Review Article

Neuronal Remodeling and Dendritic Spines: A Review

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Abstract: The neurons show remodeling in their dendritic arbor and spine/synapse number in many brain regions including the hippocampus, amygdala and the prefrontal cortex. The dendritic spine density is reported to be changed due to experiences and stressful conditions. The dendritic spines are the small protrusions arising from the dendritic shaft of the neurons. They have basic shapes as large mushroom spines, short stubby spines and thin spines. The morphology of spines changes rapidly in response to various stimuli that may be internal such as hormones and external such as environmental changes. Dendritic spine density plays a major role in classification of principal neurons i.e. multipolar and pyramidal neurons. The principal neurons may be classified as sparsely spinous, moderately spinous and heavily spinous on the basis of density of spine over the dendritic branches. In response to environment dendritic remodeling takes place in the form of spine shapes, spine turnover and spine density etc. Synaptic plasticity primarily takes place in dendritic spines and enriched environment have positive effect while social isolation have negative effect on synapse formation. Exposure of animals to environmental complexity may improve the learning and memory by providing adaptive changes in the dendritic spine density.

INTRODUCTION

The adult brain is much more active and adaptable than previously believed, and neuronal remodeling involves growth and shrinkage of dendritic trees, turnover of synapses and neurogenesis in some areas of forebrain. Dendritic spines arise as small protrusions from the dendritic shaft of various types of neuron and receive inputs from excitatory axons. Dendritic spines on neurons were first described in the 1888 by the legendary neuroanatomist Ramon y Cajal [1, 2]. Dendritic spines have variety of shapes and sizes, suggesting a high degree of functional diversity. Spines occur at various densities depending on the neuronal type and are reported in all vertebrates [3] such as reptiles [4-14], birds [15-20] and mammals [21-23]. Most of the principal neurons are classified by taking spine density as one of the classification criteria. The morphology of spines is highly variable and they are commonly classified into three types: thin, mushroom and stubby (Fig. 1) [24]. The size of dendritic spines varies among brain areas, as well as between species according to their functional aspect [25].

The basic structure of synaptic spines was established early in evolution and appears to be roughly the same in all animal groups, but they have been studied best in mammals. Typical spines have a head and narrower neck region and project from the sides of dendrites [22, 26-30] (Fig. 1). They broadly come in three basic shapes: (a) large, mushroom spines with enlarged head regions, (b) short, stubby spines without a clearly defined neck, and (c) thin spines with a relatively slender head and neck [22, 31, 32]. Stubby spines are devoid of a neck [33] and are prominent between postnatal development [34].

Dendritic spines have been a source of fascination since long time and it is believed that these anatomical structures are involved in learning and memory. The capacity to learn and remember is undeniably critical for mammalian livelihood. It has long been assumed that changes in the structure and organization of synapses can be brought about by anatomical modifications of neurons [30, 35]. Dendritic spines, small protrusions found on the shaft of dendrites in the mammalian brain, are one aspect of cellular anatomy that may play a role in the expression of memory [35].

The majority of synapses in the brain are chemical synapses found on the synaptic specializations of dendrites. A chemical synapse consists of two membranes separated by a gap called the synaptic cleft. Neurotransmitters released from synaptic vesicles on the presynaptic side of the cleft diffuse across the cleft to activate receptors in the postsynaptic membrane. Because spines represent potential sites of postsynaptic excitatory input, an increase in their number can

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translate into an increase in the number of excitatory synapses [30, 36]. Thus, changes in the density of spines can have a major impact on the amount of excitatory neurotransmission and processing of information in a particular brain region. In present review, we surveyed the morphological aspects of the dendritic spines that are used in neuronal classification. In addition to this we also discussed the changes in dendritic spine density due to external stimulus in the form of enriched environment, hormonal stress etc., that have effects on the learning and memory.

MORPHOLOGICAL DIVERSITY OF DENDRITIC SPINES

The morphology of a spine can change rapidly through activity-dependent and independent mechanisms [35, 37-40]. In addition, thin, hair-like protrusions called filopodia, which lack a bulbous head, are found on dendrites of developing neurons (Fig. 1). They are transient structures that might receive synaptic input and can develop into dendritic spines [41, 42]. The structures of spines are linked to high number of biochemical reactions taking place inside the spine [43]. Spine heads form an asymmetric excitatory synapse with a presynaptic axon [44]. Calcium dynamics in spines revealed a close relationship between spine morphology and function [40]. The spine–neck geometry is an important determinant of NMDA receptor-dependent calcium signaling in spine heads and dendritic shafts [45]. Furthermore, there is evidence that the induction of long-term potentiation (LTP) correlates with spine enlargement [46].

The final determinant of spine morphology is the cytoskeleton. Spine heads contain actin filaments that interact with the plasma membrane and the PSD at their barbed ends (Fig. 1). In spine necks, actin filaments form long bundles (Fig. 1) [47]. It was shown that actin polymerization occurs within seconds of LTP, underlying the enlargement of dendritic spines [48]. Thus, there is good evidence that, at least for hippocampal synapses, the reorganization of the actin cytoskeleton is tightly linked to synaptic efficacy [35, 49].
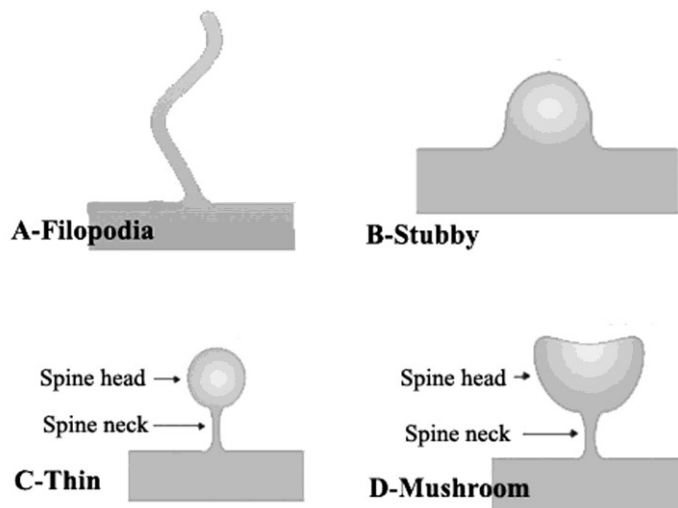

Fig 1. Structural and molecular organization of spine; Schematic drawings of spine morphologies based on the most common four-category classification

DENDRITIC SPINES AND NEURONAL CLASSIFICATION

Distribution of dendritic spines over the dendritic shaft have important role in the classification of neurons. The neurons are classified on the basis of the density of the dendritic spines present on the dendritic branches of the neuron. Neurons are sub-classified as highly spinous, moderately spinous and sparsely spinous on the basis of number of spines present in 10µm or 25 µm distance of the dendritic shaft [3, 5] (Fig. 2).

While describing medial cortex neurons in different reptiles various authors have taken the spine density as major criteria. In medial cortex of *L. pityusensis* Sparsely spinous horizontal neurons; Spinous pyramidal neurons; Spinous bitufted neurons; Small, sparsely spinous pyramidal neurons; Spinous multipolar neurons have been described [10]. In medial cortex of *P. hispanica* Heavily spiny granular monotufted, Heavily spiny bitufted neurons; Spiny bitufted neurons; Sparsely spiny bitufted neurons; Superficial multipolar neurons have been described [9]. Recent study in *M. carinata* and *H. flaviviridis*, describes the aspinous bipolar neurons; aspinous monotufted monopolar neurons; aspinous monotufted bipolar neurons; spinous monotufted monopolar neurons; spinous monotufted bipolar neurons; spinous bitufted bipolar neurons (heavily spinous bitufted bipolar neurons; spinous bitufted bipolar neurons; sparsely spinous bitufted bipolar neurons) and spinous multipolar neurons [3, 4, 6].
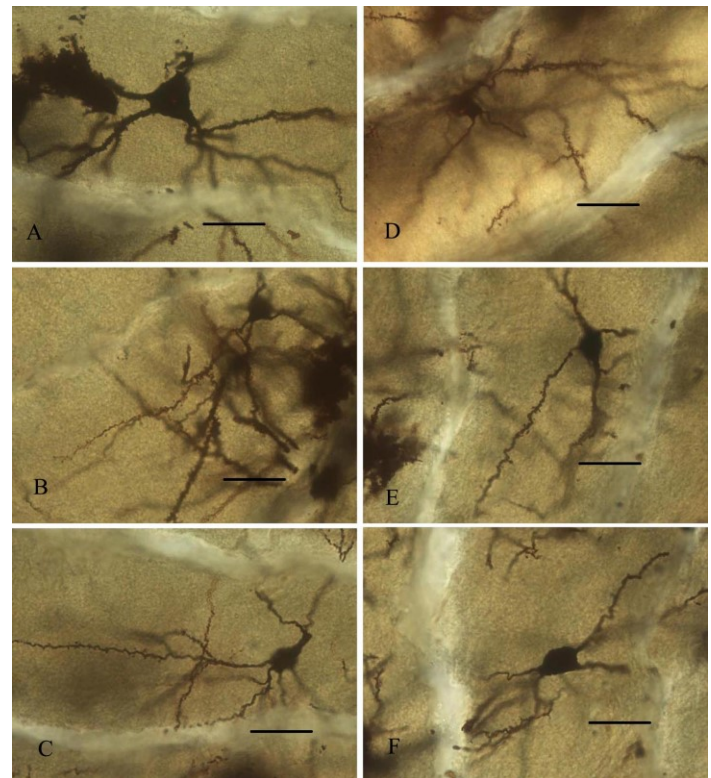

Fig. 2. Photomicrographs showing the Golgi impregnated pyramidal and multipolar neurons of the hippocampal complex of chick brain. (A) heavily spinous pyramidal neuron, (B) moderately spinous pyramidal neuron, (C) sparsely spinous pyramidal neuron, (D) heavily spinous multipolar neuron, (E) moderately spinous multipolar neuron, (F) sparsely spinous multipolar neuron, (Scale bar = 20µm)

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In the visual wulst region of bird, *Estrilda amandava* Pyramidal neurons are classified as moderately spinous and sparsely spinous; Multipolar neurons as highly spinous, moderately spinous, and sparsely spinous; Local circuit neurons (small and medium sized) as aspinous; stellate, sparsely spinous neurons [17]. However, in *Taenopygea guttata*, the multipolar type neurons which were small and medium sized with few spines, has been described as Local circuit neurons [50]. Spine density is significantly different among interlaminar basal dendrites of Indian bat. Spine density on the apical and basal dendrites of atypical pyramidal neurons is reported to be relatively higher than of typical pyramidal neurons in Indian bat [21].

ADAPTIVE CHANGES AND SPINE FLUCTUATIONS

Spine density in layer V pyramidal neurons of the primary visual cortex was found to be decreased in Golgi-stained material in mice when raised in total darkness from birth [51]. It is also shown that spine density can recover in some dendrites after few days of life in normal light conditions [52]. The spine density of dentate granule cells in the rat hippocampus, after an initial decrease due to entorhinal cortex lesions, subsequently returned to normal levels as a result of re-afferentation by sprouting of nearby axons [53]. These findings demonstrated the bidirectional nature of these morphological changes and indicated that the initial decrease in spine density was an adaptive response to changes in afferent input instead of a sign of injury to the postsynaptic neuron.

It has been shown that, at early postnatal ages, dendritic spines of cortical neurons of rat brain are highly plastic and spine turnover decreases with age [54, 55]. The total spine number is found to be stable in adults over time due to comparable rates of spine elimination and their formation [56-58]. However, experience has tremendous effect on spine density and spine remodeling occurs in the adult brain due to induction of experience [58].

NEURONAL REMODELING TO CHANGING ENVIRONMENT

The adult brain possesses a remarkable ability to adapt and the minute structural changes in the brain due to the response to the environment can be noted in the form of neuronal replacement, dendritic remodeling (dendritic spine shapes) and synapse turnover (dendritic spine density) [59]. The brain is capable of rewiring after brain damage [53] and also able to grow and change as seen by spine turnover, dendritic branching, angiogenesis and glial cell proliferation during cumulated experience [60]. More specific physiological changes in synaptic connectivity have been recognized in relation to environmentally directed plasticity of the adult songbird brain, showing seasonally varying neurogenesis in restricted areas of the brain [61-63].

Stress hormones have major effect on the function of the brain by changing the structure of neurons. The hippocampus is one of the most sensitive region of the brain which shows the effect of the stress hormones. Within the hippocampus, the input from the entorhinal cortex to the dentate gyrus is ramified by the connections between the dentate gyrus and the CA3 pyramidal neurons [64]. There is adaptive structural plasticity in dentate gyrus, where the new neurons produced continuously throughout adult life, and CA3 pyramidal cells show a reversible dendritic remodeling during hibernation and chronic stress [64-67]. This type of plasticity may be protective against permanent damage and the hippocampus undergoes a number of changes in response to acute and chronic stress to adapt new environmental conditions.

The hippocampus involves replacement of neurons such as the subgranular layer of the dentate gyrus contains cells that have some properties of astrocytes which give rise to granule neurons [68, 69]. These cells appear as clusters in the inner part of the granule cell layer, where some of them will go on to differentiate into granule neurons within few days. There are many hormonal, neurochemical and behavioral modulators of neurogenesis in the dentate gyrus, including estradiol, antidepressants, IGF-1, voluntary exercise and hippocampal-dependent learning [70-72].

Remodeling of dendrites and synapses in the hippocampus, amygdala and prefrontal cortex is also a type of structural plasticity. In hippocampus, chronic restraint stress CRS; daily for 21 days causes retraction and simplification of dendrites in the CA3 region of the hippocampus [64, 73]. Such dendritic reorganization is independent of adrenal size and found in both dominant and subordinate rats undergoing adaptation to psychosocial stress in the visible burrow system [74].

In species of hibernating mammals, dendritic remodeling is a reversible process and occurs within hours of the onset of hibernation and it is also reversible within hours of wakening of the animals from torpor [65-67, 75]. This shows that changes in dendrite length and branching are a form of structural plasticity not "damage" and the reorganization of the cytoskeleton is taking place rapidly and reversibly [59].

ENVIRONMENTAL ENRICHMENT AND NEURONAL PLASTICITY

Postischemic housing in an enriched environment significantly improves the functional outcome after permanent focal brain ischemia in the rat [76-78]. Different mechanisms may contribute to the environmental effects in the postischemic brain. Dendritic spines are the primary postsynaptic targets of excitatory glutamatergic synapses [79-81]. Dendritic spines, as bridges between axons and dendrites, were proposed as primary sites of synaptic plasticity [82]. The spine cytoskeleton consists of actin filaments, and it has been shown that the shape of spines can change rapidly [83, 84]. Spines are calcium compartments with a constantly changing ability to compartmentalize calcium [40, 85]. Housing intact animals in an enriched environment can increase dendritic branching and number of synapses and dendritic spines [86-89], whereas rearing animals in social isolation has the opposite effect [90, 91].

DENDRITIC SPINES IN LEARNING AND MEMORY

Dendritic branching patterns and spine density determine which populations of afferent axons terminate upon a population of neurons and the relative weighting of each type

of input. The vast majority of synaptic inputs onto neurons are on dendrites or dendritic spines, and the amount of synaptic input, cells receive, varies with the amount of dendritic surface available [29]. Most of the excitatory synapses are on dendritic spines, and changes in the number of dendritic spines are associated with experiences like learning or environmental complexity [92-95]. Thus, changes in dendritic morphology in the form of spine density are reliably associated with functional alterations induced by neuroendocrine changes [96-99].

There are numerous evidences in literature that behavioral training can alter different aspects of dendritic anatomy, such as length and branching of dendrites, dendritic spine density [92, 100]. There is a relationship between the presence of dendritic spines and the formation and expression of new memories due to new experiences in the life.

Environmental complexity can alter the presence of dendritic spines and these complex experiences can affect learning ability on a variety of tasks [101-103]. Moreover, animals exposed to the complex environment showed faster acquisition in the water maze task [102, 104] and spine density analysis showed that the enriched animals possessed a higher density of dendritic spines on pyramidal cells in the CA1 region of the hippocampus. Similarly, Rampon et al. [103] reported a 20% increase in hippocampal dendritic spine density as well as enhanced performance on both object recognition and fear conditioning tasks following environmental enrichment. These results suggest that experience leading to increased spine density can also improve new learning. It should be noted that enrichment also induces changes in spine number in cortical regions [87].

CONCLUSIONS

A hundred years after Ramon y Cajal, the relationship between structure and function in neurons are still being discovered. The dendritic spine morphology have major role in neuronal classification in various animal groups [3, 4, 6, 9, 10, 17, 18, 50]. The pattern of dendritic arborization is clearly related to connectivity. Similarly, the synaptic specializations extended by dendrites contribute significantly to connectivity. They allow thin dendrites to reach multiple axons such that larger numbers of synapses interdigitate in a relatively small brain volume [105]. The enormous diversity in the structure, composition, and plasticity of dendrites and their synaptic specializations suggests that the functional contributions of these structures to mind and brain are enormously diverse.

Hormonal influences in the form of stress may also be considered along with the effects of experience in understanding how the brain adapts to challenges. Stress affects brain circuits in ways that promote adaptive plasticity by remodeling dendrites. Although repeated stress can cause deleterious effects on the brain neurons, but the primary role of the stress response is to promote adaptation [106].

There are individual differences in the adaptive management in response to stress, based upon the individual experiences, early in life and in adult life. Early life experiences, positive or negative, in school, at work or in family relationships, have greater role in terms of how an individual reacts to new situations [107]. Depression and anxiety are a natural reaction to major life events and when the individual fails to "bounce back", they need treatment. Most of these effects are seen on brain structure and function [108-111].

Throughout the life span, the external environment and internal body conditions can modify dendritic form and other aspects of neural circuitry [93]. How changes in spine density would alter processes involved in learning and memory remains to be undetermined question for future researchers [112]. The presence of spines may enhance synaptic efficacy and thereby enhances the excitability of the network involved in the learning process. Thus, learning is not necessarily dependent on spine density changes, but rather changes in the presence of dendritic spines provide anatomical support for the processing of novel environmental information that will be helpful in memory formation.

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