Review Article

Molecular Mechanoneurobiology: An Emerging Angle to Explore Neural Synaptic Functions

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Neural synapses are intercellular asymmetrical junctions that transmit biochemical and biophysical information between a neuron and a target cell. They are very tight, dynamic, and well organized by many synaptic adhesion molecules, signaling receptors, ion channels, and their associated cytoskeleton that bear forces. Mechanical forces have been an emerging factor in regulating axon guidance and growth, synapse formation and plasticity in physiological and pathological brain activity. Therefore, mechanical forces are undoubtedly exerted on those synaptic molecules and modulate their functions. Here we review current progress on how mechanical forces regulate receptor-ligand interactions, protein conformations, ion channels activation, and cytoskeleton dynamics and discuss how these regulations potentially affect synapse formation, stabilization, and plasticity.

1. Introduction

In the nervous system, synapses are intercellular asymmetrical adherent junctions in transmitting biophysical and biochemical information between neurons and target cells (Figure 1). They are tight and highly dynamic structures that rapidly respond and adapt to diverse intrinsic or extrinsic complex cues. From mechanical standpoints, the synapse formation at least involves four steps [1, 2]: the elongation of neurites, physical attachments between neuronal branches and their targets, survival of the axonal branch decided by mechanical forces, and complete synapse formation. Generally, mechanical force manifests some physical properties, such as stress, tension, stretch, and stiffness [3], which may regulate axonal initiation, neurite elongation or growth, and axonal retraction [4, 5] and may also mediate synapse formation and plasticity. The dynamic coupling of the cytoskeleton with the neuron’s mechanical environment through transmembrane proteins (e.g., integrins) can exert forces on their substrates for the extension and anchorage of growth cones [1, 6, 7]. The mechanical tension, generated by the growth cones, promotes the stabilization of axon branches and regulates the topology of developing networks through cytoskeleton rearrangement, modulating subsequent formation of synapses [4, 8]. Notably, the rigidity of extracellular environment has been shown to influence the movements of neurites [9]. For example, neurite outgrowth of dorsal root ganglion (DRG) neurons was dependent on substrate rigidity [10]. Similarly, the astrocytes also respond to substrate rigidity with more complex morphology on stiffer substrates than those on more compliant substrates [11]. There is a mechanical stress threshold (∼274 pN/mm²) to trigger a series of retraction and direction-changing events for growth cones, which may be related to mechanosensitive ion channels that convert mechanical inputs into biochemical signals [12]. Mechanical cues in the microenvironment may also modulate differentiation and development of neurons [13]. Saha et al. [14] proposed that the biochemical and mechanical cues in the microenvironment can cooperatively regulate the differentiation of adult neural stem cells. These complex cues, for instance, can modulate notch activation and signaling to influence neuronal differentiation or development [15–17]. As to notch activation, Kopan and Ilagan [18] proposed two feasible models including the mechanotransduction model...
Figure 1: Schematic of a neural synapse with key molecules under external and/or internal mechanical forces. Neural synapses are very tight, dynamic, and well organized by many synaptic adhesions and signaling receptors (e.g., cadherins, integrins, and Eph/Ephrin), ion channels (e.g., NMDAR and L-type VGCC), and their associated cytoskeleton (e.g., actins). These molecules serve as mechanosensors and mechanotransducers. Cytoskeleton serves as a regulatory center that physically links membrane receptors and their associated cytoplasmic molecules (e.g., talin, PSD-95, S-SCAM, and catenin) for mechanotransduction. Mechanical forces, including extracellular forces from axon growth or other neural movements and internal forces from cytoskeletal dynamics and contractions of motor molecules (e.g., myosin), may regulate these proteins’ conformations and functions, which may further determine synaptic formation and plasticity.

Mechanical forces can also affect the physiological and pathological development of the nervous system. Franze [20] has put forward a differential expansion hypothesis: the intrinsic mechanical force produced through growth processes, such as proliferation of neurons, can fold the cortex during the cerebral development. If the mechanical properties of intracellular and extracellular environments change, folding abnormalities of the cerebral cortex give

(i.e., the mechanical strain may expose site 2 of a notch receptor for protease cleavage) and the allosteric model (ligand binding may induce an allosteric change into a protease-sensitive conformation). Indeed, Meloty-Kapella et al. [19] demonstrated that the mechanical force generated by the ligand-induced endocytosis, which was dependent on dynamin, epsins, and actin, changed notch receptor's conformations to trigger effective proteolysis.
rise to diverse clinical symptoms and cognitive deficits, such as Williams syndrome [21], autism spectrum disorders [22], and schizophrenia [23]. Likely, Alzheimer’s disease may also be related to abnormality of brain tissue stiffness [24]. It has been reported that the stiffness of neuronal cells increased significantly after the treatment with amyloid-β protein which was from proteolytic cleavage of the amyloid-β precursor protein by β- and γ-secretases [25]. This result may lead us to rethink the pathogenesis of Alzheimer’s disease from the mechanical standpoint.

Many evidences have been accumulated to suggest that neuronal developments are closely related to the mechanical cues from neurons themselves and their microenvironments. As to the neuronal disease treatment, carefully controlled force is obviously an effective stimulator to intervene the neuronal activities. However, the molecular mechanisms by which the force regulates neural functions, especially synaptic functions, are still largely unknown. This review will mainly focus on the mechanical regulation of adhesion receptors, ion channels, and cytoskeleton in synapses. We hope this paper can refresh our fundamental understanding on the molecular basis of neural synaptic functions and inspire new ideas to explore the mysterious nervous system, especially from the mechanobiology standpoint.

2. Adhesion Molecules

2.1. Cadherins. Cadherins are a family of type-I transmembrane proteins that mediate cell-cell adhesion at intercellular adherent junctions. A cadherin contains extracellular domains that bind homophilically with another cadherin and a cytoplasmic domain that binds with the catenin family (e.g., α, β, γ, or p120 catenin) [26]. The cadherin family consists of several subfamilies, such as classical cadherins, protocadherins, Fat cadherins, cadherin-like neuronal receptors, and seven-pass transmembrane cadherins [27]. They are widely expressed on various cell surfaces, including endothelial cells and neurons. Multiple classic cadherins expressed on neurons [28] mainly regulate neuronal recognition and connectivity [29]. For example, N-cadherin–mediated extracellular neuron–neuron interactions are indispensable for maintaining dendrite growth and branching [30] and synapse formation or stabilization [31]. Adjusting the expression levels of N-cadherins on neurons by overexpression or knocking-down can strengthen or attenuate spine stability respectively [32]. Moreover, the N-cadherin-induced signaling cascades regulate spine morphology, postsynaptic organization, presynaptic organization, and synapse functions [33].

Recently, many evidences have suggested that cadherins are mechanosensitive in a way that they can sense external and internal mechanical forces to trigger appropriate biological functions via a positive feedback loop (Figure 1) [26]. For example, substrate rigidity can affect the formation of cadherin junctions via changing the cellular traction forces. The softer the substrate, the less the traction forces that can be generated on cadherin adherent junctions. These traction forces are mainly generated and regulated actomyosin assembly via a positive feedback loop [34]. That is, the reorganization of the actomyosin complexes generates appropriate mechanical forces to stabilize the cadherin adhesions and the recruitment of actin fibers. Thus, the cadherin adhesion complex performs as a mechanosensor and mechanomodulator by changing its adhesion strength in response to the different rigidity of the intra- and extracellular environments.

Assisted by many biophysical studies, especially by structural and single-molecule studies, the molecular mechanism by which the cadherin complex senses mechanical cues has been gradually unveiled. An ultrasensitive biomembrane force probe, a state-of-the-art single-molecule biophysical technique, was used to measure rupture strengths of single-paired trans-bonded E-cadherins. In this study, the E-cadherin trans-interaction was found to exist a hierarchy of rupture strengths, suggesting multiple binding states, which are related to multiple biomechanical functions for E-cadherins [35]. Moreover, the cadherin ectodomain is a Ca^{2+}-switched mechanostable structure [36]. That is, at high Ca^{2+} concentrations, the ectodomain structure is fairly rigid and stable, assuring the transmission of mechanical stimuli, while, at low Ca^{2+} concentrations, it turns into a compliant structure, which attenuates effective mechanical transmission. In addition, classical cadherins form two distinct trans-binding conformations, a strand-swap dimer, and an X-dimer [37]. Interestingly, X-dimers form catch bonds (i.e., force-prolonged bond lifetimes), strand-swap dimers form slip bonds (i.e., force-shortened bond lifetimes), and ideal bonds (i.e., force-independent bond lifetimes) appear when X-dimers change to strand-swap dimers [38] (Figure 2(a)). Later, computer simulations and single-molecule force spectroscopy were combined to study the structural mechanism of cadherin X-dimer’s catch bonds [39]. Their data suggest that tensile force flexes the cadherin extracellular region of X-dimers, which induces new hydrogen bonds, resulting in a tighter contact. Recently study using optical trap-based single-molecule assay from Buckley and colleagues [40] reported that mechanical force strengthened cadherin/catenin complex binding to actin filament to resist tensile forces more efficiently via catch bonds. They also found that there were two bound states—a weakly bound state and a strongly bound state existed on cadherin/catenin complex binding to an F-actin filament. Mechanical force can switch the bound states probably through changing conformations of α-catenin which severs as a tension transducer [41]. That is, once mechanical force is exerted on the cadherin-catenin/F-actin bond, a weakly bound state can be switched to a strongly bound state, which stabilizes the cadherin-catenin and F-actin interactions [40]. Mechanical force can also enhance binding of the cadherin/catenin complex to vinculins by exposing vinculin-binding sites on α-catenins. Once vinculins are recruited to cadherin/catenin complex, actomyosins are then activated to trigger downstream molecular cascades, such as remodeling adherent interactions between cadherins. Does mechanical regulation on cadherin/catenin complex at the molecular level affect neurite growth or synapse formation in vivo? Indeed, Bard et al. [42] demonstrated that the mechanical
coupling between the cadherin/β-catenin complex with actins on primary neurons was a major determinant of growth cone advance and neurite extension through the adhesions between neuron and N-cadherin-coated substrates.

2.2. Integrins. Integrins are a large family of noncovalently associated heterodimeric adhesion receptors formed by a α- and a β-chain. Their bindings with various ligands mediate cell-cell and cell-extracellular matrix (ECM) interactions and trigger signaling pathways for cell adhesion, migration, proliferation, and differentiation [43]. 18 α and 8 β subunits have been identified in mammals, forming 24 different integrin heterodimers [44]. Each integrin subunit consists of a short cytoplasmic tail, a single transmembrane domain, and a large extracellular domain. Integrin’s cytoplasmic tail has been reported to interact with cytoplasmic proteins, such as talin and kindlin. These interactions physically connect integrins to actin cytoskeleton, transducing biophysical and biochemical signals bidirectionally across cell membrane [45].

In neurons, several types of integrins (e.g., β1 and β3 integrins) are expressed at synaptic membranes on both nascent and mature synapses and regulate neuronal functions [46–49]. These functions include neuronal migration, neurite growth [50] and path finding [51], dendritic spine plasticity [47], synaptic differentiation and maturation [52–54], synapse density [55], synaptic strength [56], and plasticity [57]. The integrin and its associated adaptor proteins can bind directly to some kinases (e.g., Arg kinase and focal adhesion kinase) to initiate signaling to mediate dynamic cytoskeleton organization and transcription [55, 58] and to modulate induced neuronal firing activities as well as trafficking of N-Methyl-D-aspartate (NMDA) and α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors [47, 59]. Such regulations may lead to synaptic scaling. But the exact roles of integrin in mediating neuron transmission still remain unclear, which is worth more investigations.
Integrins and their associated proteins have been demonstrated as mechanical sensors. They not only sense mechanical cues but also convert such cues to biochemical signals and transduce them into the cell [45]. To sense mechanical cues, an integrin can switch among multiple global conformations. Generally, integrins exist at least three states, inactive low affinity state in which an integrin adopts a compact and bent conformation with a closed headpiece [60], intermediate affinity state with extended conformations and a closed headpiece, and active and high affinity state with extended conformations and an open headpiece [61]. These conformational changes can be activated bidirectionally via the inside-out or outside-in signaling pathway [62] (Figure 2(b)). In the inside-out signaling pathway, a talin or a kindlin binds with integrin’s cytoplasmic β tail, which transduces mechanical forces from actomyosins across the membrane, separating α and β leg, extending ectodomains, and exposing ligand-binding sites [45]. In the outside-in signaling pathway, extracellular matrix (ECM) proteins (e.g., fibronectin) binding to integrin’s headpiece induces local conformational changes (i.e., α7 helix downward movement in either αA and/or βA domain). These conformational changes then propagate down to swing out hybrid domain, extend ectodomains, and separate intracellular α and β tails, leading to the talin and/or kindlin recruitment and cytoskeleton reorganisation [63]. Mechanical force can facilitate extension but impede bending of cell-surface αβ integrin when it engages with its ligand ICAM-1 (Intercellular Adhesion Molecule 1) using non-fluorescence-labeled single-molecule biomechanical assay [64]. Moreover, mechanical force can also regulate integrin’s binding to its ligands. Friedland et al. [65] found that myosin II-generated cytoskeletal force regulated the bond strength between αβ integrin and fibronectin by switching integrin from a relaxed state to a tensioned state. Later on, Zhu and his colleagues used single-molecule biomechanical force-clamp assays to demonstrate catch bond formed between αβ1, αβ2, and αβ3 integrin with their respective ligands [64, 66–68]. They also found that mechanical force accelerated downward movement of αA domain α7 helix to allosterically open the MIDAS (metal ion-dependent adhesion site) on the top of αA domain. This allosteric regulation by force is a possible molecular mechanism for αA domain containing integrin catch bonds [69, 70]. Mechanical force may enforce hybrid domain swing-out, which may also play a critical role in forming integrin’s catch bands [67]. Finally, the clustered complex switches to low-binding affinity state possibly through the phosphorylation of β3-integrin tails [71]. Therefore, the mechanical regulation for synaptic neurotransmissions, synapse formation, and plasticity through integrins may exist, but there is still lacking experimental evidences.

2.3. Eph/Ephrin. Eph receptors are known as the largest family of receptor tyrosine kinases, which consist of two subclasses, the A-subclass Eph receptors (e.g., EphA1–EphA10) and the EphB subclass receptors (e.g., EphB1–EphB6). Similarly, ephrins, as Eph ligands, also comprise two subclasses, the A-subclass ephrins (e.g., ephrinA1–ephrinA6) and the B-subclass ephrins (e.g., ephrin-B1–ephrin-B3) based on their affinities and sequence conservation [72, 73]. The most unique feature of signaling mediated by Eph/ephrin interactions is that their downstream signaling can be bidirectionally transmitted across cell membrane [74]. Moreover, Ephs and ephrins can bind each other in trans or in cis manners [75]: trans-interactions activate Eph/ephrin signaling, but cis-interactions inhibit signaling transmission. Activated Ephs usually form clusters on cell surface, which consist of different Eph members that cross activate each other [76, 77]. Within the clusters, activated Ephs can trans-phosphorylate kinase domains of inactivated Ephs, initiating the downstream signaling cascades [78].

In neurons, different types of Ephs and ephrins are expressed at diverse locations over the course of neural system development. For example, EphB2s are preferentially expressed in dendrites and dendritic spines [79], EphA4 mainly at the postsynaptic density [80], and Ephrin-A3 and EphA on dendritic spines [81]. As reported, Eph and ephrin can mediate neural development [82, 83], dendritic spine formation [84], morphology [85] and maturation [86, 87], axon guidance [88], synapse formation [89], synaptic specializations [90], synaptic plasticity [91, 92], and synaptogenesis [93, 94]. For example, Eph and Ephrin binding regulates NMDAR trafficking [95, 96]. The activation of EphB2 by ephrin-B1 induces association of EphB2 receptors with the NMDAR [90] and AMPARs [93] through PDZ domain containing proteins. EphB activation by ephrinB2 can also induce the phosphorylation of NMDA receptors through Src tyrosine kinases, which leads to increasing NMDA receptor-dependent influx of calcium in response to glutamate, and finally enhances NMDA receptor-dependent gene expression [96]. Furthermore, Eph/ephrin interactions can also regulate actin cytoskeleton reorganization to some extent [87, 97].

Similar to aforementioned membrane receptors, the Eph/ephrin complex can integrate and transmit biomechanical and biochemical signaling in response to mechanical cues. Recently, tensile strains or compressive forces were found to regulate the expression of ephrin-A2 and ephrin-B2 [98]. Moreover, Salaita et al. [99] explored the mechanical regulation of the ephrin/Eph signaling. They found that the mechanical restriction of ephrin-AIs through nanofabricated chromium metal lines changes the spatial organization of EphA2s and alters the cellular response to ephrin-A1, suggesting a spatial-mechanical regulation of the EphA2 signaling pathway. Plodinec and Schoenenberger [100] proposed that the mechanical force can modify downstream cellular activities through the Eph/ephrin complex, implying that the Eph/ephrin complex serves as a mechanical transducer to convert mechanical stimuli to biochemical signals. Moreover, Eph's downstream signals can remodel the actin cytoskeleton and induce actomyosin contraction [101]. Salaita and Groves [102] proposed that EphA2 transport induced by actin cytoskeleton alters the size and the distribution of Eph-ephrin clusters, which may generate mechanical forces on the Eph-ephrin complex. But how mechanical force regulates Eph/ephrin binding and downstream signaling that affect synaptic functions, still remains not clear, due to lack of direct experimental evidences.
3. Ion Channels

Ion channels are pore-forming membrane proteins that allow the specific ions passage, establishing a resting membrane potential and electrical excitability, and other electrical signals [103]. In general, ion channels can roughly be classified into three groups: voltage-gated channels, ligand-gated channels, and mechanosensitive channels [104]. It is known that the external or internal force is sufficient to induce conformational changes on the gating domain of an ion channel to modulate ion transportation, converting mechanical stimuli into electrical or biochemical signals [105–107]. For example, a cystic fibrosis transmembrane conductance regulator (CFTR) is robustly activated by membrane stretch, resulting in chloride transport [108]. Membrane stretch can also regulate the activity of Nav1.5 channel in a fully reversible manner, which may serve as a phasic positive feedback component in mechanotransduction [109]. Moreover, mechanical stretch increases the number of active Nav1.5 channels and peak current, slows down recovery from, and stabilizes the inactivated states [110]. And, for Nav1.5, stretch-effects can also be partially reversible [110]. By cell-attached patch–clamp experiments, Chubinskiy-Nadezhdin et al. [111] found that stretch-activated channels induced local changes in Ca\(^{2+}\) concentration, triggering nonmechanosensitive K\(^{+}\) currents. Stretch-activated channels that modulate the Ca\(^{2+}\) entry can regulate mechanical strength and the organization of focal adhesion sites between a fibroblast and a substratum [112]. For Shaker Channels, membrane stretch can accelerate their activations [113, 114]. What is more, mechanical force can also regulate the activity of TREK-1 potassium channel [115], the canonical transient receptor potential channel 1 [116], and Kv channel [117].

Recently, Martinac [118] summarized three force-transmission models to elucidate the mechanisms of ion channel activations (Figure 2(c)): (1) the bilayer mechanism (the activation of the ion channels by mechanical force is only through the lipid bilayer, not by an associated protein) [119], (2) the single-tether model (the conformation of the channel depends on deformation of lipid membrane caused by a cytoskeleton or matrix proteins pushing or pulling the cell membrane where the channel resides) [120], and (3) the dual-tether model (two anchoring points, such as the ECM and large-diameter microtubules, can exert mechanical force on the channels and activate them) [120] and proposed that the connection between cytoskeleton and ion channels is necessary to mediate mechanosensory and mechanotransduction. Moreover, mechanical forces are coupled to electrical signals through multiple binding partners of the adaptor proteins, posttranslational modifications (e.g., phosphorylation), and transport and assembly of channels [121]. And mechanical forces mediated by integrins can also activate ion channels [122]. Through magnetic pulling cytometry and high speed microfluorimetric calcium imaging techniques, Matthews et al. [123] demonstrated that the mechanical force mediated by \(\beta_1\)-integrins induces ultrarapid activation of TRPV4, triggering a rapid instantaneous calcium influx (within 4 milliseconds). They proposed that intracellular cytoskeleton may provide a physical linker between integrin and ion channels that enables direct mechanotransduction.

In neurons, ion channels (e.g., L-type voltage-gated calcium channels, small conductance calcium-activated potassium channels, gamma-aminobutyric acid receptors, \(\alpha\)-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors, and N-methyl-D-aspartate receptors) [124–128] expressed at both presynapse and postsynapse can modulate synapse strength and plasticity and signal propagation between neurons [129]. Undoubtedly, some mechanosensitive ion channels on neurons are also regulated by mechanical forces. For example, the mammalian neuronal potassium channel subfamily K member 4 is also opened by membrane stretch, mediating growth cone motility and neurite elongation [130]. Remarkably, more are known about mechanical effect on NMDAR. Stretch-induced injury indeed increases ionic currents and intracellular free calcium concentration through reducing the Mg\(^{2+}\) blockade of NMDAR [131]. NMDARs regulate long-term potentiation and long-term depression of excitatory synaptic transmission through calcium flux, which is related to synaptic plasticity [132]. Kazi et al. found that the coupling between ligands binding domains can impose mechanical force on the porelining M3 helix of NMDARs, prolonging pore opening [133]. And mechanical injury initiates specific signaling mediated by NMDA receptor which can modulate AMPA receptor desensitization [134]. Similarly, Paoletti and Ascher [135] believed that mechanical stress may be the common stimulus and mediate NMDAR-dependent signaling transduction. Moreover, subunit composition of NMDAR also can influence its mechanical responses [136]: GluN1/GluN2B NMDARs are more sensitive to mechanical force than GluN1/GluN2A NMDARs and GluN1/GluN2A/GluN2B trimeromic NMDARs, and GluN1/GluN2A/GluN2B NMDARs show an intermediate form of mechanosensitivity. And the phosphorylation of GluN2B (Ser-1323) by protein kinase Cs (PKCs) dynamically regulates NMDAR GluN2B mechanosensitivity, altering NMDA receptor activities. In detail, postsynaptic density protein 95 (PSD-95) binding with GluN2B subunit modestly affects the mechanical stimulus as a mechanical clutch through regulating cytoskeletal destabilization [136]. Therefore, mechanical force may regulate the synaptic formation and plasticity through ion channels.

4. Cytoskeleton

In a neuron, the synapse is a highly dynamic structure that rapidly responds and adapts to different intrinsic or extrinsic cues through cytoskeleton, which includes actins, microtubules, and their associated proteins. Actin filaments are enriched in both pre- and postsynaptic terminals, controlling dynamic synaptogenesis, regulating bidirectional morphological spine plasticity, and adjusting synaptic activity [137–142]. For example, during the recruitment of synaptic vesicles from the reserve pool to the readily releasable pool, actin filaments provide cytoskeletal tracks to help actin-based molecular motors (e.g., myosin) to transport the vesicles.
Moreover, during the synaptic vesicle exocytosis, actins have been found to negatively regulate the neurotransmitter release. Actin polymerization and synaptic actins likely contribute to endocytosis, which is critical to learning and memory. So dynamic rearrangement in actins plays a central role in synapse remodeling and functions [137].

An actin filament is assembled by numerous actin monomers via noncovalent interactions. It undergoes dynamic and controlled polymerization and depolymerization to accomplish appropriate organizations to adapt to mechanical stresses [143]. Previous studies have demonstrated that external forces distorted the filament structure [144], resulting in the assembly, stabilization, and reorganization of the actin stress fiber and the focal adhesion (FA). Interestingly, when bearing forces, actin filaments can survive from being severed by coflin and function as tension sensors [145]. Catch bonds in G-actin/G-actin and G-actin/F-actin may provide a mechanoregulatory molecular mechanism by which mechanical forces regulate the depolymerization kinetics of force-bearing actin filaments throughout the actin filament and further control cell functions [146]. Furthermore, tension is also crucial to actin bundle formation [147]. Actin-associated proteins, such as formin, can sense mechanical forces to mediate actin polymerization [148, 149], which further regulates the traction force at FAs during cell migration through the speed of F-actin retrograde flow [150]. Retrograde flow of actin filaments is also associated with force generation in the growth cone of a neuron [151]. Like actins, microtubules are also important in regulating the neuron activities and maintaining the cellular structure. In the nervous system, forces generated by microtubule dynamics are crucial to the axons guidance and lengthening. Paul Letourneau pointed out that microtubules generate push forces to mediate the axonal elongation [152].

In addition to actins and microtubules, cytoskeleton-associated proteins also serve as critical components in mechanotransduction pathways in living cells. For example, talins physically link the actin cytoskeleton to membrane associated proteins also serve as critical components in cell functions [146]. Furthermore, tension is also crucial to actin bundle formation [147]. Actin-associated proteins, such as formin, can sense mechanical forces to mediate actin polymerization [148, 149], which further regulates the traction force at FAs during cell migration through the speed of F-actin retrograde flow [150]. Retrograde flow of actin filaments is also associated with force generation in the growth cone of a neuron [151]. Like actins, microtubules are also important in regulating the neuron activities and maintaining the cellular structure. In the nervous system, forces generated by microtubule dynamics are crucial to the axons guidance and lengthening. Paul Letourneau pointed out that microtubules generate push forces to mediate the axonal elongation [152].

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Myosins, another large family of cytoskeleton-associated proteins, play key roles in driving the dynamics of actin filaments to organize the synaptic structures and to regulate synaptic functions. They were indicated to determine dendritic spine morphology [162], to maintain synaptic plasticity in the postsynaptic terminal [163], and to regulate neurotransmitter release [164]. From the mechanical standpoint, myosins can convert chemical energy by ATP hydrolysis into mechanical energy to power intracellular transportation or mechanical tethers. In detail, myosins can transport cargoes inside the cell on the tracks of actin filaments [165] and walk like motor proteins to generate force and displacement along actin filaments. Moreover, mechanosensitive myosin II can recruit itself into the fusogenic synapse to increase cortical membrane tension and boost fusion pore formation [166]. Takemoto et al. put forward that different kinds of mechanical force induce different effects on signaling transduction of the myosin [167]. That is, stretching and compressive stress induces phosphorylation and dephosphorylation, respectively, for myosin regulatory light chain. It has been found that force, which is produced by myosins and applied onto the complex actin network, regulates actin cytoskeleton dynamics and synaptic cargo transport [168] and results in the axonal retraction [169]. Moreover, postsynaptic myosin II applies forces onto the cytoskeleton in the spine, maintaining long-term potentiation (LTP) and stabilizing the synaptic plasticity [163]. Therefore, we believe that myosin-associated force is crucial to some signaling pathways that are closely relevant to cytoskeletal dynamics and synaptic plasticity.

5. Concluding Remarks

Growing evidences clearly demonstrate that neurons can correctly respond to their complex mechanical environments by sensing mechanical stimuli and can integrate these mechanical cues with biological signals to initiate and transduce biomechanical and biochemical signals towards the inside of the neurons to appropriately modulate diverse neural functions. Future investigations of these mechanoregulations of neural functions will lead us to a new era of unveiling the molecular basis of axon guidance, neurite growth, synaptogenesis, and synaptic plasticity [4, 5]. With rapid and significant advances of modern biomechanical technologies, especially single-molecule biomechanical methodologies, the era of the amalgamation of neuroscience with mechanobiology is coming. Such multidisciplinary researches will provide us greater insights of fundamental molecular machinery
for better understanding the physiology of neural system and the pathology of dysfunctional neural diseases [170], such as Williams syndrome [21], autism spectrum disorders [22], schizophrenia [23], and Alzheimer’s disease [24], from mechanical standpoints.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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