, either by electrical stimulation or by flash photolysis of caged glutamate. The latter stimulation also activates non-synaptic glutamate receptors, which reside on spine heads, but also on dendritic shaft (Zhang, Cudmore, Lin, Linden, & Huganir, 2015). In contrast, the entire network can be activated by protocols such as 'chemical' LTP or LTD which will cause obvious changes in a large proportion of the imaged spines, but not be specific to a given spine, and in fact can be caused by changes in soma/dendritic excitability (Frick, Magee, & Johnston, 2004). Finally, two interesting possibilities to be considered are that a cluster of adjacent spines rather than an individual one is the elementary unit of neuronal plasticity. This possibility has been alluded to recently (Cichon & Gan, 2015). Likewise, single axons making new multiple spine contacts with a given dendrite (Bartol et al., 2015; Kasthuri et al., 2015) can modify the view of the elementary unit of 'memory'.

3. Short term morphological and functional plasticity of spines: formation of new spines

Early time-lapse imaging of dendrites following LTP-inducing protocol described the formation of new spines in cultured hippocampal slices (Engert & Bonhoeffer, 1999 and see Fig. 1). The new spines were detected within 30 min after the induction of LTP in the slice, and amounted to an addition of roughly 10–15% to the existing (rather low density) population of spines. Interestingly, the authors did not report on a change in volume of the existing spines on these dendrites. Similar observations were made by Shi et al. (1999) who described NMDA receptor-dependent formation of new filopodia in response to tetanic stimulation in cultured hippocampal slices. In neither of these studies was there any indication that the growth of the new spines or filopodia is associated with formation of new synapses, although the electrophysiological responses recorded in the slice showed the typical rapid growth of synaptic responses associated with LTP generation. These issues were addressed in a study with dissociated hippocampal neurons (Goldin et al., 2001; Ovtscharoff et al., 2008) where new spines were found to be attached to synaptophysin containing terminals. Still, the issue of when do nascent dendritic spines become functional was subject to further explorations. Bonhoeffer and colleagues (Nagerl, Kostinger, Anderson, Martin, & Bonhoeffer, 2007) combined confocal microscopy with EM studies of cultured hippocampal slices to suggest that physical contacts with presynaptic fibers are made within tens of minutes after enhanced activation, but mature spines with both pre- and post synaptic elements, indicating a functional synapse, are formed only 15–19 h after the plasticity-evoking stimulation. In a similar approach, Zito, Scheuss, Knott, Hill, and Svoboda (2009), also using cultured hip-