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Molecular Mechanisms of Neuroplasticity: An Expanding Universe

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Abstract—Biochemical processes in synapses and other neuronal compartments underlie neuroplasticity (functional and structural alterations in the brain enabling adaptation to the environment, learning, memory, as well as rehabilitation after brain injury). This basic molecular level of brain plasticity covers numerous specific proteins (enzymes, receptors, structural proteins, etc.) participating in many coordinated and interacting signal and metabolic processes, their modulation forming a molecular basis for brain plasticity. The articles in this issue are focused on different "hot points" in the research area of biochemical mechanisms supporting neuroplasticity.

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This issue of *Biochemistry (Moscow)* is dedicated to molecular mechanisms of neuroplasticity, one of the most cosmic and the same time vague concepts of contemporary neurobiology. The term "plasticity", first applied to the brain in 1890 by William James [1] and then used as "neural plasticity" in 1948 by Jerzy Konorski [2], has become a kind of umbrella term covering changes to the brain structure and function throughout the life course. Neuroplasticity (brain plasticity or neural plasticity), a remarkable capacity of the brain to change and adapt, implies physiological changes in the brain resulting from interactions of the organism with the environment. This dynamic process allowing to adapt to different experiences and to learn is also a factor in recovery from brain injury, since rehabilitation is aimed at rebuilding connections between neurons, "rewiring" of the brain. The specificity of brain organization (multiformity of cells, "geographic" nature of neuronal cells outspreading sprouts at relatively long distances, communal character of neurons unable to survive "by themselves", without connections with other neurons) and the key role of brain in animal survival explain the necessity of plasticity providing for adaptive changes in brain structure and functions. On the other hand, numerous brain structures and nuclei, as well as multiple interactions and numerous functions bring about an active increase in the number of discovered neuroplasticity phenomena and reveal new phenomena during deep studies of known ones.

Neuroplasticity can be observed on multiple scales, with adaptive behavior, learning, and memory being at the top of neuroplasticity hierarchy. The basis of this pyramid is shaped of molecules and their interactions, which underlie subcellular/synaptic, cellular, and neuronal circuit and network levels. A fundamental principle underlying neuroplasticity is the plasticity of synaptic connections that are constantly being removed or recreated, the balance of these opposite processes being largely dependent upon the activity of the neurons. Different forms of activity-dependent plasticity have been documented in most areas of the brain. The activity-dependence of synaptic plasticity is one of the central points of the general neuroplasticity concept and of memory and learning theories based on experience-induced changes in synaptic structure and function. Evidences that neuroplasticity must arise from a series of interrelated molecular events, partially specific towards definite neuroplasticity phenomena, was accumulated several decades ago [3]. It became clear that long-term plasticity occurs as a result of changes in gene expression that are triggered by signaling cascades modulated by various signaling molecules during altered neuronal activity. Obviously, the "lower", molecular level of neuroplasticity is forming a basis for all the "upper" levels, and the myriads of molecular events and pathways multiplied by the unique multiformity of brain structures and cells ensure the variety of neuroplasticity phenomena.

For a neuron, a "geographic" cell possessing multiple processes defining its integration into the network, and, at the bottom, the function of the neuron, the spatial organization of molecular events and their compartmentalization are of primary significance. This is especially obvious in phenomena of synaptic plasticity, where it is localization of receptors and other proteins in different loci of the synaptic compartment that grants effective plastic conversions. A conceptual problem of biochemical level of neuroplasticity is the understanding that all known molecular mechanisms are directly or indirectly involved in plasticity realization as the adaptive capacity of the brain and, therefore, many of them are changing with alterations of the state. Thus, the main challenge is to reveal key systems and events to describe signaling and metabolic processes underlying a specific neuroplasticity phenomenon. The articles in this issue are focused on some specific hot points of biochemical mechanisms subserving neuroplasticity.

A number of neuronal functions, including synaptic plasticity, depend on proper regulation of synaptic proteins, many of which can be rapidly controlled by phosphorylation/dephosphorylation [4]. It is now clear why enzymes with broad substrate specificity play a crucial role in brain plasticity. The reason for protein kinases, protein phosphatases, as well as proteases are functioning on most significant crossroads of different signal transduction pathways and can switch between them, is their ability to catalyze conversions of different protein substrates. Indeed, the number of potential substrates for these enzyme classes reaches several thousands. Importantly, it is the nature of a substrate that defines the direction of signal transduction or metabolic changes induced by these pleiotropic enzymes [5, 6]. A potential to process different substrates makes protein kinases, protein phosphatases, and proteases key players providing for brain plasticity on the molecular level. One promising growing point in this respect is the involvement of atypical protein kinases in synaptic plasticity and long-term memory, a review presented in this issue [7]. A major target of different molecular signaling pathways is inhibitory connections of GABAergic neurons. The mechanisms of long-term synaptic plasticity in GABAergic synapses, including those mediated by different protein kinases, are critically reviewed in [8].

Analyzing long-term potentiation (LTP), the most widely studied form of neuroplasticity believed to be the substrate for learning and memory, McEachern and Shaw [9] introduced a plasticity–pathology continuum model designed to place into proper context various forms of neural modification, some leading to beneficial alterations such as may occur in learning and others that may be primarily pathological in nature. They provided a basis for evaluating the specific synaptic/cellular response modification along the continuum of events, from beneficial to detrimental, that were induced by particular stimuli. Thus, aberrations in normal plasticity during neuropathology development does not mean a disappearance of neuroplastic capacity, but just a change in its form. A decade ago, based on analysis of our own data and the results reported by other groups, we substantiated a concept concerning resemblance of basic molecular mechanisms involved in neuroplasticity and neuropathology at different levels [10]. This similarity, demonstrated on a variety of examples of plasticity and pathology phenomena, is based on the pleiotropicity of proteins and basic mechanisms. Along with the fundamental significance of this idea for understanding processes taking place both in normal brain and in neuropathological conditions, the concept is of principal importance for practical application. It allows explanation of numerous failures in development of the "pathogenetically directed" approaches to treatment of neurological and mind diseases (e.g. stroke, depression) with neglecting the similarity of the basic molecular mechanism underlying both normal and pathological brain plasticity. At present, the rapid development of connectomics confirms that the concept of the connectome and connectopathy reflects one of the highest strata of neuroplasticity. Neuronal networks forming the connectome are based on several "lower" network levels, the state and interactions of these levels stipulating the state and functioning of the connectome as well as its dynamic changes. Similar network levels can be demonstrated in connectopathies, which are examples of non-beneficial, aberrant neuroplasticity [11].

Homeostatic synaptic plasticity is maintained by a set of negative-feedback mechanisms that are used by neurons to maintain activity within a functional range. Proinflammatory cytokines, molecules classically associated with the peripheral immune system, are also involved in the modulation of homeostatic synaptic plasticity [12]. Inflammation, a well-known adaptive process, becomes non-beneficial when proinflammatory cytokines, together with other mediators of inflammation, are excessively accumulated. Neuroinflammation, affecting neuronal plasticity, is a common key link in the pathogenesis of virtually all known neurological and mind diseases Microglia is involved in synaptic plasticity representing particularly plastic cells, which can be shifted from their resting state by numerous factors. These multifunctional cells, though their main role is probably maintenance of homoeostasis, can be activated, turning into cells with a proinflammatory phenotype and secreting an excess of proinflammatory mediators [13-15]. In this issue, modulatory effects of cytokines on the mechanisms of synaptic plasticity are reviewed in [16], while the data presented by [17] demonstrate how neonatal proinflammatory stress induces neuroinflammation and impairs synaptic plasticity in juvenile rat hippocampus.

Cerebral pathologies are often (but not always) associated with limitations of adaptive capacity of neuroplasticity, e.g. because of neurodegeneration (elimination of

peripheral synapses and gradual retraction of neurites) up to neuronal cell death. However, there are situations when excessive neuronal plasticity is underlying the pathogenesis of the disease, and epilepsy is the most thoroughly studied example. Aberrant neuroplasticity during epileptogenesis and in epilepsy is based on changes in many facets of molecular, subcellular, cellular, and network levels of plasticity, some of them simultaneously contributing to the pathogenesis of comorbid pathologies [18].

This issue includes a report about NMDA receptor-associated molecular mechanisms mediating impairment of synaptic plasticity induced by epileptic status [19]. Astroglial cells are regarded as relevant players in the orchestration of synaptic plasticity; astroglial release of glutamate, ATP, and cytokines likely alters the survivability and functioning of synapses [20, 21]. Specifically, astrocytes may be regarded as a key element of aberrant plasticity in epilepsy as discussed in [22].

Revealing protein-synthesis dependence on acquisition of behavioral change was an influential discovery in the neurochemistry of behavioral modification [23], while specific alterations in the expression of synaptic proteins may be markers of different cerebral pathologies. It is believed that there is a specific need for normal macromolecular synthesis in a definite fragment of the learning process, memory consolidation, which takes place minutes to hours following acquisition. Memory consolidation processes are suggested to be associated with proteostasis, i.e. maintaining the protein structure, contents and turnover in the neuron and the synapse [24]. Since the mechanisms underlying persistent changes in synaptic transmission and plasticity depend on new protein synthesis, such changes are thought to be orchestrated by engaging the signaling pathways that regulate mRNA translation in neurons [25, 26]. Abnormal expression of proteins in the mature brain causes destabilization of neurons and their processes, leading to aberrant plasticity and aberrant wiring of brain circuitry. Many studies have confirmed the roles played by regulated proteolysis in neural plasticity and memory. A number of studies focused on the ubiquitin–proteasome system, the endosome–lysosome system, as well as autophagy relating them to synaptic remodeling [27]. Recent studies implicate extracellular proteases in synaptic plasticity, learning, and memory [28]. Thus, protein homeostasis seems to be a regulatory motif for synaptic plasticity changes that involve extensive regulation of the synaptic proteome. The advances in mass spectrometry-based proteomics in the past 15 years have contributed to a deeper appreciation of protein networks and the composition of functional synaptic protein complexes [29].

A group of proteins called neurotrophins are considered powerful molecular mediators of synaptic plasticity. Neurotrophins are proteins believed to play crucial roles in synapses, and they have been extensively studied for the last 40 years. The review of the involvement of the first discovered neurotrophin, nerve growth factor (NGF), in brain plasticity describes specific effects of NGF in the cholinergic system [30]. Among all neurotrophins, brain-derived neurotrophic factor (BDNF) stands out for its main function in the adult brain as a synaptic plasticity regulator, its structural and functional effects ranging from short-term to long lasting, on excitatory or inhibitory synapses, in many brain regions [31]. Deficits in BDNF signaling contribute to the pathogenesis of several major diseases and disorders such as Huntington's disease, Alzheimer's disease, and depression. The effects of BDNF are mediated by TrkB and p75 receptors and are coupled to the activation of several signaling pathways. BDNF regulates the transport of mRNAs along dendrites and their translation at the synapse by modulating the initiation and elongation phases of protein synthesis and by acting on specific miRNAs. The effect of BDNF on transcription regulation may further contribute to long-term changes in the synaptic proteome [32]. In this issue, the mechanisms of BDNF interaction with two key brain neurotransmitter systems, glutamatergic [33] and serotonergic [34], are reviewed and analyzed, disclosing the involvement of these mechanisms in neuroplasticity. Synaptic plasticity of glutamatergic transmission emerges as a particularly powerful mechanism for the fine-tuning of information encoding and storage throughout the brain. AMPA receptors and NMDA receptors are dynamically regulated and subject to activity-dependent long-term plasticity [35, 36], BDNF-dependent modulation being a key event. Depressive disorders are directly associated with the impairment of BDNF control of both glutamatergic and serotonergic transmitter systems; therefore, understanding the mechanisms of such impairment should provide new approaches in treatment of mind diseases. Neurotrophin-mediated mechanisms of neuroplasticity impairment may be of importance also for treatment of neurodegenerative diseases. In this connection, changes in the expression of proteins representing brain neurotrophic systems during the maturation of senescence-accelerated OXYS rats accompanied by the development of Alzheimer's disease-like symptoms in these animals have been reported [37].

Mitochondria, by generating energy, play important roles in controlling neuroplasticity phenomena, including neural differentiation, neurite outgrowth, neurotransmitter release, and dendritic remodeling. These organelles are highly mobile and move within and between subcellular compartments involved in neuroplasticity (synaptic terminals, dendrites, cell body, and axon). Data exist suggesting that mitochondria emit molecular signals (e.g. reactive oxygen species, proteins, and lipid mediators) that can act locally or travel to distant targets, including the nucleus [38]. Thus, it is not surprising that disturbances in mitochondrial functions and signaling are involved in impaired neuroplasticity and neuronal degen-

eration in Alzheimer's disease, Parkinson's disease, psychiatric disorders, and stroke. In this issue, Medvedev et al. [39] present results on the mitochondrial subproteome of Rpn10-binding brain proteins and its alterations induced by neurotoxin MPTP and neuroprotector isatin and discuss the data from the perspective of an involvement of these changes in neuroplasticity mechanisms.

Bcl-xL belonging to the Bcl-2 family of proteins, acts as an antiapoptotic protein by preventing the release of mitochondrial cytochrome c, inducing caspase activation, and ultimately, programmed cell death. In this issue [40] it is shown that optogenetic activation of neurons induces Bcl-xL expression, while another article [41] demonstrates opposing effects of stress and lithium on Bcl-xL expression in the hippocampus, down- and upregulation, respectively. These results suggest involvement of Bcl-xL in neuroplasticity.

Stress and stress hormones, glucocorticoids, exert widespread effects in the brain, ranging from the regulation of gene transcription, cellular signaling, modulation of synaptic structure, synaptic transmission, and glial function to behavior. The actions of stress hormones are mediated by glucocorticoid and mineralocorticoid receptors, which are nuclear receptors/transcription factors. The hippocampus, which expresses high levels of adrenal steroid receptors, is a flexible brain structure predominantly important for certain types of learning and memory. This structure is also vulnerable to the effects of stress hormones, which have been reported to be increased in depressed patients, particularly those with severe depression [42, 43]. Glucocorticoid resistance, a hallmark of stress-induced mind diseases, is an important link in their pathogenesis. The molecular mechanisms linking glucocorticoid resistance to impairments of neuroplasticity are analyzed in [44].

The multiformity of plasticity phenomena includes the interaction between functionally different neurons fulfilling one task cooperatively, and an example of such situation is presented in a report [45] demonstrating consecutive synthesis of dopamine by neurons, each of them containing only one enzyme of the sequential pathway of dopamine synthesis. Moreover, an even higher, organismal plasticity level can be demonstrated during a critical period of ontogenesis: the brain can be integrated in the system of norepinephrine-synthesizing organs of the organism [46]. The mutual humoral regulation of different organs results in a compensatory increase in norepinephrine secretion in the situation of inhibition of the production of this transmitter in the brain.

Neuroplasticity, which makes the brain amazingly resilient, also makes it vulnerable to extreme influences. "Negative" neuroplasticity may be one of the mechanisms underlying cognitive and neurological decline in ischemic or traumatic brain injury [47]. However, neuroplasticity is gaining popularity as a theory that, at least in part, explains improvements in functional outcomes with post-stroke or post-traumatic patients. Although there are spontaneous reparative changes following injury, these changes are rarely sufficient to support significant functional recovery. Thus, research on the basic principles of brain plasticity should lead to new approaches in rehabilitation and treating the injured brain. In this regard, analysis from the perspective of neuroplasticity of hypoxic/ischemic preconditioning of the brain, a promising approach to prevention of brain injury, is important both for the fundamental concept of brain plasticity and for its potential clinical use [48].

The human brain contains about 86 billion neurons, specifically organized into definite brain areas and nuclei. Synaptic communications between neurons in specific circuits form a basis for adaptive behaviors, learning, memory, and are impaired in neurological and neuropsychiatric disorders. Efficiency ("strength") of signal transmission at each synapse can be modulated on diverse time scales providing for different neuroplasticity phenomena [49]. The area of neural plasticity and behavior has seen tremendous advances over the last six decades, with many of those advances being specifically in the neurochemistry domain [23]. This universe of neuroplasticity phenomena and mechanisms continues to expand, and multiple growing points associated with different areas of biochemistry, molecular biology, and molecular genetics are turning to powerful branches and stems before our very eyes. The main challenge is not only to decipher molecular mechanisms of normal adaptive and aberrant/maladaptive neuroplasticity, but also to use this knowledge for preventing and treating "dysplastic" cerebral pathologies.

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