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Central Glutamatergic-Purinergic System Importance in Brain/ Neural Plasticity

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Abstract

The proteolysis of the extracellular matrix plays a key role in the synaptic neuroplasticity of the central nervous system (CNS), which results in learning and memory. Proteases from the serine family and metalloproteinases of the extracellular matrix are localized within the synapses and are released into the extracellular space in proportion to the degree of neuronal excitation. These enzymes cause changes in the morphology, shape and size, and the overall number of synapses and synthesize new synaptic connections. The proteinase also changes the function of receptors, and consequently, the secretion of neurotransmitter/neuromodulator from the presynaptic glutamatergic and/or purinergic elements are either strengthened or weakened. Neuroglia involved in homeostasis, melanin synthesis and defense of the brain contain different combinations of purinergic receptors, which contributes to many neurotransmitters. This review summarizes a concept of brain plasticity, the role of ATP and P2 receptors interaction with glutamatergic system during plasticity of the brain in the one hand and after physical exercise in the other, which may be triggering phenomena facilitative synaptic plasticity as well as potentiates an personal efficiency to react to biobehavioral adaptation and disorders.

Keywords

Glutamatergic/Purinergic System, Neuroplasticity, Physical Exercise, Neuroglia Dependences

1. Introduction

In studies that examine neuroplasticity, many that are performed directly on isolated neurons CA1 and slices of hippocampus find that changes occur at the molecular and cellular levels during long-term synaptic potentiation (LTP), changes that are dependent on N-methyl-D-aspartate acid receptors (NMDARs) and/or purinergic receptors [1]. Electrophysiological studies and the chemical induction of LTP of synaptic neurotransmissions provide key evidence that LTP is dependent on the volume of Ca^{2+} influx through postsynaptic NMDARs, in addition to the consecutive stimulation to activity and autophosphorylation of Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) and the augmentation in the density of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors on the postsynaptic membranes of neurons. The primary peculiarity of LTP in the central nervous system (CNS) excitatory synapses is the synthesis of additional AMPARs in the postsynaptic elements [1] [2].

Additionally, the proteolysis of the extracellular matrix (ECM) plays a key role in the synaptic neuroplasticity of the CNS [3]. Proteases from the serine family and metalloproteinases of the extracellular matrix are localized within the synapses and are released into the extracellular space in proportion to the degree of neuronal excitation. These enzymes cause changes in the morphology, shape and size, and the overall number of synapses and synthesize new synaptic connections. The proteinases also change the function of receptors, and consequently, the secretions of neurotransmitters from the presynaptic elements are either strengthened or weakened.

Neuroglia are the cells involved in the homeostasis, melanin production and defense of the brain and are represented by the astrocytes, oligodendrocytes, NGglia and microglia. These cells contain different combinations of purinergic receptors, which contributes to many neurotransmitters [4].

The mechanism of neuroplasticity

Brain plasticity is closely correlated with the types of excitatory or inhibitory neurotransmitters that relay impulses in synapses, which thereby modify the strength or number of synaptic connections. These neurotransmitters primarily include glutamate, which affects several types of receptors among the ionotropic AMPA and NMDA receptors, and their function is to generate excitatory potentials at the postsynaptic membrane [5] [6]. A substantial number of NMDA receptors relative to AMPA receptors results in increased susceptibility to plastic changes in the initial period of postnatal development; however, in some adults, the situation is reversed. The function of the AMPA and NMDA receptors is associated with *long-term potentiation*, LTP, which is caused by the stimulation of protein kinases by Ca^{2+} ions, and *long-term depression*, LTD, which results from the low influx of Ca^{2+} ions and the activation of phosphatases. The consequences of these processes are long-term changes in the amplitudes of synaptic potentials, which lead to a strengthening or weakening of synaptic connections; the LTP and LTD phenomena are among the basic mechanisms of learning and memory [7].

2. Neuroglia Relation among Astrocytes, Glutamate and Adenosine

Synaptic plasticity importantly conditioned by an inverse correlations among the neurons and glia. Reciprocal transmitting impulses among neuronal and glia cells has been presented in the mammalian central nervous system. In the brain, they demonstrate about 10% of the overall brain neuronal number, where they are predominant as the brain resident macrophage and facilitate the modulation of neuronal activity (maturation, developing neuronal synapses, and phagocytic function). Microglia also serve as assessors of the CNS healthiness and endlessly liaison dendritic spines to modulate morphological trans synaptic changes in vivo with studies using 2-photon laser scanning microscopy [8]. Using 3-D reconstruction of ESEM, the opposition of microglia to dendritic spines, synaptic terminals, and synaptic effects were confirmed in the visual cortex of juvenile mice during the critical period. Microglial processes preferentially interacted with smaller, developing dendritic spines. This experiment demonstrated that the spines lesioned by microglia were more often removed compared with the non-contacted spines (24% vs 7%, respectively) during a normal visual experience [4].

Paolicelli *et al.* [9] used stimulated emission depletion (STDE) microscopy and immunogold electron microscopy techniques (immune-EM) and demonstrated that microglia contribute to synaptic pruning during development. These authors also identified a significant reduction in the microglial density in the brains of fractalkine/knockout mice receptors (CX3CLI) compared with littermate controls during postnatal weeks 2 to 3; during this period, the dendritic spine density of the hippocampal CA1 pyramidal neurons was significantly enhanced ($p < 0.05$). These data propose that microglia plays a key roles in the conformational plasticity in development via the fractalkine/fractalkine receptor and the classical complement cascades [10].

Reciprocal transmitting impulses among neuronal and glia cells has been presented in the mammalian CNS. Light-evoked neural action provide to enhances in the inception of Ca^{2+} transitional in neurons. These light-elicited glial responses are substantially potentiated by adenosine. Natural stimuli may induce Ca^{2+} enhances in brain glia. Signaling in the opposite direction, it is from glia to neuronal cells, has again been established. Glia cells suspend ganglion cells by the exception of ATP, which is deregulate into adenosine by ecto-enzymes and latterly stimulates neuronal adenosine receptors.

Glutamate is the major excitatory neurotransmitter in the brain which is accountable for causing Ca^{2+} improves in astrocytes. Likewise,, glial modulation of neuronal cells in the CNS is thought to be primarily mediated by the astrocytic liberation of glutamate. ATP appears to be the primary messenger accountable for both neuron to glia signaling and glia to neuron signalizing, in the retina [11]. Similar to the CNS, the presence of signalizing between neuronal and glia cells in the retina confirms retinal glial cells may important significance in information processing [12].

3. Physical Exercise on Neuronal Plasticity Involving Glutamatergic and Purinergic System

Neural plasticity is basically the capability of neurons in the CNS to accommodate gradually with time and predominantly appears in reaction to repeated exhibition to impulses [7] [13], whereas adult ontogenesis is the after-birth development of new neuronal cells, an advantageous configuration of neural plasticity. Physical exercise advances adult neurogenesis by augmenting the synthesis of neurotrophins (compounds that promote the growth of neuronal survival), such as brain derived neurotrophic factor (BDNF), insulin-like growth factor 1 (IGF1), and vascular endothelial growth factor (VEGF) [14]. The CNS centers that exhibit the very large improvement in gray matter volume in reaction to physical exercise are the prefrontal cortex and hippocampus [15], whereas a moderate improvement occurs in the anterior cingulated cortex, parietal cortex, cerebellum, caudate nucleus, and nucleus accumbens [16]. The prefrontal cortex, caudate nucleus and anterior cingulated cortex are between the most important brain centers in the DA and NE systems that create to mental control [7] [16]. Glutamate is one of the most predominant neurotransmitters in the central nervous system and is an stimulatory substance participated in many aspects of brain activity, along with learning and memory [7]. Exercise normalizes the co-transmission of glutamate and dopamine in the nucleus accumbens [17]. In a preclinical model of neurocardiac function, exercise-induced neuroplasticity of the rostral ventrolateral medulla (RVLM) has an inhibitory effect on glutamatergic neurotransmission, which, in turn, decreases sympathetic activity. This neuroplasticity in the RVLM may represent a mechanism by which regular exercise prevents inactivity-related cardiovascular disease [18].

The capability of the CNS to alter its configuration to transformed requests and the environment it was named "neuronal plasticity" [19]. Neuronal plasticity take place, for example, during the acquisition of new abilities after injury to the brain and as a consequence of sensory deprivation. Neural plasticity it was investigated at the various organization levels of the CNS, which range from ion channels to synapses, neurons, neuronal columns, cortical maps and behavior [19].

In previous years, data from human and animal researches has proposed that physical activity and physical exercise were facilitating the impact on neural plasticity and are frequently associated with enhanced mental activity. By increasing neural plasticity, physical exercise may facilitate hardly adaptive types of learning, as well as the acquisition of fear or unwanted practices, not previously reported in humans [19].

Physical activity is a beneficial favorable treatment that influences the cerebral autogenously pharmacology of the brain to increase cognitive and emotional activity in old age. Physical exercise is associated with slower cortical neurodegeneration, better efficiency of the brain, and increased cognitive activity, and it has been argued that physical activity takes predominance of the neuronal brain's congenital capability for plasticity [16].

Brain reparation phenomenon during convalescence from disorders concerns neuronal plasticity, the development of new blood vessels and the growth and development of nervous tissue, which are phenomenon controlled by environmental stimulant impulses, such as sensory and motor stimuli through the neural tract. Physical exercise promotes neural cell survival mechanisms, while suppressing the neural apoptotic tract, for example during stroke by bettering motor enforcement and enhancement the glutamate transporter (GLT-1) expression and activeness, which modifies the neuronal circuitry of the brain [10]. Additional physical exercise increases the neural plasticity and the activity of neural tracts. It was well confirmed that glutamate is a main excitatory neurotransmitter, which intermediates a substantial most of synaptic transmission and neural plasticity, as well as higher brain functions [20]. Various current investigations demonstrate that physical training likewise features an critical importance in angiogenesis and practical restoration following cerebral stroke [21].

4. Role of Glutamate in Shaping Plasticity

The formation and development of central neuronal synapses is controlled by the glutamatergic system, with a significant contribution from purinergic signaling (adenosine triphosphate, ATP) [22]. A special role is attributed to N-Methyl-D-aspartate (NMDA) acid receptors. These receptors are localized on the postsynaptic membranes and regulate the transport of Ca^{2+} ions into the neuron and therefore, the signaling cascade initiated by these ions as a result of the strong depolarization. Under these conditions, non-NMDA receptors are easily stimulated by changes in the impulse voltage because these receptors are gated with Na^{+} and K^{+} and are therefore rapidly and transiently activated. When a long-term depolarization occurs (caused by a stronger stimulus or a simultaneous stimulation of neighboring synapses in the postsynaptic neuron), the induction of LTP and the consolidation of the synaptic connections are possible. Synaptogenesis is maintained throughout the life of the individual, and synaptic neuroplasticity may be modulated not only by glutamate but also by acetylcholine (ACh), dopamine (DA), gamma-aminobutyric acid (GABA), glycine, norepinephrine (NE) and purine, which affect the development of axons and dendrites, the stabilization of synapses, and the survivability of neurons *via* the regulation of apoptotic and other factors.

Role of glutamate in brain plasticity

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5. Role of Purines in Brain Plasticity

The purines adenosine and ATP (adenosine triphosphate) are widely recognized as a neuromodulator and neurotransmitter, respectively, for their neuromodulatory effects. In the CNS, neurons release ATP as a co-transmitter and co-release with glutamate in the hippocampus [25]. Adenosine is directly released by nucleoside transporters and channels or produced through the extracellular metabolism of nucleotide (ATP). ATP mediates astrocyte calcium waves *via* astrocyte excitability [26].

ATP and adenosine have been demonstrated to have effects on neurons *via* various receptors (P and A) and interactions with glial cells, as well as the modulation of LTP specifically in hippocampal slice preparations. Adenosine mediates a mimetic suppression of synaptic transmission. Low adenosine concentrations appear to increase basal synaptic activity *via* a decreased activation of the inhibitor A_1 receptor, which consequently makes it more difficult to induce LTP because of a lower contrast.

During high levels, the inhibition of neighboring pathways by adenosine, in combination with A_2 receptor stimulation, appears to increase the contrast of excited pathways against a nonexcited [27]. The evidence for a clear role for purinergic signaling in LTP is evident [25].

Cell surface-located triphosphate diphosphohydroxylases (NTDPase-1, -2, -3 and -8) are oligomeric entire membrane proteins accountable for signal transformation and deactivation in occurring outside a cells nucleotide intermediated "purinergic" impulses. They activate the sequential order hydrolysis of the signaling molecule ATP trough ADP to AMP [28]. In addition to its important intracellular function (metabolism), ATP and nucleotides also serve as extracellular signaling molecules that change a breadth physiological activities, such as cell proliferation (e.g., in embryonic development and cancer), pain perception

(neuropathic pain), blood clotting, inflammatory processes, immune reactions and smooth muscle contraction [29]. It is released by exocytosis or *via* transporters to the extracellular space. Cellular effects are induced by binding to two classes of P2 receptors: P2X receptors, which are ligand gated ion channels, or P2Y receptors, which are G-protein coupled receptors [30] [31] [32]. This purinergic signaling *via* ATP and other nucleotide effects are transformed and finalized *via* the subsequent dephosphorylation of nucleotides by a cascade of membrane bound enzymes [33].

Extracellular nucleotides influence a wide variety (previously described) of short-term (acute) physiological processes, including endocrine and exocrine release, immune reactions, inflammation, nociceptive mechanosensory transduction, clumping of blood platelets and endothelial-mediated vasodilatation. The long-term (trophic) processes affected include cell proliferation, differentiation, migration and death, such as in body growth, regeneration and cancer [29].

A number of extracellular nucleoside triphosphate diphosphohydroxylases (nucleotidases - NTPDases, E.C. 3.6.1.5) and more specifically the cell surface-located NTPDase 1-3 and -8 comprise the dominant ectonucleotidases relevant to P2 receptor-mediated signaling. They dephosphorylate ATP *via* ADP to AMP. ADP also acts on specific receptors, whereas no receptor has currently been identified for AMP. 5-nucleotidase (5'-NT) catalyzes the hydrolysis of AMP to adenosine. In addition to the receptors for extracellular nucleotides and nucleosides, the ecto-nucleosidases have also been recognized as pharmaceutical targets to interfere with purinergic signaling pathways (**Figure 1**) [28].

The A_1 podtype receptor, which is tonically stimulated by the resting level of adenosine, regulates basal neurotransmission; however, the A_{2x} receptor is stimulated by an increased adenosine concentration and participates in plasticity. ATP may act as an independent neurotransmitter on the $P2X_4$ receptor or *via* the $P2X_3$ subtype as a neuromodulator that affects NMDA receptor signaling. The G-protein coupled P2Y receptors also evoke a neuromodulatory effect on neuronal plasticity, which inhibits LTD in the prefrontal cortex. P2X is responsible for communication between astrocytes and synchronization of their activity. ATP and adenosine released by astrocytes act as neuromodulators both at the release site and heterosynaptically. Taken together, these multiple actions of nucleotides constitute a mechanism that regulates the homeostatic processes necessary for proper brain functioning: synaptic scaling and metaplasticity [12]. In addition to its important cellular function in metabolism, ATP also serves as an extracellular signaling substance. It is released by exocytosis or via transporters to the extracellular space, and it acts on P2X receptors, which are ligand-gated ion channels, or P2Y receptors, which are G-protein coupled receptors. These signaling pathways via ATP and other nucleotides are referred to as purinergic signaling. Extracellular nucleotides influence various short-term (acute) physiological processes, including exocrine and endocrine secretion, immune responses, inflammation, nociceptive mechanosensory transduction, platelet aggregation and endothelial-mediated vasodilatation. The long-term (trophic)

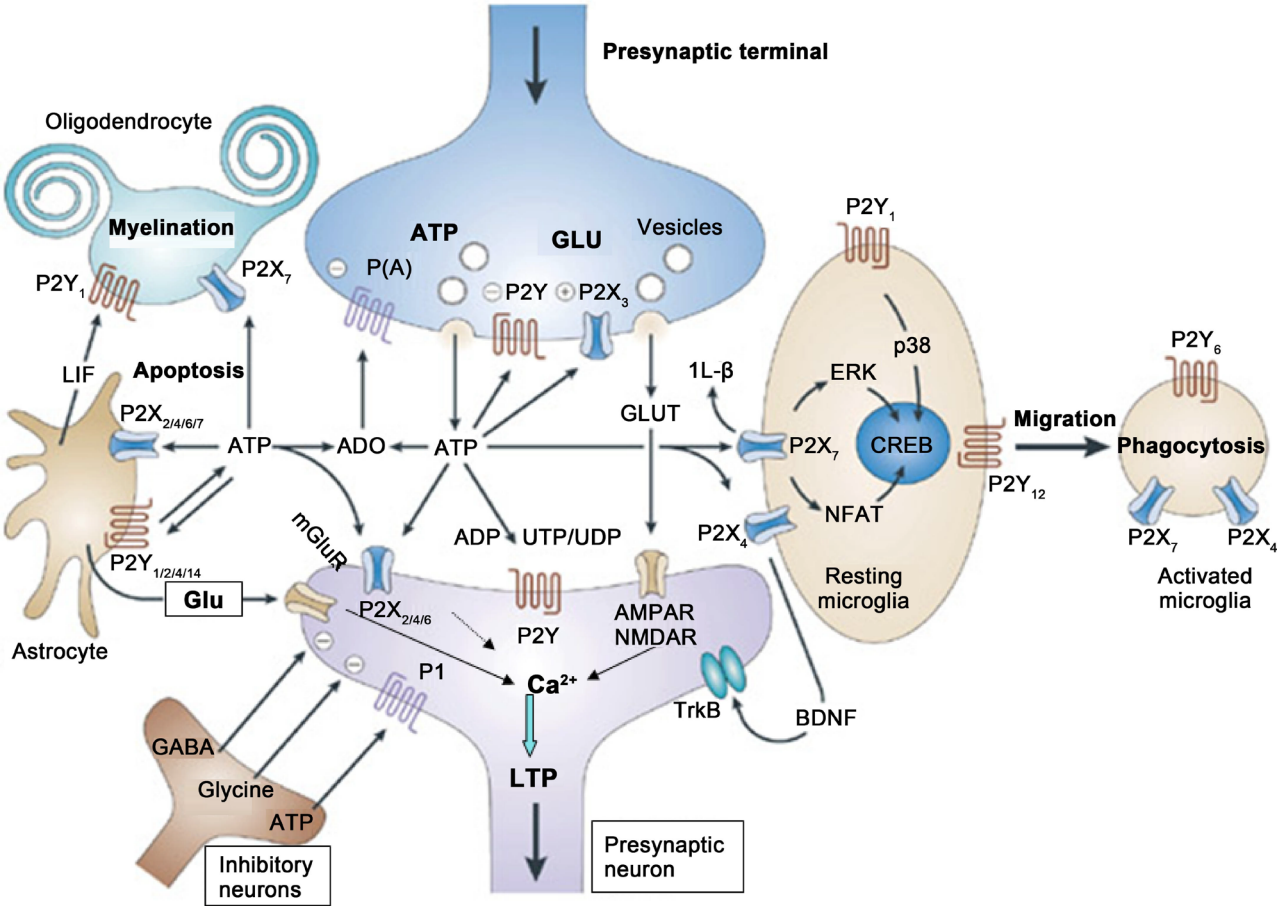

Figure 1. Hypothetical scheme of the putative glutamatergic-purinergic possible signaling pathways implicated in the induction of neural plasticity that is modulated by ATP/Glu in the brain. Presynaptic terminals of the neuron are depicted releasing Glu or a simultaneous release of Glu and ATP as cotransmitters from both presynaptic terminals and glia cells, by exocytosis. The released ATP acts postsynaptically on $P2X_{2,4,6}$ and on various P2Y receptor subtypes activated by ADP, UTP and UDP as well as ATP. Glutamate released from presynaptic terminals, astrocytes and microglia acts postsynaptically on AMPARs and NMDARs, releasing of Ca^{2+}, AMPARs phosphorylation, leading to the induction of LTP in postsynaptic neuron. ATP is broken down by ectonucleotidase to adenosine (ADO), which acts as a presynaptic inhibitory modulator through P1 (A_1) receptors, but ATP itself can act presynaptically either to inhibit the release of transmitter through P2Y receptors or to enhance the release of Glu through $P2X_3$ receptors. ATP is also released from astrocytes (and probably also from microglia) together with Glu to participate in glial-neuron interactions. Both P2X and P2Y receptor subtypes are expressed by astrocytes [acc. to Geoffrey Burnstock: Nature Review 2008, 64, 471-483 and Ref. [1] [3] [22] [28] (with proper modification).

processes affected are cell proliferation, differentiation, migration and death, such as development, regeneration and cancer.

Primarily because ATP is rapidly metabolized to ADP and adenosine, the functions of ATP as a chemical mediator in the brain are also little understood. Similarly, the pharmacological effects of ATP are difficult to determine with sufficient precision. Moreover, few substances that act as selective agonists and/or antagonists in relation to the ATP receptors have been identified, which contributes to the lack of information. One function may be an involvement in brain plasticity and nociception because the damaged tissues release ATP, which has reparatory, nociceptive effects, as a consequence of the intensification of LTP and the activation of myelin-free afferent nerve endings, which comprise P2X

receptors [34].

As a foundation for all learning and memory processes, the synaptic activity-dependent phenomenon of LTP applies to excitatory Hebbian synapses. The role of the purinergic component in synaptic transmissions has recently been stressed. ATP is released from presynaptic terminals [35], and ATP receptors are widespread in the brain [36]; therefore, ATP saturates the P2X receptors that mediate the synaptic transmission in the medial habenula and the hippocampus, which is the structure responsible for orientation in space (short-term memory) [37]. Despite this scenario, the specific physiological role of ATP receptors in the brain remains the subject of research. The activity of ATP is mediated by ionotropic (P2X) and metabotropic (P2Y) purinoceptors. The inhibition of P2X receptors does not induce LTP, in which the prior blockage of NMDA receptors is demonstrated. Therefore, the assumption is that P2X receptors interfere with the induction threshold of LTP *via* calcium-dependent inactivation of NMDA receptors.

6. Effect of Central Glutamatergic-Purinergic Interactions on Neural Plasticity

Long-term potentiation is the activating factor of the synaptic correlation with learning and memory processes because the induction of LTP requires NMDA receptor (NMDAR) activity. This receptor unblocks the plasma protein, syntaxin-1 SNAP25 vesicle protein synaptobrevin/VAMP complex (SNARE complex), dependent exocytosis of AMPA receptors (AMPAR) [38]. Nevertheless, the molecular mechanisms that mediate AMPAR exocytosis via NMDAR receptor activation remain largely unknown. The binding of complexin (synaphin), a protein that regulates neurotransmitter release, to the SNARE complex is essential for AMPAR exocytosis, which maintains the basic synaptic strength. The modulation of postsynaptic AMPAR exocytosis during LTP requires the binding of complexin to the SNARE complex [39]. In hippocampal neurons, presynaptic complexin functions in combination with synaptotagmin-1 and mediates the release of neurotransmitters. Postsynaptic synaptotagamin-1 is not essential to complexin-dependent AMPAR exocytosis during LTP [40]; however, the results obtained by Ahmed *et al.* [39] suggest that complexin-dependent molecular mechanisms of AMPAR regulation are transported to the synapses. Moreover, the mechanism of this transport is remarkably similar to presynaptic exocytosis; however, it is controlled by regulators other than synaptogamin-1.

Long-term potentiation involves both presynaptic and postsynaptic mechanisms. Neuronal depolarization and NMDA receptor activation, in addition to voltage-gated calcium channel activation cause the inflow of Ca^{2+} ions to the center of the cell from storage in the endoplasmic reticulum and the extracellular space. The activities of Ca^{2+}/calmodulin-dependent protein kinase II (CAMKII) and PKA and PKC protein kinases, as well as phosphatases, which control the functions of receptors and other proteins, are regulated by the concentration of Ca^{2+} ions. The enzyme activity leads to changes in the phosphorylation of neu-

rotransmitter receptors, the synaptic transport of AMPA receptors and the clustering of receptors in the postsynaptic membrane. In the late phase of LTP, a critical phenomenon occurs, the synthesis of new proteins, which may occur near the synapses on the mRNA matrix that is transported from the cell body of the neuron [40].

Jones *et al.* [41] recently described a novel form of heterosynaptic metaplasticity in the hippocampal CA1, in which "priming" activity at one set of synapses confers a metaplastic state that inhibits subsequent LTP both within and between the dendritic compartments. In an investigation of the roles of purinergic signaling and gap-junctions in the mediation of this long-distance communication between synapses, it was demonstrated that heterosynaptic metaplasticity requires the hydrolysis of extracellular ATP to adenosine and the stimulation of adenosine A_2 but not A_1 receptors. These previous findings indicated that an intracellular signaling cascade in acute hippocampal slices in young adult male Sprague-Dawley rats and mice underlies the long-distance communication required for this form of metaplasticity, which was also blocked by the nonselective gap-junction blockers carbenoxolone and meclofenamic acid, as well as a connexin43-specific mimetic peptide [41].

7. Conclusions

In conclusion, the interaction of glutamate and ATP in shaping long-term potentiation strongly suggests that the mechanisms in the nervous system require the mediation of ATP. Thus, additional studies should be conducted to specifically determine the processes that require ATP participation, including the processes related to dysfunctions of the nervous system.

This review summarizes concepts of brain plasticity, the role of ATP and P2 receptors interaction with glutamatergic system during plasticity of the brain in the one hand and after physical exercise in the other, which may be triggering phenomena facilitative synaptic plasticity as well as potentiates an personal efficiency to react to biobehavioral adaptation and disorders.

Conflict of Interests

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

Contribution of the Authors

The review was performed at the Hugon Kollataj Agricultural University in Cracow. Al authors (B.F.K., D.W and D.Z.) contributed to conception of design of the work, analysis or interpretation of another manuscripts or revising it critically. All authors have approved the final version of the manuscript and agree to be accountable for all aspects of the review. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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Abbreviations

A1—adenosine receptor 1;
AD2—adenosine receptor 2;
ADO—adenosine;
ADP—adenosine diphosphate acid;
AMP—adenosine monophosphate acid;
AMPAR—α-amino-3-hydroxy-5-methyl-4-isoxazole propioinic acid receptor;
ATP_—adenosine triphosphate acid;
BDNF—brain-derived neurotrophic factor;
CA1—pyramidal cells od CA1 area of hippocampus;
CAMKII—$Ca^{2+/}$calmodulin-dependent pprotein kinase II;
CNS—central nervous system;
CX3CLI—fractalkine/knockout mice receptor;
ECM—extracellular matrix;
ESEM—environmental scanning electron miscroscope;
GLT—glutamate transporter;
Glu—glutamate;
mGluR—metabotropic glutamate receptor;
IGF—insulin-like growth factor;
LTD—long-term depression;
LTP—long-term potentiation
NMDA—N-methyl-D-Aspartate;
NMDAR—NMDA receptor;
NTPDases—nucleoside triphosphate diphosphohydroxylases;
P1 (A1) —purinergic receptor 1 (adenosine receptor 1);
P2X—purinergic receptor 2X;
P2Y—purinergic receptor 2Y;
mRNA—ribonucleic acid messenger;
RVLM—rostral ventrolateral medulla;
SNARE—synaptobrevin/VAMP complex;
UDP—uridine diphosphate;
UTP—uridine triphosphate;
VEGF—vascular endothelial growth factor.