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Chapter

Homeostatic Plasticity and Therapeutic Approaches in Neurodegeneration

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Abstract

The synapses transmit signals between neurons in an ever-changing fashion. Changes of synaptic transmission arise from numerous mechanisms known as synaptic plasticity. The importance and complexity of the synapse has fueled research into the molecular mechanisms underlying synaptogenesis, synaptic transmission, and plasticity. Particularly, homeostatic plasticity refers to the local changes in synaptic activation to generate local synaptic adaptations and network-wide changes in activity to generate adjustments between excitation and inhibition. This review chapter will focus on synaptic phenomena and mechanisms that are likely to contribute to network homeostasis. In addition, it will be discussed a putative modulation of the signaling mechanisms serving a homeostatic function as a viable therapeutic approach for disease modification in neurological and neurodegenerative disorders. To sum up, the main role of the following players in homeostatic plasticity will be analyzed, based on what a growing body of evidence has suggested recently: BDNF-mediated TrkB system activation; adenosine modulation system; nitric oxide/soluble GC/cGMP signaling; astrocyte involvement—astroglial CB1 receptors; the microtubule-associated neuronal protein Tau; the signaling pathway of the Wnt protein family; extracellular vesicles in the intercellular communication; and estrogen involvement in non-reproductive functions.

Keywords: adenosine, astrocytes, BDNF, estrogens, extracellular vesicles, neurodegeneration, nitric oxide, synaptic plasticity, Tau, TrkB system, Wnt proteins

1. Introduction

The neurotransmission may be defined as the set of biochemical and physiochemical signals which establishes neuronal communication. Changes of synaptic transmission arise from numerous mechanisms known as synaptic plasticity. Synaptic plasticity is crucial for regulating synaptic transmission or electrical signal transduction to neuronal networks, for sharing essential information among neurons and for maintaining homeostasis in the body.

Synaptic plasticity in the mature nervous system includes structural and morphological modifications constituting the cellular response to the changes in neuronal activity that are thought to be responsible for learning and memory [1].

The individual synaptic connections are constantly removed or recreated depending on the neuronal environment. This plasticity is highly regulated by signals from other cells of the nervous system, mainly the astrocytes whose function is the maintenance of the neurons in a determined position [2]. This modeling ability is achieved by genetic, molecular, and cellular mechanisms that influence synaptic connections and neuronal circuits.

Various neurotransmitter receptors are functionally associated with protein kinases and other G-proteins that modulate cascades of molecules which in turn maintain essential cellular functions [3]. Modifications of the MAPK- and cAMP-related signaling pathways may affect intracellular Ca^{2+} levels, neurotransmitter receptors, transcription factors, and the cross-link between signaling pathways, among other biological functions which are essential for neuroplasticity [4].

At the structural level, synaptic plasticity entails incorporation or disassociation of α-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid (AMPA) receptors from the postsynaptic membrane and the growth or constriction of the dendritic spines where most excitatory synapses are placed [5]. At the functional level, synaptic plasticity is considered as the long-term potentiation (LTP) or long-term depression (LTD) of synaptic strength, with modifications in conductance through AMPA receptors in the postsynaptic membrane. During the term of plasticity, N-methyl-D-aspartate (NMDA) receptor activation leads to Ca^{2+} ions passage through the postsynaptic membrane to trigger intracellular signaling cascades. These events set off gene transcription, trafficking of AMPA receptor via action dynamics, cytoskeleton reorganization, and enlargement or removal of dendritic spines. The integrity of the synaptic structure, trafficking of AMPA receptor, and dendritic spine dynamics are all crucial for generating lasting synaptic plasticity modifications [5].

The AMPA receptors and NMDA receptors are the ones which synergize at postsynaptic terminals to facilitate different forms of synaptic plasticity. Constant activation of AMPA receptors by a series of impulses arriving at presynaptic terminals leads to depolarization of the presynaptic membrane, which removes the Mg^{2+} ions that are obstructed at NMDA receptors [6]. Thereon, the simultaneous excitation of pre- and postsynaptic neurons speeds up the gating of NMDA channels and reinforces the synapse. This feature is crucial in NMDA channels for being specifically associated with synaptic plasticity and its high permeability to Ca^{2+} ions. Therefore, the second messenger Ca^{2+} modulates a set of signaling pathways and the responses that collectively lead to synaptic modification [6].

Furthermore, local changes in synaptic activation to generate local synaptic adaptations and network-wide changes in activity result in adjustments between excitation and inhibition. These mechanisms are likely to contribute to network homeostasis. Therefore, this review chapter will focus on synaptic phenomena involved in homeostatic plasticity. In addition, it will be discussed a putative modulation of the signaling mechanisms serving a homeostatic function as a viable therapeutic approach for disease modification in neurological and neurodegenerative disorders.

2. BDNF-mediated TrkB system activation

Synaptic plasticity at the molecular level can be driven by increased expression of plasticity-related genes, such as brain-derived neurotrophic factor (BDNF), calcium/calmodulin kinase II (CaMKII), and cAMP response element binding (CREB) protein, as well as by an augmented expression of both AMPA and NMDA receptors on surface [7].

The escalation of the synapse is a mode of homeostatic plasticity in which a prolonged enhancement in neuronal activity leads to a compensatory decline in excitatory transmission that is often mediated by a drop in levels of the synaptic AMPA receptors. The blockage of sustained activity results in the opposite effect, that is, an enhancement in excitatory transmission that is often mediated by an augmentation in levels of the synaptic AMPA receptors [8]. The neurotrophin BDNF and its signaling partners are the main regulators of synaptic plasticity. BDNF may serve as a real mediator rather than simply a modulator of synaptic plasticity and synaptic communication. As BDNF is synthesized and released in an activity-dependent manner [9], BDNF levels could serve as signals for changes in neuronal activity and thereby mediate synaptic scaling. BDNF and neurotransmitter signaling cascades can work together in close temporal association to induce immediate and guided effects on synaptic plasticity. What is more, specifically interfering with BDNF-related signaling is a crucial strategy for neuronal and functionally restorative treatments for neurological and psychiatric disorders [10].

The main functions of BDNF are mediated by its interaction with the tropomyosin-related kinase B (TrkB) receptor [11] whose intracellular signaling cascade activation can affect synaptic transmission and synaptic contact formation [12]. TrkB receptors are typically localized within vesicles inside the cell and translocate to the plasma membrane through neuronal activity [13]. The early effects of BDNF are a result of the modification (e.g., protein phosphorylation) of components that are already present at the synapse, while the long-term effects originate from the modification of translational activity at the synapse and changes in transcription. Stimulation of high-frequency inducing LTP leads to enhancement of BDNF production [14]. Furthermore, BDNF increases neurotransmitter release and promotes synaptic transmission and LTP [15]. Thus, it is assumable that the effects exerted by BDNF on synaptic plasticity are TrkB mediated.

A recent study has investigated the features of neural network formation and functions in primary hippocampal cultures in the context of chronic BDNF application and TrkB receptor blockage [16]. It has been demonstrated that the blockage of TrkB receptors affected the structures of synapses and even mitochondria, which were not regarded as capable of participating in synaptic modulation for a long period. Nevertheless, it has been shown that TrkB-mediated signaling can affect both the ultrastructural and functional parameters of brain mitochondria, even in normal oxygen and nutrient supply conditions. Chronic TrkB receptor blockade leads to destructive ultrastructural changes in mitochondria, whereas the functional activity of organelles remains intact apparently. Long-term application of BDNF enhances the enzymatic activity of mitochondria, though this modification is not related to changes in ultrastructure of organelles. These findings might demonstrate that TrkB-mediated mitochondrial regulation is associated with functional changes of the enzymatic apparatus of the respiratory chain but not with structural reshaping of organelles. Chronic BDNF application increased the basal oxygen consumption rate via activating respiratory chain complex II [17]. Under oxygen stress conditions, BDNF increases the adaptive potential by impacting the functional parameters of the mitochondrial apparatus. Further research should address whether the TrkB-mediated pathway for influencing mitochondria is generalized (i.e., carried out through nuclear genes) or directed toward an isolated organelle.

A genetically determined high level of BDNF can provide significant adaptive potential to the nervous system, and its neuroprotective effects are induced via the TrkB receptor system [18]. To date, it has been found that BDNF-mediated TrkB system activation accounts for the formation of more complex functionally active neural networks with a great level of efficiency in synaptic transmission. Thus, the TrkB signaling system can be involved in higher cognitive functions.

Recent progress into the etiology of neurological and metabolic diseases has been made with genome-wide association studies. BDNF/TrkB signaling contribution to synaptic development and plasticity, neurite outgrowth, and dendritic spine formation is a possible anatomical correlate of hyperconnectivity in autism-spectrum disorder (ASD) [19] or of hypoconnectivity in monogenic obesity [20].

Growing evidence suggests that BDNF upregulation plays a key role in the increased trophic effects in ASD. Studies on functional image have shown that, in most young ASD patients, cortical regions appear hyperlinked, and cortical thickness and brain size are enhanced [19]. These findings indicate that developing ASD brains may occur in a modified neurotrophic environment as some ASD patients and animal models have shown enhanced levels of BDNF.

Besides that, genome association studies now reveal different candidate obesity genes, most of which are strongly expressed or known to act in the CNS, highlighting the role of the brain in propensity to obesity. In this regard, BDNF is involved in energy metabolism and eating behavior as partial BDNF deficiencies in mouse models cause hyperphagia and obesity. The first case described by disruption of the BDNF gene (11p13) in humans was that of an 8-year-old obese girl, who presented an abnormality in chromosome 11 that altered the BDNF gene in one of the chromosomal breakpoints [21]. This patient with severe hyperphagia and obesity also presented a complex neurobehavioral phenotype, including impaired cognitive function and memory and a distinctive hyperactive behavior.

3. Adenosine modulation system

Adenosine is a ubiquitous molecule that is directly involved in the key processes sustaining cellular viability and adaptability, this is it, the energy charge, redox control, DNA and RNA, and epigenetic control. The role of adenosine in the brain is of great interest since the adenosine receptors are far more abundant in the brain than in any other organ or cell type in mammals [22]. Though there are four plasma membrane metabotropic receptors such as adenosine A1, A2A, A2B, and A3 receptors [23], A1 and A2A receptors are the responsible ones for the effects of adenosine in the brain. A1 receptors (A1R) are the most abundant and widely distributed, while A2A receptors (A2AR) are more abundant in the basal ganglia and in synapses throughout the rest of the brain. Both A1R and A2AR are mostly located in synapses, particularly in glutamatergic synapses, although both receptors are also present in other synapses [24].

Adenosine acts on A1R at a pre-synaptical level decreasing calcium influx and glutamate release, at a post-synaptical level decreasing the activation of ionotropic glutamate receptors and of voltage-sensitive calcium channels as well as hyperpolarizing dendrites through a control of potassium channels. The ability of A1R to control high-frequency-induced synaptic plasticity contrasts with that of A2AR. Thus, A2AR are capable of enhancing the evoked release of glutamate in different brain areas and the function of ionotropic glutamate receptors [25]. Besides, A2AR behave as fine-tuners of other neuromodulation systems, since A2AR activation is a requirement for the synaptic effects of growth factors or neuropeptides. What is more, A2AR activation diminishes the efficiency of pre-synaptic inhibitory systems. Thus, A2AR commute pre-synaptic modulation from inhibitory to facilitatory. Another significant feature of A2AR is that they have also been found in astrocytes and microglia cells, controlling Na^+/K^+-ATPase, the uptake of glutamate, the production of pro-inflammatory cytokines, and the effects potentially contributing to the selective A2AR-mediated control of synaptic plasticity [26].

Different sources of extracellular adenosine activate each of these adenosine receptors in order to control synaptic transmission by A1R and synaptic plasticity by A2AR [27]. The predominant role of adenosine under basal conditions, in excitatory synapses, is an A1R-mediated inhibition of synaptic transmission. Then, an endogenous A1R-mediated inhibitory tonus takes place under most experimental conditions. In contrast, A2AR are only recruited upon higher frequencies of nerve stimulation triggering plastic changes of synaptic efficiency (LTP) [28]. This selectivity is consequence of the adenosine formed by synaptic ecto-nucleotidases upon release of ATP from nerve terminals; high-frequency stimulations are needed to trigger an excessive release of ATP [29] that significantly results in the production of extracellular adenosine near A2AR. These A2AR then enhance the release of glutamate and the activation of NMDA receptors, effectively reinforcing the implementation of LTP [30].

Furthermore, the particular activation of A2AR upon higher frequencies of nerve stimulation favors the solution of the increased feedback inhibitory synaptic mechanisms with increasing frequencies of synaptic recruitment. The higher the stimulation frequency, the greater the extracellular levels of adenosine and of cannabinoids since supramaximal activation of pre-synaptic A1R or of cannabinoid CB1R can block synaptic transmission. The neuromodulator adenosine, by operating high affinity adenosine receptors, restrains transmission via A1 receptor (A1R) or CB1R [31].

In spite of the selective involvement of A2AR that allows simultaneously mitigating pre-synaptic inhibition and strengthening synaptic facilitation at the single synapse level, A1R and A2AR actually collaborate to encode the relevance of information at the level of brain circuits. The implementation of a potentiated transmission in a given synapse will elicit in parallel a process of hetero-synaptic depression involving synaptic strengthening of A1R function in surrounding synapses (with respect to this potentiated synapse). The increased recruitment of a synapse set off the activation of the astrocytic syncytium. Within the domain covered by this syncytium, there will be a greater astrocytic (i.e. non-synaptic) release of ATP [32], which will be degraded by ecto-nucleotidases degrading ATP into adenosine, which is channeled into A1R, further depressing the activity of neighboring synapses (where A2AR are not engaged).

In conclusion, a predominant role of neuronal A2AR in the control of neuronal damage is supported by several studies [33]. Dysfunction and damage of synapses may be triggered by the A2AR that are located synaptically. This synapse impairment is regarded as one of the earliest alterations found in different neurodegenerative disorders ranging from Alzheimer's disease (AD) to depression. Experimentally, it has been shown that blockade of A2AR prevents memory damage in AD models. Therefore, the question arises whether A2AR antagonists might have a therapeutic potential. To give some answer, a triple transgenic AD model (3×-Tg-AD) has been used with a defined onset of memory dysfunction occurring at the age of 4 months. After the onset of memory deficits in 3×-Tg-AD mice, a treatment of 3 weeks with a selective A2AR antagonist has shown to normalize the up-regulation of hippocampal A2AR, restore hippocampal-dependent reference memory, and decrease hippocampal synaptic plasticity and global and glutamatergic synaptic markers as well. These findings may point to a therapeutic-like ability of A2AR antagonists to recover synaptic and memory dysfunction that occur in early AD [34]. It may be assumed a role for A2AR in the early steps of neurodegeneration, whereby the up-regulation of A2AR that occurs at the beginning in synapses upon noxious brain insults [27] would set off an aberrant overenforcement of synaptic plasticity that would interrupt synaptic function and favor the likelihood of excitotoxic destruction of the synapse. A2AR would facilitate synaptic plasticity under physiological conditions, while their up-regulation would

lead to a synaptic toxicity that occurs early during the course of neuropsychiatric illnesses. Moreover, the up-regulation and role of A2AR in the astrocyte and microglial control suggest an involvement of A2AR in brain damage, which might also include the control of blood flow and endothelial permeability by these receptors. This entails that multiple cellular sites of action of A2AR would participate in the ongoing process engaged in neurodegeneration [33].

4. Nitric oxide/soluble GC/cGMP signaling in synaptic plasticity

Nitric oxide (NO) plays roles in maintaining synaptic plasticity and in helping to restore plasticity in the neuronal architecture in the CNS. NO is regarded as a chemical transmitter which has essential functions in the mammalian central as well as peripheral nervous system [35]. NO is the second mediator that can activate NMDA receptors. NMDA receptor activation persistently enhances the activity of neuronal nitric oxide synthase (nNOS) in the neuronal cytoplasm. It then catalyzes the generation of endogenous NO from L-arginine followed by the enhanced release of NO from neurons. Activation of these receptors by glutamate stimulates the calcium influx into cells and the generation of NO by NOS, which rapidly stimulates guanylate cyclase and increases cGMP synthesis [36]. Other glutamate receptors, such as AMPA, can also produce NO; this pathway modulates the release of glutamate and dopamine. Nevertheless, AMPA receptor trafficking, expression, and S-nitrosylation activity are maintained by NO. Specifically, the N-ethylmaleimide-sensitive factor (NSF, an ATPase) is high in neurons which binds with GluR2 and the NSF-GluR2 interaction has shown to be important to maintain AMPA-mediated transmission at the synapse [37]. Physiologically, synaptic NSF is S-nitrosylated by NO from neuronal source in the mouse brain. Activation of NMDA receptors increases the NSF-GluR2 interaction, as well as the surface insertion of GluR2. NMDA receptors stimulate NO generation, which enhances NSF S-nitrosylation, stimulates its association with GluR2, and increases the surface expression of GluR2-containing AMPA receptors [38].

Additionally, NO is associated with the storage, uptake, and release of mediators, such as acetylcholine, noradrenaline, GABA, taurine, and a glycine. NO can stimulate its own extrasynaptic receptors, which are located some distance from sites of NO synthesis. In addition, nNOS-containing neurons actively participate in the rostral path of neuroblast migration, which involves new synaptic connections and influences neurogenesis [39]. Astrocyte migration is also regulated by the release of NO under the actions of inducible nitric oxide synthase (iNOS). NO is also recognized as critical for the formation of synapses and the growth of nerve fibers [40].

Deficits in synaptic plasticity are increasingly recognized as causes of memory loss in AD [41]. NO is produced by NOS through NMDAR-mediated calcium input. NO signaling comes into play in neurodegenerative diseases via the generation of reactive nitrogen species and cGMP signaling cascades. NO also exerts neuroprotective effects, as shown in AD mouse models, by reducing cell loss and Tau pathology [42]. In AD models, NO has shown to be altered through various mechanisms. For example, the NMDAR-mediated calcium entry that activates NOS is enhanced by abnormal ryanodine receptor-(RyR-) mediated calcium-induced calcium release. NOS and RyR protein levels are also increased in both AD mouse models and human AD brains. In AD mice, at the presynaptic level, these conditions increasing NO levels take place alongside excessive hippocampal synaptic depression. These deficits occur when homeostasis is placed at risk, such as in the presence of reduced RyR-calcium release. Consequently, the hippocampal network and cognitive function are not normal, though they appear to be so [43].

In a study on 3×-Tg-AD mice, the presynaptic terminals have shown to be the primary site of NO regulation, with increased evoked and spontaneous vesicle release, as determined by paired-pulse facilitation assays and spontaneous vesicle-release properties [44]. Moreover, NO modifies the magnitude of vesicular release by transforming spare vesicles into easily releasable vesicles [45]. In addition, NO can increase the opening of RyR channels, possibly by means of S-nitrosylation. The opposite interactions between augmented RyR-calcium signaling and enhanced nNOS expression in AD neurons can sustain an increased NO production or synthesis and also strengthen the presynaptic gain. At the postsynaptic level, the neuroprotective characteristics of NO become evident by inhibiting the excessive NMDAR-induced calcium influx and excitotoxicity via S-nitrosylation of the NR2A subunit of the NMDA receptor. At the same time, apoptosis is decreased through the S-nitrosylation of caspase-3, -8, and -9. The enhanced nNOS activity and NO levels in AD brains might be neuroprotective, as proven by the selectively preserved NOS-positive neurons in AD. Hence, continuous increases in NO exert harmful effects, such as oxidative stress, the shredder loss of synaptic function, and apoptosis [46].

All in all, the NO up-regulation or down-regulation may result in neuropsychiatric conditions, and its improvement may restore synaptic plasticity and neuronal function. Understanding the specific molecular mechanisms maintaining these effects can give some light as to identify ways to treat these neuropsychiatric conditions [47]. Particularly, pathological deficits in NO signaling have been reported in corticostriatal circuits in Huntington's disease (HD). Studies indicate that deficits in cortical and striatal nNOS activity and nitrergic transmission may contribute to the progression of corticostriatal pathway dysfunction observed in HD. In this pathology, medium-sized spiny neurons (MSNs) projecting to the external globus pallidus appear to preferentially degenerate as a consequence of accumulation of the abnormal huntingtin protein. What is interesting is that cortical stimulation increases striatal NOS activity by means of a NMDA and dopamine D1 receptor-dependent mechanism. Thus, studies on nNOS knockout mice have proven that striatal MSNs are significantly less sensitive to cortical drive when compared with wild-type controls, indicating that NO signaling plays a critical role in maintaining corticostriatal transmission [48]. Therefore, deficiencies in nNOS activity and NO signaling reported in HD could be associated with decreased excitatory corticostriatal transmission and motor dysfunction. From this concluding remark, it is likely that HD patients might benefit from pharmacotherapies aimed to favor nitrergic signaling and corticostriatal transmission.

Conversely, the protective effect of NMDA antagonists in conditions of *in vivo* cerebral ischemia supports that influx of Ca^{2+} through NMDA-receptor channels constitute the main driver of glutamate neurotoxicity, a mechanism being of pathological importance. Studies on the role of NO in NMDA-mediated neurodegeneration have given some light with the use of mice lacking individual NOSs subjected to ischemia. For instance, it has been found that nNOS contributed to the early damage, whereas endothelial NOS (eNOS) was protective, reflecting its relevance in cerebral blood flow and, likely, in inhibiting both leucocyte adhesion to the endothelium and platelet aggregation [49]. Reduced synthesis and availability of eNO may contribute to the development of dementia by favoring the onset and progression of atherosclerosis, vasoconstriction, and impaired cerebral blood flow regulation. Furthermore, the inducible isoform of NOS (iNOS) that starts to be expressed in the following days to an ischemic event appeared to provide additional damage. iNOS is expressed in macrophages and glial cells in response to pro-inflammatory cytokines or endotoxin. In the brain, widespread expression of iNOS is pathologic and has been observed in neurological diseases, such as multiple

sclerosis, stroke, and AD. Increased NO production and iNOS expression have been observed after experimental and clinical traumatic brain injury (TBI). iNOS knock-out mice showed reduction in infarct volume and motor deficits after focal ischemia compared with wild-type mice. In an exploratory phase II study trial, TBI patients treated with the most selective inhibitor of human iNOS reported to date showed significant improvement in clinical outcome [50]. These studies suggested a neuroprotective effect of iNOS inhibition after TBI.

5. Astrocyte involvement—astroglial CB1 receptors

Astrocytes are the most abundant glial cell population in the brain [51]. One of the most intriguing features of astrocytes is the control of synaptic plasticity and memory functions. Astrocytes contribute in shaping different types of synaptic plasticity that challenges the generation of experimental models enabling the distinction between the neuronal contribution and the astroglial contribution in the control of a given function [52].

The finding of a large number of astrocytes and increased expression of the α7 nAChRs subunit on these cells in hippocampus and temporal cortex of sporadic AD patients have suggested an involvement of the astrocytic α7 nAChRs in the metabolism of Aβ and a relationship with the amyloid cascade [53]. It has been proven that Aβ, at physiological levels, controls synaptic activity and acts as a positive or negative regulator post-synaptically. In fact, Aβ either activates or inhibits α7 nAChRs in a dose-dependent manner. In the healthy brain, Aβ enhances spontaneous astrocyte calcium transients, regulating neuron-glia signaling in a nAChR-dependent manner [54]. On the other hand, Aβ accumulation increases astrocytic α7 nAChRs expression and subsequently increases intracellular calcium released from intracellular stores contributing to a number of inflammatory cascades.

The nAChRs from astrocytes can be activated by the transmitters released from presynaptic terminals or neurotransmitters located in the interstitial space [52]. For instance, the nAChRs agonist acetylcholine elevates intracellular calcium in astrocytes, stimulating the release of glutamate gliotransmitter and consequently the NMDA receptor-dependent currents in neurons. It results in an increase of the efficient synaptic transmission and strength. This mechanism explains the Aβ-induced hippocampal LTP. Then, Aβ-α7 nAChRs interaction increases astrocytic activity to induce glutamate gliotransmission which contributes to synaptic plasticity and cognition [55]. However, pathological concentrations of Aβ, as occurred in AD, induces LTD as Aβ oligomers-induced glutamate release from astrocytes causes excitotoxic damage and synaptic loss in neurons. In essence, pathological levels of Aβ cause α7 nAChR-induced gliotransmission dysregulation leading to increased excitability within the hippocampal neural network [56]. What is more, endogenous stimulation of α7 nAChRs on astrocytes causes expression of further AMPA receptors post-synaptically at glutamatergic synapses of neurons. Consequently, the ratio of AMPA-evoked synaptic currents increases.

There is evidence that GABA is abundantly produced and released by activated astrocytes. A non-physiological increase in tonic GABA release from reactive astrocytes in the hippocampus may be directly responsible for the memory impairment in AD. It has been shown that alterations of kynurenic acid, an astrocyte-derived antagonist of the α7 nAChRs, are associated with the impairment of the cognitive function in AD patients. In fact, kynurenic acid at low concentrations inhibits GABAergic neurotransmission triggered by α7 nAChRs activation [57]. Therefore, prevention of GABAergic neurotransmission by α7 nAChRs inhibition through kynurenic acid may protect against AD.

The α7-specific agonists decrease IL-6 production in cell lines derived from astrocytes. Conversely, internalization of these receptors in astrocytes by binding to α7-specific antibodies could stimulate IL-6 production. The α7 nAChRs internalization might provoke neuroinflammation within the brain by inducing IL-6 production in astrocytes. Furthermore, evidence shows that treatment with different α7 nAChRs agonists prevent neuroinflammation in AD-affected brains and suppress elevated levels of astrocyte-related pro-inflammatory cytokines, such as TNF-α [58].

Microglia play different roles in the healthy brain which include neuronal synapse monitoring, phagocytosis of neuronal debris, and cell migration as well as proliferation. Microglia show a typical resting phenotype in the healthy CNS, becoming activated in response to excessive neuronal activity during neurochemical or electrically stimulations. It has been shown that increased activation of astrocytic α4β2 and α7 nAChRs drives the expression of glial cell-derived neurotrophic factor (GDNF) [59]. Astrocyte-derived GDNF binds to GDNF family receptor alpha1 (GFRα1) and activates intracellular signaling pathways that lead to inhibition of microglial activation and protection of neurons from neurodegeneration [60].

The astroglial type-1-cannabinoid (CB1) receptor signaling recently emerged as the mediator of several forms of synaptic plasticity associated to important cognitive functions [61]. The presence of CB1 and type-2 (CB2) receptors in astrocytes was first described in human and rodent primary cultures. Particularly, CB1 receptors are mainly located at presynaptic terminals of different types of neurons, inhibiting neurotransmitter release. Although the signaling of CB1 receptors in astrocytes has been partially investigated, it has been suggested that they are able to couple to different intracellular signaling pathways in this type of cells, therefore providing high adaptability to endocannabinoid-mediated responses in these cells. The first endocannabinoid identified was arachidonoyl-ethanolamide, known as anandamide [62]. Arachidonoyl-ethanolamide mimics the cannabinoid "tetrad" effects (i.e., hypolocomotion, antinociception, catalepsy, and hypothermia) in rodents. The second discovered endocannabinoid, 2-arachidonoyl-glycerol (2-AG) is considered as the main effector of most of the CB1 receptor-mediated endogenous regulation of synaptic transmission. Endocannabinoids' precursors are located in cell membranes and their transformation into actual endocannabinoids is thought to mainly occur in an activity-dependent manner. Endocannabinoids are likely produced, mobilized, and degraded by astrocytes *in vivo*, suggesting the presence of an astroglial autocrine and/or paracrine endocannabinoid signaling.

Astrocytic processes express transporters GLT-1 and GLAST for glutamate, participating in the rapid removal of glutamate released into the synaptic cleft, which is essential for both the termination of synaptic transmission and maintenance of physiological neuronal excitability. Since increased stimulation of glutamate receptors is highly toxic for neurons, glutamate uptake by astrocytes is crucial for protecting neurons against excitotoxicity. In this regard, it has been observed that pharmacological blockade of CB1 receptors reduces epileptiform discharges of hippocampal slices through a direct control on astrocytic calcium signaling, suggesting that over-activation of astroglial CB1 receptors might promote the maintenance of brain excitotoxicity [61].

Intriguingly, whereas CB1 receptors on glutamatergic neurons have been found to reduce glutamate release and excitoxicity, astroglial CB1 receptors have been shown to promote astroglial-dependent activation of glutamatergic transmission [63]. These potentially opposite effects at neurons or astroglial cells might indicate the complexity in the regulation of excitatory output by the endocannabinoid system.

However, arachidonoyl-ethanolamide has shown to reverse AMPA-induced neurotoxicity and down-regulation of GLT-1 and GLAST (glutamate transporters) mRNA in cultures of mouse astrocyte and in the spinal cord of a mouse model of

multiple sclerosis via CB1 receptor [64]. Thus, the role of astroglial CB1 receptors in the regulation of excitatory amino acids in the context of excitotoxic processes might depend on the conditions of the brain circuits involved and the specific activation of the endocannabinoid system at different sites. It might be hypothesized that astroglial CB1 receptors might exert a bidirectional control of excitatory transmission and excitotoxicity [61].

The role of astroglial CB1 receptors in the modulation of excitatory transmission in the hippocampus was first reported by Navarrete and Araque [65]. They found that hippocampal astrocytes express functional CB1 receptors that increase intracellular Ca^{2+} levels in astrocytes following electrical stimulation of adjacent neurons. CB1 receptor-dependent increase of intracellular Ca^{2+} levels in astrocytes requires activation of PLC, suggesting that the interaction of CB1 receptors with the Gαq protein subunit may be favored in astrocytes as compared to neurons. Astroglial CB1 receptors activation is necessary for NMDA receptor-mediated neuronal excitability evoked by astrocyte Ca^{2+} elevations, suggesting their importance for astrocyte-neuron excitatory signaling. However, these results do not characterize neither the endogenous NMDA receptor agonist implicated in this process nor the cellular origin and identity of the released eCBs that act at astroglial CB1 receptors in these conditions. Astroglial CB1 receptors mediate heterosynaptic potentiation at excitatory CA3-CA1 synapses in a Group I mGluR-dependent fashion. Importantly, this phenomenon coexists with depolarization-induced suppression of excitation (DSE, short-term inhibition of excitatory transmission) mediated by neuronal CB1 receptors at homosynaptic connections [66].

Finally, astroglial CB1 receptors mediate spike timing-dependent LTD (tLTD) in the neocortex. tLTD is induced by paired stimulations of the pre- and postsynaptic elements, leading to a reduction of presynaptic release of glutamate. CB1 receptor-dependent tLTD has been also described at cortico-striatal synapses and may imply astroglial CB1 signaling as well. This form of synaptic plasticity has been associated to the neuronal coding of sensory experiences *in vivo*. Interestingly, one of the major consequences of exogenous cannabinoids administration, including THC, is an alteration of perception, but little is known about the mechanisms underlying these effects [67]. Therefore, it is possible that the overstimulation of CB1 receptors impairs sensory functions by a deregulation of tLTD.

6. The microtubule-associated neuronal protein Tau

The neuronal cytoskeleton is the major intracellular structure that determines the morphology of neurons and plays a critical role in the development of the nervous system, neuronal plasticity, and neurodegenerative diseases [68]. In particular, changes in microtubule (MT) dynamics are involved not only in axon formation and axonal sprouting but also in mediating structural and functional changes of dendritic spines, which represent the major site of excitatory postsynaptic input [69].

MT dynamics are regulated by several factors affecting the assembly state of this polymer. MT-associated proteins (MAPs) promote MT nucleation and elongation in a compartment-specific manner and are also subject to regulation by posttranslational modification [69]. Tau is of particular importance since it becomes enriched in the axonal compartment during neuronal development and redistributes to the somato-dendritic compartment in a state of hyperphosphorylation during neurodegenerative pathologies such as AD and other tauopathies [70]. Strikingly, acute or chronic knockdown of Tau does not appear to affect MT stability and organization or the overall structure of a neuron to a major extent. This feature raises the

question whether Tau possesses activities beyond its direct role in regulating axonal MT polymerization, which is altered in AD and other tauopathies. In this regard, Tau is an intrinsically disordered protein, which interacts with different partners. Tau stands out for its structural plasticity allowing it to react quickly in response to changes in their environment by posttranslational modifications [71]. Then, Tau may affect various signaling and regulatory processes dependent on its modification, thereby regulating the function and plasticity of neurons during learning, memory, and degenerative processes.

In order to make a functional assessment of Tau role with regard to neuronal activity and network properties, several electrophysiological studies have been performed using Tau knock-out (KO) mice or Tau knockdown experiments. Complete absence of Tau or a decrease in the amount of Tau on neuronal activity has been studied by recordings from individual cortical neurons as well as from intact neuronal circuits in acutely isolated tissue slices. The focus in most studies was placed on the influence of Tau on LTP or LTD generation in the hippocampus both being established experimental paradigms of synaptic plasticity underlying learning and memory formation. Cantero et al. [72] has studied the involvement of Tau in shaping electrophysiological properties of neural oscillations in different neocortical regions and hippocampus during spontaneous exploratory motor behavior of 4 month old mice. They observed a significant slowdown of the hippocampal theta rhythm, which is known to play a crucial role in learning and memory function. Furthermore, they found decreased levels of gamma long-range synchronization in the KO animals, while power and peak frequency in the gamma band oscillations (30–80 Hz) recorded from neocortex and hippocampus remained unchanged. As a result, it was hypothesized that the lack of physiologically phosphorylated Tau during early stages of development may influence the maturation of parvalbumin-containing interneurons affecting the spatiotemporal structure of long-range gamma synchronization between hippocampus and neocortex.

It was recently demonstrated that Tau exerts an important mediatory role in regulating the interaction between protein kinase C binding protein 1 and GluA2, a molecular mechanism fundamental to AMPA receptor internalization [73]. Biochemical and electrophysiological assays have allowed to show that specific phosphorylation at S396 of Tau is related to and required for LTD. In addition, the absence of Tau led to the reversion of deficiencies in spatial memory, pointing out a relevant role of Tau in hippocampal LTD. Thus, Tau seems to be decisively involved in the maintenance of physiological synaptic transmission and synaptic plasticity.

For many years, in terms of location, Tau has been considered to be an exclusively intracellular protein. However, Tau can be released from neurons and it has been found in the cerebrospinal fluid of AD patients. This feature may affect network functions by directly influencing the activity of multiple neurons. Stimulation of neuronal activity can induce Tau release from healthy cortical neurons, suggesting that Tau secretion is a physiological process [74]. *In vivo* microdialysis has proven that increasing neuronal activity raises the level of extracellular Tau. The elimination rate of Tau from the extracellular space in the brain is slow suggesting that Tau can be present for long times outside of neurons and influence other cells. Extracellular Tau has a reduced phosphorylation state and is enriched in C-terminally truncated forms. Besides, it has been demonstrated that a Tau fragment resulting from the cleavage through the effector caspase-3 exhibits enhanced secretion [75]. It is not yet clear in which form Tau is present in the extracellular space and how it potentially influences other neurons. Extracellular Tau might affect network functions by acting on other cells through receptor-mediated mechanisms. Alternatively, extracellular Tau might be taken up by other neurons and modulate their signaling cascades. Several studies have reported uptake of Tau aggregates and

oligomers, which may cause network damage by propagation of protein abnormalities. For instance, it has been suggested a prion-like spreading of a pathogenic misfolded Tau in a deterministic manner to distinct brain regions [76]. However, it is not clear whether or not extracellular soluble Tau is internalized by neurons at physiological conditions. Application of exogenous Tau from cerebral cortex of AD brain evoked a strong LTP inhibition at CA3-CA1 synapses in hippocampal brain slices being elicited by theta burst stimulation. Moreover, a short exposure to oligomers, but not monomers, of extracellular recombinant human Tau causes a concentration-dependent impairment of LTP in the CA3-CA1 pathway and memory formation [77]. These effects were reproduced both by Tau oligomers from AD human specimens, as well as those produced in mice overexpressing the human Tau. *In vitro* conditions has evidenced that oligomerized Tau passes the cell membrane and is internalized by neurons. However, it is unclear whether extracellular Tau acts in these experiments through receptor-mediated mechanisms or after internalization.

With all of it, it appears clear that Tau exerts systemic effects and modulates network functions both in the CNS and the peripheral nervous system. Consequently, changes in the Tau level will produce various side effects. Though most available data are still controversial at length, general trends begin to become apparent from several experimental approaches. The course of motor impairments as a consequence of reduced Tau levels at advanced age might be caused by an impact on the peripheral motor system. Mild cognitive and memory deficits and a disruption of physiological synaptic transmission and synaptic plasticity have been repeatedly reported. Even posttranslational modifications of Tau possessing pathologic effect may serve protective functions for synapses, which would be impaired in circumstances of Tau depletion. Experiments with hibernating animals have rendered evidence for a protective function of Tau phosphorylation, providing a striking model for extreme plasticity, as numerous synaptic contacts are lost during hibernation and regenerated in a brief period of time after animal awakening. In these animals, a physiologically adaptive process associated with synaptic plasticity seems to be supported by a reversible hyperphosphorylation of soluble Tau [78].

Furthermore, a small amount of Tau has been localized and accumulated in the nuclear compartment, in both the soluble and chromatin-bound fractions. A putative role of Tau in both nucleolar organization and DNA damage protection and chromosome stability have been proposed, since wild-type Tau prevents DNA damage under oxidative stress or hyperthermic conditions. Recently, it has been observed that promoting Tau nuclear translocation and accumulation, by Tau overexpression or disengagement from MTs, enhances the expression of the vesicular glutamate transporter VGluT1 [79], a disease-fundamental gene directly involved in glutamatergic transmission. Significantly, the P301L mutation in Tau gene, linked to frontotemporal dementia FTDP-17 [80], disturbs this mechanism leading to a function loss. This fact demonstrates a direct physiological role of Tau on modulating gene expression, particularly the expression of the vesicular glutamate transporter VGluT1, which is known to be strongly upregulated in early phases of tauopathies. Thus, alterations of this mechanism may be at the basis of the onset of neurodegeneration.

Taken together, though most current approaches to target Tau are based on its actions on MTs and are aimed at counteracting the aggregation of its soluble pool, unlinked functions of Tau to its MT-binding properties have been suggested lately. Therefore, in view of the evidence supporting considerable modulatory and potentially protective functions of Tau at physiological conditions, the strategies aimed at modulating the amount and modification of Tau should be carefully taken into consideration when planning Tau-based therapies.

7. The signaling pathway of the Wnt protein family

In humans, Wnts are a family of secreted glycolipoproteins (19 members) that are evolutionarily conserved [81]. Wnts are essential for axon pathfinding, dendritic development, and the formation and function of synapses [82]. The contribution of Wnts to synapse development in different model systems has been supported widely [83].

Several Wnt proteins (Wnt7a, Wnt5a, and Wnt3a) that signal through different receptors promote pre-synaptic differentiation [84]. Besides, Wnts signaling promotes excitatory synapse formation and spine growth [85]. Unlike Wnt7a, Wnt5a promotes inhibitory post-synaptic assembly by increasing GABA$_A$ receptor clustering and enhancing the amplitude of inhibitory postsynaptic currents [86]. Members of the Wnt family might regulate excitatory and inhibitory post-synaptic properties, differentially. Moreover, Wnts act bidirectionally to promote the assembly of both sides of the synapse [84].

Regulation of synaptic transmission by Wnt proteins has been demonstrated by electrophysiological recordings. Members of the Wnt family can modulate neurotransmission pre-synaptically and post-synaptically [84]. For instance, gain of function of Wnt7a has shown to promote transmitter release in cultured neurons. Post-synaptically, Wnt7a enhances synaptic strength by increasing the number of AMPA receptors at the post-synaptic membrane in hippocampal neurons and Wnt5a potentiates post-synaptic NMDAR-mediated currents through RoR2 receptors in hippocampal neurons.

Members of the Wnt family are regulated by neuronal activity. Thus, neuronal activity modulates the mRNA and protein levels of Wnts and their receptors in different model systems. Wnt blockade completely abolishes activity-mediated synapse formation in cultured neurons [87]. Blockade of endogenous Wnt proteins, with secreted frizzled-related proteins (Sfrps), severely impairs LTP [88]. Conversely, addition of Wnt proteins can facilitate LTP [89].

Research is been currently focused on identifying the mechanisms by which Wnts modulate LTP. In this regard, Wnt5a has been shown to regulate NMDAR-mediated synaptic transmission in acute hippocampal slices [89]. However, it does not affect endogenous synaptic AMPAR localization or dendritic spine size in hippocampal cultured neurons [88]. Then, it is suggested that Wnt5a may contribute to later stages of LTP.

Endogenous Wnt signaling is required for structural and functional plasticity during LTP as it has been demonstrated. A study shows that Wnt7a/b regulate the early stages of NMDAR-dependent LTP [88]. Acute blockade of endogenous Wnts with Sfrps attenuates LTP induced by stimulating acute hippocampal slices at high frequency or LTP induced by glycine application in hippocampal neurons. Changes in dendritic spine structure, augmented synaptic strength, and synaptic localization of AMPA receptors are inhibited in the presence of Sfrps during LTP. Intriguingly, gain of function via single-particle tracking and super-ecliptic pHluorin-tagged AMPA receptors in hippocampal neurons has proven that Wnt7a quickly enhances dendritic spine growth, recruitment of synaptic AMPA receptors, and synaptic strength, similar to the early phases of LTP [88].

A proper balance between canonical and non-canonical Wnt signaling might determine whether synapses are lost or only their function is affected [84]. A mouse model characterized by a Wnt deficiency in the adult brain has demonstrated that Wnt proteins constitute a requirement for synapse stability and synaptic plasticity [90]. Transgenic mice expressing the Wnt antagonist Dickkopf-1 (Dkk1) protein in hippocampus display a loss of excitatory synapses, altered LTP, enhanced LTD, and deficits in long-term memory [91]. Acute blockade of endogenous Wnts by Sfrps

does not affect the number of excitatory synapses but inhibits LTP induction. This is not due to acute versus long-term exposure to Wnt antagonists, as Dkk1 also rapidly induces synapse loss in mature neurons [92]. Both antagonists have a different mechanism of action. While Sfrps inhibits Wnt function by means of binding to Wnt proteins, Dkk1 affects a canonical Wnt signaling pathway by blocking the low density lipoprotein receptor-related protein 6 (LRP6), an essential Wnt co-receptor.

Growing evidence suggests that deficient Wnt signaling affects synaptic integrity in the adult brain. In AD, particularly, decreased levels of Wnt signaling could weaken synaptic function resulting in the subsequent degeneration and loss of synapses characteristic of this condition. Expression of the endogenous Wnt antagonist Dkk1 is increased in the brain of AD patients. On other hand, Aß quickly induces Dkk1 expression and blockade of Dkk1 protects synapses from Aß [92]. Besides, a variant of LRP6 has been linked to late onset AD [93] and deletion of LRP6 magnifies pathology in an AD mouse model [94]. These findings along with those obtained from mice expressing Dkk1 [91] demonstrate that deficits in Wnt signaling affect synaptic integrity in the adult brain. In AD, diminished levels of Wnt signaling could mine synaptic function leading to the subsequent degeneration and synapse loss which is characteristic of this condition. Reactivation of Wnt signaling might restore connectivity after substantial synapse degeneration. In fact, the ceasing of Dkk1 expression in transgenic mice that express Dkk1 fully restores the structural and functional plasticity and hippocampal-dependent memory [91]. Together, these studies prove the regenerative capacity of neurons in the adult hippocampus to assemble synapses within functional circuits after degeneration.

8. Extracellular vesicles in the intercellular communication

In the CNS, extracellular vesicles (EVs) have emerged as key players in the intercellular communication that underlies physiological processes such as synaptic plasticity, maintenance of myelination, and neuronal and glial response to brain injury. EVs are secreted membrane-enclosed 'packages' that contain cytosolic proteins, membrane proteins, mRNAs, noncoding RNAs, and even DNA [95].

In order to modulate synaptic plasticity, neuronal EVs can transfer cargo to other neurons. It has been suggested an uptake of neuronal EVs by microglia to enhance microglial pruning of synapses. Moreover, increased astrocytic uptake of glutamate may result from internalization of neuronal EVs into astrocytes. In turn, EVs from astrocytes have been shown to contain cargo-mediating neuroprotection under neuronal stress. Oligodendrocyte-derived EVs increase neuronal firing mediate as well as neuronal stress resilience [96]. Moreover, oligodendrocyte-derived EVs may behave as auto-inhibitors in expansion of myelin. As for microglial EVs, they may modulate neuronal firing, and also propagate inflammation and destabilize synapses in a CNS injury setting. In terms of neurodegenerative diseases, EVs are involved in both the spreading and clearance of neurotoxic protein aggregates [97]. EVs have also been shown to cross the blood-brain barrier particularly under inflammatory conditions, enabling molecular crosstalk between brain cells and the periphery [98].

The coupling of neuronal EV release to synaptic activity could be functionally relevant for plasticity-associated processes. For instance, activity-dependent disposal or transfer of AMPA receptor components, which have been shown to flow throughout EVs, may constitute a mechanism for the adjustment of synaptic strength [99]. Moreover, it has been suggested that neuronal EVs act as transsynaptic carriers of signaling proteins involved in synaptic plasticity. In a series of

in vivo studies at the *Drosophila* neuromuscular junction, it has been shown that the Wnt-family signaling protein Wingless was protected driving toward EVs by the trafficking protein Evi/Wntless for trans-synaptic transport and hampering this trafficking impaired synaptic bouton formation [100]. In the same model system, synaptotagmin 4 has been found to drive on EVs from the presynaptic motor neuron to the postsynaptic muscle, and this directional transport was fundamental for activity-dependent growth of presynaptic structures.

Plasticity-associated local protein synthesis at synapses appears to be affected by the activity-dependent trafficking of specific RNAs into EVs. In one study, depolarization of differentiated neuroblasts has been found to be correlated with a depletion of specific miRNAs from neurites, associated with an enhancement of a specific subset of these miRNAs in EVs. Furthermore, neuronal EVs have been recently shown to package mRNA in association with the activity-regulated cytoskeleton-associated protein (Arc), described as a master regulator of synaptic plasticity [101]. Arc appeared to self-assemble into capsids as if it were a viral group-specific antigen (Gag) protein, encapsulating its own mRNA or other highly abundant mRNAs, and trafficking between cells by means of EVs. The blockage of Arc trafficking from presynaptic terminals to the postsynaptic muscle, at the Drosophila neuromuscular junction, caused aberrations in synapse maturation and activity-dependent plasticity [102]. Therefore, Arc capsid-containing EVs may constitute a retrovirus-like mechanism for trans-synaptic transfer of at least Arc mRNA during processes associated with synaptic plasticity. The biological origin and composition of Arc-containing EVs, as well as the scope of the EV-associated Arc transport in the mammalian brain, have yet to be studied in the future.

It is intriguing that neuronal EVs can also transfer cargo to other cells in the brain, modulating their behavior with a potential impact on synaptic activity. One study found that the uptake of neuronal miR-124a-carrying EVs into astrocytes was correlated with overexpression of excitatory amino acid transporter 2/glutamate transporter-1 (EAAT2/GLT1), which could modulate synaptic activity via an increased uptake of glutamate into perisynaptic astrocytes [103]. Moreover, EVs from differentiated PC12 cells seemed to promote microglial phagocytosis of degenerating neurites by means of increasing the microglial expression of complement component 3 (C3), a factor associated with synaptic pruning. The release of EVs from active neurons could thereby serve to the removal of less functional synapses during developmental or learning-associated remodeling of neuronal connections, although validation of this finding is warranted in at least primary neurons.

With regard to glial EVs, they have been described to provide neurons with support and feedback on synaptic activity. And so, for example, oligodendrocytes contain multivesicular endosomes at sites near the axonal surface, and secrete EVs particularly in response to glutamate. While microglia appeared to degrade oligodendrocyte-derived EVs, neuronal internalization of these EVs led to functional cargo retrieval along with an increase in neuronal firing rate and modified gene expression of several plasticity-related targets, such as VGF nerve growth factor inducible and BDNF [104]. Microglial microvesicles (MVs), for its part, released in response to ATP and increased excitatory neurotransmission through stimulation of neuronal sphingolipid metabolism and a consequent increase in the presynaptic release of neurotransmitters. The functionality of the MVs seemed to depend on a lipid or a surface component since sheared MVs retained the functionality [105]. In another study, microglial EVs have shown to carry the active endocannabinoid N-arachidonoylethanolamine on their surface, which bound to presynaptic type 1 cannabinoid receptors, and thereby decreased the release of the neurotransmitter GABA. Overall, glial EVs seem to influence both excitatory and

inhibitory neurotransmission, providing regulatory feedback particularly on pre-synaptic activity [95].

As remarkable, EVs have emerged as possible therapeutic agents in inflammation-mediated demyelinating diseases, such as multiple sclerosis (MS). Increasing evidence suggests that EVs display anti-inflammatory properties, reducing the number of activated inflammatory microglial cells, supporting oligo-dendrocytes and protecting neurons. A very recent study illustrates a putative therapeutically role for EVs. Intravenously administered EVs derived from mesen-chymal stem cells (MSCs) from human adipose tissue might mediate recovery in Theiler's murine encephalomyelitis virus (TMEV)-induced demyelinating disease, a progressive model of MS [106]. Intravenous EV administration in SJL/J mice improved motor deficits, lowered brain atrophy, enhanced cell proliferation in the subventricular zone, and decreased inflammatory infiltrates in the spinal cord of animals infected with TMEV. In addition, EV treatment was capable of modulating neuroinflammation, given glial fibrillary acidic protein and Iba-1 staining were reduced in the brain, whereas the expression of myelin was increased. Modifica-tions of morphology in microglial cells from the spinal cord may indicate that EVs also modulate the activation state of microglia. EV administration attenuates motor deficits through immunomodulatory actions, diminishing brain atrophy and pro-moting remyelination.

So far, there is no evidence regarding the therapeutic potential of EVs during the neurodegenerative phase of MS. Further studies are necessary to establish EV delivery as a possible therapy for the neurodegenerative phase of MS.

9. Estrogen involvement in non-reproductive functions

Estrogens from neural origin are involved in a variety of non-reproductive functions including regulation of neurogenesis, neuronal development, synaptic transmission, and plasticity in brain regions not directly related with the control of reproduction [107]. Estrogens regulate the expression of genes for various specific subtypes of dopamine (DA) receptors and 5-HT receptors in a region-specific manner to contribute to behavioral responses to changes of the internal and external environment.

DA neurotransmission of the ventral tegmental area (VTA)-nucleus accumbens (NAc) pathway associated with motivation is modulated by estrogens, which results in functional differences of the mesolimbic dopaminergic pathway and explains numerous sex differences in reward processing and related behavior described in human and animal studies [108]. Generally, increased circulating levels of estrogens in rodents, either during their estrous cycles or by estrogen treatment, have shown to contribute to elevated dopaminergic signaling. Estrogens influence manifold aspects of dopaminergic neurotransmission both presynaptically and postsynaptically, including: (a) DA synthesis, release, and degradation; (b) presyn-aptic and postsynaptic receptors; and (c) DA transporters that uptake DA from the synapse to terminate DA neurotransmission. Nuclear and membrane-associated estrogen receptors (ERs) may constitute the mechanisms by which estrogens affect the dopaminergic system. Precisely, ERs are distributed in dopaminergic pathways involved in reward, what is pertinent to the effects of estrogens on the CNS reward system [109]. In male mice, dopaminergic projections from the VTA to the ventral caudate express the ERβ isoform, while dopaminergic projections to the dorsal caudate do not. Dopaminergic projections to the basolateral amygdala also express ERβ. Estrogens also act rapidly through membrane-associated ERs on dopaminergic neurons in the striatum to affect DA release. Estrogens increase the activity of the

tyrosine hydroxylase (TH) and thus DA synthesis in the NAc by means of both nuclear ERs and membrane ER; induce presynaptic DA release in the striatum; and decrease DA turnover in the NAc and reduce degradation of DA so that DA remains longer at the synapse [108].

Estrogens upregulate the expression and activity of tryptophan hydroxylase (TPH) to increase 5-HT biosynthesis. Estrogen administration has been found to increase the TPH mRNA level [110]. In ovariectomized (OVX) guinea pigs, estrogen treatment alone increases the protein expression of TPH at the dorsal raphe nucleus (DRN). Surprisingly, while treatment with estrogen alone increases levels of TPH mRNA and TPH protein, it does not modify 5-HT content; rather, the treatment combining estrogen plus progesterone enhances 5-HT levels at both the DRN and the projected medial basal hypothalamus in guinea pigs [111]. Thus, there is a disparity in the sex hormone regulation of TPH mRNA and TPH protein levels versus 5-HT production in estrogen-treated animals, likely due to activity of TPH that is regulated by means of phosphorylation by protein kinase A (PKA) [112]. Since only phosphorylated TPH possesses catalytic activity, progesterone treatment might increase PKA expression and activity of TPH. After loss of ovarian function in many women, there may be an adjustment in the serotonergic neurons so that TPH protein levels recover. This also may indicate that the decline in TPH expression is a potential point of vulnerability in pre- and postmenopausal women who experience mental disorders such as depression related to the decreased level of 5-HT.

Estrogens regulate the 5-HT receptors, 5-HT2A and 2C, which display classic features of G protein-coupled receptors. The 5-HT2A receptor has been associated with suicide and depression, and its mRNAs are found in brain areas fundamental for the mood control, mental state, and cognition [113]. In humans, 5-HT2A receptor mRNA is found in the cortex and hippocampus, but not in the DRN, striatum, substantia nigra, or cerebellum [114]. Estrogens increase 5-HT2A receptor mRNA and binding site densities in the male rat brain. Healthy men have shown significantly higher levels of 5-HT2A receptor binding capacity than healthy women in the frontal and cingulate cortices, according to determinations by PET and radiotracer 18F-labeled altanserin [115]. Human studies suggest that estrogens increase 5-HT2A binding in higher forebrain regions.

The NAc receives major inputs from the amygdala and projects to the cortex and hypothalamus. These regions are fundamental for the cognitive function, emotion, mental state, mood, and neuroendocrine control. Thus, increase in 5-HT2A receptor densities by estrogen stimulation in these stated regions would control behavior and mood. A single administration of estradiol to OVX rats induces a significant increase in 5-HT2A receptor labeling in the NAc, the amygdala, DRN, anterior frontal, anterior cingulate, and primary olfactory cortex [116]. Moreover, concomitantly with the spontaneous estrogen-induced LH surge, 5-HT2A receptor densities increase compared to diestrous females or males in the frontal and cingulate cortex, olfactory tubercle and NAc. OVX produces a reduction of 5-HT2A receptor mRNA and protein levels, and long-term estrogen replacement reverses this effect in the frontal cortex [117]. The receptor 5-HT2C, a relevant contributor of many psychiatric and neurological disorders, is the most prominent 5-HT receptor subtype in the rat brain. 5-HT2C mRNA and protein are found in discrete regions of the rat brain. In the primate hypothalamus, dense populations of 5-HT2C mRNA-labeled cells are found in the anterior hypothalamus, periventricular nuclei, ventromedial nucleus, dorsal hypothalamic area, lateral hypothalamus, arcuate nucleus, and infundibular nucleus [118].

Estrogens regulate 5-HT auto-inhibition via the 5-HT1A auto-receptor. The 5-HT1A auto-receptor suppresses 5-HT synthesis by inhibiting firing of

serotonergic neurons at the DRN and median raphe and inhibiting 5-HT release in the hippocampus [119]. Therefore, the blockage of 5-HT1A receptors results in an antidepressant-like activity. Estrogen treatment lowers the 5-HT1A mRNA level in the dentate gyrus, CA2 region of the hippocampus, and DRN of OVX rats and in the DRN and median raphe of castrated rhesus monkeys, according to measurement by in situ hybridization. The 5-HT1A auto-receptor is linked to an inhibitory G protein of the Gi/o/zfamily [120].

Estrogen treatment reduces 5-HT uptake to presynaptic cells by means of decreasing gene expression, translation, protein phosphorylation, trafficking, and stability of the serotonin transporter (SERT) [121]. Estrogens reduce SERT mRNA signal in the DRN of castrated rhesus monkeys treated with estrogen compared to the castrated control group and decrease [^{3}H]-paroxetine binding, a selective indicator of 5-HT reuptake sites, in the hippocampus of estrogen-treated rats. Acute estrogen administration decreases SERT mRNA levels and 5-HT1A mRNA levels and binding. Thus, estrogen replacement therapy in postmenopausal women might decrease expression of the SERT gene and SERT protein [107]; thus 5-HT may remain longer in the extracellular space to continue neurotransmission. However, such argument does not support the observations that humans with depression have lower levels of 5-HT reuptake sites than healthy humans [122]. It might be that there is a mitigated 5-HT release and reduced levels of 5-HT in humans with depression to begin with, and a less 5-HT reuptake [107].

As we described, estrogens enhance 5-HT signaling via increasing 5-HT biosynthesis, upregulating expression and binding of receptors 5-HT2A and 5-HT2c, downregulating activity and expression of the 5-HT1A auto-receptor, decreasing expression of SERT gene and SERT protein allowing 5-HT to remain in the extracellular space for a longer period of time to continue neurotransmission, and decreasing 5-HT metabolism [107]. Consequently, the hypothesis of estrogen protection [123] claims that adjunctive estrogen treatment is beneficial at improving both symptoms of schizophrenia and the cognitive function, most notably in women. So far, the majority of studies on hormone replacement therapy for mood disorders have shown a positive response. Thus, estrogen has been demonstrated to improve mood in multiple mental illnesses, including major depressive disorder. Most recently, adjunctive estradiol treatment has been suggested as a promising treatment for women with comorbid depression and schizophrenia. In this direction, exploration of the impact of estrogen on serotonergic and other neurochemical pathways plus brain circuitry may guide not only the development of new hormone treatments but also assist in understanding the etiology of premenstrual dysphoric disorder, postnatal and perimenopausal depression, and even schizophrenia in women.

On the other hand, estrogens have shown that they do not always improve learning and memory. As an experimental example, acute administration of high doses of 17β-estradiol and progesterone can impair performance in the memory test of Morris water maze. And most importantly, there is coherence among human studies since high endogenous levels of 17β-estradiol are associated with poor performance on spatial tasks and cognitive function (Montreal Cognitive Assessment scale) and high dose of exogenous 17β-estradiol impairs recognition memory. It is fundamental to assume that estradiol exerts a curvilinear influence on hippocampal-dependent performance, with low and high levels impairing versus a medium dose improving performance on a variety of tasks [124]. Similar dose response has been observed in the rapid effects of estrogens on dendritic spines, therefore, studies on the effects of estrogens on cellular morphology should take dose response into account. Furthermore, long-term exposure to estrogens can similarly result in dose-dependent responses on learning and memory, with low

levels of 17β-estradiol reinforcing spatial working memory and high levels of estradiol hampering spatial working and reference memory. Studies have also shown that, whereas there is a dose-dependent facilitation in contextual fear conditioning by 17β- and 17α-estradiol, estrone results in dose-dependent impairments in contextual fear conditioning. Thus, it is essential to consider that the dose, frequency of administrations, and type of estrogen(s) utilized along with the type of memory task performed and the time point estrogens are administered (during acquisition or retrieval), are critical to the learning outcomes [124].

10. Conclusion

This review has concentrated on some cellular processes and signaling pathways acting during homeostatic molecular remodeling and their potential involvement in the maladaptive plasticity occurring in multiple neuropathologic conditions such as neurodegeneration and neuropsychiatric disorders.

There seem to be independent mechanisms for regulating presynaptic and postsynaptic strength, and there is evidence for independent homeostatic mechanisms operating on global and local spatial scales.

Involvement of different pharmacological approaches to compensate neurotransmission imbalance are under study, which may be considered as potential therapeutic approaches in neuropathologic conditions.

Acknowledgements

Conflict of interest

Nothing declared.

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