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Introduction to Neural Plasticity Mechanism

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Abstract

In researches that examine neuroplasticity, many studies that are performed directly on isolated neurons in the pyramidal cells of CA1 area (CA1) and slices of the hippocampus indicate that changes occur at the molecular and cellular levels during long-term synaptic potentiation (LTP), and these changes are dependent on N-methyl-D-aspartate (NMDA) acid receptors and/or purinergic receptors. 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 NMDA receptors, in addition to the subsequent activation and autophosphorylation of Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) and the increase in the density of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors on postsynaptic neuronal membranes. The primary peculiarity of LTP in the central nervous system (CNS) excitatory synapses is the synthesis of additional AMPA receptors in the postsynaptic elements. Furthermore, the proteolysis of the extracellular matrix (ECM) has an important role in the synaptic neuroplasticity of the CNS. 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, as well as 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 strengthened or weakened.

Keywords

Neuroplasticity, Heterosynaptic Metaplasticity, Subjects

1. Introduction

Brain plasticity or neuroplasticity is the inherent capacity of nerve tissue to form new interneuronal connections or synapses (*synaptogenesis*) or replace useless, nonfunctional (*neurodegeneration*) neurons in the brain with new neurons (*neurogenesis*). Synaptic plasticity is the ability to change the synaptic strength. Changes in the strength include neurotransmitters. Neuroplasticity comprises an important neurochemical basis of learning and memory. The effect of neuroplasticity is to reorganize the functions of neurons to permit rapid adaptation and self-repair, which may translate into learning and memory processes at all levels of the nervous system. It also comprises the intrinsic excitability of a neuron with influences on information storage.

Neuroplasticity is the brain's ability to form new neural connections throughout life, which is influenced by intrinsic or extrinsic stimuli, or the capacity of neurons and neural networks in the brain to change their connections and behavior in response to new information, sensory stimulation, development, damage or dysfunction [1].

Accordingly to Jones *et al.* [2], experience-dependent forms of synaptic plasticity, such as LTP and long-term synaptic depression (LTD), are widely regarded as cellular mechanisms of learning and memory. LTP reflects an increase in the synaptic strength and requires the activation of glutamate receptors or other receptor subtypes. In contrast to LTP, LTD reflects a persistent decrease in the synaptic strength (**Figure 1**).

Metaplasticity is a term coined by Abraham and Bear [3] to refer to the plasticity of synaptic plasticity to different synapses, which are all controlled *via* the same mechanisms, and is defined as Hebbian plasticity [4]. In general, metaplasticity refers to activity-dependent changes in neural function that modulate subsequent synaptic plasticity, such as LTP and LTD. Metaplasticity entails a change in the physiological or biochemical state of neurons or synapses that alters their ability to generate synaptic plasticity [3].

Synaptic plasticity had previously referred to the plastic nature of individual synapses. The idea is that the synapse's previous history of activity determines its current plasticity. Therefore, the thresholds for LTP and LTD induction are plastic and may be strongly regulated by the history of neural activity through processes referred to as "metaplasticity" [3]. Their mechanisms may increase or diminish plasticity thresholds to promote information storage, discriminate salient and non-salient events and, in the extreme, avoid neuronal damage [2].

Homeostatic metaplasticity is a fundamental principle regarding the maintenance of the overall synaptic weight in the physiological range after Murakami *et al.* [5] in neuronal networks and has been demonstrated at the cellular and system levels predominantly for excitatory synaptic neurotransmission. Plasticity in both excitatory and inhibitory circuits in the human motor cortex are regulated by homeostatic metaplasticity, and priming effects on inhibition contribute to the homeostatic regulation of metaplasticity in excitatory circuits [5].

Heterosynaptic metaplasticity. Earlier synaptic plasticity was subject to activity-

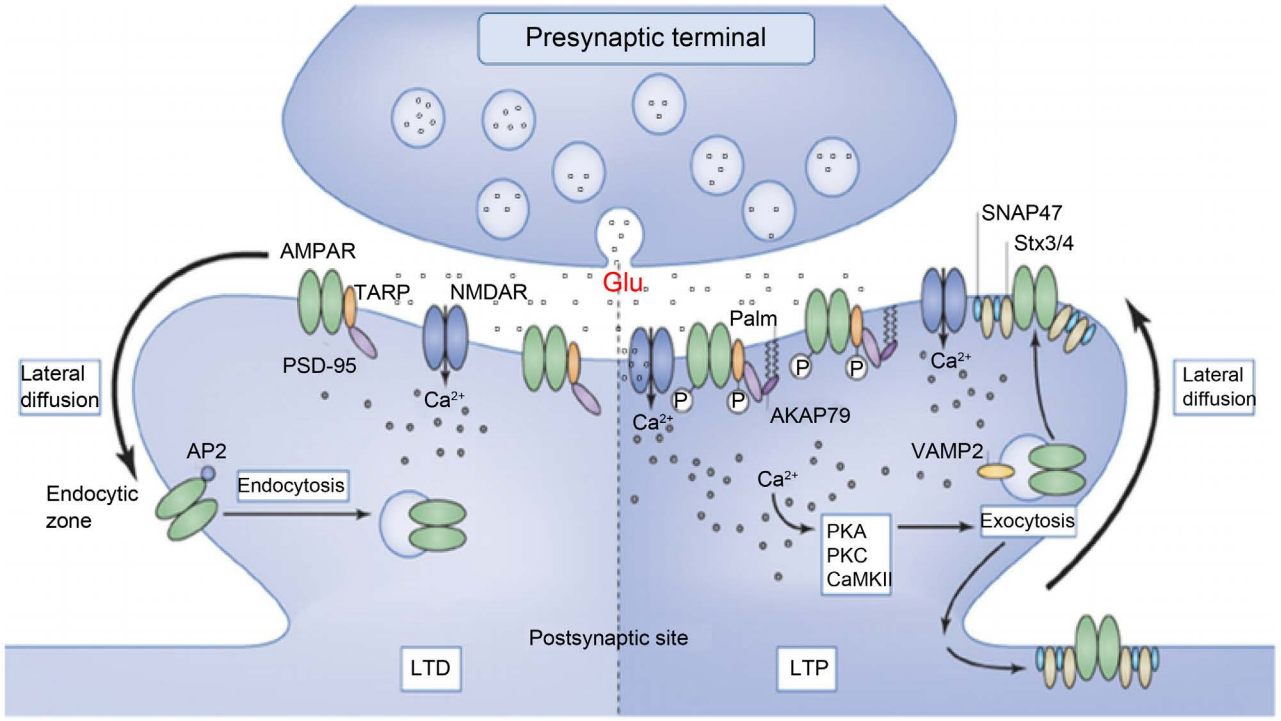

Figure 1. Hypothetical diagram of pre- and postsynaptic elements and putative glutamatergic (Glu)/purinergic signaling pathway implicated in the induction key roles of synaptic neuroplsticity that is modulated by Glu/ATP in the brain. Presynaptic terminals of the neuron depicted releasing Glu or a simultaneous release of Glu and another cotransmitters from both presynaptic terminals and glia cells, by exocytosis. Glutamate released from presynaptic terminals, astrocyte and microglia acts post-synaptically on AMPAs and NMDARs, releasing Ca^{2+} into synaptic cleft, AMPARs phosphorylation, leading to the induction of LTP in postsynaptic neuron (details in the text). *Abbreviation*: AKAP79—A kinase anchoring protein AKAP79 as a signaling complex AKAP79/150 may facilitate Ser845 phosphorylation); AMPAR—*α*-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor; TARP-transmembrane AMPA regulatory protein; NMDAR-N-methyl-D-Aspartate Rceptor; PSD-95-; Ca^{2+}—calcium ion; Palm-promoting active learning@mentoring; P-; SNAP-47—novel member of the QGc SNARE family synaptosomal-associated protein 47; Stx3/4-syntaxin 3/4 (cellular receptors for transport vesicles—a new regulator for retrograde signaling); VAMP2—vesicle-associated membrane protein 2 (synaptobrevin2); PKA—protein kinase A (regulates calcium permeability of NMDARs. PKA regulates the induction of LTP *via* increased the early phase of NMDARs-dependent LTP at hippocampal-collateral-CA1 synapses); PKC—protein kinase C (capable for modulating exocytosis and endocytosis of neurotransmitter vesicles); CaMKII—Ca^{2+} dependent CaMKII—Ca^{2+}/calmodulin-dependent protein kinase II is a serine/threonine-specific protein kinase that is regulated by the Ca^{2+}/calmodulin complex an important mediator of learning and memory; LTP—long-term potentiation; LTD—long-term depression; PSD—95-postsynapptic density protein 95 (is essential for synaptic maturation and plasticity); AP2—adaptin complex AP2 (is critical for the recruitmment of integral membrane pproteins into clathrin—coated pits); (accordingly to: Burnstock 2008, Jones 2013, Kolb 2011; in propre modification).

dependent long-term modification (metaplasticity). The degree of persistence for metaplasticity ranges from minutes to many days [3] and typically occurs in a previously stimulated synapse. Activity at one set of synapses may also affect heterosynaptic metaplasticity. Cell-wide modifications in the threshold are driven by the history of postsynaptic cell firing, and cell-wide homeostatic processes adjust plasticity thresholds to maintain the overall level of synaptic at one cell within a range. Jones *et al.* [2] 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 dendritic compartments. Heterosynaptic metaplasticity requires the

hydrolysis of extracellular ATP to adenosine, as well as the stimulation of adenosine A_2 but not A_1 receptors.

2. Historical Overview

Santiago Ramon and Cajal stated [6] that the axons of individual neurons do not connect with one another (the neuron doctrine), and each axon always ends at the dendrite of an adjacent neuron(s). The protoplasm of the two neurons does not mix, and the axon and the dendrite are separated from each other by a narrow gap, which is referred to as the neural synapse (an interneuron connection) [6]. Nerve impulses "cross" this gap *via* transmitter release from the molecular stores in the presynaptic location of the nerve fiber.

According to the discoverer of neural synapses, "In the adult centers, the nerve paths are something fixed, ended, and immutable. *Everything may die, nothing may be regenerated*." However, this statement is contradictory to the current state of knowledge regarding brain plasticity; in 1998, the development of new neurons in the adult brain was documented, as well as the finding that existing neurons developed new branches [7].

The basic synaptic pattern between various centers in the nervous system develops during the development of an individual based on a genetic program. However, the neural circuits and pathways remain plastic and are modified throughout the lifetime of an individual. This characteristic may serve, at least in part, as the initial step in the challenge to repair and compensate for damage to the nervous system [8] [9] [10].

Neural plasticity occurs when the properties of neurons permanently change as a result of impulses that originate from the environment [11], also epigenetic modification are important for neural plasticity. According to the previously quoted author, the first characteristic of nerve cells that react to incoming stimuli is their excitability, which is initiated by a defined cycle of changes. As defined by Santiago Ramon and Cajal, the second property is *plasticity*, in which, when stable, functional transformations occur in specific neuronal systems as a result of specific stimuli or the combination of stimuli; the corresponding changes are *plastic changes.* Within the following year, Hebb [12] demonstrated that effective and repeated postsynaptic neuron stimulation (action potential) preceded by presynaptic stimulation is required to change the strength of an interneuron connection (**Figure 1**). The result of this phenomenon is biochemical changes, which are followed by anatomical adaptations that reinforce the connections between neighboring neurons. Thus, effective stimulation results in stronger interneuronal connections. The strength of the excitation impulse must exceed a threshold value to increase the synaptic efficacy and the stability of the connections between neurons. However, when neurons are stimulated only with subthreshold stimuli, the overall activity of the synapse may decrease.

In 1969, Raisman [13] demonstrated that a unilateral lesion of the hippocampus results in the formation of new synapses (*synaptogenesis*) by the axons from the remaining contra-lateral hippocampal system. Thus, the postsynaptic portion

of a synapse continues to function properly despite the degeneration of the presynaptic region, and the surviving axons form new synapses. The fibers that form the (new) synapses are homologous to the damaged synapses, which may significantly facilitate the restoration of normal function. In subsequent research, sprouting was discovered, which comprises the formation of new axons and the growth of new branches (sprouts) in undamaged, intact axons, and synaptogenesis was identified in the afferent and efferent pathways of the hippocampus [14].

The potency of brain plasticity mechanisms within the optic nerves of young cats and monkeys was demonstrated by Wiesel and Hubel [15]; a very strong reorganization of the neural pathway of the visual system occurs when one eye of an animal is covered early in life to prevent its use.

3. Modern Neuro-Biological Definition of Neuroplasticity

The most recent definition of neuroplasticity is based on the permanent changes in the properties of nerve cells that occur as a result of environmental stimuli or from a break in the continuity or other damage to the nervous system [16].

Systemic neuroplasticity is an inherent feature of the nervous system that enables the system to adapt to changing environmental conditions by affecting, in particular, the processes of learning and memory, as well as a self-repair capacity. These characteristics apply to neurons at all levels of the nervous system, and various types of neuroplasticity are recognized as follows: developmental plasticity, post-injury plasticity of a fully developed brain (compensatory plasticity), neuroplasticity caused by repeated sensory (inputs) or motor (outputs) experiences, plasticity associated with the processes of learning and memory, plasticity formed during the development of addiction, and pathological neuroplasticity induced by the development of epilepsy (*epileptogenesis*) or neuropathic pain. The changes in the strength of interneuronal connections, with modifications in the strength (efficacy) and the number of synaptic connections (nerve synapses), comprise the underlying foundation of these neuroplastic changes [17].

During the prenatal development of the nervous system, the quantity of developing neurons exceeds the number of neurons that survive. The neurons "compete" with each other for the chance to form synaptic connections with other neurons (*synaptogenesis*), and the neurons that do not produce these connections experience programmed (and controlled) cell death (*apoptosis*). The key factor in the formation of synapses at both the cellular and molecular levels is *long-term potentiation* (LTP) [18].

4. Object of Neural Plasticity

Based on studies of the structure and function of the brain, dynamic modifications of this organ occur under the influence of different factors. The plasticity of the brain is defined as nerve pathway reorganization in response to external stimuli, which is primarily expressed in the modulation of the density and quantity

of neural pathways with changes in the mode of synaptic communication. Moreover, morphological changes occur in neurons.

Plastic changes in the nervous system are a consequence of the natural development and life of an organism; however, paradoxically, these changes may also result from various types of damage and injury, repeated activity (experience) in response to environmental stimuli, learning and memory processes, or addiction. The nervous system is particularly vulnerable to these factors during developmental stages; however, this capacity is preserved in the adult brain. Stimuli that alter the neural structure include psychoactive drugs, diet, disease, stress, growth factors, anti-inflammatory agents, sex hormones, and organic brain damage.

Changes in behavior are associated with changes in the organization and/or properties of the brain, primarily by the modification or creation of new elements, which may result in an anatomical imprint. These changes are primarily present at the level of the synapse. The examination of these changes is difficult because the area of interest will always be too limited relative to the extremely substantial number of synapses, which for the human brain consists of 100 billion nerve cells that may each produce several thousands of synapses. The simple, neuron staining technique of Golgi is used to estimate changes in the quantities of synapses that depend on changes in the dendritic length or dendritic spine density. Using this method, a significant difference is identified in the number of synapses in specific brain regions of pet animals placed in environments that are rich or poor in stimuli. In the enriched environments, e.g., in which a stimulating element, such as a running wheel, is introduced, a two- to threefold increase occurs in the number of hippocampal neurons [19]. Various stimuli, such as different odors, affect not only the number but also the life span of neurons in the medulla oblongata. Subsequent studies on animals at different stages of development have identified quantitative and qualitative differences in the organization of synapses in animals placed in identical environments that were rich in stimuli [20] [21].

In adults and older animals, the length of dendrites and the density of nerve synapses in the sensory and motor cortices increase in response to stimuli; in contrast, in young animals, the dendrites grow in length, but the density of dendritic spines decreases. Therefore, the conclusion is that even mild stimulation, such as treatment with a small brush three times a day for 15 minutes at a young age, improves motor and cognitive functions in adult animals, which suggests that anatomical changes occur in the nervous system [22] [23] [24] [25] [26].

Recently, it was discovered that dendrosomatic sonic hedgehod (Shh) signaling by secreted protein and special molecule like small Rho GTP-ases or modification of chromatin that controls the pattering of neural progenitor cells, and their neuronal and glial progeny, regulates axon elongation in the hippocampus; also, has key roles in the formation and plasticity of neuronal circuits important in learning and memory [27] [28].

Several past studies of animal models suggest potential therapeutic applications

of sonic hedgehod (Shh) signaling central receptor agonists and/or AMPA receptors (AMPARs) and NMDA receptors (NMDARs) antagonists [27] [28] in several neurological disorders such as Parkinson Disease, schizophrenia, autism and others. It can be note, in this context the considerable mechanistic overlap between neuroprotective preconditioning effects which prevent excitotoxicity and metaplasticity [2].

References

[1] Malhotra, M. (2013) Physical Exercise and Neuroplasticity. Examining the Role of Exercise on Long-Term Brain Function. Physical Therap@rehab Medicine.

[2] Jones, O.D., Hulme, S.R. and Abraham, W.C. (2013) Purinergic Receptor- and Gap Junction-Mediated Intercellular Signalling as a Mechanism of Heterosynapticmetaplasticity. *Neurobiology of Learning and Memory*, **105**, 31-39. https://doi.org/10.1016/j.nlm.2013.05.010

[3] Abraham, W.C. (2008) Metaplasticity: Tuning Synapses and Networks for Plasticity. *Nature Reviews Neuroscience*, **9**, 387-399. https://doi.org/10.1038/nrn2356

[4] Yger, P. and Gilson, M. (2015) Models of Metaplasticity: A Review of Concepts. *Frontiers in Computational Neuroscience*, **9**, 1-14. https://doi.org/10.3389/fncom.2015.00138

[5] Murakami, T., Mùller-Dahlhaus, F., Lu, M.K. and Ziemann, U. (2012) Homeostatic Metaplasticity of Corticospinal Excitatory and Intracortical Inhibitory Neural Circuits in Human Motocortex. *J Physiol*, **590**, 5765-5781. https://doi.org/10.1113/jphysiol.2012.238519

[6] Cajal, R.S. (1890) Sobre la existentia de cellulas nerviosas especiales en la primera capa de las circonvolutiones cerebrales. *Gac Med Cat*, **13**, 737-739.

[7] Walenzuela, M.J., Breakspear, M. and Sachdev, P. (2007) Complex Mental Activity and the Aging Brain: Molecular, Cellular and Cortical Network Mechanisms. *Brain Research Reviews*, **56**, 198-213. https://doi.org/10.1016/j.brainresrev.2007.07.007

[8] Burnstock, G. (2008) Purinegic Signalling and Disorders of the Central Nervous System. *Nature Reviews*, **7**, 575-590.

[9] Burnstock, G. (2007) Physiology and Pathophysiology of Purinergic Neurotransmission. *Physiological Reviews*, **87**, 659-697. https://doi.org/10.1152/physrev.00043.2006

[10] Burnstock, G. (2007) Purine and Pirymidine Receptors. *Cellular and Molecular Life Sciences*, **64**, 471-483. https://doi.org/10.1007/s00018-007-6497-0

[11] Konorski, J. (1948) Conditioned Reflexes and Neuron Organization. Cambridge University Press, Cambridge.

[12] Hebb, D.O. (1949) The Organization of Behavior. Willey, New York.

[13] Raisman, G. (1969) Neuronal Plasticity in the Septal Nuclei of the Adult Rat. *Brain Research*, **14**, 25-48. https://doi.org/10.1016/0006-8993(69)90029-8

[14] Kossut, M. (1992) Plasticity of the Barrel Cortex Neurons. *Progress in Neurobiology*, **39**, 389-422. https://doi.org/10.1016/0301-0082(92)90013-5

[15] Wiesel, T.N. and Hubel, D.H. (1965) Comparison of the Effects of Unilateral and Bilateral Eye Closure on Cortical Unit Responses in Kittens. *Journal of Neurophysiology*, **28**, 1029-1040.

[16] Kolb, B. and Gibb, R. (2011) Brain Plasticity and Behavior in the Developing Brain. *Journal Academy Child Adolescence Psychiatry*, **20**, 265-276.

[17] Ziemiańska, K., Konopka, A. and Wilczyński, G.M. (2012) The Role of Extracellular Proteolysis in Synaptic Plasticity of the Central Nervous System. *Postępy Higieny i Medycyny Doświadczalnej*, **66**, 959-975. https://doi.org/10.5604/17322693.1021851

[18] Doroszewska, J. (2008) Neurogenesis and Synaptic Plasticity of CNS. In: Kozubski, W. and Doroszewska, J., Eds., *Apoptosis in Central Nervous System Disorders*, Czelej, Lublin, 45-64.

[19] Ming, G.L. and Song, H. (2011) Adult Neurogenesis in the Mammalian braIn: Significant Answers and Significant Questions. *Neuron*, **70**, 687-702. https://doi.org/10.1016/j.neuron.2011.05.001

[20] Kolb, B., Gibb, R. and Gorny, G. (2003) Experience-Dependent Changes in Dendritic Arbor and Spine Density in Neocortex Vary with Age and Sex. *Neurobiology of Learning and Memory*, **79**, 1-10. https://doi.org/10.1016/S1074-7427(02)00021-7

[21] Kolb, B., Gorny, G., Li, Y., Samaha, A.N. and Robinson, T.E. (2003) Amphetamine or Cocaine Limits the Ability of Later Experience to Promote Structural Plasticity in the Neocortex and Nucleus Accumbens. *Proceedings of the National Academy of Sciences of the United States of America*, **100**, 10523-10528. https://doi.org/10.1073/pnas.1834271100

[22] Kolb, B., Morshead, C., Gonzalez, C., Kim, N., Shingo, T. and Weiss, S. (2007) Growth Factor-Stimulated Generation of New Cortical Tissue and Functional Recovery after stroke Damage to the Motor Cortex of Rats. *Journal of Cerebral Blood Flow and Metabolism*, **27**, 983-997. https://doi.org/10.1038/sj.jcbfm.9600402

[23] Kolb, B., Cioe, J. and Comeau, W. (2008) Contrasting Effects of Motor and Visual Learning Tasks on Dendritic Arborization and Spine Density in Rats. *Neurobiology of Learning and Memory*, **90**, 295-300. https://doi.org/10.1016/j.nlm.2008.04.012

[24] Kolb, B. and Whishaw, I.Q. (2009) Fundamentals of Human Neuropsychology. 6th Edition, Worth, New York.

[25] Kolb, B. and Gibb, R. (2010) Tactile Stimulation Facilitates Functional Recovery and Dendritic Change after Neonatal Medial Frontal or Posterior Parietal Lesions in Rats. *Behavioural Brain Research*, **214**, 115-120. https://doi.org/10.1016/j.bbr.2010.04.024

[26] Kolb, B. and Stewart, J. (1991) Sex-Related Differences in Dendritic Branching of Cells in the Prefrontal Cortex of Rats. *Journal of Neuroendocrinology*, **3**, 95-99. https://doi.org/10.1111/j.1365-2826.1991.tb00245.x

[27] Yao, P.J., Petralia, P.S. and Mattson, M.P. (2016) Sonic Hedgehog Signaling and Hippocampal Neuroplasticity. *Trends in Neurosciences*, **39**, 840-850. https://doi.org/10.1016/j.tins.2016.10.001

[28] Yao, P.J., Petralia, R.S., Ott, C., Wang, Y.X., Lippincott-Schwartz, J. and Mattson, M.P. (2015) Dendrosomatic Sonic Hedgehod Signaling in Hippocampal Neurons Regulates Axon Elongation. *Journal of Neuroscience*, **35**, 16126-16141. https://doi.org/10.1523/JNEUROSCI.1360-15.2015

Abbreviations

CA1-pyramidal cells of CA1 area of hippocampus;
NMDA-N-methyl-D-Aspartate;
LTP-long term potentiation;
CaMKII-Ca^{2+}/calmodulin-dependent protein kinase II;
AMPA-α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid;
CNS-central nervous system;
ECM-extracellular matrix;
LTD-long-term depression;
ATP-adenosine triphosphate acid.