testing spatially accurate computer simulations of complex biochemical signaling machinery (71, 72). We have come a long way toward understanding how synapses work, but we still have far to go.

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REVIEW

Actin-Based Plasticity in Dendritic Spines

Andrew Matus

The central nervous system functions primarily to convert patterns of activity in sensory receptors into patterns of muscle activity that constitute appropriate behavior. At the anatomical level this requires two complementary processes: a set of genetically encoded rules for building the basic network of connections, and a mechanism for subsequently fine tuning these connections on the basis of experience. Identifying the locus and mechanism of these structural changes has long been among neurobiology's major objectives. Evidence has accumulated implicating a particular class of contacts, excitatory synapses made onto dendritic spines, as the sites where connective plasticity occurs. New developments in light microscopy allow changes in spine morphology to be directly visualized in living neurons and suggest that a common mechanism, based on dynamic actin filaments, is involved in both the formation of dendritic spines during development and their structural plasticity at mature synapses.

Dendritic spines are the contact sites for most excitatory synapses in the brain (1, 2) where they occur in vast numbers, estimated to be

on the order of 10^{14} for the human cerebral cortex. Spines are particularly associated with neurons where inputs from diverse sources converge, such as pyramidal cells in the cerebral cortex, whose dendrites commonly have several thousand spines, each representing an excitatory synapse (3-6)(Fig. 1, A and B). Characteristically, spine morphology consists of an expanded head connected to the dendrite shaft by a narrower neck (Fig. 1, C and D), but "stubby" spines lack the neck, whereas filopodia-like "headless" spines also occur, especially during development (4, 7-9). This distinctive architecture depends on a specialized underlying structure of cytoskeletal filaments. In contrast to the dendritic shaft, whose cytoplasm is

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dominated bymicrotubules (Fig. 1B) (4, 10), the spine cytoskeleton consists of microfilaments that form longitudinal bundles in core regions of the head and neck and a meshwork of fine fibers at its periphery (4, 11). As in other cell types, these microfilaments are composed of actin, which is present throughout the spine cytoplasm (12-14) and is closely associated with the postsynaptic density (PSD) (Fig. 1, C and D), a disk-shaped organelle attached to the postsynaptic membrane that provides a structural framework for localizing functional molecules including neurotransmitter receptors and ion channels (15-20).

Immunohistochemical and cell transfection studies indicate that actin levels in spines are far higher than in neighboring structures (13, 14, 21) (Fig. 1B). This concentrated spine actin consists exclusively of the cytoplasmic isoforms, β and γ , which are targeted to spine heads by a sequence-specific mechanism (21). High actin concentrations at cell margins are often associated with dynamic changes in cell shape (22-24), and time-lapse imaging of living neurons has revealed spontaneous shape changes in dendritic filopodia and spines (25-28) which are sensitive to drugs that block actin dynamics (26, 27). With the use of actin coupled to green fluorescent protein (GFP-actin), dynamic activity of the actin cytoskeleton in spines has been directly visualized, confirming its capacity for driving changes in synaptic morphology (26). In these imaging studies the rapid and spontaneous changes in spine shape contrast conspicuously with the relative morphological stability of the underlying dendrite, supporting the hypothesis that dendritic spines may be especially equipped for subserving morphological plasticity (5, 6, 19, 29-36).

Dendritic Spines and Developmental Plasticity

During brain development neuronal circuits are established in three distinct phases. The first involves the initial "wiring up" of the nervous system during embryogenesis. This occurs independently of neuronal activity through mechanisms that involve secreted and surface-bound molecular guidance cues (37, 38). The second phase takes place postnatally during a relatively short critical period when synaptic connections are refined by sensory and motor experience (39-42). The importance of this activity-dependent process for the correct patterning of neuronal circuits has been demonstrated by experiments in which axons from the eye, surgically rerouted into the auditory system, were shown to respecify circuits in the auditory cortex so that they acquired response properties characteristic of the visual cortex (43, 44). In the third phase, adulthood, plasticity is much reduced, but substantial changes in synaptic connectivity can nevertheless occur both after damage to sensory input pathways and as a result of training (45-47).

Experimental data suggest that actin-based motility may be involved in all three of these stages. Growth cone turning, which underlies pathfinding by developing axons and dendrites in the embryonic nervous system, depends on localized rearrangements of the actin cytoskeleton in response to concentration gradients of target-derived guidance molecules (48-51). Because in the past cell culture experiments focused on the large axonal growth cones of sensory neurons, there was a tendency to regard axons as the predominantly active partner in circuit formation. However, time-lapse imaging of hippocampal neurons developing in cell culture has shown dendrites initially making a plethora of motile filopodia extending and retracting within minutes (25, 52). After a week in culture this activity gradually diminished as the filopodia were replaced by spines of mature morphology, suggesting that dendritic filopodia may act as spine precursors. The timing of this conversion in culture roughly matches the chronological age at which a similar transition from filopodia to spines of mature appearance occurs on dendrites in the developing brain (9, 53).

How might this motility of spines and filopodia at nascent synapses influence patterns of connectivity during brain development? A recent study of dendrites in the sensory cortex of living rats provides fresh insights (28). As with neurons maintained in culture, dendritic spines and filopodia in the developing brain show constant protrusive activity. To assess the effect on dendrite morphology of sensory experience, time-lapse recordings of dendrites in the cortical area where inputs from the whiskers arrive were made 1 to 3 days after cutting off the whiskers. This had no significant effect on spine number, but the level of motility in both spines and filopodia was decreased by $\sim 40\%$. This effect was prominent 11 and 13 days after birth, the time when animals begin to use the whiskers for exploratory activity, but was far less pronounced either before or after this period (28). There is thus a strong correlation between enhanced morphological plasticity in spines and experience-dependent refinement of circuit connectivity. Moreover, the major effect was on protrusive activity, which is characteristic of actin-based mechanisms.



Fig. 1. Structural features of spinebearing neurons. (A) A living hippocampal neuron in cell culture expressing γ-cytoplasmic actin tagged with GFP-actin. The myriad fluorescent dots on the dendrites are spine heads where actin accumulates. Bar, 15 µm. (B) Part of a dendrite from a GFP-actin-expressing cell that was fixed and then stained with antibodies against the dendrite-specific microtubule protein MAP2. Red MAP2 labeling shows microtubules concentrated in the shaft of the dendrite compared to green actin-GFP labeling of actin present in dendritic spine heads. Bar, 5 µm. (C) A single spine synapse seen by electron microscopy, and (D) a diagram of a spine structure. The neurotransmitter glutamate (pink) is stored within synaptic vesicles and released into the synaptic cleft where it activates receptors located in the postsynaptic density (PSD). Actin filaments are represented by the barbed lines. ax., axon; pre., presynaptic bouton; dend., shaft of dendrite; s.v., synaptic vesicle. [Images: (A) H. Brinkhaus; (B) S. Kaech; (C) from a micrograph given to the author by the late E. G. Gray]

Glutamate Receptors Regulate Spine Formation and Stabilization

Recent data implicate receptors for glutamate, the neurotransmitter at excitatory synapses, in both the initial formation and the subsequent stabilization of dendritic spines. Glutamate receptors of the N-methyl-D-aspartate (NMDA) subtype appear to be involved in regulating spine outgrowth. Several recent studies have suggested that stimulation protocols leading to long-term potentiation (LTP) (54, 55) are associated with increased production of dendritic spines and filopodia and, like LTP itself, this increased spine production is blocked by NMDA receptor antagonists (56-58). A link between these two phenomena and actin-based spine motility is suggested by studies showing that drugs that inhibit actin dynamics suppress LTP (59, 60). These effects first become significant during the maintenance phase of LTP beginning \sim 20 min after stimulation (60), a delay suggestively similar to that required before outgrowth of new spines becomes apparent after LTP-inducing stimulation (56-58).

Other studies implicate glutamate receptors of the α -amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) subtype in maintaining spines at established synapses. In hippocampal tissue slices, spines were found to degenerate over a period of days after axons were cut, but this effect could be largely prevented by the addition of micromolar concentrations of AMPA (61). Conversely, pharmacological blockade of AMPA receptors led to spine loss at rates comparable to that produced by cutting axons. Exposing neurons to tetrodotoxin, which blocks activity-evoked release of neurotransmitter, had no effect on spine morphology, but treating cells with botulinum toxin, which blocks neurotransmitter release entirely, mimicked the spine loss induced by cutting axons or blocking AMPA receptors. These results suggest that the low level of AMPA receptor stimulation produced by glutamate spontaneously released from presynaptic boutons is sufficient to maintain spine morphology at mature synapses (61). In constrast to the period of days required for spines to regress after AMPA receptor blockade, blocking synaptic activity for several hours was found to lead to a large increase in spinelike protrusions from dendrites in hippocampal slices (2). These two sets of experiments are not necessarily contradictory because both the extension and retraction of cell extensions involve actin-based motility. Together, these observations raise interesting questions about the innate spine-producing capacity of dendrites and the underlying mechanism that determines the balance between spine production and suppression.

The potential involvement of actin in regulating the morphological stability of spines is supported by recent experiments in which micromolar concentrations of AMPA were found to reversibly block actin motility in spines of hippocampal neurons (62). AMPA also effectively inhibited spine motility when NMDA receptors were blocked, suggesting that NMDA receptor-induced outgrowth of new spines and AMPA receptor-dependent stabilization of established spines may involve distinct mechanisms.

Calcium Links Synaptic Activity to Morphological Plasticity

Like LTP-related spine induction, which depends on activation of Ca^{2+} -permeable NMDA receptor channels (56–58), AMPA receptor–induced stabilization of spine morphology also depends on Ca^{2+} influx, in this case through voltage-dependent Ca^{2+} channels (62). Ca^{2+} thus appears to be involved in both the initiation and the subsequent stabilization of dendritic spines, a situation reminiscent of its effects, at an earlier stage of neuronal development, on actin-based growth cone motility when differing levels of cytoplasmic Ca^{2+} can produce opposite turning responses to the same local stimulus (63, 64).

Synaptic contacts are generally made onto the tips of spine heads (Fig. 1, C and D) so that ion currents elicited by receptor activation originate at the periphery of the spine and are spatially isolated from the shafts of dendrites. The potential significance of this arrangement is evident from calcium imaging studies showing that postsynaptic Ca²⁺ fluxes evoked by "weak" stimuli occur primarily within individual spines, whereas stronger stimuli recruit Ca²⁺ responses in additional spines and in local areas of the dendritic shaft (65-69). In this way spines perform two distinct functions: first, as biochemical compartments where Ca²⁺ levels can be regulated independently of the underlying dendrite; and second, as summation units capable of integrating inputs arriving from various sources according to their strength (33, 70-74). An important feature of this process is that during synaptic activation the Ca^{2+} ion undergoes a subtle role change, from serving as a charge carrier passing through an ion channel to acting as a signal transduction molecule capable of influencing a wide variety of metabolic and structural functions inside the postsynaptic cell. Thus, the characteristic morphology of the spine, in which the head is spatially separated from the dendrite by the neck, makes it possible for excitatory synaptic transmission to influence cellular events over a wide range, stretching from individual synapses to the entire dendritic tree.

The stabilization of spine morphology by AMPA receptor activation occurs through the suppression of actin-rich protrusions from the surfaces of spine heads, which round up as dynamic actin at the periphery collapses, leaving intact more stable actin filaments in the center of the spine (62, 75). This is consistent with both the effects of actin-blocking drugs on spine morphology (26, 76) as well as the bipartite arrangement of actin filaments in the spine cytoplasm (11) and suggests a model in which a stable core of actin is capped by a corona of dynamic filaments (36). This arrangement could account for the differing effects on spine morphology of AMPA- and NMDA-receptor activation: the former suppressing motility by disassembling peripheral actin filaments through local increases in Ca²⁺ levels; the latter perhaps activating mechanisms that lead to spine growth by producing higher levels of Ca^{2+} in the spine cytoplasm. Still higher levels of NMDA receptor activation produce pathological changes in neurons mediated by Ca2+ influx (77, 78), with degenerative changes in spines among the earliest events (79). Inhibition of the calcium-dependent phosphatase calcineurin protects spines from this excitotoxic damage (79), suggesting calcineurin as a potential mediator between postsynaptic Ca^{2+} fluxes and the actin cytoskeleton.

Synaptic Activity and the Regulation of Spine Morphology

A potentially important factor in the successive induction and stabilization of dendritic spines, particularly during development, is the sequential appearance of different glutamate receptor subtypes. When excitatory synapses are first formed they show only NMDA receptor currents and, because these receptors require strong stimulation for activation, they appear to be functionally "silent" (80-82). Activation of NMDA receptors induces newly formed synapses to acquire AMPA receptor-mediated responses, apparently through physical insertion of receptors into the postsynaptic membrane (83-85), suggesting that spine maturation may involve AMPA receptor-dependent mechanisms.

How might the sequential appearance of glutamate receptor subtypes at nascent synapses influence spine morphology? Figure 2 presents a hypothetical scheme incorporating salient aspects of the data discussed above. Figure 2, A and B, represents the initial step of spine outgrowth, which appears to be promoted by activation of NMDA receptors (56, 57). At least during development, nascent spines predominantly occur as motile filopodia (Fig. 2B) (9, 25, 28) whose role may be to "search" the developing neuropil for appropriate presynaptic partners (86). The subsequent activity-dependent acquisition of AMPA receptors (Fig. 2C) (83-85) provides a mechanism that may stabilize spine morphology by suppressing actin-based spine motility (Fig. 2, C and D) (62). The steps shown in Fig. 2, B and C, may mark the transition to a state in which spine maintenance depends on continued stimulation of AMPA receptors (61). Current evidence suggests that each of the transitions in this se-

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quence is reversible if stimulation from the presynaptic terminal fails (61, 62). Such a scheme may help to explain experience-dependent shaping of neuronal circuits because it would make sense to require a mechanism that depends on strong stimulation, like that of NMDA receptor activation, for the initiation of new connections but to then support them with a mechanism sensitive to low rates of neuronal activity, like that of AMPA receptor activation. Learned responses could thus be maintained during periods when they are not actually being used. Similarly, should synaptic stimuli fall below a certain threshold indicative of disuse, it would be appropriate for synaptic connections to be broken and re-formed in new configurations.

Various interesting questions remain to be answered. One of them concerns the extent to which postsynaptic glutamate receptors regulate spine morphology. In contrast to hippocampal pyramidal cells, where interrupting synaptic transmission leads to extensive loss of spines (61, 87), dendritic spines of mature morphology still develop on cerebellar Purkinje cells when axonal inputs are absent (88-90). This suggests that diverse mechanisms regulate spine plasticity at different brain locations. Among the factors potentially involved are neurotrophins, which destabilize dendrites and spines when overexpressed (91). Mechanisms of spine plasticity may also differ between development and adulthood because in tissue slices from older animals, NMDA receptor-dependent LTP appears to promote outgrowth of dendritic spines without the intermediate filopodial state so prominent during development (57, 58).

Dendritic Spine Plasticity in Adulthood

Studies on slice cultures (27) and in living brain (28) indicate a significant decline in dendritic spine motility during the postnatal period, raising the question of how much of the plasticity evident during development remains in adult brain tissue. One indication is the presence of high concentrations of actin in dendritic spines at synapses in adult brain (12-14). This need not imply that spines are constantly motile. A key feature of actin function is its ability to support both motile and stable structures. The actin in spines at synapses in the adult brain may thus represent the supporting cytoskeleton of a stable structure that nevertheless retains the potential for morphological plasticity under circumstances where adaptive changes in synaptic connectivity become appropriate. Large-scale rearrangements in cortical connectivity that take place when sensory input pathways are damaged (45, 47, 92, 93) demonstrate this potential being realized in practice. More significant for normal brain function are changes in the brain representation of sensory receptor fields that accompany the learning of new skills. For example, it has been demonstrated that the area of somatosensory cortex responding to finger stimulation increases after tactile training in monkeys (94) and Braille



Fig. 2. Hypothetical scheme for the effect of glutamate receptors on dendritic spine development. (A) Stimulation of NMDA receptors (white boxes) promotes actin accumulation at nascent synaptic sites leading to (B) the outgrowth of motile filopodia. (C) Acquisition of AMPA receptors (black boxes) and the formation of synaptic contacts is accompanied by reduced motility. (D) Activation of AMPA receptors suppresses actin motility and stabilizes spine morphology. ax., axon; dend., dendrite; filop., filopodium; pre., presynaptic bouton; sp., spine; s.v., synaptic vesicle. Neurotransmitter molecules (glutamate) are represented by small black spots inside synaptic vesicles and the synaptic cleft. Actin filaments are represented by the chevrons inside the spine.

learning in humans (95).

Whether adaptive processes in the adult brain involve actin dynamics is now a question of considerable interest, particularly with respect to learning and memory. It is remarkable that during memory formation the transient electrical signals carrying information through the brain's circuitry are converted into stable records that are immediately available for recall yet are capable of lasting for many years. Actin, with its ability to transit between dynamic and stable states of cellular structures, is a good candidate for mediating this apparently instantaneous transition from fleeting perception to enduring memory. The new techniques for imaging dynamic activity at brain synapses may soon allow this hypothesis to be tested.

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