Dendritic Spine

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Dendritic spines are small, bulbous protrusions along neuronal dendrites where most of the excitatory synapses are located. Dendritic spine density in normal human brain increases rapidly before and after birth achieving the highest density around 2–8 years. Density decreases during adolescence, reaching a stable level in adulthood. The changes in dendritic spines are considered structural correlates for synaptic plasticity as well as the basis of experience-dependent remodeling of neuronal circuits. Alterations in spine density correspond to aberrant brain function observed in various neurodevelopmental and neuropsychiatric disorders. Dendritic spine initiation affects spine density. In this review, we discuss the importance of spine initiation in brain development, learning, and potential complications resulting from altered spine initiation in neurological diseases. Current literature shows that two Bin Amphiphysin Rvs (BAR) domain-containing proteins, MIM/Mtss1 and SrGAP3, are involved in spine initiation. We review existing literature and open databases to discuss whether other BAR-domain proteins could also take part in spine initiation. Finally, we discuss the potential molecular mechanisms on how BAR-domain proteins could regulate spine initiation.

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1. Introduction

Dendritic spines are tiny protrusions along neuronal dendrites. In spiny neurons, dendritic spines form the site for excitatory synapses. Spines are dynamic structures and their shape, size, and density change with developmental age, location, and synaptic activity [1][2][3]. Studies on electron microscopy (EM) have classified dendritic spines into three types based on their morphological features: mushroom, thin, and stubby spines [4]. Mushroom spines are defined by a large head and short, thin neck, whereas thin spines have a small head and long, thin neck. Stubby spines do not have a well-defined head and neck due to their wide neck, with approximately the same diameter as the head. Several imaging studies have shown that dendritic spines arise from dendritic filopodia [5][6][7]. These newly formed filopodia are highly dynamic, and repeatedly extend and retract to form connections with the presynaptic axons [8]. Changes in actin dynamics are central for structural and functional alterations of dendritic spines as actin is a major cytoskeletal component of dendritic spines [9][10][11].

The Bin/Amphiphysin/Rvs (BAR) domain protein superfamily consists of a large and diverse set of multi-domain proteins known for dynamically remodeling the cellular membranes [12]. Unique structural and functional features of BAR proteins in addition to their specialized role in various cellular processes related to membrane deformation make them a highly relevant protein family also in the context of dendritic spine initiation.

In this review, we will first discuss the physiological importance of dendritic spines. Then we will review the known molecular pathways underlying dendritic spine initiation. We will further discuss whether BAR domain-containing proteins could have a broader role in spine initiation. The first aim of this review is to identify unknowns—gaps in knowledge which should be studied in future. These open questions are listed at the end of each section. The second aim of this review is to identify BAR domain-containing proteins which could take part in spine initiation. Based on the literature review, we identified six BAR-domain proteins, ABBA, SrGAP1, SrGAP4, Toca1, GAS7, and FER, which are good candidates to be novel spine initiation factors.

2. Brain Development

Human brain development is characterized by a rapid increase in synapse density in early development and then a decline to the stable adult level. Electron microscopy study quantitated synaptic density of layer 3 of the middle frontal gyrus in 21 human postmortem brains ranging from newborn to age 90 years [13]. Synaptic density in neonatal brains was already high—in the range seen in adults. Synaptic density increased during infancy, reaching a maximum at age of 1–2 years which was about 50% more than the adult mean. Synaptic density declined between ages of 2 and 16 years, and was constant throughout adult life (ages 16–72 years). There was a slight decline in synaptic density in the brains of aged people (ages 74–90 years) [1][13]. Tang et al., 2014 analyzed the spine density of children of age 3–8 years and 13–18 years. This analysis revealed that spine density decreased significantly with the age of the children [14]. The data suggest that in humans, spine density increases during early development, reaching a maximum density at around 2–8 years, and after this, spine density decreases between 8 and 18 years, reaching the density which is maintained through adulthood. It is unclear why this “overproduction” of dendritic spines occurs during early development, but one possibility is that excessive connections create a “preliminary” network of connections which can then be defined by experience-based pruning of spines.

Orner et al., 2014 quantitated spine density for the first year of mouse life starting from postnatal day 15 (P15). They showed that in mice, there is first a faster decrease in spine density between P15 and P90, and then a slower decline between P90 and P360 [15]. Mice are considered to reach adulthood at around the age of P90. Spine morphology shifted from filopodia to mushroom spines as the animals matured [15]. Although the spine density is maintained at similar level during adulthood, individual spines can still be remodeled. Some spines are formed *de novo*, some stabilized, some change and some are eliminated [16].

Open questions: How does the increase in spine number change to a decrease in spine number during adolescence? Is it due to change in spine initiation rate, stabilization rate or pruning rate? If it is due to change in spine initiation rate, does the spine initiation factor change (e.g., expression of different proteins) or only the regulation of initiation (e.g., changing phospholipid composition)?

3. Defects in Spine Initiation May Play a Role in Neurological Diseases

Dysregulation of dendritic spine shape, size, or number has been strongly associated with various neurodevelopmental, neuropsychiatric, and neurodegenerative disorders [17][18][19][20][21]. Alterations in dendritic spine initiation rate can directly affect spine density and therefore cause aberration in the number of synapses, signaling, and plasticity mechanisms, as well as defects in neural circuitry, ultimately leading to disease-associated cognitive and behavioral symptoms [1][21]. Here, we first review in general some examples of the diseases that have been associated with alteration in dendritic spine density and then discuss how aberrant spine initiation might be directly or indirectly linked with the disease pathogenesis.

3.1. Autism Spectrum Disorder (ASD)

ASD is a spectrum of neurodevelopmental conditions characterized by repetitive, stereotyped behavior and deficits in communication and social interaction. ASD affects 0.9% of children and diagnosis typically occurs around 2–3 years of age [22]. Accumulating evidence from family and twin studies suggests that genetics has an important role in ASD pathogenesis [23]. Numerous ASD susceptibility genes converge on the cellular pathways modulating proper synapse formation and function [22][23]. Interestingly, ASD brain is associated with significantly high dendritic spine density in various brain regions, such as the frontal, temporal, and parietal lobes [24], as well as the lateral nucleus of the amygdala [25]. This is consistent with other studies showing that infants and young children with ASD often show signs of early brain overgrowth [26][27]. Moreover, functional magnetic resonance imaging (fMRI) studies in children with ASD have provided evidence for functional hyperconnectivity within various cortical and subcortical areas of the brain [28]. Greater functional connectivity in the brain has also been linked to more severe social impairment, suggesting that this might be the underlying reason behind limited flexibility, or the need for rigidity and sameness typically observed in the behavior of ASD patients. Likewise, several studies suggest that altered functional connectivity could be the origin of hyper- or hypo-sensitivity of ASD patients to external sensory stimuli [29][30]. At the same time, hyperconnected brain circuits might result in over-focused and undivided attention, allowing some portion of ASD diagnosed people to have certain extraordinary cognitive abilities at the expense of dynamic social interactions [28][31][32].

Open questions: How often is increased spine initiation the underlying cause of increased spine density in ASD? Are spine initiation factors associated with ASD? Or is the cellular signaling regulating spine initiation altered in ASD (e.g., PTEN, which dephosphorylates PI(3,4,5)P3 to PI(4,5)P2, is strongly associated with ASD (48)).

3.2. Schizophrenia

Schizophrenia is a heterogenous neurodevelopmental disorder with impairments in thought, perception, cognition, affect, and motivation [33]. The symptoms of schizophrenia typically emerge during late adolescence or early adulthood, and it occurs in about 0.5–1% of the world population [19]. Schizophrenia has a strong genetic component, with 6–17 times higher risk among first-degree relatives and 40–50 times higher risk in the monozygotic twin of an affected individual compared to the general population [19][34]. Meta-analysis of several magnetic resonance imaging (MRI) studies has revealed that people with schizophrenia have reduced hippocampal and overall brain volume and increased ventricular volume compared to that of the healthy controls

[35]. The robust loss of cortical gray matter during adolescence [36] might partly account for decreased brain volume. Moreover, schizophrenia has been characterized by decreased dendritic spine density in various brain regions, including prefrontal cortex and auditory cortex [37][38][39], suggesting reduced connectivity and functional hypoactivity.

Open questions: How often is decreased spine initiation the underlying cause of decreased spine density in schizophrenia? Are spine initiation factors associated with schizophrenia? Do their expression levels decrease in schizophrenia?

3.3. Alzheimer's Disease (AD)

AD is the most common form of dementia and is characterized by progressive memory loss along with cognitive, behavioral, and affective changes [18]. Although early-onset AD may occur, it is typically diagnosed in people over the age of 65 [17]. The exact cause of AD is not known, but it is likely to be the result of both genetic and environmental factors—about 70% of the risk of developing AD is attributable to genetics [40], and the rest is attributable to several acquired risk factors, including cardiovascular diseases, hypertension, diabetes, obesity, and dyslipidemia [41]. Accumulation of β-amyloid plaques, neurofibrillary tangles (NFTs) in various brain regions, including the hippocampus and cortex, and the loss of synapses and dendritic spines are the major pathophysiological hallmarks of AD brain [42][43].

Open questions: Are there changes in expression levels of spine initiation factors in AD? Why does spine initiation not compensate the loss of spines?

3.4. Intellectual Disability (ID)

ID was previously termed mental retardation (MR). It is a neurodevelopmental disorder that causes significant impairment in cognitive abilities and adaptive skills [44]. ID can be part of a clinical syndrome together with various other congenital abnormalities (neuroendocrine and psychiatric symptoms, body and brain malformations, metabolic defects) or non-syndromic with no other obvious anatomical or functional abnormalities [45]. ID affects about 2–3% of children and young adults, and the level of severity and underlying causes are extremely heterogeneous [46]. Various environmental and genetic factors including premature birth, fetal alcohol syndrome, prenatal infections, chromosomal abnormalities, and single-gene mutations can cause ID. In many cases, etiology cannot be established [47]. The most common genetic cause of ID is trisomy of chromosome 21, which causes Down's syndrome, and the most common single-gene-caused ID is fragile X syndrome, caused by trinucleotide CGG repeat expansion of *FMR1* gene [45]. Neuronal cells in the brain of patients with various forms of ID consistently show abnormalities in dendrite/dendritic spine morphology and densities [48][49]. Despite extreme heterogeneity in terms of causes and symptoms of ID, striking similarities in spine pathologies have led to the idea that the deficits associated with ID disrupt the common intracellular pathways leading to the development of the dendrite and dendritic spine cytoskeleton [45][48][50].

3.5. Neuropathic Pain

Neuropathic pain arises from a lesion or disease of the somatosensory system and is notoriously difficult to treat [51][52]. Neuropathic pain tends to last far beyond the time of injury and can become lifelong. This persistent state suggests that the body has learnt the pain and keeps the learnt memory trace active although the cause of the pain has been cured. A two-photon in vivo imaging study showed that neuropathic pain first triggers a transition from spine elimination to increased *de novo* spine formation (at day 3), which is followed by an increase in mushroom spine formation (at day 7) [53]. Aberrant dendritic spine formation seems to be a general mechanism underlying chronic pain as increased spine density was observed in several preclinical neuropathic pain models, including diabetic peripheral neuropathy, spinal cord injury (SCI), peripheral nerve injury, cutaneous burn, and chemotherapy-induced peripheral neuropathy [54][55][56][57][58][59]. Each of these models displays a similar pattern of spine changes, including a greater number of stable/mature mushroom-shaped spines, an increase in overall spine density, and redistribution of spines toward the dendritic branches closer to the soma [60]. Based on these results, proteins regulating formation and maintenance of dendritic spines are considered as potential targets of novel pain therapeutics [53][59].

Open questions: SrGAP3 is involved in the formation of neuropathic pain (see below), but are there other initiation factors that could be involved? Can we find clinically relevant means to inhibit the pain-induced “learning” by finding ways to inhibit spine formation?

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