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IP International Journal of Comprehensive and Advanced Pharmacology

Journal homepage: https://www.ijcap.in/

Review Article

Advances in neurotransmitter detection and modulation: Implications for neurological disorders

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ARTICLE INFO

Article history:
Received 10-08-2024
Accepted 21-09-2024
Available online 26-11-2024

Keywords:
Neurotransmitters
Neurological disease
Detection
Parkinsons
Alzheimer's

ABSTRACT

Neurotransmitters are chemicals that amplify, transmit, and transform cellular impulses, facilitating communication across the neurological system. Over the last century, hundreds of these compounds have been identified, with continuous study focussing on their effects on brain health. Neurotransmitters are known to control a variety of processes, including emotions, thoughts, memory, learning, and movement. As a result, abnormalities in neurotransmitter levels have been related to a variety of neurological and neurodegenerative illnesses. This paper seeks to explore the most significant neurotransmitters, categorized into two broad groups: canonical and noncanonical. Additionally, it discusses the connection between these neurotransmitters and key neurological conditions. A concise review of recent advances in neurotransmitter detection methods is also provided, along with insights into how modulating these substances may help restore homeostasis.

1. Introduction

The central nervous system (CNS) is the primary control centre for all activities in the human body, processing information received from and transmitted to the peripheral nervous system (PNS). This intricate system governs various physiological functions, including muscle control, secretion regulation, and organ function, through signal conduction between neurons. These signals are passed across specialized junctions known as synapses, where communication is mediated by chemical messengers called neurotransmitters (NTs). This process, known as synaptic transmission or neurotransmission, forms the basis for the CNS's ability to control smooth, skeletal, and cardiac muscles, manage bodily secretions, and regulate organ function.[1]

NTs are endogenous chemical messengers that serve as the primary mediators of communication within the nervous system. These tiny molecules play an important role in transferring and enhancing impulses between neurones and other cell types, such as muscle or gland cells. They regulate and communicate sensory, motor, and integrative neural information, impacting a wide range of body activities, such as emotions, thoughts, memories, movements, and sleep patterns. In addition to these roles, NTs also play an essential part in the regulation of neuronal growth, differentiation, and survival, making them critical for the overall functioning of the brain.[2]

The significance of NTs in maintaining the proper functioning of the nervous system cannot be overstated. Their roles extend beyond simple signal transmission; they are integral to maintaining homeostasis in the brain, allowing neurons to communicate effectively and ensuring the body responds appropriately to external and internal

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https://doi.org/10.18231/j.ijcaap.2024.035

stimuli. The diversity of NTs reflects the complexity of the CNS, where each neurotransmitter has specific functions and targets. The balance and homeostasis of these chemicals are vital to normal brain function. When this balance is disrupted, it can lead to a range of physical, psychotic, and neurodegenerative diseases.[3,4] For instance, an excess or deficiency of specific NTs can result in mood disorders like depression or anxiety, while neurodegenerative conditions such as Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD) have also been linked to neurotransmitter imbalances. Over the past century, extensive research has led to the identification of hundreds of NTs, classified into two broad categories: canonical and noncanonical NTs. Canonical NTs include amino acids, monoamines acetylcholine, purines, soluble gases and neuropeptides. These NTs have long been recognized for their role in transmitting signals within the CNS and PNS and have been studied extensively for their involvement in various neurological functions and disorders. Glutamate, for example, is the primary excitatory neurotransmitter in the brain, while GABA is the major inhibitory neurotransmitter. Dopamine is well-known for its role in reward, motivation, and motor control, while serotonin is involved in mood regulation, sleep, and appetite.[4–6]

In contrast, noncanonical NTs have only recently gained attention and are less understood compared to their canonical counterparts. These include molecules such as exosomes, steroids, and D-aspartic acid, which, although not traditionally considered NTs, have been found to play critical roles in neuronal communication and regulation.[7] Exosomes, for instance, are small vesicles that carry various molecular signals between cells, influencing processes such as neuroplasticity and neuroinflammation. Steroids, which are typically recognized for their role in hormonal regulation, have been shown to modulate neurotransmission, particularly in stress responses. D-aspartic acid, a non-protein amino acid, is involved in synaptic plasticity and has been linked to neurodevelopmental processes. Given the essential functions that NTs perform in the brain and nervous system, it is no surprise that abnormalities in their levels and functions can have severe consequences. Dysregulation of neurotransmitter systems is implicated in a wide array of neurological and psychiatric conditions.[8] For example, a deficiency in dopamine is a hallmark of PD, a neurodegenerative disorder characterized by motor impairment, while an imbalance in serotonin levels is associated with mood disorders such as depression. Similarly, abnormal glutamate signaling is implicated in neurodegenerative diseases like AD, where excitotoxicity (overactivation of glutamate receptors) leads to neuronal damage and cognitive decline.

Understanding the complex roles of NTs and their involvement in these diseases is crucial for developing effective therapeutic strategies. In recent years, there has been significant progress in the development of novel methods for detecting NTs, which has opened new avenues for research. These detection methods include advanced imaging techniques, biosensors, and electrochemical approaches that allow for the real-time monitoring of neurotransmitter levels in different regions of the brain. Such advancements have enhanced our understanding of neurotransmitter dynamics in both healthy and diseased states. Furthermore, efforts to modulate neurotransmitter levels as a treatment strategy have gained significant attention.[9,10] Pharmacological agents that target specific neurotransmitter systems, such as SSRIs for depression or dopamine agonists for PD, have become standard treatments for various neurological and psychiatric conditions. Additionally, non-pharmacological approaches, such as deep brain stimulation and transcranial magnetic stimulation, are being explored as ways to restore neurotransmitter balance and improve symptoms in patients with neurological disorders.[11]

In this context, this review aims to provide a comprehensive overview of the known canonical and noncanonical NTs, emphasizing their roles in neurological and neurodegenerative diseases. Additionally, novel detection methods for NTs will be discussed, alongside potential strategies for modulating neurotransmitter levels to restore homeostasis and treat associated neurological conditions. Through a deeper understanding of neurotransmitter systems, we can better address some of the most pressing challenges in neuroscience and neuropharmacology.

2. Neurotransmitters

NTs are molecules that play a critical role in amplifying, transmitting, and converting signals within cells, making them essential for brain function, behavior, and cognition. Since their discovery in 1921, more than 200 of these chemical messengers have been identified, although the precise number remains unknown. This uncertainty is largely due to the continuous discovery of new biomolecules exhibiting neuroactive properties, which are added to the growing list of recognized NTs.[12]

To be categorised as a neurotransmitter, a chemical must satisfy several fundamental criteria: (i) it must be created and released by the same neurone, with storage taking place at the presynaptic terminal; (ii) it should cause a particular response in the postsynaptic neurone; (iii) its exogenous administration should produce the same effect as its endogenous counterpart; and (iv) there must be a specific mechanism to terminate its action on the postsynaptic cell.[13]

Over time, various types of NTs have been identified and studied for their influence on brain health. NTs are broadly classified into two categories: canonical and noncanonical. Canonical NTs include small molecules that

are widely recognized as NTs, while noncanonical NTs represent neuroactive compounds that have only recently been identified and are still subject to ongoing research and debate [14]

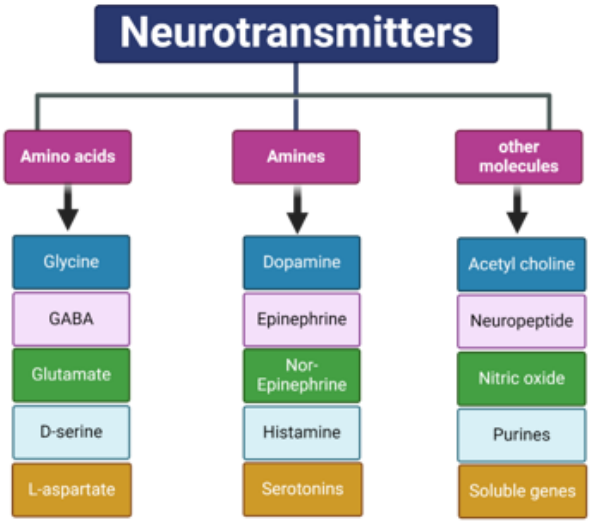

Figure 1: Classification of Neurotransmitters

2.1. *Canonical Neurotransmitters*

Several types of NTs have been identified, each with distinct functions and areas of production within the brain. From a chemical standpoint, NTs are commonly grouped into categories such as amino acids, amines, and other molecules. Functionally, they can also be classified as either excitatory (positive) or inhibitory (negative) NTs, or according to whether they act centrally in the brain or peripherally in other parts of the nervous system. The next sections will explore the main canonical NTs, categorized based on their chemical nature and functions. [6]

2.1.1. *Amino acid*

Amino acid NTs are vital to the CNS, playing crucial roles in brain function and the development of various disorders. Among these are α-amino acids, such as glutamate and glycine, and GABA, which are engaged in important brain functions and contribute to the development of certain neurological disorders. [15]

Glutamate is the principal excitatory neurotransmitter in the CNS, synthesised from glutamine and acting as a precursor to GABA. Presynaptic neurones release it into the synaptic cleft, activating NMDA and AMPA receptors. This activation promotes the inflow of calcium and sodium ions into postsynaptic neurones. However, high glutamate can cause overactive calcium signalling in postsynaptic neurones, resulting in hyperactive neuronal firing and excitotoxicity. This excitotoxicity has been linked to neurological illnesses such as ALS and PD. [15,16]

Astrocytes regulate extracellular glutamate levels through both release and absorption processes. They take excess glutamate from the synaptic cleft and convert it to glutamine, which is subsequently delivered back to the presynaptic neurones. Furthermore, a part of the glutamate is released into the extracellular space via multiple mechanisms. This cycle helps control glutamate homeostasis in the tripartite glutamatergic synapse, hence preventing detrimental excitotoxicity. [17,18]

GABA, another key amino acid neurotransmitter, is produced by the enzyme glutamate decarboxylase or synthesized by commensal gut microbiota. Interestingly, although GABA is known as the primary inhibitory neurotransmitter in the brain, early studies have shown that it initially exhibits excitatory properties, Inducing stimulation rather than inhibition in certain brain areas. A lack of GABA is linked to neuronal hyperexcitability, contributing to conditions such as anxiety and epilepsy. [19–21]

Glycine is the primary inhibitory neurotransmitter in the spinal cord, whereas in the brainstem and medulla, it acts as a neurotransmitter and co-agonist at NMDA receptors with glutamate. Glycine, like GABA, shows excitatory activity throughout early development before switching to an inhibitory function in maturity. It is responsible for a variety of tasks, including voluntary muscular control, sensory processing, and regulation of the auditory, cardiovascular functions. [22,23]

D-serine is another neurotransmitter, released by glial cells, whose role in higher organisms has been only recently explored. It is synthesized from L-serine by the enzyme serine racemase, particularly in regions of the brain rich in NMDA-glutamate receptors. Another neurotransmitter, L-aspartate, has been a subject of debate due to conflicting findings regarding its localization and function. Some studies suggest that L-aspartate acts as a neurotransmitter in the visual cortex and cerebellum, while others propose that it functions both as a neurotransmitter and a neuropeptide-like modulator in the hippocampus. [24]

2.1.2. *Amines*

Monoamines are a group of NTs that play critical roles in regulating motor functions, emotional responses, motivation, and behavior. These NTs are synthesized by presynaptic neurons and act by binding to specific receptors on the postsynaptic membrane(24). Any excess monoamines remaining in the synaptic cleft are degraded by enzymes such as MAO or COMT. Dysregulation of this process is linked to several severe neurological disorders, including AD, PD, HD, and schizophrenia. [25]

Dopamine is one of the most important neurotransmitters in mammals, impacting almost all physiological activities in the CNS, either directly or indirectly. It is created and released by dopaminergic neurones, which are mostly found

in the substantia nigra pars compacta and ventral tegmental region. Dopamine is necessary for homeostasis and acts as a precursor to other catecholamines, including norepinephrine and epinephrine. Any imbalance in dopamine levels can lead to many behavioural and neurological diseases, including drug addiction, schizophrenia, Parkinson's disease, and hypertension.[26]

Serotonin is another vital monoamine neurotransmitter, known for its role in modulating a wide range of physiological processes. It influences sleep-wake cycles, gastrointestinal secretion, respiration, vasoconstriction, behavior, and overall neurological function.[27] Enterochromaffin cells in the gut create the vast majority of serotonin, with the tryptophan hydroxylase enzyme playing a critical role in its production. Serotonin has a wide-ranging effect on the CNS, regulating other NTs by inhibiting dopamine release, modulating glutamate and GABA transmission, and influencing glutamate release in various brain regions, such as inhibiting glutamate release in the frontal cortex while increasing it in the prefrontal cortex.[28]

Epinephrine and norepinephrine are monoamines that operate as both neurotransmitters and hormones. Norepinephrine neurones are mostly found in the locus coeruleus and send signals to many regions of the brain, including the limbic system, which is involved in emotional regulation.[29] While epinephrine is also produced by specific neurons in the brain, its role as a neurotransmitter remains less understood. Both of these NTs are crucial in the body's response to stress and are involved in the "fight or flight" response.[30]

Histamine is another monoamine signaling molecule that functions as a neurotransmitter within the CNS. It is involved in various physiological processes, including regulating sleep-wake cycles, immune responses, and inflammatory reactions. Although its role in the CNS is not as extensively studied as other monoamines, histamine is increasingly recognized for its importance in maintaining overall neurological health and function. In summary, monoamines are fundamental NTs in the CNS, playing crucial roles in behavior, cognition, and physiological homeostasis. Dysregulation of monoamine systems is implicated in numerous neurological and psychiatric conditions, highlighting the need for continued research into their functions and therapeutic potential.[31]

2.1.3. Other molecules as a neurotransmitters

In addition to the above-mentioned NTs, numerous additional compounds have been discovered as NTs. Acetylcholine, the first chemical to be characterised and recognised as a neurotransmitter in the PNS, is one of the best-studied. Acetylcholine is produced by post-ganglionic neurones in the parasympathetic nervous system and is required for muscle contraction at the neuromuscular junction. Acetylcholine is important in the CNS for awareness and cognitive activities such as attention, learning, memory, voluntary movement, and sleep. Cholinergic neurones, which produce acetylcholine, are dispersed across various brain areas, including the striatum, cranial nerves, and vestibular nuclei.[32]

Acetylcholine is stored in synaptic vesicles within cholinergic presynaptic neurones and, after neuronal depolarisation, is released into the synaptic cleft to permit neurotransmission via acetylcholine receptors. It serves as a neuromodulator in several areas of the forebrain, influencing motor and cognitive activities via cortico-striato-thalamocortical circuits. Acetylcholine imbalances have been associated to neurological illnesses such as Alzheimer's disease, Parkinson's disease, hypertension, schizophrenia, myasthenia gravis, as well as learning, attention, memory, and sleeping difficulties.[33,34]

In addition to acetylcholine, several compounds are recognised as NTs. These include purines like adenosine triphosphate (ATP), soluble gases known as gasotransmitters (e.g., carbon monoxide [CO], nitric oxide [NO], and hydrogen sulphide [H2S]), and different neuropeptides such as somatostatin, substance P, and neuropeptide Y. A brief description of a specific example from each category suggests below.

ATP, sometimes known as the "energy currency" of the cell, is required for several key activities within organisms and cells, such as intracellular signalling, active transport, muscular contraction, and DNA/RNA synthesis. Synaptic transmission, an energy-intensive mechanism, requires ATP at the presynaptic terminal to sustain ion gradients that assist shuttle NTs into vesicles and prepare them for release by exocytosis. at the central nervous system, ATP is recognised as an excitatory neurotransmitter at neuronal synapses. Insufficient ATP release has been associated to different dysfunctions, including brain traumas, strokes, PD and AD.[35,36]

Among soluble gases, nitric oxide (NO) stands out as a well-established neurotransmitter and signaling molecule, crucial in regulating synaptic plasticity. NO also plays a role in modulating the biosynthesis of D-serine, another important neurotransmitter. Serine racemase, the enzyme responsible for converting L-serine to D-serine, is physiologically nitrosylated by NO, which inhibits its activity and lowers the conversion rate. NO is produced in response to NMDA receptor activation and diffuses to D-serine-producing cells, providing a form of feedback inhibition. Given its wide-reaching effects, NO is crucial for maintaining proper synaptic function and neurochemical balance.[37,38]

Neuropeptide Y (NPY) is one of the most extensively expressed NTs in the nervous system, as well as the most abundant peptide in the mammalian brain. NPY is implicated in a wide range of biological activities, including

cortical excitability, stress response, food intake control, circadian rhythms, and cardiovascular function. Abnormal regulation of NPY is linked to a range of neurological conditions, such as epilepsy, and is implicated in other disorders like obesity, anxiety, and mood disturbances. NPY's widespread influence makes it an important target for research into neurophysiological and neuropsychiatric disorders.[39,40]

2.2. Noncanonical Neurotransmitters

Noncanonical NTs have recently garnered increasing attention in scientific research and debate due to their complex roles in brain function, intercellular communication, and potential involvement in neurodegenerative diseases.[41]. Among the most notable of these nontraditional NTs are exosomes, which are small bilayered extracellular vehicles (EVs) that serve as long-range messengers. These vesicles have been implicated in a range of critical functions, including the control of growth and development, intercellular communication, antigen presentation, inflammation, and cancer. Although exosomes were first researched for these biological tasks, new research indicates that they also have a role in neurotransmission and synaptic control.[42]

Exosomes share functional similarities with synaptic vesicles but differ in that they are released into the extracellular space by their parent cells rather than within synapses. Exosomes contain diverse molecular cargo, including proteins, lipids, and RNAs that influence synaptic plasticity and neuronal communication. In addition to their role in synaptic plasticity, neuronal exosomes have been proposed as direct mediators of neurotransmission.[43] Exosomes, like classical neurotransmitters, are released by presynaptic neurones in response to action potentials. They can carry neuropeptides and ligands that activate G protein-coupled receptors (GPCRs), initiating intracellular signalling cascades.[44] Exosomes, once released, can raise intracellular calcium (Ca2+) levels in postsynaptic neurones by promoting Ca2+ release from the endoplasmic reticulum via inositol 1,4,5-triphosphate (IP3) receptors and activating calcium channels on the cell membrane. This rise in Ca2+ causes quick reactions in postsynaptic neurones and allows for long-term changes in synaptic strength via controlling the number of receptors and the activity of certain ion channels.[45]

Exosomes also contribute to a variety of physiological processes in the CNS, such as neurone regeneration, synapse maintenance, and immunological responses. Their participation in neurodegenerative illnesses including AD and PD has prompted worries regarding their possible harmful impact.[46] Certain exosomal proteins, including Alix and Flotillin-1, have been linked to the propagation of AD and PD. These proteins may facilitate the spread of misfolded proteins like amyloid-beta in AD or alpha-synuclein in PD, contributing to the progression of these diseases.[47]

Another noncanonical neurotransmitter class is steroids, which exhibit neurotransmitter-like properties. Steroids can signal within the brain and the nucleus, activating intracellular signaling cascades and modulating calcium release.[48] The neuroactive effects of steroids are not limited to their role in the endocrine system; they also play a part in synaptic transmission, influencing neuronal excitability and synaptic plasticity.[49]

D-aspartic acid, a noncanonical neurotransmitter, is another molecule with potential neuroactive effects. This amino acid has been found in nervous tissues of several animal species as well as in human brains.[50] Although its exact role as a neurotransmitter is still being studied, D-aspartic acid has been suggested to participate in neurotransmission and may contribute to neural development and plasticity.[51]

The exploration of noncanonical NTs, such as exosomes, steroids, and D-aspartic acid, continues to expand our understanding of brain function and neural communication. These molecules challenge traditional definitions of neurotransmission and open new avenues for research, particularly concerning their roles in neurodegenerative diseases. Understanding the mechanisms through which these molecules influence neuronal signaling may provide valuable insights into potential therapeutic targets for neurological and psychiatric disorders.[52]

3. Neurotransmitter Disorders of the CNS

NTs are integral to various diseases, such as epilepsy and multiple sclerosis (MS), which arise from disruptions in NT metabolism. These disruptions can affect NTs like amino acids, monoamines, cholinergic transmission, purines, and others. These imbalances may be genetic, or they can develop over time due to issues like impaired neuronal receptors, faulty intracellular signaling, vesicle release problems, or other synaptic dysfunctions.[53]

3.1. Epilepsy

Epilepsy is a devastating neurological illness marked by seizures produced by a sudden and transient synchronisation of neuronal activity. The illness is largely impacted by an imbalance of excitatory and inhibitory neurotransmitters, especially glutamate and GABA. Glutamate is the primary excitatory neurotransmitter in the CNS, and excess activity promotes neuronal excitability, which contributes to seizure onset. To address this, contemporary anti-seizure drugs target ion channels, transporters, and receptors to restore balance between these NTs, resulting in symptomatic relief.[54,55]

3.2. Multiple sclerosis

Multiple sclerosis (MS) is a chronic, autoimmune-driven inflammatory disease that affects the central nervous system. Although the specific aetiology is unknown, it involves both genetic and environmental factors. MS is characterised by demyelination, astroglial proliferation, and neurodegeneration in the CNS. One key feature of MS is glutamate excitotoxicity, which is caused by high extracellular glutamate levels. Research has found that single nucleotide polymorphisms (SNPs) in glutamate transporter genes can disrupt the expression of EAAT1/2 transporters, which regulate glutamate uptake. This dysregulation leads to excitotoxicity and worsens tissue damage in MS.[56,57]

GABA, another key NT, has also been implicated in MS. Lower GABA+ levels are common in people with relapsing-remitting MS (RRMS), and aberrant GABAergic neurotransmission may contribute to cognitive impairment. GABAergic interneurons help stabilize the brain's inhibitory neural network by providing recurrent inhibition to pyramidal neurons. When this network is disrupted, cognitive function suffers, particularly in individuals with RRMS.[58]

Genetic studies have identified several genes linked to MS, including those coding for human leucocyte antigens (HLA) class I and II, T-cell receptor β, and other immune-related molecules like CTLA4, ICAM1, and SH2D2A. Understanding how neurotransmitter imbalances relate to MS pathology is critical in developing more targeted and effective treatments for the disease.[59]

3.3. Autism

Autism spectrum disorders (ASD) are complex neurodevelopmental and neurobehavioral conditions marked by challenges in social interaction, communication, restrictive behaviors, and altered sensory processing. The heterogeneity of ASD suggests multiple potential underlying causes, with neurochemical imbalances playing a key role in its pathophysiology. Variable levels of GABA and glutamate in children with ASD contribute to an imbalance of excitatory and inhibitory neurotransmission.[60] Prenatal exposure to GABAA receptor inhibitors has been linked to ASD-like behaviors in offspring. Additionally, glutamatergic circuits connecting the frontal regions and the striatum are involved in regulating compulsive behaviors, such as stereotypy, often seen in ASD.[61] changes in genes like GRIN2A and GRIN2B have been connected with these illnesses, whereas glutamatergic dysregulation is also linked to changes in genes involved in synapse development and maintenance.

Monoamine neurotransmitter abnormalities are also implicated in ASD, with disruptions in dopamine, norepinephrine, and serotonin balance contributing to altered sleep, mood, and behavior. Autistic people have diminished dopamine release in the prefrontal cortex and impaired neuronal responses in the nucleus accumbens. A recent hypothesis proposes that ASD behaviors may result from dysfunctions in the midbrain dopaminergic system, where mesocorticolimbic (MCL) circuit dysfunction leads to social deficits, and nigrostriatal (NS) circuit dysfunction contributes to stereotyped, repetitive behaviors.[62]

3.4. Alzheimer's disease

AD is a neurodegenerative ailment that predominantly affects the neocortex, characterised by gradual memory loss, behavioural abnormalities, and a high death rate. The specific aetiology of AD remains unknown; however, its pathology is intimately related with the formation of Aβ plaques and hyperphosphorylated tau protein clumps. Other contributing factors include synaptic protein changes, neurotransmitter loss, oxidative stress, mitochondrial dysfunction, calcium deregulation, inflammation, and cerebral disease. Several hypotheses attempt to explain AD pathogenesis. The amyloid cascade hypothesis suggests that increased production of amyloidogenic Aβ42 leads to neuronal death and synaptic loss. The calcium hypothesis of AD proposes that neurodegeneration is driven by disruptions in cellular calcium homeostasis, contributing to synaptic dysfunction and cell death.

Neurotransmitter imbalances are key to understanding AD's cognitive and behavioral symptoms. Cholinergic dysfunction, marked by acetylcholine deficits, is linked to cognitive decline and exacerbates amyloid-beta and tau pathology. Damage to cholinergic signaling results in impaired memory and cognition. Dopaminergic deficits are also tied to cognitive impairments and may contribute to AD-related behavioral changes, such as apathy and mood disturbances, as dopamine plays a role in the brain's reward and motivation circuits[63,64]

Serotonergic dysfunction in AD has been implicated in neuropsychiatric symptoms, including depression and agitation. Restoring serotonin levels has been shown to alleviate both cognitive and behavioral symptoms, making it a potential target for AD therapy.[63] Addressing these NT deficits might offer therapeutic strategies for managing AD's complex neurodegenerative profile.

3.5. Parkinsons disease

Parkinson's disease is a progressive neurodegenerative disorder characterised by the degradation of dopaminergic neurones in the substantia nigra pars compacta, which results in dopamine insufficiency in the striatum and the production of Lewy bodies. This results in a range of symptoms, including motor disturbances, hyposmia (reduced sense of smell), autonomic dysfunction, sleep disorders, and psychiatric or cognitive impairments. In

addition to dopamine, other NTs like glutamate, GABA, serotonin, histamine, acetylcholine, and epinephrine are also affected in PD.[64,65]

One emerging aspect of PD pathology is the disruption of glutamate homeostasis in the striatum. Inflammatory processes contribute to astrocytic glutamate excitotoxicity by altering the expression of glutamate transporters and receptors.[66] The accumulation of α-synuclein, a protein associated with PD, increases the presynaptic release of glutamate in a calcium-dependent manner, which activates extra synaptic NMDA receptors and leads to neuronal damage. Elevated glutamate levels also stimulate AMPA receptors, further promoting glutamate release. Additionally, α-synuclein enhances the mobilization of glutamate-containing vesicles, causing overstimulation of mGluR5 receptors, contributing to excitotoxicity and neuronal injury.[67]

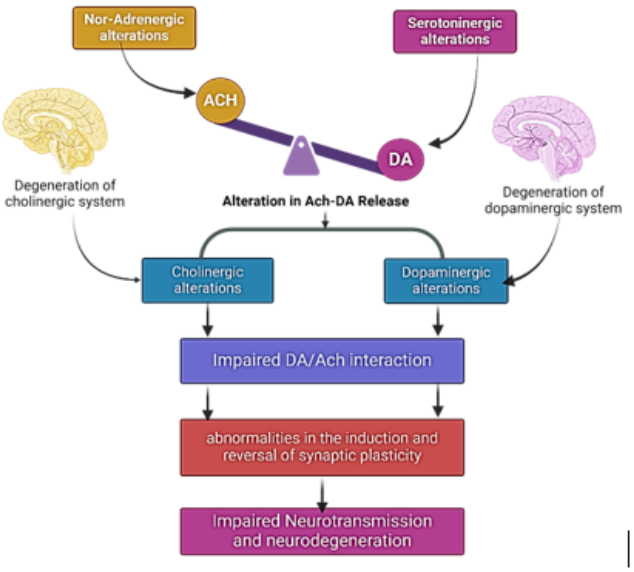

Figure 2: illustrates Parkinson's disease's neurotransmitter imbalances

cholinergic hyperactivity due to acetylcholine (Ach) excess, dopaminergic deficits from dopamine (DA) loss, disrupted DA/Ach interactions causing motor issues, and impaired synaptic plasticity, affecting learning and motor adaptation.

3.6. Huntington's disease

Huntington's is a neurodegenerative disorder caused by an expansion of CAG trinucleotide repeats in the first exon of the huntingtin gene, leading to polyglutamine expansions and toxic aggregation of the huntingtin protein in neurons, particularly in striatal and cortical motor regions, as well as prefrontal areas. The abnormal body movements observed in HD arise from disruptions in the balance between the direct and indirect pathways of motor control, accompanied by altered levels of several NTs in the striatum.

The most severe neurodegeneration occurs in the caudate and putamen, areas known for their rich dopaminergic innervation and high concentrations of dopamine receptors. In the early stages of HD, the heightened thalamocortical glutamatergic signaling contributes to hyperkinetic (excessive) movements. As the disease progresses, hypokinesia (reduced movement) develops as both the direct and indirect pathways become compromised. Research suggests that the interaction between dopamine and glutamate pathways, particularly through the activation of D1 receptors, may exacerbate neurotoxicity, further contributing to the progression of the disease.[68–70].

3.7. Schizophrenia

Schizophrenia is a severe neurodevelopmental condition with unknown origins that is frequently diagnosed during adolescence. It manifests as a variety of symptoms, including hallucinations, delusions, social isolation, lack of desire, and cognitive deficits. Cognitive deficiencies, such as difficulties with working memory, executive function, learning, long-term memory, and sensory perception, are substantial predictors of long-term functional outcome in schizophrenia.[71]

The cognitive symptoms of schizophrenia are thought to stem from primary deficits in NMDA receptor glutamatergic signaling, particularly in layer 3 pyramidal neurons of the prefrontal cortex. These deficiencies impede executive cognitive skills as well as working memory maintenance. Furthermore, abnormalities in GABA neurotransmission may lead to working memory problems. Working memory is strongly related with gamma frequency oscillations in the prefrontal cortex, which are decreased in persons with schizophrenia. Reduced GABAergic neurotransmission is linked to increased dopamine synthesis, and abnormalities in both presynaptic and postsynaptic dopaminergic systems have been associated with the onset of schizophrenia. Dysregulation of the dopaminergic system is considered a major factor in the etiology of the disorder.[72–76]

3.8. Depression

Depression is a complex and multifaceted disorder associated with various biological mechanisms beyond behavioral factors. This involves inflammatory reactions, hypothalamic-pituitary-adrenal axis dysregulation, abnormalities in sympathetic and parasympathetic and endothelial dysfunction accompanied by platelet activation. Neurobiological research has indicated that depression is associated with neuronal shrinkage in cortical and limbic brain areas, as well as impaired brain connections and network function. These changes are attributed to structural, functional, and neurochemical deficits,

particularly involving dysfunctions in the GABA and glutamate systems.[19,77]

One hypothesis regarding depression emphasizes the role of monoamine NTs. It suggests that low levels of serotonin, dopamine, and norepinephrine are associated with depression, and these neurotransmitter levels can be increased by antidepressant medications. However, research on monoamine levels has produced mixed results, with some studies contradicting this link. On the other hand, alterations in GABAergic and catecholaminergic pathways have shown more consistent diagnostic value in understanding depression.[78]

3.9. Amyotrophic lateral sclerosis

ALS is a chronic neurological disease with a complicated pathophysiology. Initially thought to be a pure motor neurone disease, it has since been recognised as a multisystem condition with clinical, inherited, and neuropathological fluctuation. ALS causes motor neurone degeneration, muscular atrophy, paralysis, and severe metabolic dysregulation. ALS's mechanisms comprise ROS-associated oxidative stress, dysfunction of the mitochondria, compromised homeostasis, axonal and vesicular transport dysfunction, excitotoxicity of glutamate, proteostatic deficits, altered RNA metabolism, low Ca2+ buffering capacity, a high number of AMPA receptors in motor neurones, neuroinflammation, and neurotrophin depletion.[79,80]

Approximately 2% of ALS cases have a genetic component, including mutations in SOD1 and other prevalent risk factors. Treatments focused on reducing NT concentrations have been developed, with riluzole being the sole disease-modifying medicine licensed in the majority of European nations. This medication has been shown to increase patient lifespan by 3 to 6 months, however it includes adverse effects such as nausea, diarrhoea, exhaustion, disorientation, and liver damage.[81,82]

4. Neurotransmitters Detection

Diagnosing brain disorders chemically presents considerable challenges due to the difficulty of analyzing brain chemistry in living organisms and the protective blood-brain barrier that limits direct access to the CNS. Despite these obstacles, early detection of NTs is crucial for the prevention and management of neurological disorders. Recent research has aimed to overcome these challenges by developing and refining tools for the direct detection of chemical biomarkers associated with these conditions.[9,83]

Several advanced techniques have been employed to facilitate the diagnosis and detection of NTs. Electrochemical methods are used to measure changes in electrical properties that occur when NTs interact with specific sensors. Fluorescence Resonance Energy Transfer (FRET) utilizes the transfer of energy between two fluorescent molecules to detect specific biomarkers, offering high sensitivity and specificity. Chemiluminescence involves the emission of light resulting from chemical reactions, making it useful for detecting low concentrations of NTs. Chromatography separates NTs based on their chemical properties, which aids in their identification. Mass Spectrometry provides precise detection by analyzing the mass-to-charge ratio of NTs. Capillary Electrophoresis separates NTs based on their size and charge using an electric field, allowing for accurate analysis. Surface-Enhanced Raman Spectroscopy (SERS) enhances Raman scattering to detect NTs even at very low concentrations. Near-Infrared (NIR) Biosensing employs NIR light to analyze NTs, while Microdialysis allows for the collection and measurement of NTs from the extracellular fluid in the brain.[84]

In addition to these techniques, advancements in nanomaterial-based detection systems are showing great promise. Carbon-Based Nanosensors use carbon materials to achieve high sensitivity and selectivity in detecting NTs. Metal-Based Nanosensors employ metals to enhance detection capabilities, while Metal-Oxide-Based Nanosensors offer high performance in identifying various NTs. Polymer-Based Nanosensors provide flexibility and customization for specific applications, and Enzyme-Based Nanosensors use enzymes to selectively interact with NTs, allowing for precise measurements. These innovations are significantly improving the ability to detect and monitor NTs, thereby enhancing the diagnosis and management of neurological disorders.[85,86]

5. Modulation of Neurotransmitters and Neurotransmitter Transporters as a Therapeutic Strategy

Neurotransmitter transporters (NTTs) are integral to maintaining the delicate balance of within the brain. These transporters are responsible for regulating extracellular NT concentrations by facilitating their uptake into cells, which helps in limiting receptor activation and ensuring appropriate downstream signaling. Consequently, NTTs have emerged as promising targets for therapeutic interventions aimed at treating a range of neurological and neuropsychiatric disorders.[87]

Some of the important NTTs are glutamate transporters, notably the glutamate-aspartate transporter and glutamate transporter-1, as well as their human homologs, excitatory amino acid transporters 1 and 2. These transporters are mostly expressed in astrocytes and serve an important function in controlling extracellular glutamate levels.[88] By facilitating the uptake of glutamate from the synaptic cleft, these transporters prevent excessive accumulation and thereby mitigate the risk of excitotoxicity—a condition where excessive glutamate causes neuronal damage and

death.[89] Enhancing the production and function of these transporters has been investigated as a therapeutic approach. Several pharmacological drugs, including β-lactam antibiotics, selective oestrogen receptor modulators, growth factors, histone deacetylase inhibitors, and translational activators, have demonstrated the ability to modulate these transporters. For instance, β-lactam antibiotics like ceftriaxone have been reported to upregulate GLT-1 expression, thereby providing neuroprotection in conditions such as ALS and other neurodegenerative diseases.[90]

Monoamine transporters (MATs) are another crucial target for therapeutic interventions. These transporters regulate the levels of key monoamines, including serotonin, dopamine, and norepinephrine, which are implicated in a variety of neuropsychiatric disorders. MATs are targeted by various drugs, including antidepressants and substances of abuse. Such as SSRI act by inhibiting serotonin reuptake, therefore increasing its availability in the synaptic cleft and reducing mood and anxiety symptoms[91] Caffeine, a well-known psychoactive substance, also modulates NT systems, particularly in the mesocorticolimbic brain regions, which are involved in reward and addiction pathways. While moderate caffeine consumption can enhance dopaminergic signaling and offer neuroprotective benefits, excessive intake may lead to neurotoxicity, negative behavioral effects, and other health issues. Therefore, careful dosing and monitoring are essential when using caffeine as a therapeutic agent.[92] Recent research has highlighted the influence of gut microbiota on NT regulation through the gut-brain axis. Prebiotics and probiotics have emerged as potential modulators of NT levels. For instance, the probiotic Lactobacillus rhamnosus has been shown to affect GABA receptor expression, increasing GABAB1b mRNA in certain brain regions while decreasing its expression in others. This modulation has implications for stress-related disorders such as anxiety and depression.[93] Similarly, prebiotic chito-oligosaccharides, derived from chitin, have demonstrated strong inhibition of acetylcholinesterase, an enzyme responsible for the breakdown of acetylcholine. This inhibition suggests that prebiotics could be beneficial in preventing or treating cognitive disorders like AD by maintaining higher levels of acetylcholine in the brain.[94]

Drugs can also mimic the action of NTs, altering neurotransmission by interacting with specialized receptors and transporters. This mimicry can be harnessed therapeutically to modulate NT systems and address neurological and psychiatric conditions. However, drug abuse and addiction can disrupt these systems, leading to significant physiological and psychological dysfunctions. Therefore, understanding the precise mechanisms through which drugs interact with NT systems is crucial for developing effective therapeutic strategies.[95]

In summary, the modulation of NTs and their transporters presents a promising avenue for therapeutic intervention in neurological and neuropsychiatric disorders. By enhancing or inhibiting specific transporters and leveraging the influence of external agents such as drugs, probiotics, and prebiotics, it is possible to achieve more targeted and effective treatment outcomes. Continued research and development in this field has the potential to revolutionise the management of numerous brain illnesses, providing hope for a better quality of life for those affected.

6. Conclusion

NTs are chemical messengers that transport and amplify information throughout the nervous system, influencing feelings, ideas, perceptions, movements, learning, sleep cycles, behaviour, consciousness, excitement, blood flow, and respiration. Abnormalities in levels of neurotransmitters can cause serious disorders that affect both people and entire health systems. Variable amounts of NTs that include glutamate, GABA, dopamine, serotonin, norepinephrine, histamine, and acetylcholine are related with a range of illnesses, including autism spectrum disorders, schizophrenia, epilepsy, ALS, PD, HD, AD, drug addiction, depression, and sleep problems. Early detection and monitoring of neurotransmitter imbalances are crucial to prevent complications. Despite this, diagnosing brain disorders chemically remains complex, necessitating further research into the mechanisms of neurotransmitter action and strategies for modulating their levels. Overall, NTs are fundamental to understanding and treating numerous neurological and neurodegenerative conditions, and interdisciplinary research is key to developing effective treatments that can improve the quality of life for millions of patients globally.

7. Source of Funding

None.

8. Conflict of Interest

None.

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Cite this article: Bhagwat A, Tambe P, Vare P, More S, Nagare S, Shinde A, Doke R. Advances in neurotransmitter detection and modulation: Implications for neurological disorders. *IP Int J Comprehensive Adv Pharmacol* 2024;9(4):236-247.