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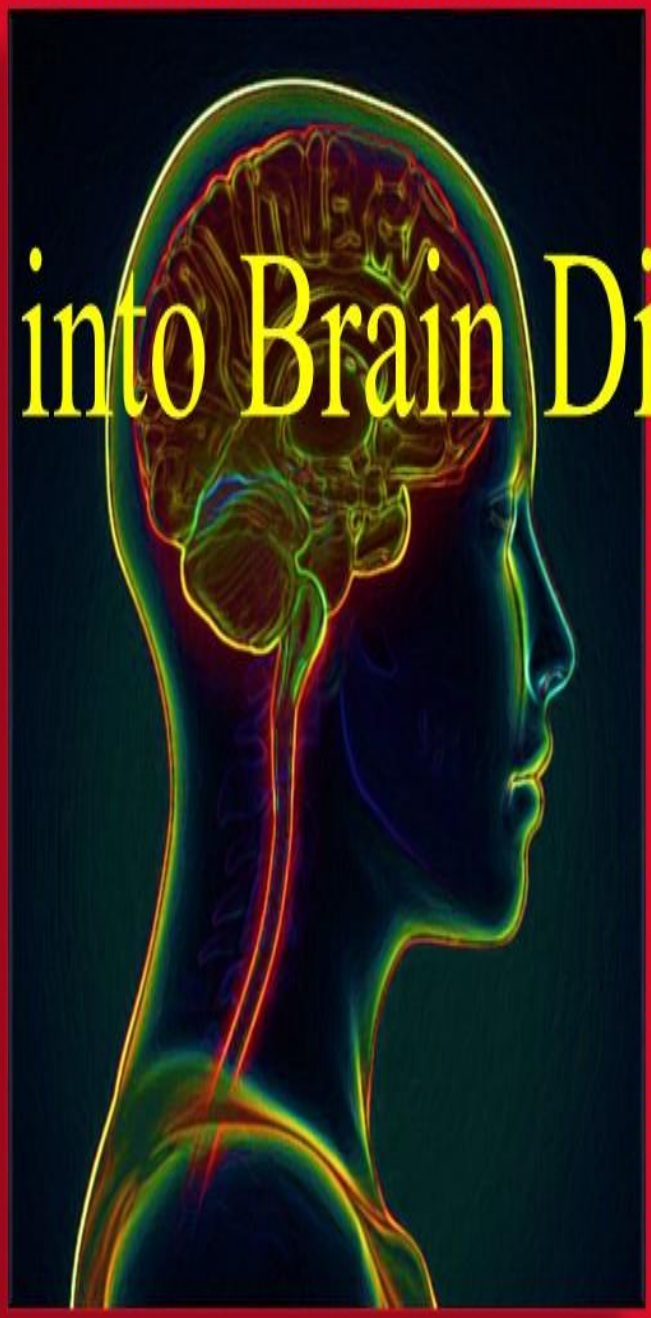
Insights into Brain Disorders



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Insights into Brain Disorders

Atef Sobhy Iskander

Brain disorders are major causes of morbidity and disability that affect millions of people globally. These disorders, including Parkinson's, Huntington's, and Alzheimer's diseases, arise from the changes in the architecture and function of the brain. The harmony of neurons interactions is vital for the development of neural networks and neural functions. Among the various factors that causes neurological disorders are the spatial patterns of dendrites; the hyperphosphorylation of both inositol 1,4,5-trisphosphate receptors and the tau protein; and the mutant huntingtin protein. Understanding the architecture and function of the brain require understanding how individual neurons interact with one another. This study provides a brief overview of neuronal signaling in the brain including the basic processes underlying neuronal communication and the neuronal actions of several neurotransmitters, and neurotrophic factors, as well as other vital topics. Finally, hypothetical scenarios are presented, which may have potential therapeutic targets.

Keywords: Neuronal signaling, Neurotransmitters, Neurotrophins, Brain disorders, Spatial patterns of dendrites, Tau protein, Mutant huntingtin protein, BBB, Cobalt nanoparticles,

1. Introduction

Brain disorders are a major cause of the global burden of diseases that affect millions of people world-wide. The diversification of these disorders ranges from neuropsychiatric disorders such as eating disorders, obsessive compulsive disorder, depression, schizophrenia, bipolar disorder, to neurodegenerative diseases including Parkinson's, Huntington's, and Alzheimer's diseases.[1,2] These disorders arise from the changes in the architecture and function of the brain. In fact, the brain has the ability to dynamically reorganize itself by forming new neural connections throughout life, a phenomenon known as "neuroplasticity" that allows the neurons in the brain to compensate for injury and adjust their activity in response to new situations or changes in their environment. The different forms of neural plasticity can take place in the human throughout the central nervous system (CNS), from the cerebellum (the area of the brain that coordinates the sensory information) to the spinal cord.[3] Within the cerebellum, the interactions between its cells are vital for normal

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cerebellar function. The total number of neurons in the average human brain is about 130 billion, while the number of cerebellar neurons constitutes some 109 billion neurons in the typical cerebellum.[4-7] Nerve cells, (neurons), in the brain are classified into three main classes: sensory, motor, and interneurons. The sensory neurons respond to stimuli, that affect the cells of sensory organs, and transmit signals to the nervous system which then performs the appropriate action. Whereas motor neurons receive signals from other neurons, and then pass them on to the target cells including the muscles, glands or other organs. The interneurons are found only in CNS, which are responsible for connecting different types of neurons within the same region of the brain and the spinal cord. The interactions between these neurons are crucial for cerebellar function. The harmony of these interactions is essential for the proper development of the neurons, which profoundly affects the formation of neural networks and neural functions. Thus, understanding the architecture of the brain requires understanding how individual neurons interact with one another. To begin with, I provide a brief overview of neuronal signaling in the brain including the basic processes underlying neuronal communication and the neuronal actions of several neurotransmitters, as well as neurotrophic factors, and other vital topics. Also, I shall discuss some proposals which may have potential therapeutic application in manipulating neural plasticity to treat a variety of conditions.

2. Neural communication

Nerve cells are responsible for rapid communication of information through a combination of electrical and chemical signals. Neurons have specialized patterns of arbor morphology branches of dendrites and axons. These branches are used by the nervous system to transmit messages between neurons, or from neurons to muscles. Within the brain, neurons receive chemical input from other neurons through dendrites and communicate information to other cells through axons. These arbor morphologies determine the efficacy with which the information is transmitted to the soma (cell body). Electrical signals that have travelled along the axon are rapidly converted into chemical ones through the release of chemical molecules, causing a specific response in the receiving neuron. These chemical molecules (*i.e.* neurotransmitters) influence a nerve cell in an excitatory, inhibitory, or modulatory way. An excitatory transmitter promotes the generation of an electrical signal known as “action potential” in the receiving neuron, while an inhibitory transmitter prevents it. Whether a neurotransmitter is excitatory or inhibitory depends on the receptor it binds to in the small gap between the synapses of the nerve cells, *i.e.* “synaptic cleft”. Neuromodulators regulate populations of neurons without restriction to the synaptic cleft, operating over a slower time course than excitatory and inhibitory transmitters.

Being excitable cells, the neuronal surface membrane contains many ion channels, which allow small charged particles to pass through from one side of the membrane to the other when the voltage across the cell membrane changes. A subtype of these “voltage-gated” channels allows the neuron to produce a rapid signal, *i.e.* the action potential (Figure 1).[8]

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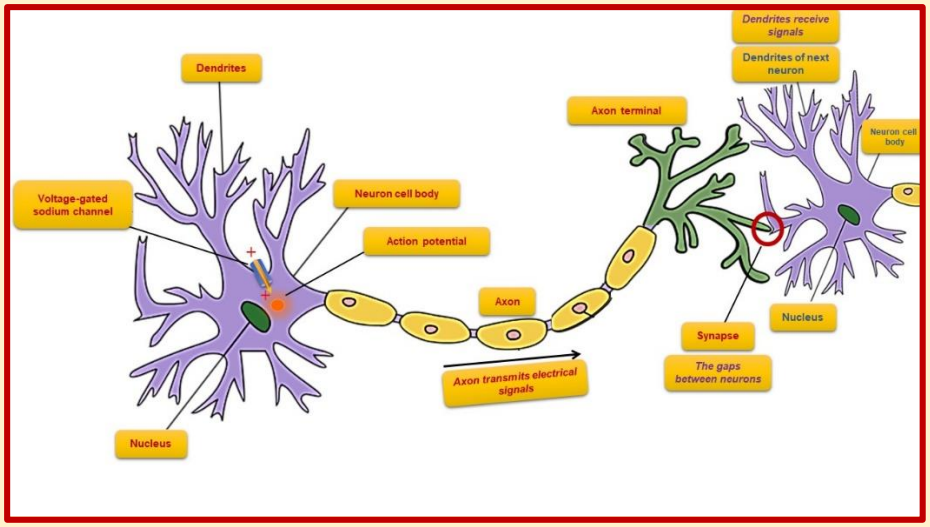

Figure 1. Schematic drawing of a neuron receives chemical input from other neuron through dendrites; and axon terminal communicates information to other neuron cells. Voltage-gated sodium channels in the membrane of the neuron cell body, axon, and axon terminal permit positively charged sodium ions to enter the neuron and produce rapid conduction of the excitatory action potential to the terminal. This signal stimulates neurotransmitter release at the axon terminal.

Communication between neurons takes place at small synaptic gaps where specialized parts of the two cells (*i.e.* the presynaptic and postsynaptic neurons) come within nanometers of one another to allow for chemical transmission. The presynaptic neuron releases a neurotransmitter (a chemical molecule) that is received by the postsynaptic neuron's specialized proteins called neurotransmitter receptors (Figure 2). The neurotransmitter molecules bind to the receptor proteins and alter postsynaptic neuronal function.

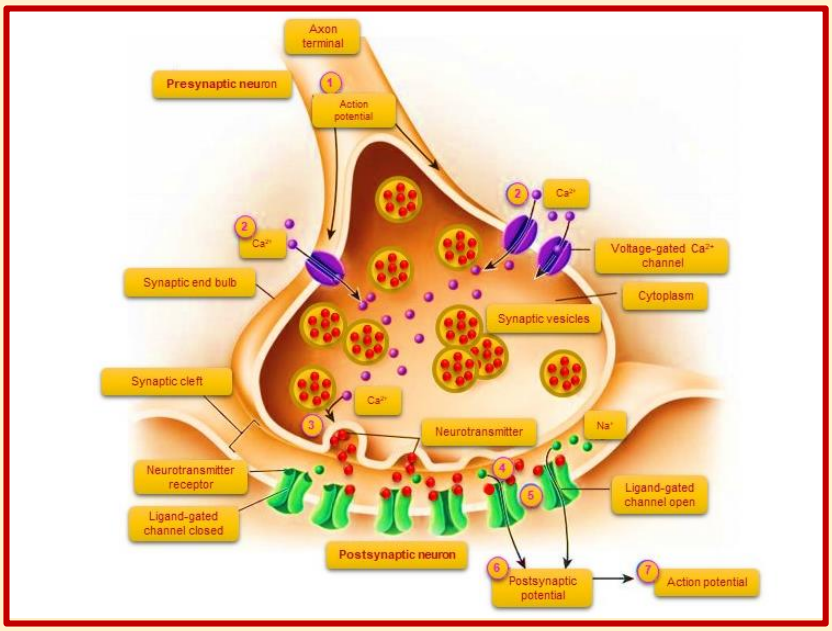

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Figure 2. Schematic drawing of a synapse between two neurons. 1) The action potential arrives at axon terminal; 2) action potential stimulates voltage-gated Ca^{2+} channel open and Ca^{2+} enters the cell; 3) Ca^{2+} stimulates the vesicles containing neurotransmitter to fuse with the cell membrane and release the neurotransmitter into the small synaptic cleft between cells; 4) neurotransmitter molecules cross the synaptic cleft and bind to neurotransmitter receptors known as ligand-gated ion channels (LGICs) on the postsynaptic neuron; 5) transduction of the neurotransmitter chemical signal into an electrical response; 6) the receptor activation leads to an influx of sodium into the cell, causing the membrane potential to depolarize, bringing it nearer to the action potential threshold; 7) postsynaptic potential fires an action potential.

Two types of neurotransmitter receptors exist: ligand-gated ion channels (LGIC), which permit rapid ion flow directly across the outer cell membrane, and G-protein–coupled receptors (GPCRs), which set into motion chemical signaling events within the cell (Figure 3). Several molecules are known to act as neurotransmitters in the brain. Neuronal development and function also are affected by peptides known as neurotrophins and by steroid hormones.

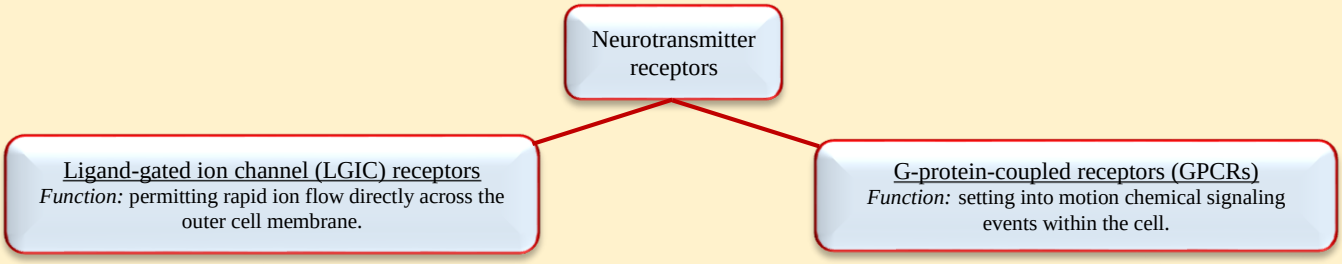

Figure 3. The two major classes of neurotransmitter receptors.

The synaptic transmission is mediated by LGICs and behaves as excitatory or inhibitory, depending on whether their net effect is to make it more or less likely that the postsynaptic neuron will fire an action potential.[8,9] The strong excitatory synaptic transmission allows positively charged ions to flow across the membrane, leading to an influx of sodium into the cell. This event causes the membrane potential to depolarize, bringing it nearer to the action potential threshold. Whereas, inhibitory synaptic transmission usually is mediated by receptors with channels permeable to negatively charged ions (usually chloride). GPCRs are specialized for binding the neurotransmitter molecule and subsequently producing intracellular biochemical reactions *via* G-proteins, that can influence a variety of cellular functions. The synaptic transmission mediated by GPCRs often is termed neuromodulatory.
Neurotransmitters are rapidly removed from the synapse after their release to produce short and discrete synaptic signals. Most synapses in the brain contain neurotransmitter transporters that mediate this removal and directly reloaded them into vesicles at the presynaptic terminal.[9] In some cases, however, non-neuronal support cells, such as glial cells, participate in such removal, or enzymes that degrade the neurotransmitter to constituent molecules that do not themselves activate receptors.

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Other associated chemical substances include steroid hormones and neurohormones, which are involved in intercellular communication, and have a variety of actions in the body and brain. For example, corticosteroids are released from the cortex of the adrenal glands located on top of the kidneys in response to external stress and are carried by the bloodstream to their sites of action throughout the body and brain.[10] The neurohormones are synthesized in neurons and secreted into the bloodstream which carries them to distant tissues. The best example is the hypothalamic releasing hormone oxytocin. Oxytocin stimulates uterine contractions to speed up the process of childbirth and fosters the bond between mother and child immediately following birth.[11]

3. Neurotransmitters

A wide variety of small organic molecules, amino acids, or peptides serve as neurotransmitters, engaged in many functions of the nervous system and influencing bodily functions.[9] This section focuses on discussing specific neurotransmitter molecules, that play a key role in the human nervous system. Figure 4 depicts their chemical structures.

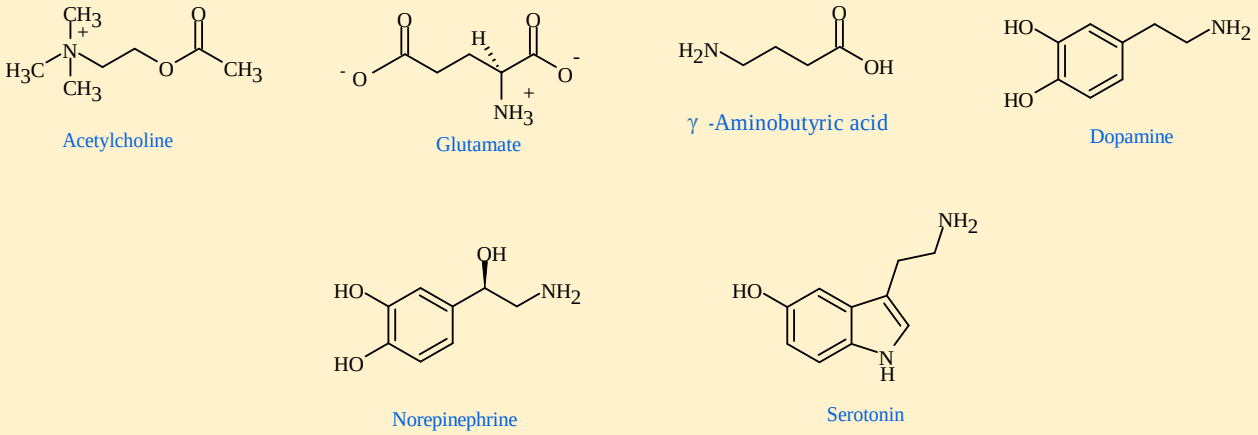

Figure 4. The structures of key neurotransmitters in the brain.

3.1. Acetylcholine (ACh)

Acetylcholine is the neurotransmitter at neuromuscular junctions, at synapses in the ganglia of the visceral motor system, and at a variety of sites within the CNS. It is the chemical that motor neurons of the nervous system release in order to activate muscles. In the brain, ACh functions as a neurotransmitter and as a neuro-

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modulator. The brain contains a number of cholinergic areas, each with distinct functions; such as playing a key role in attention, memory, arousal and motivation.[12] ACh plays a vital role in the normal functioning of muscles, and regulates the sleep cycle.
It is synthesized in nerve terminals from acetyl coenzyme A and choline in a reaction catalyzed by choline acetyltransferase. Choline is present in plasma, and is taken up into cholinergic neurons by a high-affinity Na^+/choline transporter. ACh are packaged into vesicles by a vesicular ACh transporter. ACh exerts its effect by binding to and activating its specific receptors, nicotinic and muscarinic. The postsynaptic action of ACh at many cholinergic synapses are not terminated by reuptake, but by a powerful hydrolytic enzyme, acetylcholinesterase (AChE). This enzyme is concentrated in the synaptic cleft, ensuring a rapid decrease in ACh concentration after its release from the presynaptic terminal. AChE has a very high catalytic activity, and hydrolyzes ACh into acetate and choline.[13]

3.2. Glutamate (Glu)

Glutamate is the key excitatory neurotransmitter in the brain, mediating the rapid synaptic excitation of almost brain neurons. Such the rapid synaptic excitation resulted by Glu involves the activation of three major subtypes of LGICs: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)*-, kainate-, and *N*-methyl-D-aspartic acid (NMDA)*-type.
At excitatory synapses, Glu released from presynaptic vesicles crosses the synapse and binds to AMPA-type glutamate receptors, which activates the ion pore intrinsic to this protein and produces a rapid depolarization of the postsynaptic neuron that increases the probability that this neuron will fire an action potential.
At most glutamatergic synapses, the NMDA-type glutamate receptors perform the same function as AMPA receptors, in which the invasion of the pre-synaptic terminal by an afferent action potential releases Glu into the synaptic cleft, followed by binding of glutamate to NMDA receptors on postsynaptic neuron. However, this event alone does not open the NMDA receptor's intrinsic cation channel, since at near-resting membrane potentials, the channel is blocked by magnesium ions.[14] Only when the depolarization of post-synaptic cell is sufficiently strong, the NMDA receptor pore will become unblocked, and ion flux through this receptor-channel also can participate in activating the postsynaptic neuron. The ion pore of the NMDA receptor is especially permeable to calcium ions that can activate a variety of intracellular signaling cascades, including protein kinases.[8,9]
The AMPA and NMDA receptors have crucial roles in producing long-lasting changes in synaptic function belonging to the molecular mechanisms of learning and memory, such as long-term potentiation.
Glu also can activate GPCRs known as metabotropic glutamate receptors (mGluRs).[9] Eight mGluRs are known to exist and can be separated into three groups termed I, II, and III. The group I mGluRs couple through the G_q-type G-protein subtype to activate phospholipases enzymes.

* Both of AMPA and NMDA are specific agonists (molecules) that bind and activate specific receptor.

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These receptors mainly are on postsynaptic structures, where they serve to activate intracellular signaling that modifies ion channel function and biochemical processes including the generation of second messengers** from cell membrane lipids. The group II and III mGluRs couple to $G_{i/o}$-type G-proteins. Members of these latter two mGluR subgroups reside predominantly on presynaptic axon terminals, where they act to inhibit neurotransmitter release.[15]

3.3. The neurotransmitter γ-aminobutyric acid (GABA)

GABA is a main inhibitory neurotransmitter, which mediates the majority of fast synaptic inhibition in the brain, specifically through activation of $GABA_A$ receptors. The intrinsic ion channel contained in the $GABA_A$ receptor protein is permeable to Cl^- and other anions. Activation of the receptor can hyperpolarize neurons through the influx of negative charges at membrane potentials below the threshold for action potential generation. This inhibition generally counteracts the effect of Glu and other depolarizing, excitatory synaptic influences. $GABA_A$ receptors are formed by the confluence of five subunit proteins: two α-, two β-, and one γ-type. There are 20 subunits in the brain, which each of them has a slightly different amino acid sequence.[16] The $GABA_A$ receptor channel contains numerous sites for allosteric modification. GABA also can act through a GPCR, the $GABA_B$ receptor, which acts to inhibit neuronal activity.[8]

3.4. Dopamine

The neurotransmitter dopamine has a large impact on brain function, including brain mechanisms of reward, evaluation of environmental stimuli, general behavioral activity levels, and disorders such as Parkinson's disease and schizophrenia.[9] Dopamine acts exclusively as a neuromodulator *via* activation of GPCRs. There are five dopamine receptors that is classified into two subclasses: those that activate G_s/G_{olf}-type G-proteins (D1 and D5) and those that activate $G_{i/o}$-type G-proteins (D2-4).[17] In general, the two classes of receptors produce separate, and often opposing, effects on neuronal physiology. Dopamine, working through these two receptor subtypes, has key roles in controlling performance of actions.

3.5. Serotonin

The neurotransmitter serotonin, 5-hydroxytryptamine (5 HT), is made by small discrete clusters of neurons located at the base of the brain. These serotonergic neurons connect to other neurons located throughout the

** A second messenger system is a method of cellular signaling, whereby a diffusible signaling molecule is rapidly generated/released which can then go on to activate effector proteins within the cell to exert a cellular response.

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CNS, which has the capacity to influence a variety of brain functions including sensations related to environmental stimuli, pain perception, learning and memory, as well as sleep and mood. The brain has 15 serotonin-activated GPCRs, which activate a wide variety of G-protein subtypes.[18] Different subtypes of these GPCRs are found on presynaptic and postsynaptic neuronal structures in different brain regions. By activating these receptors, serotonin can enhance or inhibit neurotransmitter release at certain synapses and can produce slow hyperpolarizing or depolarizing synaptic responses at others. Intracellular signaling *via* serotonin-activated GPCRs also can influence the function of intracellular enzymes as well as alter gene expression.
Serotonin also can activate a single type of LGIC-type neurotransmitter receptor, *i.e.* 5-HT_3 receptor.[19] This receptor contains a channel that is permeable to positively charged cations and thus produces fast activation of neurons when bound to serotonin. Activation of these presynaptic 5-HT_3 receptors leads to a rapid release of GABA that will then inhibit downstream neurons.

3.6. Norepinephrine

Norepinephrine, also known as noradrenaline, is an excitatory neurotransmitter used by the sympathetic nervous system, and produced by the brainstem, hypothalamus, and adrenal glands, and release into the bloodstream. The noradrenergic neurons in the brain form a neurotransmitter system, that, when activated, exerts effects on large area of the brain. These effects are manifested in alertness, arousal, and readiness for action. The important source of norepinephrine in the brain is locus coeruleus, which sends projections to every part of the brain and the spinal cord.[20] Norepinephrine has been implicated in mood disorders such as depression and anxiety, in which case its concentration in the body is abnormally low.

4. Neurotrophins

In addition to neurotransmitters that alter neuronal physiology, intracellular signaling, and gene expression on a relatively fast time scale, a variety of neurotrophins in the brain can also be secreted by neurons that act as growth factors. They play pivotal roles in the formation and plasticity of neuronal networks.[21]
Neurotrophins are homodimeric polypeptide, which are thought to be secreted from different neuronal structures, including both axon terminals and dendrites.[22] They include nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), neurotrophin-4/5 (NT-4/5).
There are two different classes of neurotrophin receptors, a low-affinity transmembrane glycoprotein, a non-selective pan-neurotrophin receptor, $p75^{NTR}$, which serves as a common receptor for all the known neurotrophins, and a high-affinity receptor, which belongs to the tropomyosin-related kinase (Trk) family, having a tyrosine kinase activity, and is different for each neurotrophic factor.[22] (Trk) family consists of TrkA, TrkB, and TrkC, and together with the neurotrophic factors play critical roles in tumor progression and/or suppression in various cancers.[23]

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4.1. Structure, associated ligands, and signaling pathway of neurotrophin receptors

The $p75^{NTR}$ is a type I transmembrane protein, with a molecular weight of 75 kDa, which consists of an extracellular domain, a transmembrane domain and an intracellular domain.
The extracellular domain of $p75^{NTR}$, which can bind to NGF, BDNF, NT-3, and NT-4, has a stalk domain connecting the transmembrane domain and four cysteine-rich regions which are negatively charged, a property that facilitates neurotrophin binding (Figure 5A). The intracellular part is a global-like domain, which consists of two sets of perpendicular helixes arranged in sets of three. It connects the transmembrane domain through a flexible linker region N-terminal domain.[24]
Each of the Trk receptors consists of an extracellular domain, a transmembrane region and an intracellular region containing the tyrosine kinase domain. The extracellular domain contains a cysteine-rich cluster followed by three leucine-rich 24-residue repeats (LRR1–3), another cysteine-rich cluster and two immunoglobulin-like domains (Figure 5B). The intracellular region contains five key tyrosine residues: three within the activation loop of the kinase domain, which are necessary for full kinase activity, and two on either side of the tyrosine kinase domain, which serve as phosphorylation-dependent docking sites for cytoplasmic adaptors and enzymes.[25,26] Each of the four neurotrophins have specificity for a particular Trk and bind to it with high affinity. NGF binds to TrkA, both BDNF and NT-4 bind to TrkB, and NT-3 binds to TrkC. The NT-3 can bind to all three Trk receptors but has highest affinity for TrkC and is its sole ligand.[26]
Upon neurotrophin binding, the Trk receptors are activated, setting into motion a variety of signaling mechanisms, which some of these signaling pathways have effects locally within a particular subcellular compartment. Other signals (e.g., those involving transcription factors) are transmitted to the nucleus. There is evidence that neurotrophin-bound Trk receptors are internalized and translocated to the nucleus, where they can participate in signaling that regulates gene expression.[27] Internalization of neurotrophin-bound receptors also is believed to be a major mechanism by which the neurotrophins are removed from the extracellular space and ultimately degraded by intracellular peptidases. The diversity of signaling pathways activated by Trk receptors allows them to participate in a variety of neuronal functions, including not only cell survival and growth but also synaptic formation and plasticity, and axon and dendrite growth.[8]
The cytoplasmic domains of Trk receptors contain several sites of tyrosine phosphorylation that recruit intermediates in intracellular signaling cascades. As a result, Trk receptor signaling activates several small G proteins, including Ras, Rap-1, and the Cde-42-Rac-Rho family, as well as pathways regulated by MAP kinase, PI 3-kinase and phospholipase C-γ (PLC-γ) (Figure 5). Interestingly, Trk receptor-mediated signaling interplays with signaling promoted by the pan-neurotrophin receptor $p75^{NTR}$. $p75^{NTR}$ activates a distinct set of signaling pathways within cells that are in some instances synergistic and in other instances antagonistic to those activated by Trk receptors. Several of these are pro-apoptotic but are suppressed by Trk receptor-initiated signaling. $p75^{NTR}$ also influences the conformations of Trk receptors; this modifies ligand-binding specificity and affinity with important development consequences.[21]

Two types of neurotrophins thought to be most heavily involved in neurodegenerative diseases (*i.e.* NGF and BDNF) and are briefly discussed in the following section.

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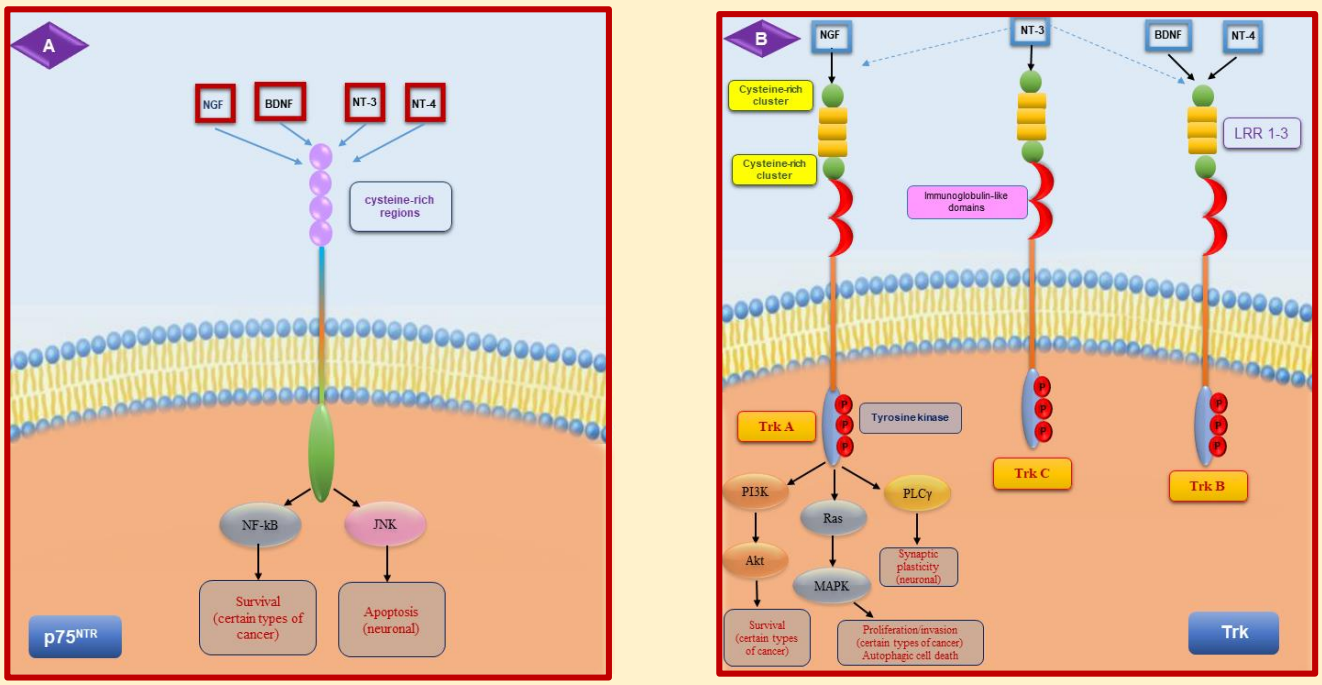

Figure 5. The molecular structures and signal transduction of $p75^{NTR}$ and Trk receptors. A) Neurotrophins binding to $p75^{NTR}$ receptor activate a range of intracellular signaling proteins including nuclear factor-kappa B (NF-κB), and N-terminal kinase (JNK), which are thought to be the predominant downstream factors involved in $p75^{NTR}$ signalling. B) Neurotrophins binding to Trk receptors activate a variety of intracellular signaling proteins, which, in turn, activate transcription factor proteins that act on the nucleus to alter gene expression, as well as promote the growth and differentaition of neuron. Activation of neurotrophin-Trk-intracellular signaling pathways also promotes long-lasting plasticity of synaptic transmission. Both receprtors along with the neurotrophic factors are involved in tumor progression and/or suppression in certain types of cancers.

4.2. Nerve growth factor (NGF)

Nerve growth factor (NGF) is one of the most important biologically active molecules in the nervous system. It activates signaling that regulates cell growth, survival of sympathetic and sensory nerves, and plays a crucial role in promoting brain development, damage nerve regeneration and functional recovery, as well as promotion of the germination of nerves. NGF is the prototypical neurotrophin that defines the properties and functions of the class of growth factors. NGF is synthesized and released from target tissues in both the peripheral (PNS) and the central nervous systems (CNS). In the PNS, the target tissues are typically non-neuronal cells while in the CNS, the targets are neurons such as the sympathetic, sensory, and cholinergic basal forebrain neurons.[28]

It is synthesized as a precursor pro-NGF that is further processed to a mature polypeptide, and each form has distinct activities. ProNGF contains a potential *N*-glycosylation site, which helps to secrete the endoplasmic

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reticulum. ProNGF undergoes post-translation modifications at the N-terminus and C-terminus to form biologically active mature NGF. There are 6 cysteine residues in the mature NGF chain, which can form 3 pairs of intra-chain disulfide bonds. The formation of disulfide bonds is a necessary condition for NGF to be activated.

The biological action of NGF is mediated by both of TrkA and $p75^{NTR}$. Binding of NGF to $p75^{NTR}$ activates additional signaling pathways that, in the absence/reduced expression of coexpressed TrkA on NGF-target cell, might trigger apoptosis. The effect of NGF on target cells depends on the ratio of these two receptors co-distributed on cell surface. Thus, the reduced transport of NGF, produced by NGF-target/innervated tissues can lead to damage of nervous cells, as observed in peripheral neuropathies.[28]

NGF expression in the brain has a wide range of protective effects: i) enhancing the activity of free radical scavenger such as glycopeptide peroxidase, which reduces the damage of ischemic nerve cell, and increasing the activity of catalase, superoxide dismutase, and glutathione,[29-31] ii) antagonizing the neurotoxicity of excitatory amino acids by regulating the cytoplasmic Ca^{2+} levels in neurons through various ways and means, thereby protecting the injured neurons and inhibiting programmed cell death, and iii) increasing cerebral blood flow and improving damage caused by cerebral ischemia.

4.3. Brain-derived neurotrophic factor (BDNF)

Brain-derived neurotrophic factor (BDNF) is vital to the survival, growth, and maintenance of neurons in key brain circuits involved in emotional and cognitive function. However, BDNF might be partly responsible for degenerative processes of certain disorders, as evidenced by the abnormal BDNF levels in the brains of patients with neurodegenerative disorders, e.g. Huntington's Disease. Furthermore, circulating concentrations of brain-BDNF have been linked to certain types of cancer.[32] The synthesis of BDNF occurs in both the central and peripheral nervous system by target neurons under physiologic conditions and by astrocytes following injury, inflammation, or administration of antidepressants.[33] In the brain, neurons are considered a significant cellular source of BDNF, and synthesis occurs in regions that participate in emotional and cognitive function (e.g., hippocampus and frontal, parietal, and entorhinal areas). Several brain regions retrogradely transport BDNF from their projection areas.

BDNF is synthesized as a precursor (pre-pro-BDNF protein) that results from cleavage of a 32 kDa pro-BDNF protein. Pro-BDNF can be proteolytically cleaved intracellularly by enzymes (e.g., PC7, furin, and proconvertases) and secreted as the 14 kDa mature form or it can be secreted as pro-BDNF and subsequently cleaved extracellularly by proteases (e.g., metalloproteinases and plasmin). Both forms of BDNF (pro-BDNF and mature) are sorted and packaged into vesicles for activity-dependent secretion. Pro-BDNF can be internalized and stored by astrocytes and later released as the immature (pro-BDNF) or mature (BDNF) form.

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Pro-BDNF mediates its biological actions through binding to low-affinity $p75^{NTR}$ receptors, whereas mature BDNF binds with higher-affinity Trk-B receptors. Once bound to its cognate receptors, BDNF is internalized along with its receptor and transported *via* retrograde axonal transport mechanisms to the soma wherein it can initiate a multiplicity of effects within the nucleus.[34]
The functional importance of differential binding to either $p75^{NTR}$ or Trk-B receptors is underscored by their opposing effects. Pro-neurotrophin binding to $p75^{NTR}$ reduces spine complexity and density, induces long-term depression (LTD), promotes neuronal cell death, and facilitates the resculpting of neuronal circuits. These biological actions are accomplished via activation of a receptor complex that is composed of $p75^{NTR}$ and sortilin. In contrast, mature neurotrophin binding to Trk-B receptors increases cell survival and differentiation, dendritic spine complexity, long-term potentiation (LTP), synaptic plasticity, and the resculpting of networks.[34] Localization of Trk-B receptors significantly increases at synaptic sites following neuronal activity.

5. Some factors that cause brain disorders

Among the various factors that cause brain disorders include: i) the spatial patterns of dendrites that affects the formation of neural networks and neural functions; ii) the abnormal phosphorylation of the tau protein[35,36] and iii) mutant huntingtin protein, which is the most disruptive to nerve cells, causes Huntington's disease (HD) and neurodegeneration. These factors are discussed in short further.

5.1. Shaping the dendritic morphology

The spatial patterns of dendritic morphology determine the number and patterns of synapses received by individual neurons and the efficacy with which synaptic information is transmitted to the soma. The growth of the dendritic arbor is a dynamic process that is regulated by various environmental cues, including synaptic activity and molecular signals from adjacent cells.[37,38] Several neuronal functions are regulated by inositol 1,4,5-trisphosphate (IP_3) receptors (IP_3Rs) including synaptic plasticity, axonal extension, and nerve growth cone guidance.[38-40] IP_3, as an intracellular second messenger, is produced as a result of the hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP2) in response to cell surface receptor activation. IP_3 mediates the release of Ca^{2+} from intracellular Ca^{2+} storage organelles, mainly the endoplasmic reticulum, by binding to its receptor (IP_3R). In these IP_3/Ca^{2+} signaling cascades, IP_3R works as a signal converter from IP_3 to Ca^{2+}.[41] Three different IP_3R subtypes have been identified, and are capable of forming homo- and heterotetramers: IP_3R1, IP_3R2, and IP_3R3, with IP_3R1 being the predominant subtype in the central nervous system (CNS), especially in cerebellar Purkinje cells. The growth of dendritic arbor of Purkinje cells, which they interact with other neurons such as parallel fibers, is essential for cerebellar function.

It is known that BDNF production by AMPA receptor (AMPAR) stimulation is further augmented by costimulation with metabotropic glutamate receptor (mGluRs).[42,43] Furthermore, stimulation of AMPA receptor increases the cytosolic Ca^{2+} concentration *via* depolarization induced Ca^{2+} entry, which facilitates the activation of Ca^{2+}-dependent proteins, PLC and IP_3Rs, that function under mGluR signal pathway.[44] It

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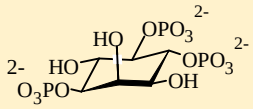

The inositol trisphosphate trianion (IP_3)

has been shown that activation of AMPAR and mGluR increases BDNF expression through IP_3R1-mediated signaling in cerebellar granule cells, which contributes to the dendritic outgrowth of Purkinje cells intercellularly, possibly by modifying parallel fiber-Purkinje cell (PF-PC) synaptic efficacy.[45]

To gain an insight into regulation of the IP_3/Ca^{2+} signaling pathway, I briefly focus on the activation of IP_3R in the following section.

5.1.1. Activation of IP_3Rs

IP_3R is a tetrameric intracellular IP_3-gated Ca^{2+} release channel with reversible transition between two distinct structures, windmill and square structure, and is predominantly localized in the endoplasmic reticulum (ER).[46] IP_3, produced by phospholipase C after cell activation by hormones, growth factors or neurotransmitters, diffuses into the cytosol, binds to and activates the IP_3R, leading to Ca^{2+} release from the ER. The three IP_3R isoforms demonstrate different IP_3- binding affinities and sensitivity.
The IP_3R proteins are structurally and functionally divided into 5 distinct domains: the N-terminal coupling domain (suppressor domain), the IP_3-binding core, the internal coupling domain (the modulatory and transducing domain), the channel-forming domain with six membrane-spanning regions, and the C-terminal coupling domain (the gatekeeper domain).[47] Residues 226-578 of IP_3R1 subtype are assigned to the IP_3 binding core, leading to activation of IP_3R1, and inducing a substantial conformational change, which may cause channel opening. In addition to this channel opening, such IP_3-induced conformational change has been assumed to be responsible for degradation of IP_3R.[47]
The increase in the cytoplasmic Ca^{2+} concentration resulting from IP_3R activation regulates a wide variety of cellular processes, such as synaptic plasticity, secretion, proliferation, differentiation, fertilization, development and cell death.[41,48] Such a complex regulation of Ca^{2+} signals has been to some extent attributed to the diversity of IP_3R isoform expression, assembly of heterotetrameric complexes of IP_3R isoforms, subcellular distributions of IP_3R, and regulation of IP_3R by Ca^{2+} itself, ATP, and phosphorylation. IP_3R channels are also regulated by their interacting proteins, such as calmodulin dependent protein kinase, and other regulatory protein.[47] These protein-protein interactions regulate the IP_3/Ca^{2+} signaling pathway and contribute to the specificity of intracellular Ca^{2+} dynamics.
IP_3R isoforms have multiple consensus sites for phosphorylation and several docking sites for protein kinase and phosphatases on their sequences. For example, Ca^{2+}/CaM-dependent protein kinase II (CaMKII) is a serine/threonine kinase, that existed at a slightly percentage compared to all proteins in the brain, and is highly sensitive to Ca^{2+} and calmodulin. CaMKII plays a role in neurotransmitter secretion, transcription factor regulation, and glycogen metabolism. Colocalization of CaMKII and IP_3R induces phosphorylation of

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IP_3R in N-terminal region, which, in turn, significantly reduces the open probability in lipid bilayers. Such an event may indicate that CaMKII acts negatively on Ca^{2+} oscillations.[49]

5.1.2. Regulation of intracellular Ca^{2+} concentration

The charged ions have low solubility in the hydrocarbon core of the phospholipid bilayer of plasma membrane, thereby having low permeability coefficients across the bilayer. Due to a large difference in the electric potential between the two sides of the membrane, the passage of ions across the membrane and equilibrated both its sides is achieved through ion channels, which is basically a fluid-filled hole in the membrane through which the charged ions can pass, and ion pumps like Na^+/K^+ pumps. Opening and closing of the ion channel is usually controlled chemically or mechanically. Depending on the type of ion channel, its conformational change may occur because of changes in the membrane potential (voltage-gated channels), ligand binding (chemical activation) or ligand-driven stretching of the membrane (stretch-activated ion channels). Body response to the external stimuli can be linked to the regulation of ion channel activity. Ion channels play a vital role in different physiological processes, such as flow of nerve impulses, muscle contraction, cell division and hormone secretion.[50] The intracellular concentration of Ca^{2+} depends on electrical gradients driven in turn by Na^+ and K^+ channels.

Na^+ ions are mainly present at high concentrations outside the cell, unlike K^+ ions that are present at high concentrations inside the cell. Gradients for these cations across the cell membrane provide the energy source for action potentials generated by opening of Na^+ and K^+ channels, and for transporting solutes and other ions across the cell membrane *via* coupled transporters. The cytosol is surrounded by two big Ca^{2+} stores: the extracellular space, where the Ca^{2+} concentration is ~ 1.8 mM, and the sarco-endoplasmic reticulum, where the Ca^{2+} concentration varies from 300 μM to 2 mM.[50,51]

There are four main types of Ca^{2+} channels including voltage-activated, receptor-activated, store-operated and second messenger-operated channels. Receptor-activated, store-operated and second messenger-operated channels are ubiquitous, whereas voltage-activated calcium channels are specific for excitable cells. Voltage-activated calcium channels open when the plasma membrane is depolarized. Receptor-activated calcium channels open when a ligand binds to the channel, whereas store-operated calcium channels, and archetype calcium release-activated channels are activated when the level of Ca^{2+} within the lumen of the ER decreases below a threshold level.[50] Another type, second messenger-operated channels (e.g., arachidonic acid-regulated Ca^{2+} current) are activated by intracellular second messengers like arachidonic acid.

Neurons are excitable cells, so Ca^{2+} depends on the voltage-activated channels, whereas the other channels play an important role, especially in case of immune cells, in keeping Ca^{2+} at an optimal level in order to maintain the cellular functions in parallel with Na^+/K^+ pumps.[52] When an action potential reaches the axon terminal and stimulates an increase in the concentration of calcium, this ion stimulates, in turn, the vesicle to fuse with the cell membrane and release the neurotransmitter into synapses. The time between neurotransmitter binding and opening of the voltage-activated channel is on the order of microseconds to milliseconds. Thus, at synapses using receptor-activated channels, the time between action potential depolarization of the axon terminal and the beginning of the current flowing through the postsynaptic LGIC is a matter of 1 to 2 milliseconds. This type of synaptic transmission produces a rapid and strong influence on postsynaptic neuron function.[8]

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5.2. *The tau protein*

The tau protein is microtubule-associated protein located primarily in neuronal axons. The protein is recognized as a multifunctional molecule that interacts with microtubules in addition to actin, and is involved in the organization of the cytoskeletal network. Tau binds with tubulin, through its carboxy-terminal assembly domain, to promote aggregation and assembly to form microtubules in a dynamic stability manner, exerting important roles for axonal transport and function.[53] Tau consists of four parts: the N-terminal region, the proline-rich domain, the microtubule-binding domain, and the C-terminal region. Tau is a phosphoprotein with a wide variety of phosphorylation sites. Most of these phosphorylation sites exist in the proline-rich middle region.[54] This region contains multiple threonine-proline or serine-proline motifs that are the targets of proline-directed kinases.[55] Hyperphosphorylated tau leads to aggregation, which, in turn, can assemble into paired helical filaments and eventually form neurofibrillary tangles, affecting excitatory postsynaptic currents, as manifested in the neuropathological changes that are found in patients with Alzheimer's disease (AD).[56]
Tau dramatically induces an increase in the viscosity of actin filaments, and has the ability to bundle microfilaments. In addition, tau induces changes in the organization and stability of neuronal actin filaments. There are evidences that both the proline-rich domain and the microtubule-binding domain are involved in the association of tau with actin.[57] Tau also has the potential for liquid-liquid separation and does so under the control of its phosphorylation state, where proline-rich domain is considered as the regulator of condensate formation.[58] Such condensates can create finely tuned molecular locales to regulate cellular architectures under the control of microtubules. In numerous neurodegenerative conditions, tau undergoes a liquid-to-solid phase transition, most prominently Alzheimer's disease.

5.3. *Mutant huntingtin protein*

Mutant huntingtin (mHTT) protein contains an expanded polyglutamine tract and causes neuronal dysfunction and death, producing the progressive and ultimately fatal combination of behavioral, cognitive, and motor symptoms that characterize Huntington's disease (HD).[59] The normal huntingtin protein (HTT) contains 10-35 glutamines, and acts as a signaling scaffold for cellular processes, including autophagy, vesicle transport, and mitotic spindle orientation.[60] In contrast, mHTT contains 40 or more glutamine repeats, resulting from the genetic mutation, *i.e.* the cytosine-adenosine-guanine (CAG) trinucleotide repeat expansion in protein-coding segments of *HTT* gen. HTT is ubiquitously expressed protein, but the mutant form of the protein causes toxicity mainly in the brain, leading to neuronal dysfunction and cell loss. The neuropathology in HD is characterized by neuronal death in the striatum, the cerebral cortex, and the hypothalamus.[61]

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6. Hypothetical scenarios targeting some of brain disorders

In view of the aforementioned brief overview, there are some major causes leading to neurological disorders: i) although IR_3R plays a vital role in the regulation of several neuronal functions, its hyperphosphorylation, as a result of its multiple consensus sites for phosphorylation, leads to reduce the open probability of the channels, which, in turn, negatively impacts Ca^{2+} oscillations; ii) activation of IP_3R occurs *via* its binding to IP_3, leading to Ca^{2+} release, as well as its conformational change, which is supposed to lead to its degradation; iii) generated the action potential takes place by changing the electrical gradients across the cell membrane *via* opening of Na^+ and K^+ channels resulting in depolarization of the membrane and opening of voltage-gated calcium channel. Consequently, irregular opening of Na^+ and K^+ channels leads to devastated consequences.; iv) hyperphosphorylation of tau protein leads to formation neurofibrillary tangles, which affect excitatory postsynaptic currents; v) the abnormal regulation of proline-rich domain of tau, as a result of the hyperphosphorylation, causes the protein to lose its tenability locals, and undergoes a liquid-to solid phase transition, which negatively affects the cellular architectures; and vi) the genetic mutation of huntingtin protein causes neuronal dysfunction mainly in the brain.
Aside from neurological disorders, IP_3R also play an important role in several different cancers and gynecological disorders due to increased circulating BDNF concentrations relative to controls.[62] It is known that AMPAR and mGluR cooperatively activate the signaling pathway for IP_3R-mediated BDNF production.[45]
Therapeutic intervention targeting these disorders confronts three barriers belonging to the function and regulation of CNS: the cerebral microvascular endothelium (blood–brain barrier, BBB), the choroid plexus epithelium (blood–cerebrospinal fluid barrier), and the avascular arachnoid epithelium (cerebrospinal fluid–blood barrier). As a result of these natural barriers, particularly the BBB, transporting the drug molecules into the brain tissue makes them extremely difficult. Thus, it is important to shed the light on BBB.

6.1. The Blood-Brain Barrier

The blood-brain barrier (BBB) intricately regulates the movements of ions, nutrients, and cells between the blood and the brain. The BBB consists of cerebral endothelial cells, pericytes, astrocytes, and basement membrane (Figure 6). The BBB acting together with neurons and glial cells forms the complete neurovascular unit (NVU) which is crucial for the function of the brain.[63]
The cerebral endothelial cells are non-fenestrated, contain a large number of mitochondria, and form tight junctions that highly regulate the molecule transport across the endothelium. The inter-endothelial space is characterized by the presence of transmembrane protein complexes composed of occludin, claudin, and junction adhesion molecules. These specialized tight junction proteins undertake homophilic interactions to form an intricate tight barrier that is exclusive to the cerebral endothelial cells. Pericytes are smooth muscle cells that regulate the activity of endothelial cells. While astrocytes have a characteristic star-shaped morphology and play a crucial role in enhancing the BBB integrity. The astrocytes secrete soluble factors, such as β-2 microglobulin and transforming growth factor beta (TGF-β), which upregulate the expression level of tight junction proteins on endothelial cells.[63]

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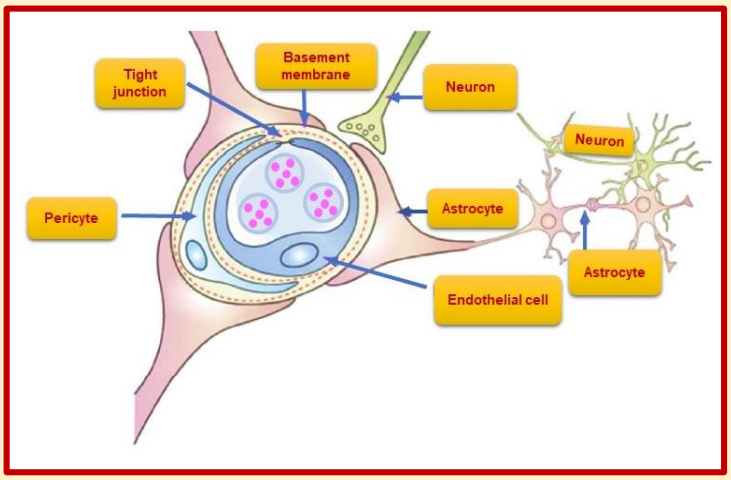

Figure 6. Schematic drawing of the neurovascular unit. The endothelial cells are interconnected via tight junctions, while the basement membrane (basal lamina) surrounds the endothelial cells and embeds pericytes that span several endothelial cells. Astrocytic end-feet are in contact with the endothelial cells. On the luminal side of the endothelium, ligands bind to the receptors on the plasma membrane and are internalized through the formation of vesicles. These vesicles are subsequently transported through the cytoplasm of the cells and then release the ligands on the basolateral side.

The Transport Mechanism

Transport of substances through endothelial cells can be broadly divided into two categories: paracellular and transcellular pathways. The paracellular pathway involves the transport of molecules through the intracellular space between the cells. The transport through the paracellular pathway is strictly limited in the BBB due to the presence of tight junctions which forces the majority of the transport through transcellular pathways. Substances are transported through the BBB via one of the three following transcellular pathways: carrier-mediated transcytosis, receptor-mediated transcytosis, or adsorptive-mediated transcytosis.[63]

Carrier-mediated transcytosis

Transporter protein carriers located on the luminal and basolateral sides of the endothelial cells are named nutrient and efflux transporter proteins, respectively. Nutrient transporter proteins are specific to solutes such as glucose, hormones, and amino acids. These solutes bind to their respective transporter proteins triggering a reversible conformational change. Upon cellular uptake of the solutes, they are transported to the basolateral side of the membrane, following high to low solute concentration gradient. On the other hand, a diverse range of ATP-binding cassette transporters or efflux pumps are employed to actively transport non-specific substrates and drugs out of the endothelial cells. These efflux pumps are found on the luminal side of the brain capillaries and bind to a variety of substrates, and they effectively prevent drug accumulation in endothelial cells and hamper the transport of drugs to the brain.[63]

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Receptor-mediated transcytosis

Cerebral endothelial cells express highly specialized receptors for macromolecules such as hormones, enzymes, and plasma proteins. On the luminal side of the endothelium, ligands bind to the receptors on the plasma membrane and are internalized through the formation of vesicles. These vesicles are subsequently transported through the cytoplasm of the cells and then release the ligands on the basolateral side. The internalization of cargos through endocytosis can occur via clathrin- or caveolin-dependent pathways. Transcytosis of most ligands follows the clathrin-dependent pathway. Only a few compounds, such as folate, undertake the caveolin-dependent pathway that is mediated by the caveolin protein and results in the formation of uncoated vesicles. However, this pathway is more relevant to leaky BBB in neurological diseases.[63]

Adsorptive-mediated transcytosis

Substrates that are positively charged can undertake adsorptive-mediated transcytosis. It is triggered by electrostatic interactions between the positively charged substrate surface, usually polycationic proteins and the negatively charged heparin sulfate proteoglycans present on the plasma membrane surface of the endothelial cells. This is a relatively slower process in comparison to carrier- or receptor-mediated transport and has a lower transport capacity.[63]

In the light of the above discussion, some hypothetical scenarios are proposed, that may pave the way for discovering appropriate drug molecules for some of the neurological disorders.

6.2. Targeting the hyperphosphorylation of IP_3R and tau protein

The inhibition of IP_3 production may be an option to control the hyperactivity of IP_3R. Furthermore, hydrolysis of the proline-rich middle region of tau protein, which contains multiple threonine-proline or serine-proline motifs that are the targets of phosphorylation, may be an effective means of reducing the aggregation of the protein, which, in turn, inhibits the formation of neurofibrillary tangles.

As a hypothetical scenario, the use of cobalt nanoparticles (Co NPs) with appropriate capping agents may have the ability to coordinate with phosphate groups of IP_3 as well as the bond hydrolysis of threonine-proline or serine-proline of the tau protein, leading to restricted phosphorylation sites. In addition, Co NPs may exert electrocatalytic activity on the electrical gradients across the cell membrane, which, in turn, may induce depolarization of the membrane and assist the opening of the voltage-gated channels.
On the other hand, Co NPs may occlude glutamines from further mutation through interaction with their amino groups. Besides, they may exert hydrolytic activity on the cytosine-adenosine-guanine (CAG) trinucleotide. In fact, the hydrolytic cleavage of phosphate esters plays a crucial role in DNA repair,[64] and RNA splicing.[65] Such a particle size of less than 90 nm, whether used as cobalt nanoparticles or cobalt nanocomposites, can penetrate the BBB.

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6.3. *Synthesis of Cobalt nanoparticles*

The synthesis of Co NPs can be carried out in many different ways, which can be modified to produce potential therapeutic targets. For example, the synthesis of colloidal Co NPs has been reported by reduction of $CoCl_2.6H_2O$ using hydrazine (N_2H_4) in a basic solution of ethylene glycol (EG).[66] The obtained colloidal particles were spherical and monodispersed with an average diameter of 2–7 nm. It should be pointed out that pH, reaction temperature and molar ratio of N_2H_4 to Co^{2+} influenced the reduction rate. An alkaline medium, a temperature around 80°C, and high molar ratios of N_2H_4 to Co^{2+} promoted the formation of colloidal Co NPs.
Monodisperse Co NPs in the size range 3–10 nm have been obtained by "hot injection" method, namely by thermal decomposition of $Co_2(CO)_8$ at 168–182°C in the presence of oleic acid, (9Z)-octadec-9-enoic acid, (OA). The size of Co NPs can be tuned by careful control of the temperature of the hot OA solution into which the Co precursor is injected.[67] The monodisperse NPs can be coated with surfactants (*i.e.* oleic acid) and polymers (*i.e.* dextrin, polyethylene glycol (PEG)) to enhance biocompatibility, provide functionality and prevent agglomeration.[68]
Co NPs on ethylene diamine-based porous organic polymers (EPOP) were prepared at variable temperatures. The NPs were stabilized by the amine groups on the porous organic polymers.[69]
The size-control synthesis of Co NPs encapsulated inside hollow carbon spheres (HCS) by using polystyrene-*b*-poly(acrylic acid) (PS-*b*-PAA) nanospheres was reported.[70] The latter were prepared from polystyrene spheres by functionalization with acrylic acid and used for the synthesis of Co_xO_y/polymer composites, which were heated to 600°C at a rate of 10°C/min and kept isothermal for 2 h to pyrolyse and carbonise the resorcinol–formaldehyde (RF) forming a carbon shell that encapsulates the Co nanoparticles. The size of the Co NPs is affected by the concentration of poly(acrylic acid) (PAA) in the polymer. For example, Co NPs encapsulated inside HCS (Co@HCS) obtained by using PS-*b*-PAA with 8 mol% of PAA (PS-*b*-PAA_8) and 12 mol% of PAA (PS-*b*-PAA_{12}) have an average size of 5.4 and 6.1 nm, respectively. It should be noted that the Co@HCS involves not only metal NPs, but also oxides of cobalt NPs such as CoO and Co_3O_4, whose variation of composition influences the NPs' size and metal loading.
The hexagonal Co NPs were synthesized by reduction of anhydrous cobalt(II) chloride with $NaBH_4$ in 2,5,8,11,14-pentaoxapentadecane (tetraglyme) at temperatures in the range of 200–270°C under a nitrogen–hydrogen atmosphere.[71]
A series of colloidal Co NPs having average diameter ranging from 1.8 to 2.8 nm were synthesized by a modified polyol method using $NaBH_4$ as a reducing agent, and by varying the conditions, namely, the gas atmosphere, either inert or oxidative, and the reduction temperature.[72]

Various types of capping agents, including surfactants, ligands, polymers, dendrimers, cyclodextrins, etc., have been used in colloidal synthesis. The Co NPs can be coated by polymers, such as PEGylated liposomes, to form hybrid nanoparticles, which can penetrate BBB. Specific ligands such as surfactants, antibodies, and peptides can be conjugated onto Co NPs to promote recognition by receptors on the endothelial cells, leading to transcytosis and thus BBB crossing. For instance, PEG has the ability to improve blood circulation time and colloidal stability. Polysorbate 80 (PS80, Tween 80) is a common surfactant used to pass through the BBB.[73] Furthermore, appropriate aptamers can be used to facilitate BBB penetration, such as the RNA-based aptamer, A15[74], and a transferrin-receptor aptamer-functionalized liposomes.[75] Small molecules such as glutathione, glucose, and natural polymers like chitosan have also shown to enhance the BBB penetration of

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nanoparticles. Glucose-conjugated nanoparticles can bind to the highly expressed BBB receptor GLUT-1 to promote transcytosis with increased biocompatibility.

7. Conclusions

The focal point of this study is to introduce hypothetical scenarios targeting some neurological disorders, which may potentially have therapeutic application in manipulating neural plasticity to treat a variety of disorders. Important topics have been discussed including neural communication, neurotransmitters, neurotrophins, tau protein, mutant huntingtin protein, the blood-brain barrier, and some other vital factors that cause brain disorders. In view of this discussion, some hypothetical scenarios are proposed for targeting the hyperphosphorylation of IP_3R and tau protein using cobalt nanoparticles coated with appropriate agents. As supporting arguments for these scenarios, Co NPs may have the ability to coordinate with phosphate groups of IP_3 leading to inhibition its binding to IP_3Rs, which, in turn, restricted the overexpressing activity of this receptor. Furthermore, Co NPs may reduce the phosphorylation sites of the tau protein through bond hydrolysis of threonine-proline or serine-proline of the protein. In addition, Co NPs may induce depolarization of the membrane and assist the opening of the voltage-gated channels through exerting electrocatalytic activity on the electrical gradients across the cell membrane. I speculate that Co NPs are ideally suited for biological hydrolysis reactions. They may also exert hydrolytic activity on the active site of mutant huntingtin protein, namely, the cytosine-adenosine-guanine (CAG) trinucleotide repeat expansion in the protein-coding segments of *HTT* gen, which may occlude glutamine from further mutation.
Various synthetic routes for Co NPs are highlighted as well as the capping agents. The challenges associated with penetrating BBB, can be overcome through modifying these synthetic methods to produce potential therapeutic targets for some of the neurological disorders.

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