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Review article

Epigenetic signature in neural plasticity: the journey so far and journey ahead

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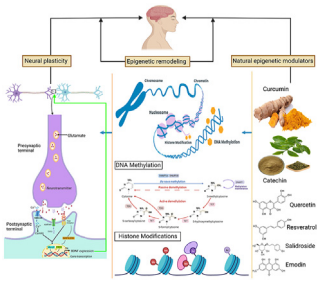
HIGHLIGHTS

- Neural plasticity, remodeling neural network is associated with learning and memory.
- Neurons reorganize the strength and efficacy of synaptic transmission.
- Epigenetic reprogramming is an established mechanism of neural plasticity.
- Epigenetic signature proteins are the hallmark of epigenetic remodeling.
- Natural bioactive compounds potentially modulate the epigenetic mechanism.

GRAPHICAL ABSTRACT



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ABSTRACT

Neural plasticity is a remarkable characteristic of the brain which allows neurons to rewire their structure in response to internal and external stimuli. Many external stimuli collectively referred to as 'epigenetic factors' strongly influence structural and functional reorganization of the brain, thereby acting as a potential driver of neural plasticity. DNA methylation and demethylation, histone acetylation, and deacetylation are some of the frontline epigenetic mechanisms behind neural plasticity. Epigenetic signature molecules (mostly proteins) play a pivotal role in epigenetic reprogramming. Though neuro-epigenetics is an incredibly important field of emerging research, the critical role of signature proteins associated with epigenetic alteration and their involvement in neural plasticity needs further attention. This study gives an integrated and systematic overview of the current state of knowledge with a clear idea of types of neural plasticity and the context-dependent role of epigenetic signature molecules and their modulation by some natural bioactive compounds.

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1. Introduction

It is "Neuroplasticity" that marked the year '1990–2000' as the decade of the brain.

Nobel Prize winner, Prof. Eric Richard Kandel, (Physiology and Medicine, 2000).

The brain is not a static organ and is being remodeled and changes over time according to our lifestyle, experiences, and environment by perceiving its functions, structures, or connections by neuron. Neurons are the structural and functional units of the central nervous system. The intercellular junction between neurons is referred to as synapse which facilitates impulse transmission and communication between neurons and finally establishes neuronal circuit. Strengthening and weakening of synapse maintains the plasticity in neuron [1]. While some structural remodeling and developmental patterns like neurogenesis, migration of neurons, and synaptogenesis are more dominant in the fetal brain, functional neural plasticity, mostly in response to the environment, is prominent in the adult brain [2]. Earlier it was believed that neurogenesis is terminated immediately after birth, but now it is revealed that the brain never stops creating new connections and new neurons as it possesses the remarkable capacity to reorganize pathways. This unique and adaptive feature of the brain establishes a new neural network that is influenced by various intrinsic or extrinsic stimuli [3]. Such capacity of the brain to change its function in response to environmental stimuli by rewiring its structure is called neural plasticity, also known as brain plasticity [4]. In contrast, the malleability of the individual synapse to alter the efficacy and strength of synaptic communication at the single-cell level is called Synaptic plasticity.

Neural plasticity is an exceptional mechanism that encourages the mature brain to respond to the different environmental stimuli and repairs itself after injury, and slows down the aging process [5]. Neural plasticity plays a central role in the initial development of neural networks and compromised neural plasticity is a major contributor of several distinguished neuropsychiatric diseases [6]. Without this ability, any brain would be unable to develop from infancy through adulthood or recover from brain injury. Neural plasticity means the ability of our brain to learn new things, improve the existing cognitive responses, and recover from various strokes and brain injuries.

It occurs through a diverse range of activity-dependent mechanisms. Neural networks change their connections and behavior in the brain in response to new information, sensory stimulation, and neuronal dysfunction, which modifies subsequent thoughts, feelings, and behavior [6]. The synaptic connections are persistently being reorganized [7] and result in memory formation [8]. Various genetic and epigenetic mechanisms are associated with altered neural plasticity. It is also important to mention here that among different organs, the brain is highly affected, remodeled, and contrived by various epigenetic factors [9]. Many extrinsic factors like diet, exercise, environmental variations, and stressors can alter neural activity in the embryo, adolescent, adult, and during aging. These epigenetic factors exert their effect through "Epigenetic mechanisms" [10] and drive epigenetic processes that coordinate several translational pathways. Epigenetic mechanism mainly comprises DNA methylation and demethylation, protein acetylation and deacetylation, non-coding RNAs, and microRNAs (miRNA) activities.

Indeed, epigenetic mechanisms epitomize the development of the brain more than any other structure and thereby play a central regulatory role in neural plasticity. One such epigenetic mechanism is DNA methylation. The beauty of this regulation is that epigenetic marks/tags can be read, written, and erased (this is reversible) [3]. However, it is still ambiguous to understand how exactly neural plasticity contours the physiology and morphology of the brain, in spite of intense research on related mechanisms of neural plasticity. Despite its importance in remodeling brain structure and function, neural plasticity has been a long ignored area of research [11] However, there is a recent spark in this domain because of several neurobiological aspects like developmental plasticity in brain, pathogenesis of neurodegenerative and psychological disorders, context dependent learning and above all memory formation are linked to neuroplasticity. Moreover, there is tremendous potential for the modulation of neuroplasticity through epigenetic intervention.

Thus, studying synaptic and neural plasticity is very important to underpin the cellular and molecular mechanisms regulating plasticity in the nervous system. By understanding the mechanism of neural plasticity and associated dynamics involved in this mechanism the synaptic dysregulation can be controlled with an appropriate intervention [12]. Recently, epigenetic processes within the brain were investigated because of their acknowledged implications in basic biology, psychology, and neuropharmacology. Neuroepigenetics is an emerging area of neuroscience research and has potential to provide new insight behind the neurological remodeling; both spontaneous as well as context dependent learning. The complex and dynamic crosstalk among neurons, neuronal plasticity and epigenomic mechanism is well evident, however, the research to identify the specific epigenetic driver and the underlying mechanism behind such processes is still in its stage of infancy. Hence, a comprehensive understanding of the dynamic nature of epigenetic modifications associated with neural plasticity is required. This review, therefore, comes up with an integrated and collated overview of the current state of knowledge with a focus on various types of neural plasticity, different epigenetic mechanisms behind them, the context-dependent role of epigenetic signature molecules like Methyl CpG binding protein 2 (MECP2), Histone acetyltransferase (HAT), Histone deacetylase (HDAC), Brain-derived neurotrophic factor (BDNF), Repressor Element-1 Silencing Transcription factor (REST), Myocyte enhancer factor 2 (MEF2), Ten-eleven translocations (TET), and their modulation by some natural bioactive compounds as epigenetic modulators. The development of a conceptual framework on epigenetic reprogramming as a potential driver of neural plasticity and identification of specific signature molecules to uncover the incremental insights and extension of future research in this direction is the ancillary goal of this review.

This compilation is based on an in-depth search on various databases such as PubMed, Scopus, Science Direct, Web of Science, ERIC, Directory of Open Access Journals (DOAJ), and various search engines such as Google Scholar and IQ Education. The key terms we used to search the literature are epigenetics, neural plasticity, epigenetic modulator, MECP2, HAT, HDAC, BDNF, REST, TET, MEF2 and natural bioactive compounds.

2. Neural plasticity

Neural plasticity is the capability of the brain to be remodeled or changed. This change can either be pre-synaptic or post-synaptic. Based on experience in the environment, either internally or externally, neural plasticity is categorized into the following three major types as explained and represented in Figure 1.

3. Synaptic neural plasticity

It indicates the changes in the associations between neurons. This can occur quickly in milliseconds. Synaptic neural plasticity occurs in two different forms (Short term and long-term), as explained below.

3.1. Short-term plasticity

Short-term plasticity (STP) refers to the changes in the synaptic strength which occur on a sub-second timescale and modulate the synaptic strength in an activity-dependent manner [13, 14]. This may be further categorized as mentioned below.

3.1.1. Post-tetanic potentiation (PTP)

Post-Tetanic Potentiation (PTP) is short-lived. With high-frequency (approximately 200 ms to 5s) trains of stimulation (10–200 Hz), this

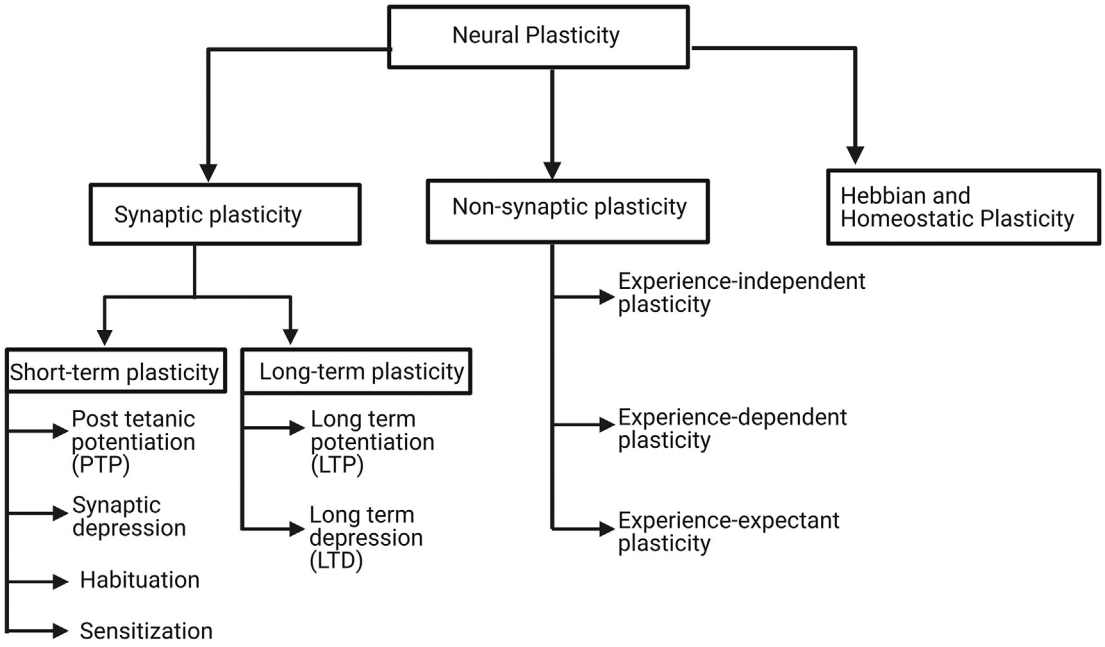


Figure 1. Types of neural plasticity.

long-lasting form of plasticity is observed [15]. The increasing numbers of tetanizing stimuli influenced by action potential are due to increased Ca2+ influx in the pre-synaptic terminal [15]. Sometimes when a continuous synapse activation repeatedly occurs, it induces depression and can continue for several seconds or minutes [15].

3.1.2. Synaptic depression

Synaptic depression is a type of short-term plasticity expressed due to feedback activation of presynaptic receptors or postsynaptic processes. A decline in the postsynaptic potentials after repetitive stimulation of a synapse leads to short-term synaptic depression (STD). It has a different impact on network computations. Benita JM and co-workers in 2012 suggested that STD is modulated by cortical activity. This type of synaptic transmission is directly related to the probability of transmitter release [15]. STD is a feature of both excitatory and inhibitory synapses [16, 17].

3.1.3. Habituation

Habituation is the easiest behavior for the study of memory. It describes the progressive decrease of physiological and behavioral responses to repeated sensory stimulation. This results in a reduction in responsiveness to an environmental stimulus after prolonged exposure or becoming accustomed to any behavior or condition [18, 19].

3.1.4. Sensitization

Sensitization defines the process by which repeated administration of a stimulus increase in progressive amplification of a response. The fast reaction to a potentially threatening stimulus can be enhanced by a sense of fear [20]. Sensitization can also trigger synaptic transmission when an irritating stimulus leads up to an innocuous environmental stimulus.

3.2. Long-term plasticity

Long-lasting, activity-dependent change in synaptic strength is called Long-term synaptic plasticity. It can modify synaptic strength-either by increasing Long Term Potentiation or decreasing Long Term Depression [21]. Further, this may be categorized as mentioned below.

3.2.1. Long Term Potentiation (LTP)

Long-term synaptic plasticity was identified first by Timothy Bliss and TerjeLomo. When the post-tetanic potentiation lasts for days, due to repeated synaptic activity strengthening of synapses occurs, this is otherwise called as LTP [22]. This is associated with increased influx of Ca^{2+} in the post-synaptic terminal [23] which increases the synaptic strength. This type of potentiation develops very rapidly and is most commonly seen in the hippocampus.

3.2.2. Long Term Depression (LTD)

Long-term depression (LTD) is characterized by a weak synaptic strength in which synapses become less efficient for the transmission of neuronal signals. It is important for adopting synaptic networks for different physiological activities following a long-patterned stimulus. Glutamate-mediated LTD can be induced by the activation of *N*-methyl-D-aspartate receptors (NMDAR) [24].

4. Non-synaptic neural plasticity

It refers to the changes in the neurochemicals, particle channels, axons, dendrites, and other physiological variables connected to neuronal systems. The scale of time varies even from milliseconds to minutes. Sometimes, it extends for hours and days also. It is categorized into three types in the normal brain according to the functional organization, behavior, neurogenesis, dendritic organization, synaptic structure, and gene expression.

4.1. Experience-independent plasticity

Experience-independent plasticity is largely a prenatal developmental process. It involves the changes in the brain that takes place regardless of the environmental factors and unfolds in a tightly regulated manner. It is independent of external sensory input. In the cat, the development of the eye-specific multilayers of the lateral geniculate nucleus (LGN) is an example of experience-independent plasticity [25].

4.2. Experience-dependent plasticity

Experience-dependent plasticity is associated with the process of changing the neuronal unit via several cellular mechanisms. This change is a continuous process, including the organization and creation of neuronal connections which occur from life experiences. Once an animal receives stimuli, that will precede a reinforced motor action for which

representational changes can be seen in the sensory cortex of adults [26]. This plasticity occurs when animals receive extreme environmental variations, injury [27], or in response to psychoactive drugs [28] in different parts of the brain.

4.3. Experience-expectant plasticity

Experience-expectant plasticity happens due to the integration of environmental stimuli during the developmental process. Ocular dominance columns present in the primary visual cortex contribute a combined mechanism for the inputs from the right and left eyes to produce binocular vision. It is revealed that if one eye is closed just after birth, the other open eye enlarges its territory, which leads to subsequent shrinkage to the closed eye as observed in kittens. Finally, the vision of the closed eye is compromised [29].

5. Hebbian and Homeostatic synaptic plasticity (Figure 2)

Hebbian plasticity (introduced by Donald Hebb) is another type of synaptic plasticity that includes both LTP and LTD [30]. It creates a positive feedback loop and mostly bear a resemblance to fast synaptic alternation which is required for experience-dependent plasticity. Homeostatic processes are very slow and last for hours or days. Homeostatic plasticity also influences the release of a neurotransmitter, the sensitivity of the postsynaptic receptor, and the density of the ion channel. It operates over hours to days and promotes network stability by adjusting global synaptic strength [31]. A negative feedback mechanism related to homeostatic plasticity conserves the network stability by controlling the synaptic strength of the neurons [32].

6. Basic aspects of neural plasticity and its various mechanisms

Neural plasticity is responsible for learning and memory. It is the capacity of neurons for strengthening of the existing synapses to encode and retain memories. In the brain, neuronal impulse is transmitted through synaptic junction is comprises presynaptic and postsynaptic terminals interspaced by a synaptic cleft. A single neuron can collect thousands of synaptic inputs from presynaptic cells. Consequently, each cell can combine information from different sources before passing the detailed information as an electrochemical code. In the brain, the

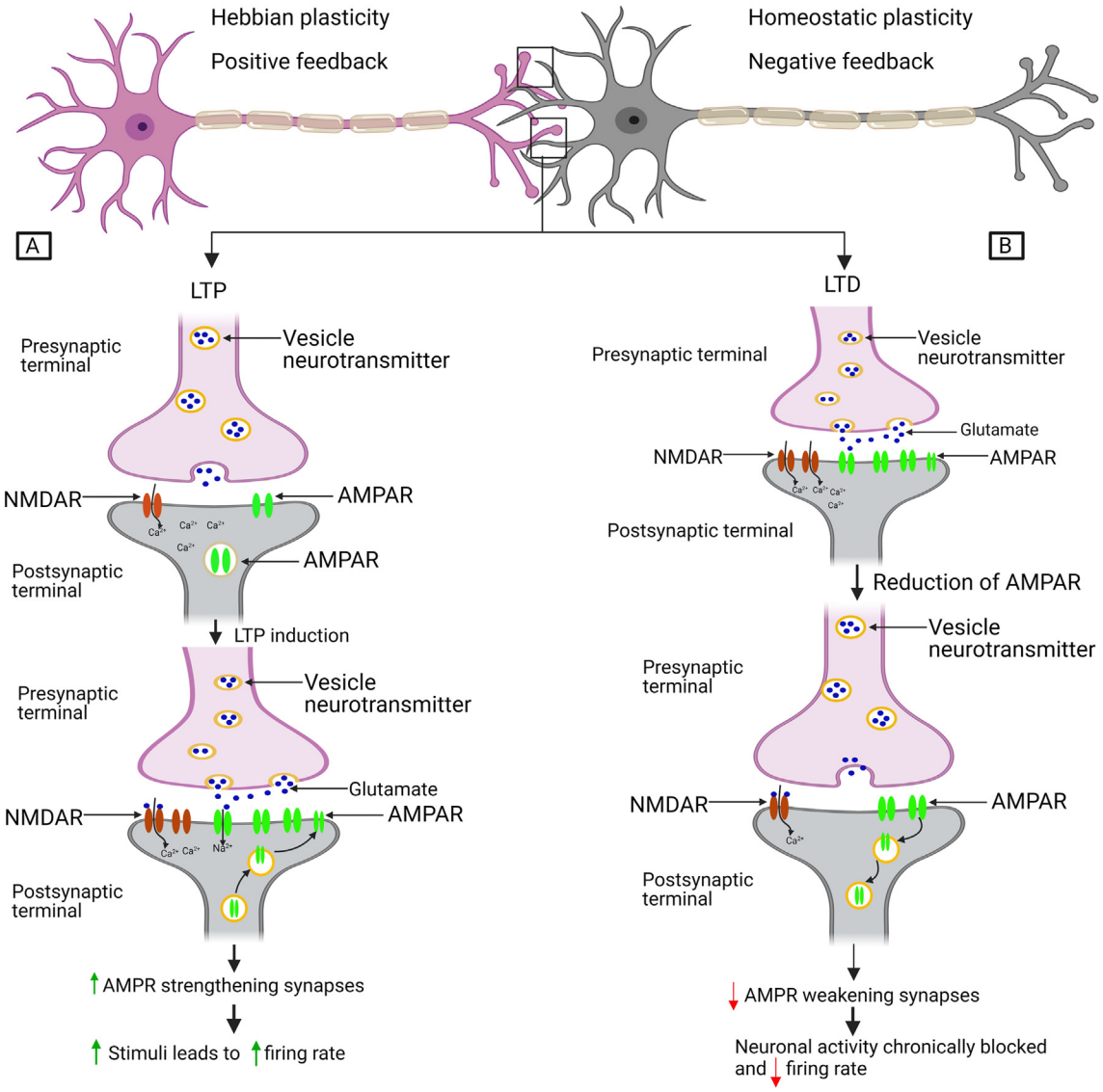


Figure 2. Hebbian and Homeostatic neural plasticity: A) Long Term Potentiation (LTP) induces Hebbian plasticity, during which *N*-methyl-D-aspartate receptors (NMDARs) activates α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors (AMPARs) and strengthen synapses. Increased stimuli (↑) enhance the firing rate. B) In homeostatic neural plasticity, postsynaptic reduction in AMPARs weakens (↓) the synapses and maintains homeostasis and firing rate.

transmission of information passes through neurons by specialized synapses. Neurotransmitters are filled in small vesicles at the presynaptic terminal. Also, specific receptors for specific neurochemicals are present at the postsynaptic terminal. Neurons conduct electrical impulses called an action potential, which is started at the cell body (Cyton) and moves down the axon. Voltage-dependent release of neurotransmitter-filled vesicles due to an action potential converts an electrical impulse into a chemical signal at the synapse. Subsequently, at the synaptic cleft, the neurotransmitter diffuses and binds to receptors by creating an electrical impulse in the postsynaptic neuron. After acquiring a minimum electrical threshold required for firing, the postsynaptic neurons fire an action potential. Based on the molecular process and type of molecules involved in neural plasticity, five different mechanisms have been proposed, as described below.

6.1. Regulation of synaptic strength by NMDAR-dependent Long-Term Potentiation and Long-Term Depression (LTP/LTD) (Figure 3)

The neural plasticity which occurs through LTP/LTD has been extensively studied in the glutamate neurons, where glutamate is the major excitatory neurotransmitter throughout the central nervous system (Approximately 5–15 mmol glutamate per kg brain tissue). Glutamate

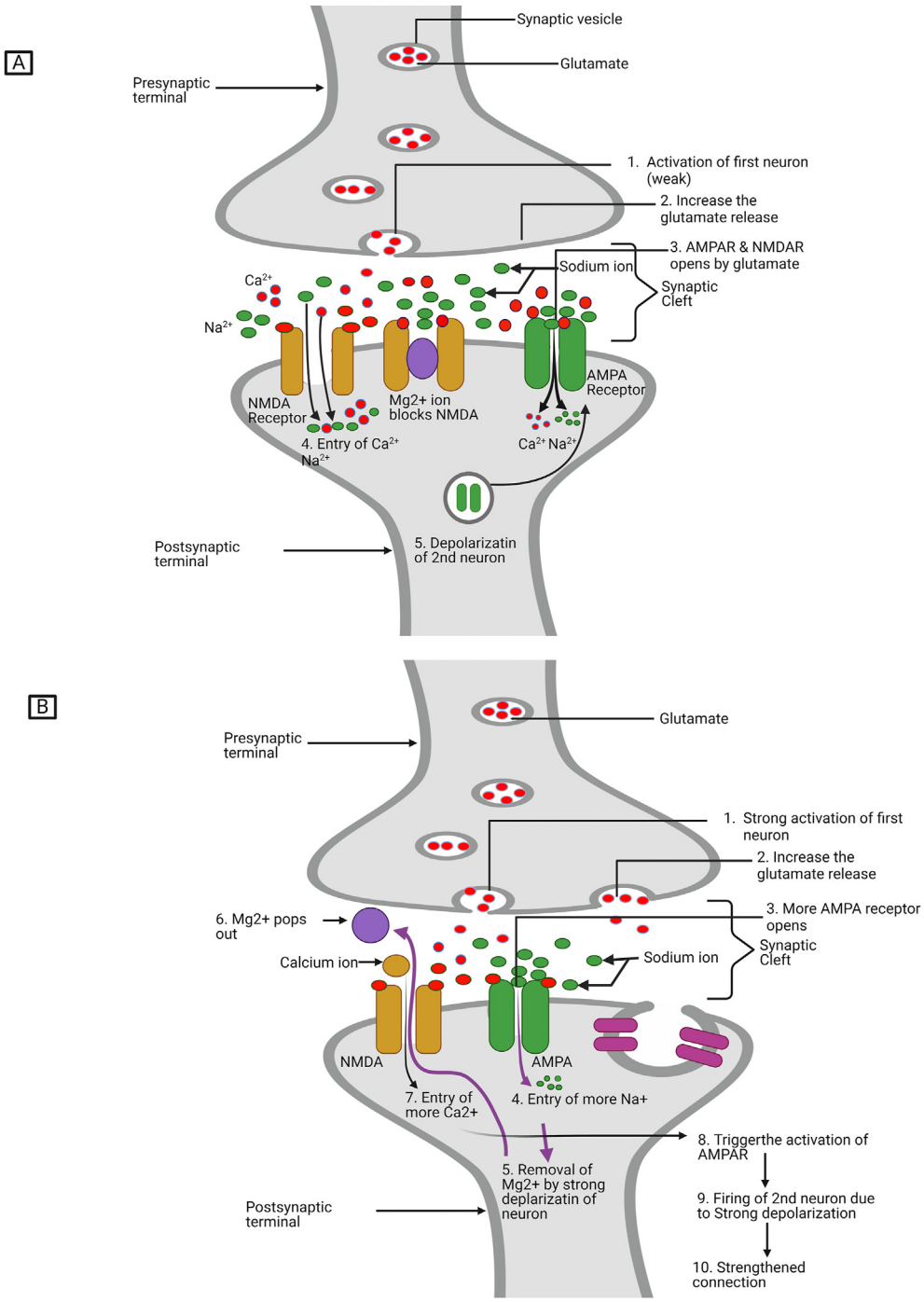


Figure 3. Glutamate-mediated activation of LTP and LTD by NMDARs and AMPARs. Glutamate released from presynaptic terminal acts postsynaptically on NMDARs and AMPARs and releases Calcium ions (Ca^{2+}) into the synaptic cleft. Calcium triggers the production of AMPARs facilitating the entry of Na^{2+} ions into the post synaptic terminal resulting the strengthening of synapse. A) Weak activation of neuron B) Frequent activation of neuron.

plays a critical metabolic role in the brain, and it works as the crossways between various biochemical pathways [33]. It has excitatory effects on nerve cells [34] and controls the delivery of signals within nerve cells. There are two main types of glutamate receptors like NMDARs and AMPARs (Figure 3). The NMDAR is a crucial ionotropic glutamate receptor and ion channel protein found in neurons. LTP occurs after the attachment of glutamate molecules to NMDA receptors due to a low firing rate of the presynaptic neuron. AMPARs are the predominant ionotropic glutamate receptors that mediate the basal synaptic transmission. When both receptors are triggered at a time, the NMDA receptor opens, allowing influx of calcium to post synaptic neuron and initiation of LTP [35]. Calcium stimulates the production of more AMPA receptors, which facilitates further influx of calcium and sodium ions to the postsynaptic neuron. When firing occurs from the first neuron strongly and at high frequency, the depolarization through the AMPA receptors is strong enough, which pops the magnesium out from blocked NMDAR. Now, opened NMDAR allows more sodium and calcium to the neuron at the postsynaptic terminal. The positive charge of sodium ions depolarizes enough and triggers a cascade effect to fire the second neuron (Figure 3). The influx of calcium enhances the deposition of more AMPA receptors by the second neuron at the synapse. The above cascade/sequential events contribute towards the strengthening of synapse. NMDARs also play a crucial role in triggering LTD and regulate the presynaptic and postsynaptic firing [36, 37]. The induction of LTP or LTD, depends on the concentration of calcium ion present in the postsynaptic neuron. Moderate concentration of Ca2+ below its threshold level, leads to LTD [38]. NMDAR-dependent LTD increases endocytosis of AMPAR, which is responsible for synaptic depression [24]. NMDAR-dependent LTD also increases STP which strengthen the neuronal responsiveness of previously depressed synapses [24].

6.2. Dendritic spine enlargement: another mechanism of neural plasticity (Figure 4)

Ramon y Cajal characterized dendritic spines as tiny, protruded neurons for the first time in 1888 by using their Golgi method to label spines [39]. Dendrites and dendritic spines of neurons perform vital functions in the brain connection. They are recognized as the site of long-term, memory-related synaptic plasticity. Dendritic spines provide sites of synaptic contact and are comprised of actin filaments. These are distributed throughout the nervous system, indicating the synaptic locations, and are mainly linked with convergent neurons. In the central nervous system (CNS), more than 90% of excitatory synapses occur only on dendritic spines [40]. Larger dendritic spines have synapses with more neurotransmitter receptors and a larger post synaptic density (PSD) protein, therefore stronger synaptic transmission occurs in larger dendritic spines than the smaller one (Figure 4).

6.3. Brain-derived neurotrophic factor (BDNF)-dependent activation of neural plasticity (Figure 5)

Plasticity of dendritic spines is required for memory formation, which occurs in the medial prefrontal cortex (PFC) and the hippocampus [41]. Memory changes according to the estrogen levels in the female during their life span. The elevation in estrogen levels enhances the dendritic spine density and memory performance in the PFC and hippocampus. BDNF is a member of the neurotrophin family, which promotes dendritic spine formation and improves memory performance. LTP-induced alternation in synaptic structure and function requires BDNF which is believed to alter the synaptic proteome [42]. In the area of cognitive domain, BDNF can be used as a marker for progression of the mnemonic symptoms [43]. Estrogen also enhances PFC and hippocampal BDNF concentrations. In activity-dependent plasticity BDNF acts as an important regulator at excitatory synapses in the central nervous system [44]. BDNF also promotes the growth, maturation, survivability, and maintenance of neuronal cells. The synaptic development and activity-dependent changes in the structure and function of the synapse are also controlled by BDNF. BDNF shares common targets, effects, and mechanisms of action for both Estrogen (ERs) and Tyrosine kinase B (TrkB) receptors. Both receptors, are associated with the differentiation and plasticity of neurons found in the hippocampus. They control general neurobiological functions in learning and memory. Their co-expression trigger the activation of various

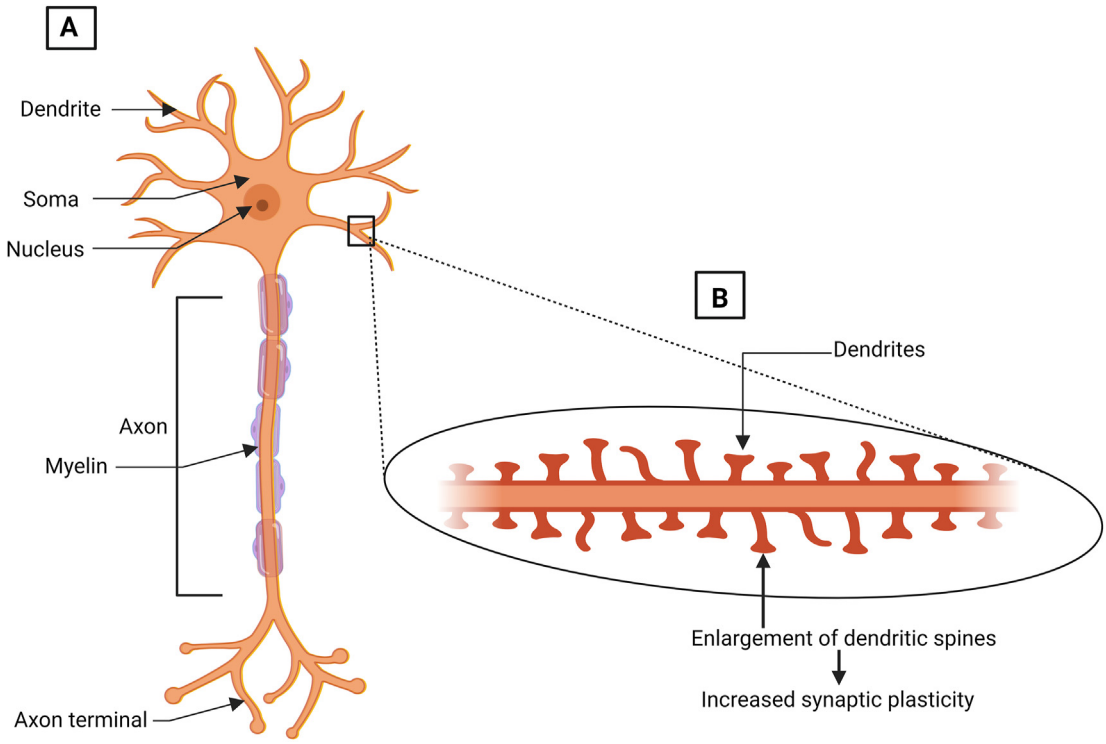


Figure 4. Schematic diagram of a mature neuron: A) A mature multipolar neuron. B) A part of the Enlarged dendrite indicating high density of dendritic spines which creates functional connections and increase neural plasticity.

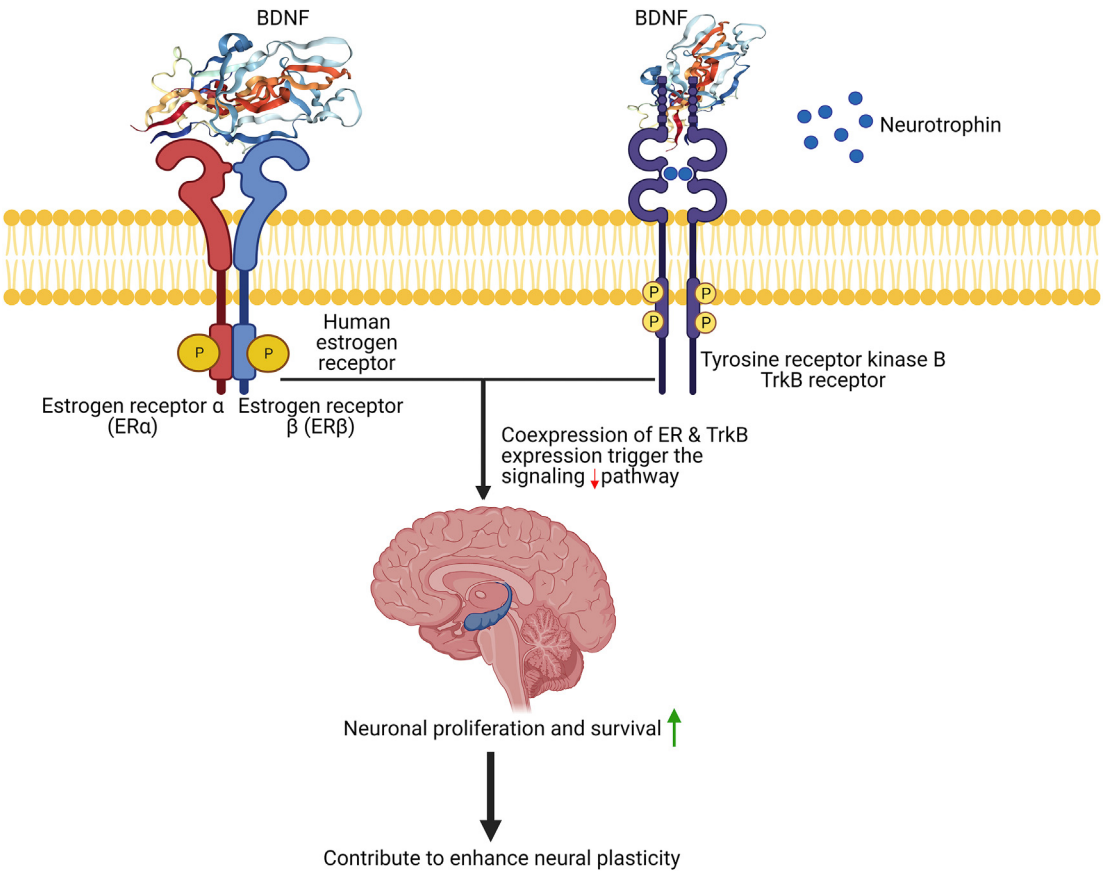


Figure 5. Estrogen receptor (ER) and tyrosine receptor kinase (TrkB) mediated neural plasticity: Combined role of Estrogen & TRK in BDNF dependent neural plasticity.

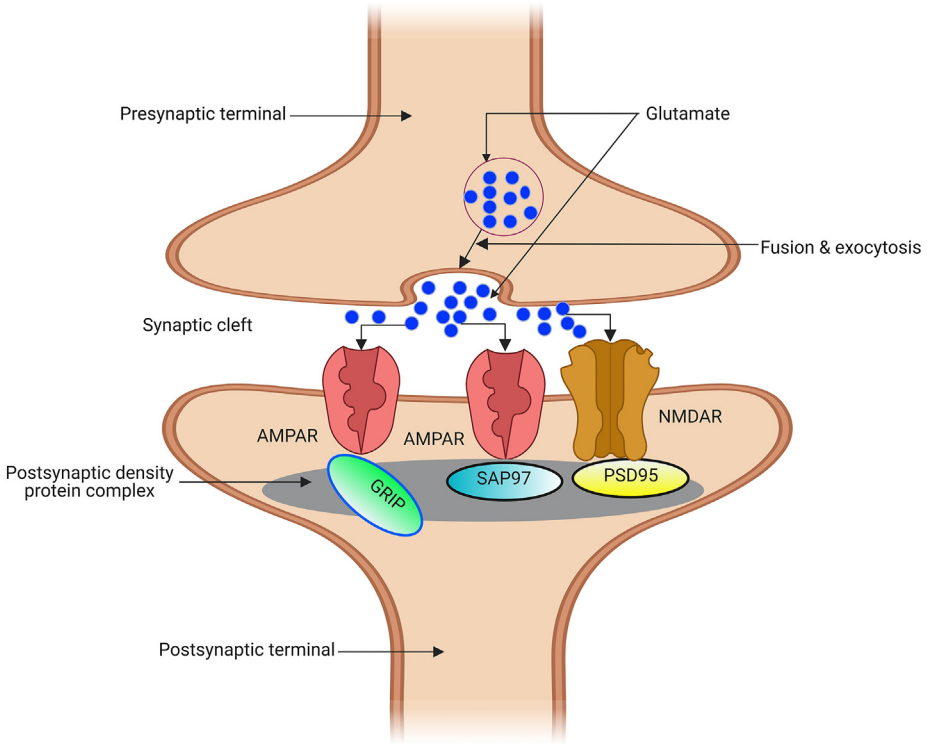


Figure 6. Post Synaptic Density (PSD) proteins anchor AMPA and NMDA glutamate receptors and strengthen the synapses. Neural plasticity is regulated by interactions of glutamate with Postsynaptic density protein 95 (PSD-95), Synapse-associated protein 97 (SAP97), and Glutamate receptor-interacting protein (GRIP).

signaling pathway in the brain [45]. Mature BDNF binds with TrkB receptor and induces TrkB phosphorylation. BDNF and/or TrkB expressions are influenced by estrogen in the developing hippocampus [46]. The action of estrogen on neurons during development occurs through interactions with growth factors and their communication (Figure 5). The ligand-mediated dimerization of the complex activates various intracellular signaling pathways associated with increasing neural plasticity.

6.4. Post Synaptic Density (PSD) protein-mediated neural plasticity (Figure 6)

Thousands of interlocking proteins in the postsynaptic neuron construct a large complex of PSD proteins. PSD proteins plays a vital role in anchoring and stabilizing glutamate receptors such as AMPA and NMDA receptors [47]. Interactions of glutamate receptors with postsynaptic density proteins like Postsynaptic density protein 95 (PSD-95), Synapse-associated protein 97 (SAP97), and other multi-domain proteins such as glutamate receptor-interacting protein (GRIP) forms the glutamatergic signal transduction machinery. This interaction regulates the activity-dependent and activity-independent receptor targeting and trafficking which are required for neural plasticity. It has been reported that, PSD 95, in particular regulates the function of AMPA-type glutamate receptors by increasing synaptic strength and stops LTP [48] and PSD-95 knockdown downregulate the expression of AMPARs and synaptic strength [49].

6.5. Neuroligins and neurexins-dependent neural plasticity (Figure 7)

Coordination of synaptic connectivity in the brain is performed by cell adhesion. The functional interaction between presynaptic neurexins and postsynaptic neuroligins from either side of the synapse performs a vital role in trans-synaptic transmission and brain plasticity. These transmembrane molecules are extracellularly connecting one another to enhance adhesion between dendrites and axons (Figure 7). Neuroligin alone may lead to the development of completely functioning presynaptic terminals, while neurexin may cause postsynaptic differentiation and receptor clustering in dendrites. This interaction between neuroligin and neurexin is thought to be a bilateral trigger for the formation of functional synapses [50].

7. Epigenetic basis of neural plasticity

Since the last decade, the neuroepigenetics field has emerged as a central area of research pertaining to the covalent and non-covalent modifications of DNA and histone proteins. Epigenetic factors influence overall chromatin structure, gene programs, synaptogenesis, and neural plasticity. In general, this refers to the heritable changes in the cell, which have a direct influence on gene expression without altering the DNA sequence. DNA methylation specifies the attachment of a methyl (CH_3) group at 5′-carbon of the pyrimidine ring of cytosine nucleotide through DNA methyltransferases (DNMTs), which subsequently modify the function of DNA. However, it represses gene transcription in the

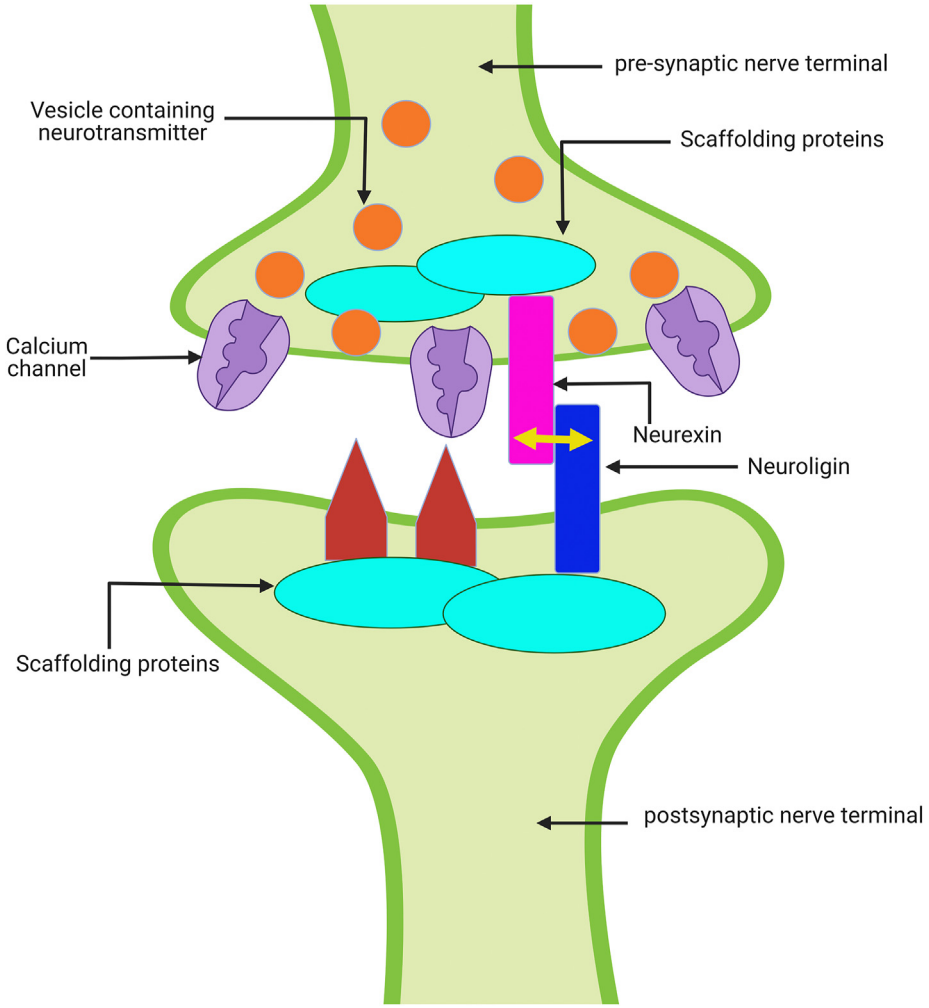


Figure 7. "Neurexin-Neuroligin" dependent functional synapse. Neurexins from the presynaptic membrane interact with Neuroligins on the post-synaptic membrane resulting receptor clustering and establishment of functional synapse.

promoter regions [51]. It is reported that, loss of *Dnmt3a*, from excitatory neurons of mouse alters the expression of the synapse-associated genes, supress the synapse maturation, and leads to impaired learning and memory [52]. Several factors, including food, microbiota, physical activities, and environmental pollutants can largely influence epigenetic changes. Epigenetic modifications can also affect one another by adding extra layers of epigenetic regulation [53]. Epigenetic processes being reversible and labile, are regulated by different signature proteins or molecules. To explain the role of such proteins in modulating neural plasticity, the following context-dependent examples are given for a better understanding of the epigenetic control of neural plasticity.

8. Role of different epigenetic signature molecules in neural plasticity

Epigenetic mechanisms are dynamic, reversible, and regulated by the action of various epigenetic modulators. The number of epigenetic modulators has been characterized to exhibit promising data in the regulation of neural plasticity in animal model. Epigenetic modulator-mediated signals from cellular stress, environmental agents, inflammation, injury, and aging alter the chromatin structure [54]. The modification in chromatin plays a vital role in the developmental process and neurological disorders. The epigenetic studies have been focused on gene expression, DNA methylation, and patterns of post-translation modifications of histones (acetylation or deacetylation). Various enzymes, including histone acetyltransferase (HAT), histone deacetylase (HDAC), histone methyltransferase (HMT), and kinases are linked to the addition or removal of molecular flags from the histone-DNA complex, which regulates the "epigenome" in the brain.

Synaptogenesis plays a central role in associative learning and memory formation. However, biochemical pathways that underlie synaptogenesis are complex and incompletely understood. Epigenetic remodeling triggered by various epigenetic modulators is being increasingly linked behind synaptic plasticity. In this context, we are particularly focusing on a few important epigenetic signature molecules like MECP2, HATs & HDAC, BDNF, REST, MEF2, and TET. The role of

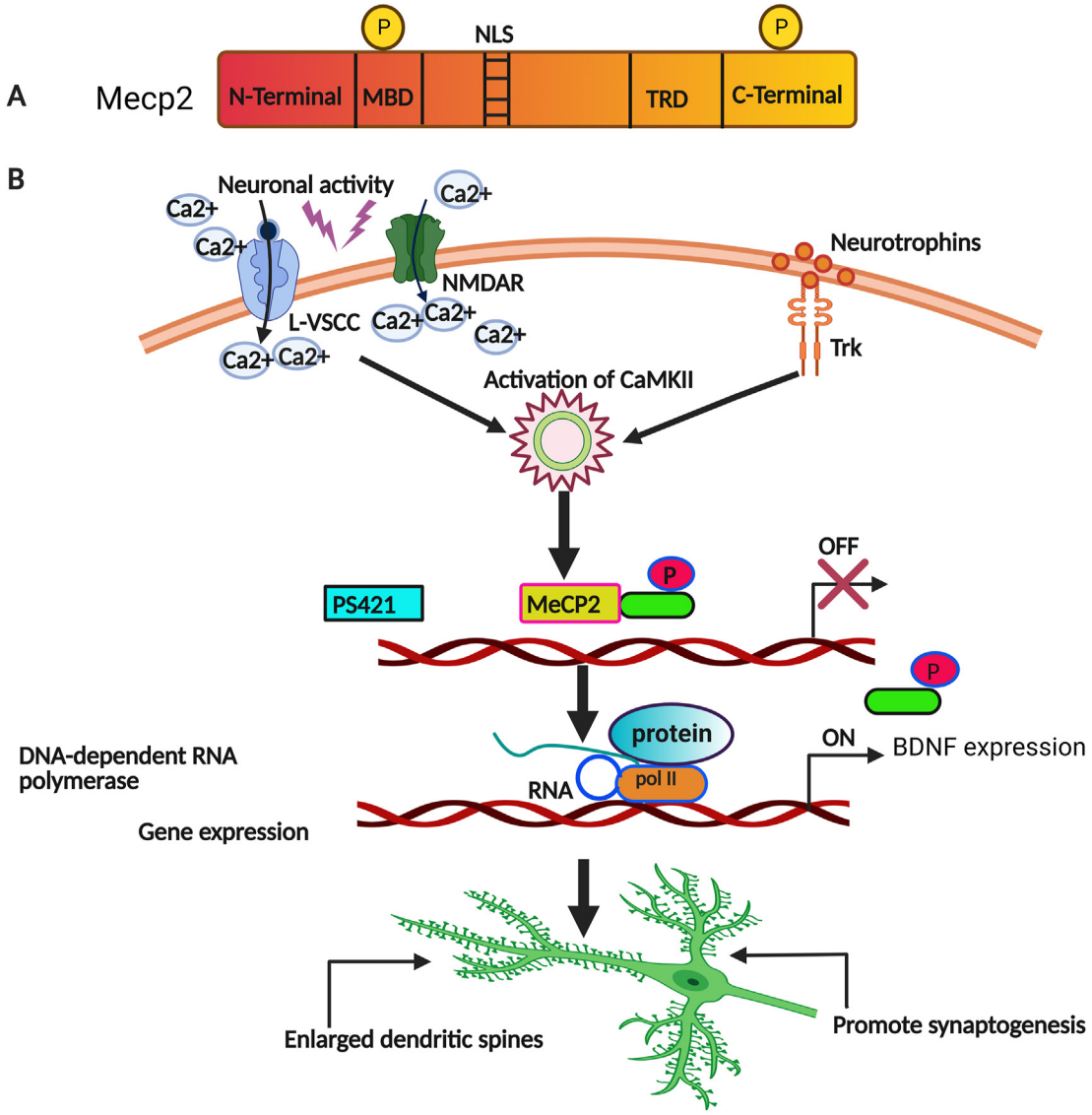


Figure 8. MeCP2-mediated regulation of dendritic patterning, spine morphogenesis, and activity-dependent gene expression. **A)** A Functionally characterized domains of human methyl-CpG binding protein 2 (MECP2) showing the methyl-CpG binding domain (MBD), transcriptional repression domain (TRD), and nuclear localization signal (NLS). **B)** Entry of Ca^{2+} through L-type voltage sensitive calcium channels (L-VSCC), *N*-methyl-D-aspartate receptors (NMDAR) and entry of neurotrophin through TrkB receptor combinedly activate calcium-dependent protein kinase II (CamK II) which in turn phosphorylates MeCP2 resulting enlarged dendritic spine and enhanced synaptogenesis.

some natural bioactive compounds like curcumin, catechin, quercetin, resveratrol, salidroside, emodin, wogonin, oleanolic acid, osthole and garcinone D are also discussed here, as they are greatly involved in modulating neural plasticity.

8.1. Neuronal activation and synaptogenesis through epigenetic marker, MeCP2 (Figure 8)

MECP2 is a member of the Methyl binding domain (MBD) protein family and is an essential mediator of the biological activities of the specific methylome of the brain. It is the most common epigenetic marker of the adult brain and links DNA methylation with the chromatin structure through interactions with chromatin modifiers [55]. In particular, MECP2 plays an essential role in the modulation of synaptical transmission in the CNS for spontaneous neurotransmission and short-term synaptic plasticity. Post-translational modifications like phosphorylation, acetylation, and SUMOylation are some of the processes through which MeCP2 modulates the synaptic transmission. It is a nuclear protein with multiple functionally identified domains, including methyl binding domain (MBD) and the transcriptional repression domain (TRD), that controls the function of MECP2 (Figure 8a). MeCP2 contains a Nuclear Localization signal (NLS) region specifically designed for the nuclear localization. It is evident from recent studies that the nuclear localization region of MeCP2 may be determined by the MBD domain, other than the NLS sequence [56]. MECP2 is phosphorylated at 2 regions, serine 80 (S80) and serine 421 (S421). When phosphorylation is induced at S421, it reduces phosphorylation at S80. After S80 is dephosphorylated, MECP2 weakly interact with chromatin regions. It has been observed that phosphorylation of MeCP2 at these two sites triggers the transition between the resting and the depolarized states of neurons [57]. Increased synapse numbers enhance the synaptic strength and results in the neuronal gain of MECP2 in neurons [58]. It is reported that expression of BDNF is transcriptionally induced by activity-dependent phosphorylation of serine 421 (S421) in MECP2 [59] (Figure 8b). Neuronal calcium influx through L-type voltage sensitive calcium channels (L-VSCC) and NMDAR, and binding of neurotrophin (BDNF) with TrkB receptor induces phosphorylation in the cytoplasmic domain of TrkB receptor which activates the calciu m-dependent protein kinase II (CamK II). Consequently, CamK II phosphorylates MECP2 at S421 [57]. Neural plasticity is controlled by loss or and gain of MeCP2 function and associated with excitatory/inhibitory balance. The bidirectional effect of neurotransmission indicates that regulation of neural transmission is sensitive to MeCP2 levels [60].

8.2. Synaptic regulation by histone modification (Figure 9)

Histone acetyltransferase (HAT) is greatly responsible for acetylation of the N-terminal tail of Lysine residues in histones, which weaken the electrostatic interaction between the histone tails (positively charged) and DNA (negatively charged). This allows the transcriptional machinery and transcriptional activators to bind more strongly to the DNA increasing the gene expression [61, 62]. The acetyl groups can also be erased by HDACs in a reversal process, promoting gene silencing. Histone

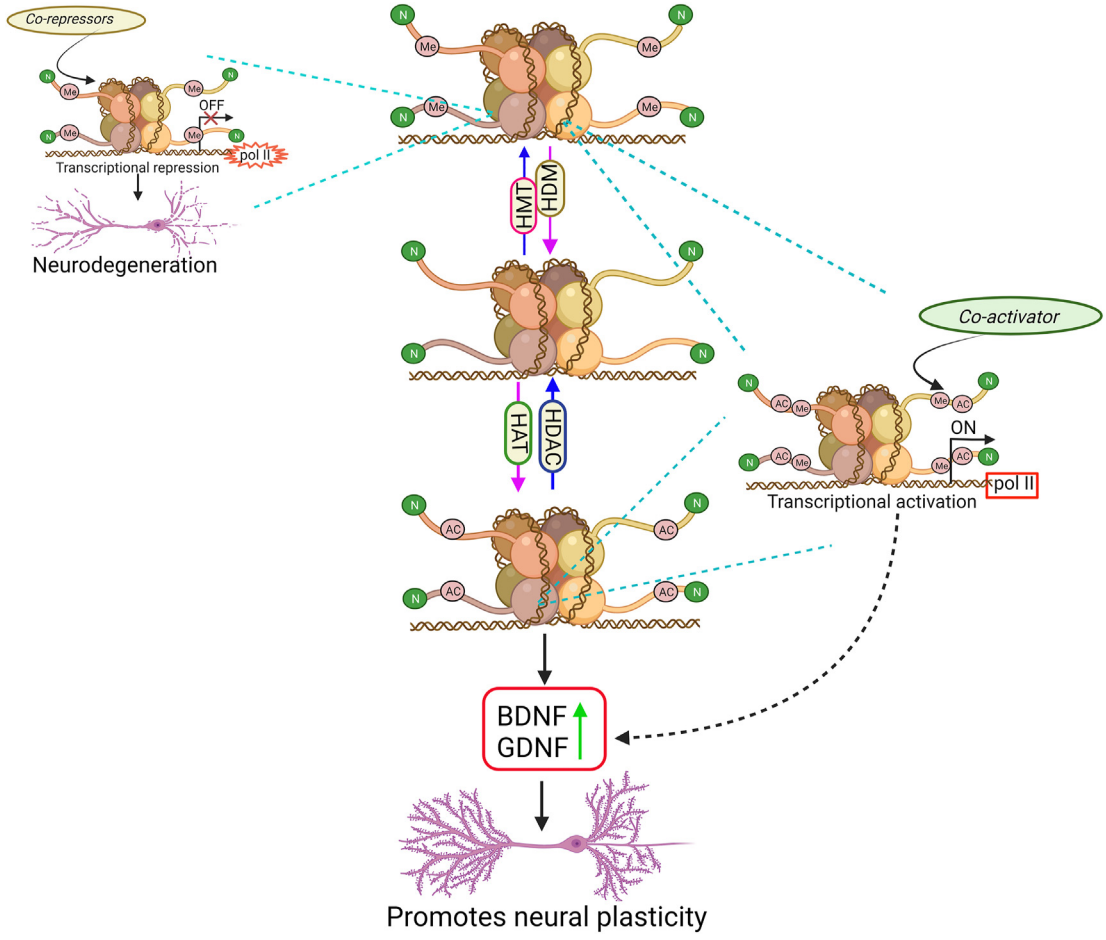


Figure 9. Transcriptional regulation by Histone modifications. Post-translational histone modifications. Histone methyltransferases (HMTs) and histone demethylases (HDMs) and their effect on gene transcription. HMT enzymes recruit transcriptional co-repressors, which block the transcriptional machinery. The HAT enzyme recruits transcriptional activators and post-translational modification creates a repulsive force between neighboring histones and DNA, which structurally loosens the chromatin to give access to the transcriptional machinery and transcriptional activators.

acetylation is a reversible posttranslational modification mechanism regulated by HATs which transfer the acetyl moiety of acetyl-CoA to lysine residues. HDACs reverse this process catalytically [63]. Histone methylation and demethylation are catalyzed by HMTs and HDMs, respectively, and their actions are residue-specific in gene transcription. Histone acetylation is the best-known chromatin modification linked with memory, learning and modifications in neural plasticity [64], as it is associated with active transcription [65]. It is evident that, administration of HDAC inhibitor increases histone acetylation and enhances LTP which further led to greater memory performance [66]. Conversely, overexpression of HDAC2 reduces the number of synapse and ultimately decreases the neural plasticity, and impaired memory [67].

8.3. Regulatory role of BDNF in neural plasticity: role of DNA methylation (Figure 10)

BDNF plays a central role as an epigenetic modulator in the brain. It is a basic neurotrophin, widely expressed as a neurotransmitting modulator [44]. It modulates neuronal survival, neuronal development, growth, and neural plasticity [68]. BDNF acts as an activity-dependent modulator in LTP [69]. The human BDNF gene is made up of eleven exons and each one of them is specific to generate transcripts for different stimuli [70]. Pre-pro-BDNF is the precursor form of BDNF, which is synthesized and folded [71] in the endoplasmic reticulum and further translocated to the Golgi apparatus. The pre-sequence of the signal peptide is cleaved and forms pro-BDNF (30 kDa), which enter the trans-Golgi network (TGN) after being processed by the Golgi apparatus [72]. Then prodomain cleaved off and mature BDNF is translocated into the extracellular space [73]. Epigenetic remodeling of the BDNF regulatory site has a critical role in gene transcription. Martinowich and colleagues reported that higher BDNF level in the neurons decreases the CpG methylation within the regulatory site of the BDNF gene resulting in active transcription [74]. It is also evident that neuronal activity has an impact on the activation of BDNF transcription. Tyrosine receptor kinase B (TrkB) is expressed in the cerebral cortex, pituitary gland, hippocampus, hypothalamus, and visual system [75]. TrkB acts as a receptor for BDNF and neurotrophin-4 (NT4) ligands [76]. NTs are critical mediators for survival and neuronal development by activating Trk receptors. This ligand-dependent dimerization of the complex happens when BDNF interacts with TrkB. Specific tyrosine residues of TrkB in the cytoplasmic domain get phosphorylate, leading to activation of intracellular signaling events [77]. Activation of the TrkB receptor by phosphorylation at Tyr 490 and Tyr 515 TrkB induces the docking of Shc adaptor protein at the tyrosine sites and recruits growth factor receptor-bound protein 2 (GRB2), which binds to Ras and forms a complex, causing ERK activation [78]. Then ERK activation triggeres mitogen-activated protein kinase MAPK/ERK pathway, which subsequently, activate cAMP response element-binding protein (CREB) transcription factor by phosphorylation [79, 80]. Now the phosphorylated CREB, binds to the BDNF promoter and induces BDNF expression [81], which promotes neuronal survivability and synaptic plasticity [82].

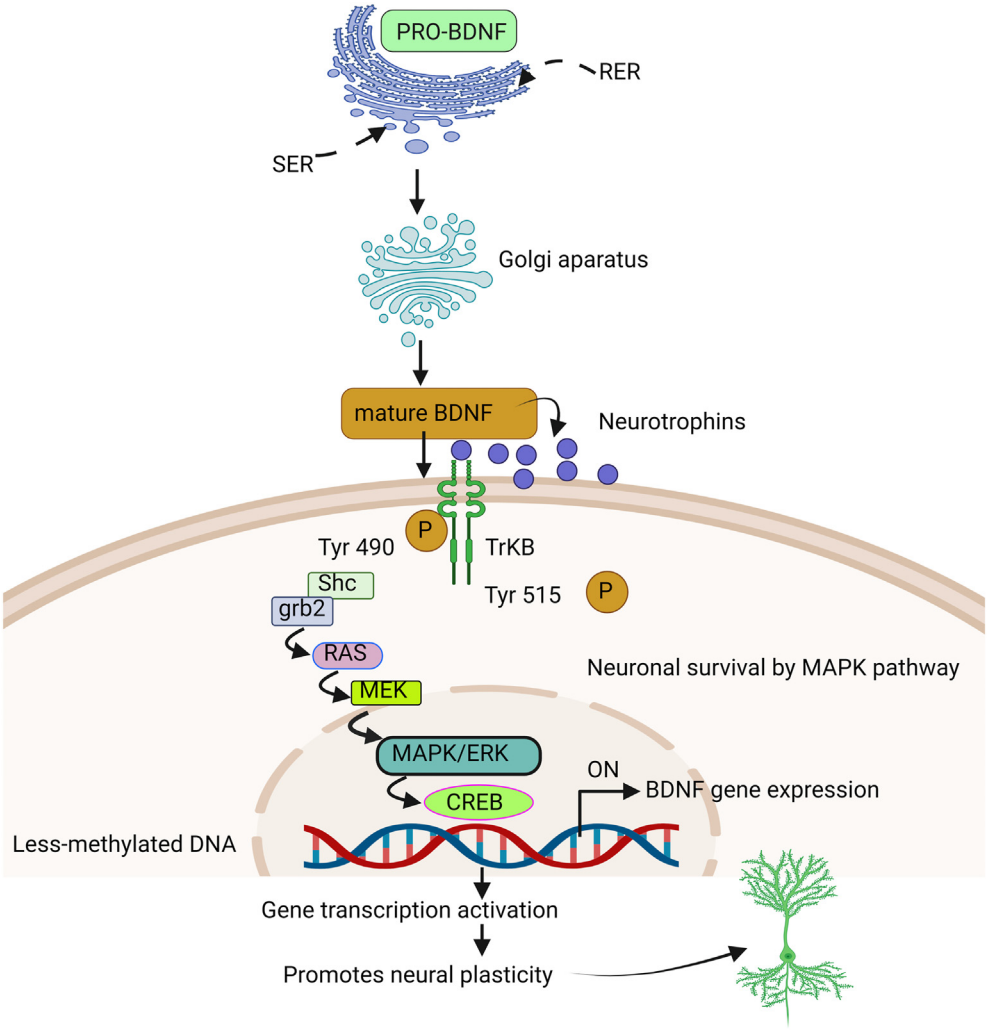


Figure 10. BDNF dependent TrkB receptor activation promotes the association of Shc adaptor protein to GRB2 and RAS to form a complex, which further triggers the MAPK/ERK pathway activating the CREB transcription factor and promotion of neural plasticity by sustained expression of BDNF.

8.4. BDNF-dependent neural plasticity through TET-mediated DNA demethylation (Figure 11)

A highly conserved family of enzymes called DNMT catalyzes the DNA methylation process, as a covalent modification that occurs on cytosine located in CG dinucleotides (CpG). A methyl group from S-adenyl methionine (SAM) to the carbon-5 of a cytosine residue is transferred by the DNMT enzyme to form 5-methyl-cytosine (5mC) [83]. Then, 5-mc is oxidized in a series to synthesize 3 chemically distinct forms, 5-hydroxymethylcytosine, 5-formylcytosine, and 5-carboxycytosine [84, 85, 86]. Ten-eleven translocation (TET) family proteins (Tet1-3), which oxidize 5-methylcytosine (5mC) into 5-hydroxymethylcytosine (5hmC) initiate the active DNA demethylation process [87, 88]. It is further regulated through the base-excision DNA repair pathway in neurons [89] and in other different cells [90, 91]. Co-localization of TET1 and NeuN (Neuronal marker) is observed in the hippocampus indicating their pivotal role in DNA demethylation-dependent neural plasticity [92]. Overexpression of TET1 enhances the conversion of 5mC to 5hmC in the central nervous system [93]. There is no spontaneous conversion of 5mC and its 3 derivatives like 5hmC/5fC/5caC into a normal one. Rather, 5fC and 5caC are identified and excised with the help of DNA repairing enzyme, thymine DNA glycosylase (TDG) coupled with the Base-excision repair (BER) pathway and completes the demethylation process [94, 95]. It is also essential for fibroblast growth factor 1 (FGF1) and BDNF promoter demethylation and its expression [96] (Figure 11). TET3 is also the most highly expressed enzyme in the brain, involved in the process of active DNA demethylation to regulate of impulse transmission across synapses [97].

8.5. Role of myocyte enhancer factor 2 (MEF2) in neural plasticity (Figure 12)

MEF2 is a well-known transcription factor that regulates the expression of array of genes involved in growth and development of various tissues, including brain. It has three functional domains, while the N-terminal contains the MCM1, Agamous, Deficiens, and SRF (serum response factor) (MADS)-box and MEF2 domain, which are responsible for DNA binding, dimerization, and co-factor interaction, the C-terminus contains the transcriptional activation domain. MEF2 has been shown to actively regulate neurite outgrowth [98] and influences the formation of synapses [99]. MEF2 is a highly promiscuous protein regulated by phosphorylation [100, 101], acetylation [102], and SUMOylation like covalent modifications [103]. Activated MEF2 promotes neuronal survival and neural plasticity upon cell activation and activates calcium entry through NMDAR. By recruiting several chromatin-modifying enzymes, MEF2 modifies the expression of the target gene at the promoter region in a calcium-dependent manner [104]. Mitogen-activated protein kinase (MAPK) is a potent activator of MEF2 activity. Upon phosphory-

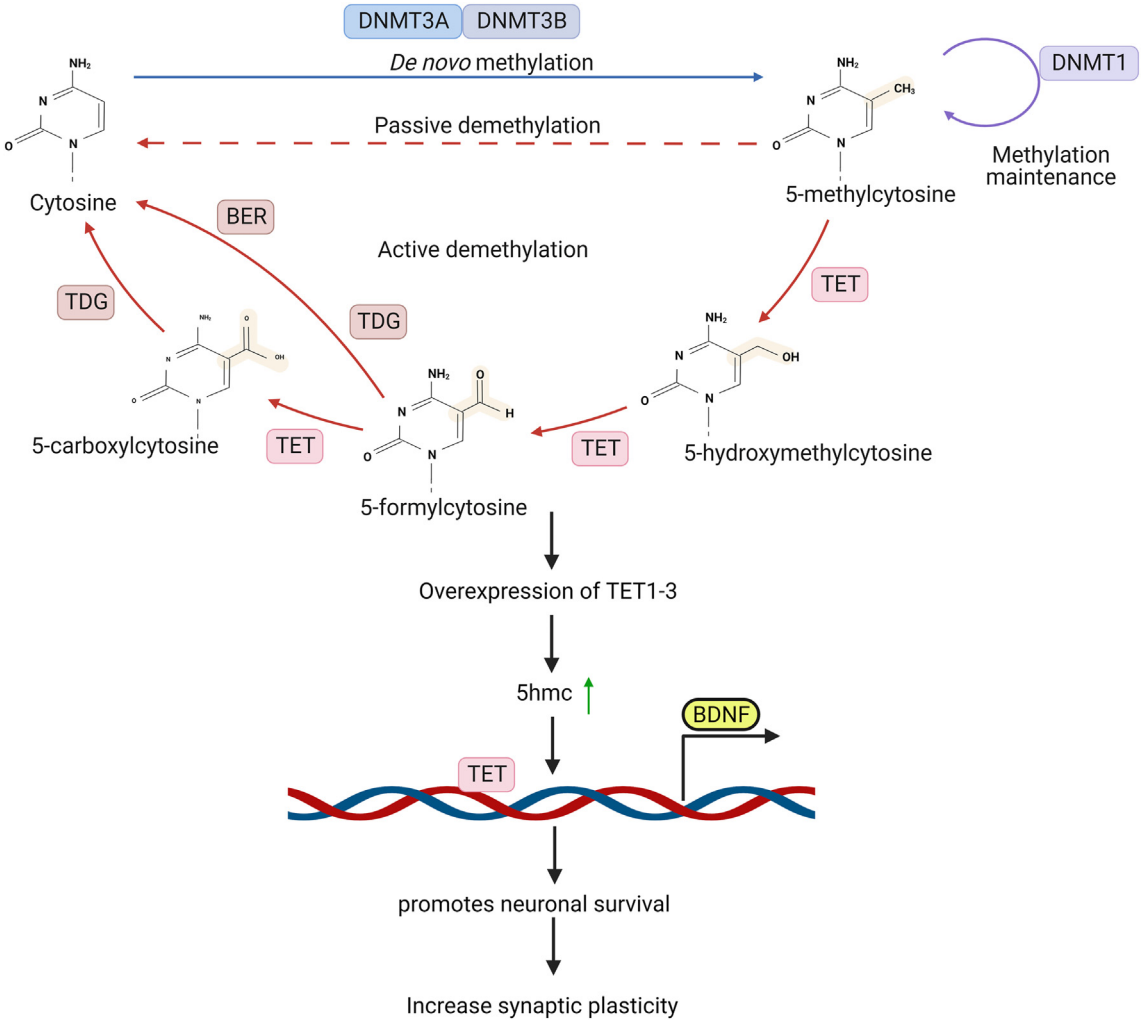


Figure 11. The pathway of DNA demethylation activated by thymine DNA glycosylase (TDG) in association with Base-excision repair (BER). Overexpression of Ten-eleven translocation (TET) enzymes and increased 5hmC content result in demethylation of the BDNF promoter that promotes neural plasticity.

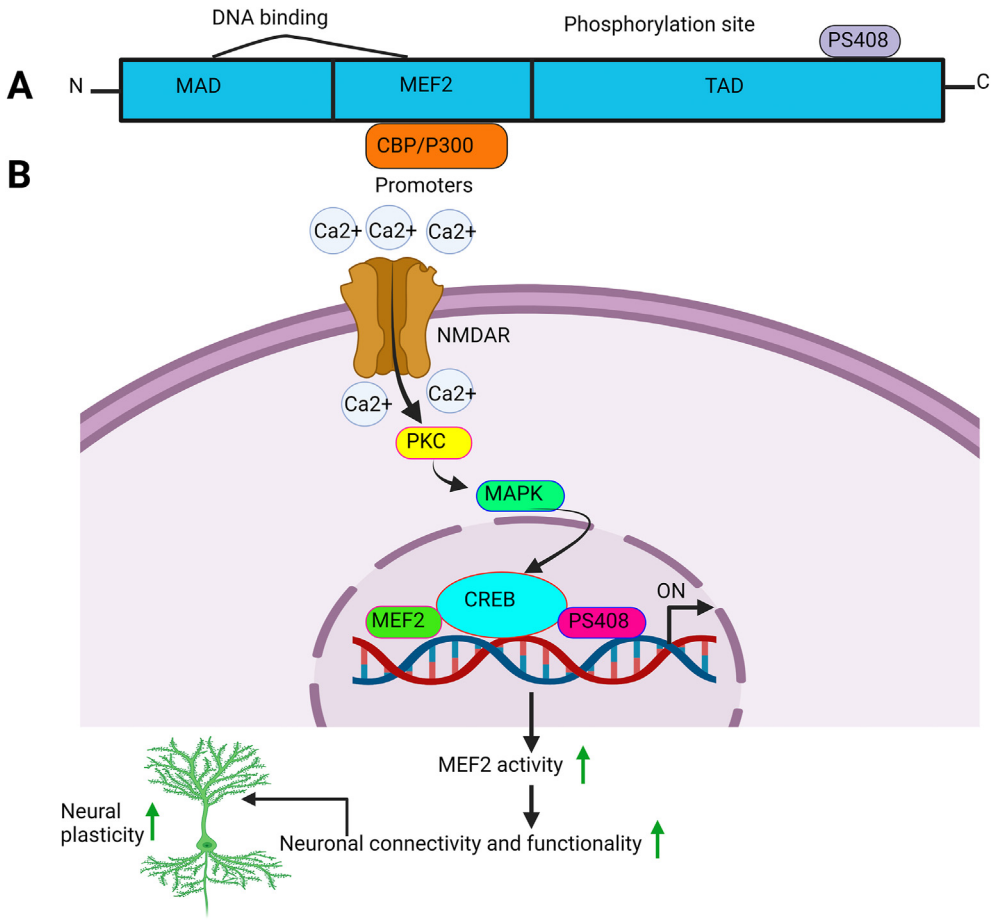


Figure 12. A) Three functional domains of MEF2: The N-terminal domain comprises of MADS-box and MEF2 domains, responsible for DNA binding, dimerization, and co-factor interaction, whereas the C-terminal domain contains key phosphorylation sites. B) Entry of calcium through NMDA receptor activates protein kinase C (PKC) and MAPK pathway. This promotes translocation of MEF2 protein to the nucleus and activates MEF2-dependent transcription through CREB transcription factor and promotes neural plasticity.

lation by PKC, MEF2 is free to interact with the transcriptional coactivators, CREB-binding protein (CBP) at serine 408 (S408), and promotes MEF2-dependent gene transcription (Fig. 12a & b).

8.6. RE1-silencing transcription factor (REST)-mediated neural plasticity (Figure 13)

REST is a transcriptional regulator of more than 2000 neuron-specific genes, encoding the proteins associated with neural plasticity [105, 106]. REST-mediated transcription is a unique process that shapes and regulates neuronal gene expression in neuronal homeostasis [107, 108]. The minimum REST concentration allows upregulation of selective target REST genes. REST regulates neural differentiation and cell specification by repressing neuronal genes associated with neuronal differentiation and maturation [109]. It includes three functional domains, DNA-binding domain (DBD) and two N-and C-terminal repressor domains. Eight zinc fingers (ZFs) present in the DBD allow the protein to link with 21-base pair consensus element-1, RE1 [110] (Figure 13). Then gene suppression is triggered by the recruitment of 2 corepressor complexes like mammalian mSin3 and CoREST, followed by their binding with chromatin-modifying enzyme [111]. REST and the cofactor complexes simultaneously control the expression of neuronal genes in target cells during neural growth and plasticity. REST maintains synaptic plasticity and regulates the glutamate receptor. It has been reported that, reduced expression or absence of REST could lead to the impaired neural plasticity [112].

9. Neural plasticity and neurological disorders

Neuronal dysfunctions are associated with several pathologies such as Alzheimer's disease (AD), Huntington's disease (HD), Parkinson's disease (PD), depression, hearing impairment, stroke, spinal cord injury, Rett syndrome, multiple sclerosis, and amyotrophic lateral sclerosis (ALS) [113, 114, 115, 116, 117, 118]. Multiple risk factors like oxidative stress, protein fibril formation, DNA damage, hyperphosphorylation, hypoglycemia, altered gene expression, and neurotrophic factor (NTF) deficiency are responsible for damage and death of neuronal cells [113, 117]. Mental illness is represented as a primary contributor to the Global burden, which provides a life-threatening and alarming signal [119]. Globally, 4.4% of individuals suffer from a depression disorder and 3.6% of individuals suffer from anxiety disorder [120].

10. Role of epigenetic modulators in the regulation of neural plasticity

Epigenetic modulators transduce signals through various modifiers and influence the process of inflammation, aging, injury, and other stress-related disorders through epigenetic reprogramming. Diet can alter and coordinate several translational processes in neural plasticity by driving epigenetic processes. Recently several studies have demonstrated epigenetic modifications induced by natural polyphenols and other bioactive phytocompounds with the introduction of the term "epigenetic diet" [121, 122] and epidrugs [123], respectively. It is pertinent to mention over here that some natural phenolic compounds mostly studied for their healthy properties are curcumin, a phenolic acid present in the rhizome of Curcuma longa Linn (family Zingiberaceae), epigallocatechin-3-gallate (EGCG), the flavonol present in green tea, and Quercetin (plant flavonol) from the flavonoid group of polyphenols. Curcumin has been extensively used for the treatment of various ailments, including neurological dysfunctions. Curcumin and catechins are responsible for modulation NF-KB expression and chromatin remodeling through HDACs and

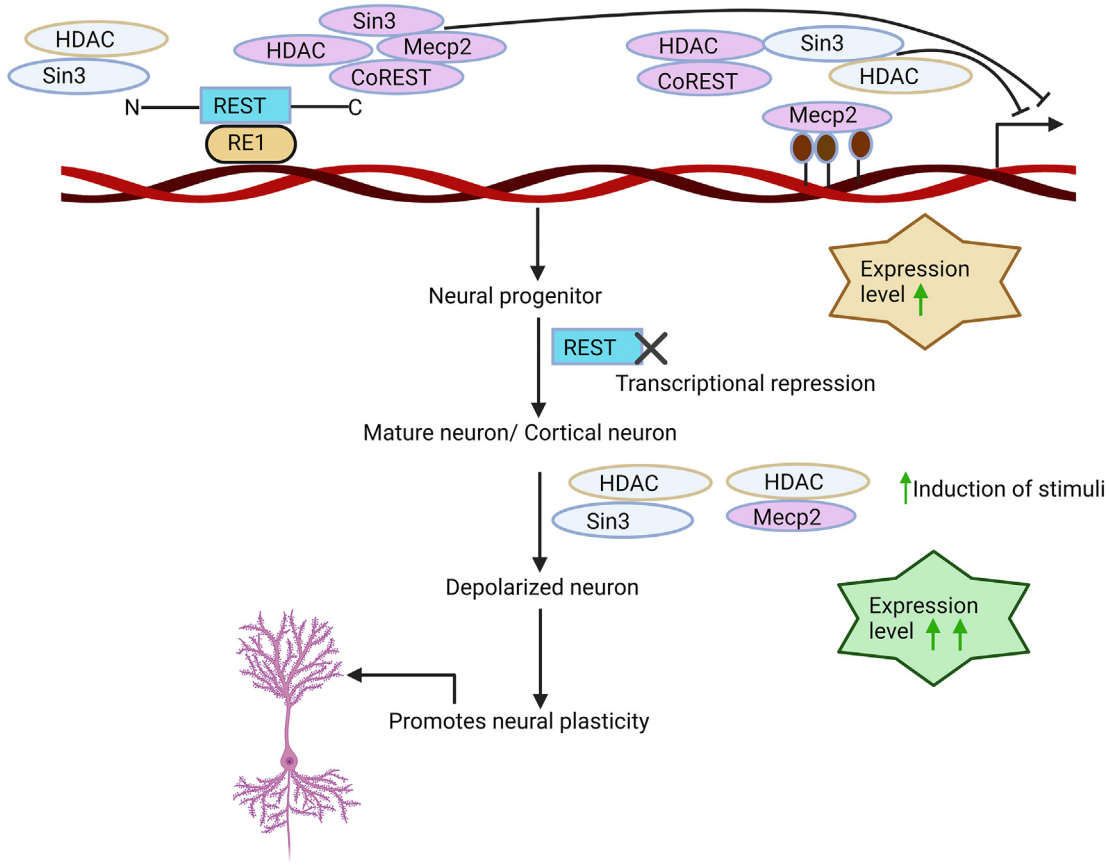
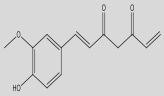
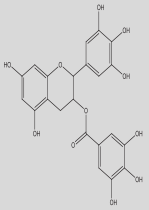


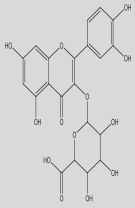
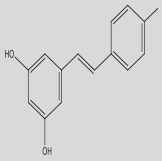
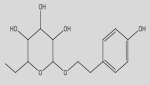
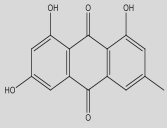
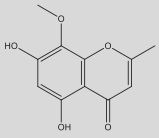
Figure 13. REST and its co-factor complexes regulate neuronal gene expression in neural plasticity: The amino terminus of REST recruits Sin3-histone deacetylases (HDACs) to mediate active repression of neuronal genes. Carboxyl terminus recruits a large complex through the specific corepressor, CoREST, which includes Sin3-HDAC and the methyl-DNA-binding protein MeCP2 to regulate neural plasticity through epigenetic modifications.

Table 1. Natural phytocompounds used in various neurological dysfunctions.

Natural compound	Category	Source	Structure	Neurological disorders	Mechanism and effect	Signaling pathway	Reference
Curcumin	Phenolic	Curcuma longa Linn (turmeric)		Alzheimer's disease Parkinson's disease Depression and anxiety Stroke Multiple sclerosis Rett syndrome Huntington's disease	↑BDNF, ↑glutathione-S-transferase activity, ↓oxidative damage, ↓oxidative stress, ↓phosphorylation of ERKs, ↓ROS, ↑DOPAC, ↓MDA, ↑Dopamine, ↑Serotonin, ↑CAT, ↑SOD, ↑GPx ↑5-hydroxytryptamine (5-HT) 1A receptor, the mutation in the MeCP2.	↑hippocampal neurogenesis (activate ERKs and p38 kinases) ↑ neurite outgrowth (reggie-1 and ERK1/2 pathway)	[126, 127, 128, 129] [130, 131] [126, 132] [133, 134, 135] [136, 137, 138] [139] [140, 141]
Epigallocatechin-3-gallate	flavonoid	Camellia sinensis (green tea)		Alzheimer's disease Parkinson's disease Depression and anxiety Stroke Multiple sclerosis Rett syndrome	↓ROS, ↓Oxidative stress, ↑CAT, ↑SOD, ↑GPx.	↑hippocampal neurogenesis (PI3K/Akt signaling)	[142]

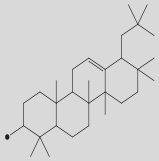
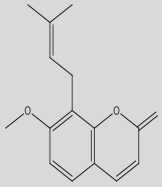
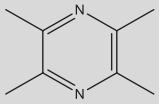
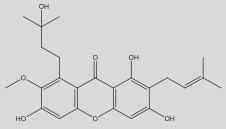
(*continued on next page*)

Table 1 (*continued*)

Natural compound	Category	Source	Structure	Neurological disorders	Mechanism and effect	Signaling pathway	Reference
				Huntington's disease			
Quercetin-3-O-glucuronide	glucuronide	grapes, apples and berries		Alzheimer's disease Parkinson's disease Depression and anxiety Stroke Multiple sclerosis Rettsyndrome Huntington's disease	↑BDNF, ↑glutathione-S-transferase activity, ↓oxidative damage, ↓oxidative stress.	increase NSC proliferation via the Akt/cyclin D1 and BDNF signaling pathway and promote migration (↑CXCR4)	[143]
Resveratrol	polyphenol	grapes, peanuts, pine trees, and cassia		Alzheimer's disease Parkinson's disease Depression and anxiety Stroke Multiple sclerosis Rett syndrome Huntington's disease	↓glutamate levels, ↓MDA, ↑Dopamine, ↑Serotonin, ↑CAT, ↑SOD, ↑GPx.	induce SIRT1 activation (↑ Nestin, Musashi, CD133, GFAP, NF-M, MAP-2, KCNH1), PKA-GSK3β and β-catenin signaling (CREB phosphorylation and pERK1/2 induction)	[144, 145]
Salidroside	phenylpropanoid glycoside	Rhodiolarosea L		Alzheimer's disease Parkinson's disease Depression and anxiety Stroke Multiple sclerosis Rettsyndrome Huntington's disease	↓synaptophysin loss, ↑DOPAC, ↓glutamate levels, ↓MDA, ↑Dopamine, ↑Serotonin.	induce neuronal differentiation by ↓Notch and ↑BMP signaling (↑NSE, MAP-2, β-tubulin III, Smad 1/5/8; ↓ Notch1, Hes1) induce differentiate into dopaminergic neurons (↑ DBH, DDC, TH ↑ BDNF, NT3, NGF mRNAs)	[34, 146]
Emodin	anthraquinones	Polygonummultiflorum		Alzheimer's disease Parkinson's disease Depression and anxiety Stroke Multiple sclerosis Rett syndrome Huntington's disease	↓Oxidative stress, ↑CAT, ↑SOD, ↑GPx.	PI3K/Akt/GSK-3β pathway (↑ tubulinβ III, CREB phosphorylation)	[147]
Wogonin	flavonoid	Scutellariabaicalensis		Alzheimer's disease Parkinson's disease Depression and anxiety Stroke Multiple sclerosis Rett syndrome	↑BDNF, ↑glutathione-S-transferase activity, ↓oxidative damage, ↓oxidative stress, ↓phosphorylation of ERKs, ↓ROS.	induce differentiation and neurite outgrowth (↑ neurofilaments, presynaptic protein, synapsin I and postsynaptic protein)	[148]

(*continued on next page*)

Table 1 (*continued*)

Natural compound	Category	Source	Structure	Neurological disorders	Mechanism and effect	Signaling pathway	Reference
				Huntington's disease			
Oleanolic acid	triterpenoid	Ligustrumlucidum		Alzheimer's disease Parkinson's disease Depression and anxiety Stroke Multiple sclerosis Rett syndrome Huntington's disease	↓ROS, ↑DOPAC, ↓glutamate levels, ↓MDA, ↑Dopamine, ↑Serotonin, ↑GABA, ↑adenosine, ↑CAT, ↑SOD, ↑GPx,↑5-hydroxytryptamine (5-HT) 1A receptor.	induce differentiation of NSCs to neurons by Nkx-2.5-dependent mechanism (↑ tubulin-βIII, Mash1; ↓ GFAP) inhibit differentiation into astrocyte by down-regulating JAK/STAT signaling pathway (↑Ngn1, ↓p-STAT3/STAT3)	[149, 150]
Osthole	coumarin	Cnidiummonnieri (L.)		Alzheimer's disease Parkinson's disease Depression and anxiety Stroke Multiple sclerosis Rett syndrome Huntington's disease	↑DOPAC, ↓glutamate levels, ↓MDA, ↑Dopamine, ↑Serotonin, ↑GABA, ↑adenosine, ↑CAT, ↑SOD, ↑GPx.	promote neuronal differentiation and inhibit apoptosis via activation of Wnt/β-catenin signaling (↓ GSK-3β)	[151]
Tetramethylpyrazine	alkaloid	LigusticumwallichiiFranch		Alzheimer's disease Parkinson's disease Depression and anxiety Stroke Multiple sclerosis Rett syndrome Huntington's disease	↑BDNF, ↑glutathione-S-transferase activity, ↑Dopamine, ↑Serotonin, ↑GABA, ↑adenosine, ↑CAT, ↑SOD.	induce neuronal differentiation through activation of PI3K/Akt/Sp1/TopoIIβ pathway (↑ tubulinβ III, MAP-2)	[152, 153]
Garcinone D	xanthone	Garciniamangostana L. (Mangosteen)		Alzheimer's disease Parkinson's disease Depression and anxiety Stroke Multiple sclerosis Rett syndrome Huntington's disease	↓oxidative damage, ↓oxidative stress, ↓ROS, ↑DOPAC, ↓glutamate levels, ↓MDA, ↑Dopamine, ↑Serotonin.	Promote proliferation (STAT3/Cyclin D1 pathway and Nrf2/HO-1 pathway)	[154]

The chemical structure of the above given bioactive compounds were drawn by Chem draw ultra 12.0.2 using the canonical SMILE for each compound from PubChem (https://pubchem.ncbi.nlm.nih.gov/).

DNMTs activity [124]. Some of the recent studies from our laboratory have demonstrated that curcumin can potentially modulate the epigenetic process by regulating the expression of DNA methylating proteins and other molecules associated with DNA methylation [125].

The following table (Table 1) summarizes the systematic assessment of some natural compounds and their role in neuroprotection, as evident from various studies. Though these studies have analyzed various parameters related to redox regulation and inflammation concerning neuronal dysfunction, the epigenetic link to underpin such mechanism should be the future research to establish the linkage among neural plasticity, epigenetic reprogramming, and mod ulators.

11. Conclusion

Neural plasticity is responsible for the functional organization, reconstitution, and maturation of synaptic connectivity. It can alter both the structures and functions of the brain and allows for modifications in neural circuitry including number of synaptic connections that neurons receive. The performance of brain function depends upon the synaptic strength, intrinsic excitability, and synaptic density, which can be modulated by epigenetic reprogramming. These mechanisms (molecular, genetic, and epigenetic) are involved in altering neural plasticity positively or negatively associated with various epigenetic modulators. Overall, the preceding discussion focuses on different types of neural plasticity, their functional relevance and regulatory mechanism of some epigenetic events behind neural plasticity, particularly through the modulation of synaptic genes and epigenetic signature molecules. Role of some natural compounds as putative epigenetic modulator in promoting redox balance and neuroprotection has also been discussed in the narration.

As we understand there is an increasing link between epigenetic regulatory molecules, machineries and neuroplasticity; future study should focus on the specific epigenetic drivers and epigenetic modulators like BDNF, MECP2, DNMTs and HDAC inhibitors and their specific role in neural plasticity. BDNF is essential for neuronal growth, survival, cognitive function, learning and memory and also serves as a neurotransmitter modulator. MeCP2 is another important neuronal modulator abundantly expressed in the brain. Studies on cross talk among various epigenetic pathways (like DNA methylation, histone modifications and miRNA formation) and modulators will help us to understand the epigenetic process and consequences associated with neurodegenerative and neuropsychiatric disorders.

Environmental toxins, metabolic disorders, disrupted "microbiota-gut-brain axis" and aging-driven compromised neuronal performance and associated neural plasticity are also some of the upcoming areas of interdisciplinary neuroscience research. Prenatal, neonatal as well as early childhood challenges from various stressors also have remarkable effect on adult brain and susceptibly to neurodegeneration. The underlying epigenetic mechanisms will provide us with important insights for the development of targeted epidrug.

Though the role of phytocompounds as epigenetic modulators has been discussed with redox regulation and neuronal dysfunction, their epigenetic link needs to be explored further in a context-dependent manner. This study has important implications for clinical and therapeutic interventions which will improve our mental health. In sum, neuroepigenetic research will be an extensive and incredible area of investigation to bridge the existing gap between basic neuroscience and clinical epigenetics.

Declarations

Author contribution statement

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Data availability statement

No data was used for the research described in the article.

Declaration of interest's statement

The authors declare no competing interests.

Additional information

No additional information is available for this paper.

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