



Current advances in the detection of neurotransmitters by nanomaterials: An update

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ARTICLE INFO

Article history:

Available online 6 December 2019

Keywords:

Neurotransmitters
Nanomaterials
Sensing techniques
Real samples
Simultaneous sensor

ABSTRACT

Neurotransmitters (NTs) are chemical messengers in the synaptic transmission process. NTs play important roles in human activities, and imbalanced NTs levels in the body lead to severe diseases such as Alzheimer's and Parkinson's diseases. The accurate diagnosis of NTs imbalances has been identified only after patient death through identifying plaques in the brain. Hence, the diagnosis and monitoring of NTs concentrations is important for avoiding serious illnesses. Many researchers have explored the use of robust diagnostic tools with various nanomaterials and techniques. Herein, we investigated the mechanism of reactions between NTs and nanomaterials, the role of nanomaterials in diagnostic tools and the different techniques used in the accurate detection of NTs. Furthermore, we discussed the simultaneous detection of NTs in a single sensing channel, detection in biological samples and future perspectives for nanomaterials in NTs detection.

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1. Introduction

Neurotransmitters are chemical messengers that enhance, transmit and convert signals in cells and play an important role in brain functions, behavior, and cognition. At the early stage of neural disorders, over 100 NTs are involved in synaptic transmissions of the human body thus understanding the functions of NTs is a great challenge in neuroscience research [1]. Variations in the molecule levels, production, and metabolism and secretions of chemicals cause many diseases such as Alzheimer's, Parkinson's, Huntington's, schizophrenia epilepsy, glaucoma, thyroid hormone deficiency, and congestive heart failure. The monitoring and detection of NTs at early disease stages are essential to avoid risk factors in diseases such as Alzheimer's disease and Parkinson's disease. For example, the symptoms of AD are memory loss, cognitive impairment, dementia, and loss of the capacity for daily life. Currently, 35 million people have been identified as having AD, and researchers have estimated that 115.4 million people will be affected by AD in 2050. Currently, the best biomarkers used to identify NTs are

contained in CSF and human blood samples [2]. The biomarkers are needed to understand the diagnosis of NTs-related diseases.

As in various technology segments, nanomaterials have established their specific advantages in biosensing applications, such as sensitivity, selectivity, and lower detection limits [3]. In the last few decades, multidesign nanomaterials have massively influenced sensor and biosensor fields. Their well-controlled physiochemical properties such as surface area, surface charge, surface modification, shape, size, and dimensions are receiving more attention [4]. Their unique optical, magnetic, electrical, electrochemical and thermal properties help target NT biomarkers in biological samples with high sensitivity. Physical signals produced by conversion of target binding events, that can be amplified and detected which could be the mechanism behind the sensor [5]. Physiochemical properties provide the main advantages for the immobilization of biomolecules, leading to the enhancement of sensitivity. In that some of the nanomaterials and its characterization, which is influent in the biosensor are gathered in the Table 1. Different types of nanomaterials have been used to design for various sensor applications. Nanomaterials including but are not limited to carbon, metal, metal oxide, polymer, and enzyme-based nanomaterials. The functionalization, surface modification, and different compositions play additional roles in performing the functions of the sensing system [6]. Controlled and targeted functionalization is critical to obtaining better performance. Various analytical tools

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List of abbreviations			
5-HT	serotonin	GSH	Glutathione
AA	Ascorbic Acid	HPLC	High performance Liquid Chromatography
Ach	Acetylcholine	Lac	Lacasse
AchE	Acetylcholine esterase	LC	Liquid Chromatography
AD	Alzheimer's disease	LD	Levodopa
ATP	Adenosine triphosphate	LOD	Limit of detection
ChO	Choline oxidase	MS	Mass Spectrometry
CV	Cyclic Voltammetry	NAD ⁺	Nicotinamide adenine dinucleotide
Cys	cysteine	NE	Norepinephrine
DA	Dopamine	NTs	Neurotransmitters
DA quinone	Dopaminoquinone	PANI	Polyaniline
DAN	Diaminonaphthalene	PBCB	poly brilliant cresyl blue
DNA	Deoxyribose Nucleic Acid	PEDOT	Poly (3,4-ethylenedioxythiophene)
DPV	Differential Pulse Voltammetry	PL	Photoluminescence
DXEP	Deoxyepinephrine	ppb	Parts per billion
ECL	Electro-chemiluminescence	ppm	Parts per million
EP	Epinephrine	PPy	Polypyrrole
FCS	Fluorescence Correlation spectroscopy	PPy-MIP	Polypyrrole molecularly imprinted polymer
FI	Fluorescence Intensity	PTC	Perylenetetracarboxylate
FLIM	Fluorescence Lifetime imaging	PTh	Polythiophene
FRET	Fluorescent Resonance Energy Transfer	PVS	Polyvinylsulfonate
GA	Glutamic Acid	SPR	Surface plasmon resonance
GABA	γ - Aminobutyric acid	SWV	Square wave Voltammetry
Gly	Glycine	T _{rec}	Recovery time
Glu	Glutamate	T _{res}	Response time
		UA	Uric Acid
		UHPLC	Ultra High performance Liquid Chromatography

have been involved in the diagnosis and detection of NTs in direct and biological samples including electrochemical methods, FRET, chemiluminescence, chromatography, and capillary electrophoresis [7]. To avoid and overcome drawbacks and limitations such as high expense, poor sensitivity and selectivity and difficulties in the manufacturing of current sensing techniques, much research is being conducted to solve these problems. The simultaneous detection of NTs has only been partially developed due to the challenging presence of major electroactive compounds such as AA, UA, and purine. In this review, we have discussed the functions, process, and quantitative analysis of some specific NTs such as DA, EP, NE, GABA, Gly, Glu ATPs, etc. (Table 2).

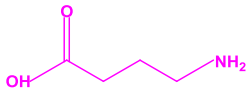
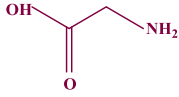
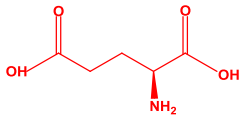
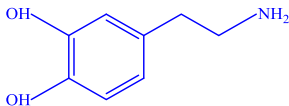
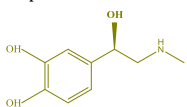
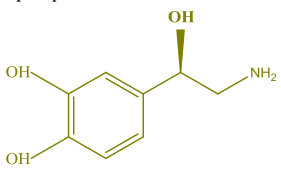
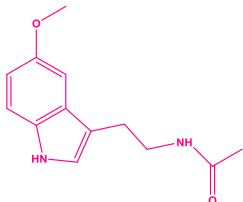
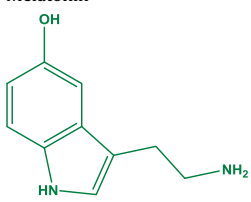
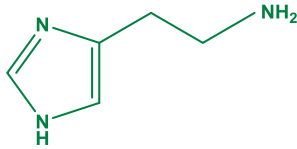
The present review attempted to gather and critically discuss NTs functions, nanomaterials involved in the detection of NTs and techniques involving the NTs sensors. The roles, functions and active sites of NTs were discussed individually. The mechanism behind the detection of NTs using nanomaterials is explained in detail. Different techniques used to carry out NTs sensing in biological samples through the use of nanomaterials are discussed. The main roles of the nanomaterials and techniques are identified in the simultaneous detection of NTs in biological samples. Therefore, recent publications related to the most common NTs detected using nanomaterials by various detection techniques were summarized and discussed in this review.

Table 1
Different Nanomaterials and its characterization.

Nanomaterials	Optical characterization	Morphological characterization
CoPhMoRe@SWCNTs	Fluorescence spectroscopy, Raman spectroscopy,	Visible-Wavelength TIRF Microscopy, nIR epifluorescence microscope, TEM, FE-SEM.
CD@rGO	UV–vis) spectrophotometer, Fluorescence Spectrometer, XPS, X-ray diffraction, FTIR and Raman spectroscopy.	
Carbon Nanopipette.	HPLC, cyclic Voltammogram.	SEM
3D mITO	cyclic Voltammogram	SEM
N-doped reduced graphene oxides	XPS, ATR-FTIR, BET,	SEM.
Cu ²⁺ -BTC based MOF	XRD, FTIR, TGA, cyclic Voltammogram.	TEM.
Au-Pd/NPSS	XRD, cyclic voltammogram.	FE-SEM, EDX.
Ag@HCSs	XPS, XRD, BET, cyclic voltammogram	FE-SEM, TEM, EDS.
FeNPs/NC	XRD, TGA, XPS, Raman Spectra, BET.	SEM, TEM.
GO with six amino acids	UV–Vis absorption, FTIR, XPS, surface analysis spectrometer, Raman spectra, PL spectroscopy, ELISA.	AFM, element analysis, TEM.
Co ₃ O ₄ /Fe ₃ O ₄ /C-loaded g-C ₃ N ₄ nanocomposites	FTIR, XRD, Raman spectra, XPS, BET, cyclic voltammogram.	FE-SEM, HR-TEM, EDX

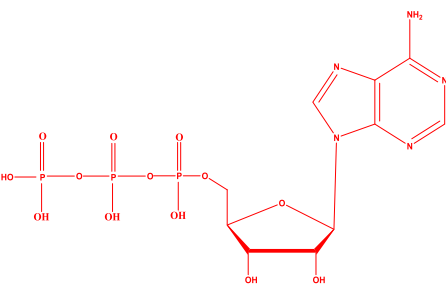
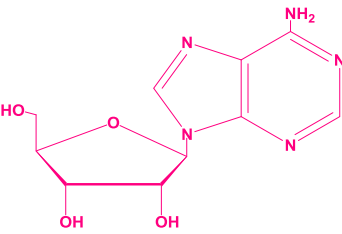
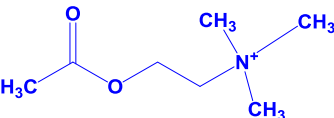
Table 2

Function, associated disease and range of various NTs.

Neurotransmitters	Role	Associated Disease/Treatment	Normal range
 GABA	Inhibitory chemical messenger reduces neuronal excitability, regulate muscle tone	Epilepsy, Mood Disorders.	$0.97 \pm 0.39 \mu\text{M}$.
 Glycine	Inhibitory neurotransmitter participates in motor and sensory functions	Glycine encephalopathy	$15.15 \pm 1.4 \mu\text{M}$
 Glutamate	Excitatory messenger, Plays a role in cognitive functions such as learning and memory	Alzheimer's disease, Autism, Ischemic cascade	10,000–12,000 $\mu\text{mol/L}$
 Dopamine	Involves in the coordination of body movements posture, modulates mood, plays a central role in positive reinforcement and dependency.	Parkinson's disease, Drug addiction, Schizophrenia.	0.5–25 nM (CSF)
 Epinephrine	Plays a role during stress, afraid.	Treatment of anaphylaxis, cardiac arrest.	0–140 pg/mL (764.3 pmol/L)
 Norepinephrine	Alertness, in the body's fight or flight response, body mobilization, guides the brain to in times of danger	Increases blood pressure, Treats septic shock	70–1700 pg/mL (413.8–10048.7 pmol/L).
 Melatonin	Regulation of sleep-wake cycles	Alzheimer's Disease, Circadian Rhythms, Diabetes type 2	10–40 pg/mL
 Serotonin	Regulate mood, social behavior, appetite digestion, sleep, memory, sexual desire	Insomnia, Fibromyalgia, Irritable Bowel	93–902 pg mL ⁻¹ (CSF) 1.37–4.44 ng mL ⁻¹ (Plasma)
 Histamine	Plays a role in allergic reactions, immune response to pathogens	Migraine, hives	388.05 $\pm$ 51.19 pmol mL ⁻¹ (CSF) 39.19 $\pm$ 20.22 pmol mL ⁻¹ (Plasma) 182.4 $\pm$ 126.4 pmol mg ⁻¹ (Urine)

(continued on next page)

Table 2 (continued)

Neurotransmitters	Role	Associated Disease/Treatment	Normal range
 ATP	Autonomic control, sensory transduction, communication with glial cells	neural Dysfunction- Alzheimer's Disease, Parkinson's Disease	2–4 mM
 Adenosine	suppressing, arousing, improving sleep.	Huntington's disease, multiple sclerosis, Lesch-Nyhan syndrome, Creutzfeldt-Jakob disease	30–300 nM
 Acetylcholine	muscle movements, memory, learning.	Alzheimer's disease, Myasthenia gravis	0.1–6 nM
Neuropeptides	Play a diverse role depending on their origin and release	Alzheimer's disease (AD), Huntington's disease, and Parkinson's disease.	Depends on their origin and release
Nitric Oxide (NO)	Affects smooth muscles, dilates blood vessels, increase blood flow	Amyotrophic lateral sclerosis (ALS), Huntington's disease, Ischemic brain injury. Treats pulmonary hypertension, respiratory distress syndrome	The normal range of NO fluctuates, since it is unstable
Carbon Monoxide (CO)	Modulate the body's inflammatory response.	Parkinson's disease	Trace amount
Hydrogen sulfide (H ₂ S)	Regulates intracellular calcium concentration in brain cells	Protects neurons from ischemia –reperfusion injury	50–160 μmol/L

2. Neurotransmitters

Neurotransmitters are a type of chemical messenger that carries, conveys, boosts and balances signals between the neurons to other body cells. They play a major role in everyday life from breathing to body gestures. In addition to their significance in everyday life, they play major roles in several neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, dementia, and epilepsy. Researchers do not yet know how many NTs exist because biomolecules that possess the characteristics of neurochemicals are frequently added to the list of NTs. This nature of neurochemicals urges researchers to study, quantify, and determine their characteristics through the use of diverse techniques. Among the various techniques, the nanomaterial-based approach is acquiring a remarkable place and is becoming more used day by day. Herein, the determination of familiar NTs using different nanomaterials has been discussed. The recognized NTs have been categorized into 6 groups, as shown in (Fig. 1).

2.1. Amino acid neurotransmitters

Amino acid neurotransmitters such as glycine, GABA (gamma-aminobutyric acid), and glutamate are inhibitory and excitatory messengers which play significant roles in the central nervous

system (CNS) as transmitters [8]. Therefore, developing a simple and universal method for the quantitative analysis of amino acid NTs has important applications. The techniques utilized for amino acid NTs detection was micro-dialysis coupled with high performance liquid chromatography (HPLC), in which glutamate was measured directly in the human. It is used to administer testing drugs locally to explore their basic mechanisms of action related with a particular neurotransmitter. In case of GABA determination, the common technique used to measure GABA is micro-dialysis coupled with HPLC, since it is neither fluorescent nor electroactive. Nevertheless, this technique to detect AA NTs faced important disadvantages like much slower, prolonged sample collection time about 20 min and the probe size causes tissue injury and glial scar. To overcome such difficulties analytical and clinical based determination of NTs has been carried out using nanoparticles [9].

Nickel oxide nanoparticles (NiONPs) with large surface area and high conductivity was used to modify glassy carbon electrode (GCE) which together the NiONPs/GCE possesses stable and strong mediation properties was applied for the constant-potential amperometric detection of glycine with the LOD of 0.9 μM and sensitivity of 24.3 nA μM⁻¹, which implies high sensitivity, and no mutual interference has been observed between Gly and other amino acids (AA) [10].

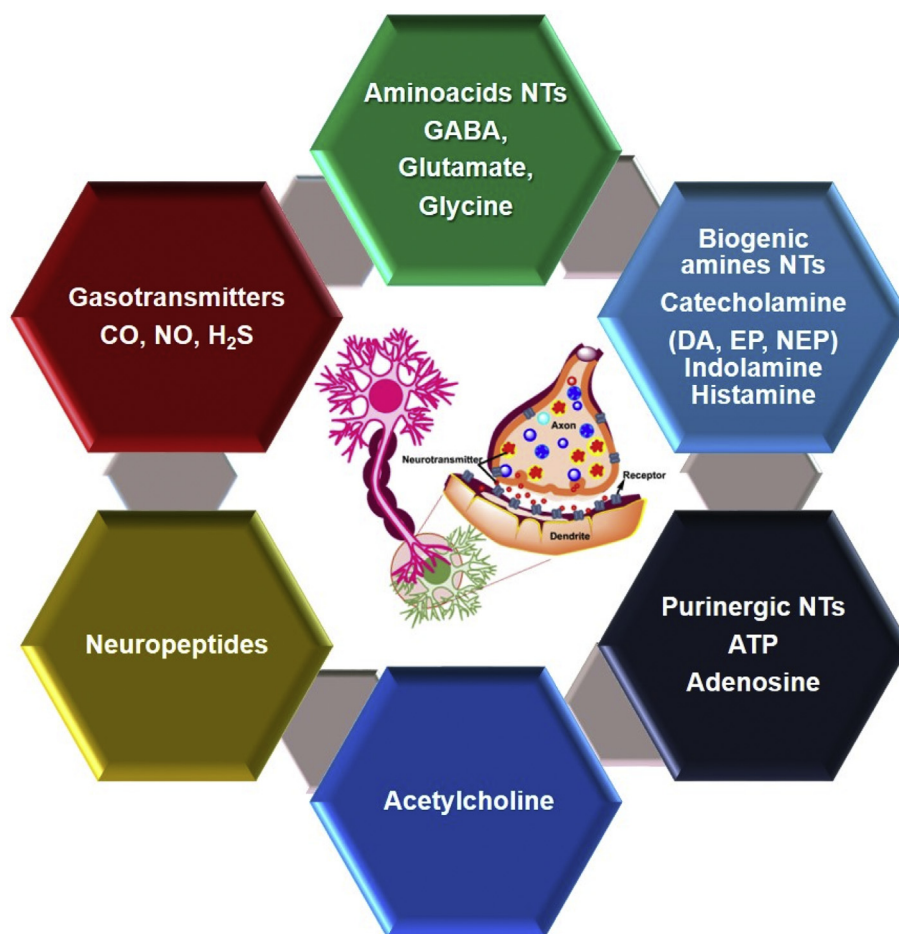


Fig. 1. Different NTs associated with Neurogenic diseases.

It is anticipated that CuNPs with different geometries will affect the specifically chelating status for β - or γ -AAs on the Cu^{II}O surface, which is useful for the detection of α -, β - and γ -AAs. Following this in a report cubic copper nanoparticles (CuNPs) were electro-deposited on screen-printed carbon electrodes (SPEs) using direct-reduction and reduction-oxidation method. Compared with the other CuNPs/SPEs, the RO6-CuNPs/SPEs with the cubic CuNPs characterized by the geometric parameters of a 353 nm-long S_{na} and a Cu^I2O (200)/Cu^I2O face ratio of 0.17 exhibit the largest electroactive area and obvious electrochemical response for detection of GABA based on the high oxidative ability and complexation mechanism, which was in the range of 100–1000 μ M. The superior quality of this approach is the utilization of a surfactant-free method to coat CuNPs onto SPEs, yet the researchers failed to discuss real sample analysis [11]. To overcome difficulty in GABA detection, GABA (isoelectric point (pI) 7.30) was prepared with a positive charge by dissolving in a medium with pH lower than the pI value and silver nanoparticle (AgNPs) which have gained much interest since they have a high extinction coefficient at a low cost, were citrate-capped which possess negative charge causes aggregation of AgNPs due to electrostatic interactions and thus color of solution changed from yellow to green which results in spectrophotometric detection within the linear range of 100–500 mgL^{-1} with the LOD of 57.7 mgL^{-1} . The predominant characteristic of this technique is that it requires a minimal time period of approximately 1 min, follows simple colorimetric procedure to sense GABA when compared to previous report discussed [12]. A tricobalt tetroxide nanoparticles (Co_3O_4 NPs), graphene (GR), and chitosan

(CS) nanocomposite-modified glassy carbon electrode (GCE) was fabricated and possessed high electric conductivity and a large surface area, upon which glutamate was oxidized to form H_2O_2 in the presence of glutamate oxidase (GLOx); this result led to the determination of glutamate within the linear working range of 4.0×10^{-6} to 6.0×10^{-4} M with a detection limit of 2.0×10^{-6} M and a sensitivity of 0.73 $\mu\text{A}/\text{mM}$, along with a low response time of approximately 25 s [13]. Carboxyl-terminated reduced graphene oxide (Crbxl-rGO) and platinum nanoparticles (PtNPs) were used as a supporting and catalyzing medium for the ultrasensitive detection of glutamate, in which it was oxidized to form H_2O_2 in the presence of glutamate dehydrogenase (GLDH), so the linear range was determined to be 0.004–0.9 mM, with a LOD of 0.1 μM and a sensitivity of $973 \pm 4 \mu\text{A}/\text{mMcm}^2$ [14].

2.2. Biogenic amine neurotransmitters

Biogenic amines are low-molecular weight nitrogenous compounds formed by the decarboxylation of amino acids and the transamination of aldehydes and ketones. They include three subclasses of neurotransmitters, which are catecholamines (dopamine (DA), norepinephrine (NE) and epinephrine (EP)), indolamines (serotonin, melatonin) and histamine. These transmitters play salient roles in the central nervous system (CNS) as NTs and take part in a wide spectrum of prominent neuro functions and cognitive phenomena [15]. Since the last decade, nanomaterial-based detection has become more prevalent in the sensing of these NTs.

2.2.1. Catecholamines

The development of DA sensor in presence of excess ascorbic acid (AA) remained a challenging task, which taken into account, an electroanalytical approach incorporated gold nanoparticles (AuNPs) into an anionic polymer on gold electrode which facilitates fast electron transfer kinetics on the surface of the AuNPs and provides electrostatic discrimination between a cationic analyte DA and an anionic interferent AA, which permitted the detection of DA with a LOD of 2 μM in presence of higher concentration of ascorbic acid (1 mM). This method thus paved the way for *in vivo* applications in biological experiments [16]. Graphene-AuNPs composite where graphene possesses good potential as an electrode material and AuNPs provide excellent catalytic activity which together used for GCE modification for electrocatalytic detection of DA. This constructed DA sensor showed a wide linear range (5–1000 μM) and a low detection limit of 1.86 μM and sensitivity was calculated to be 510.2 $\mu\text{A mM}^{-1} \text{cm}^{-2}$ [17]. An edge-plane pyrolytic graphite electrode (EPPGE), which was modified with acid-functionalized single-wall carbon nanotubes (SWCNT) and electrochemically deposited iron (III) oxide nanoparticles (Fe_2O_3), was designed for the electrocatalytic detection of DA. The electronic interaction between the Fe_2O_3 nanoparticles and CNTs enhanced the electrocatalysis of the EPPGE, and the added advantage was that the dihydroxy catechol group of DA is chelated with ferric ion, which allowed the detection of DA within the range of 0.36 μM (LOD) with a sensitivity of 3.44 $\mu\text{A}/\mu\text{M}$, and this modified electrode can be potentially used for DA drug formulation [18]. The fluorescence turn-on detection of DA is based on the intercalating dye Gene-finder (GF), dsDNA and silver nanoparticles (AgNPs), which together called GF/dsDNA-silver nanohybrids, and it has been demonstrated by the Lin group [19]. In this method, upon the addition of DA, which possess high reactivity with AgNPs through catechol interactions, the nanohybrid causes fluorescence enhancement by the release of the GF-dsDNA complex from the nanohybrid, resulting in the determination of DA within the linear range from 0 to 200 nM; the LOD is 6×10^{-9} M. This technique for detecting DA has led to a decrease in the use of sophisticated equipment. An advanced one-pot microwave-assisted synthesis of photoluminescent silicon nanoparticles (SiNPs) was utilized to detect DA in accordance with the principle of fluorescence quenching, in which DA was oxidized to form DA quinone, thus leading to Förster resonance energy transfer from the SiNPs. This approach is simple, cheap and highly selective for detecting DA, with a detection limit of 0.3 nM. The highly fluorescent water soluble nature, zero-dimensional nanostructure, photostable characteristic played the major role in energy transfer during DA detection [20]. Recently, attention has been focused on upconversion nanoparticles (UCNPs) because it shows advantages such as good photo and thermal stability, long luminescence lifetime, narrow emission bandwidth and good signal-to-noise ratios and in consequence of these properties UCNPs have been used for the detection of biomolecules and metal ions. One such type of UCNP, near-infrared-excited $\text{NaYF}_4:\text{Yb}^{3+}, \text{Tm}^{3+}$ nanoparticles were synthesized for the label-free detection of DA. This approach directly detects DA by quenching the luminescent signals of the UCNPs, and it does not require complex modification and functionalization. The luminescent probes revealed a linear relationship between the interference and DA concentration within the range from 0.25 to 150 μM , with an LOD of 124 nM [21].

Cerium-doped hydroxyapatite (Ce-HA) nanoparticles synthesized by the hydrothermal method have applications as a novel biosensor to detect NE with the aid of a glassy carbon electrode. Ce-HA nanoparticles enhance the electrocatalytic activity towards NE due to the strong adsorptive ability and larger surface concentration and undoped HA nanoparticles crystalline structure of about

258 Å and particle size about 40–50 nm also plays a prominent supporting role in NE detection, thus this method exhibits a good linear range of detection of 0.1–200 μM , with a detection limit of 0.058 μM [22].

The characteristics such as good biocompatibility, strong super paramagnetic property, low toxicity, easy preparation and high adsorption ability of NiFe_2O_4 nanoparticles have gained an increasing interest in construction of sensors and biosensors. NiFe_2O_4 with an inverse spinel structure shows ferrimagnetism that originates from magnetic moment of anti-parallel spins between Fe^{3+} ions at tetrahedral sites and Ni^{2+} ions at octahedral sites. Such NiFe_2O_4 NPs exhibit high surface area and low mass transfer resistance was deposited on screen-printed carbon electrode ($\text{NiFe}_2\text{O}_4/\text{SPCE}$) for the sensitive detection of NE, in which NE is electro-oxidized in the presence of NiFe_2O_4 NPs. Using differential pulse voltammetry (DPV), NE was detected with the detection limit of 0.07 μM [23]. The two-dimensional graphene sheet which exhibits extraordinary thermal and electrical conductivity, mechanical stiffness, high specific surface area, electrocatalytic activity and also it holds great potential as window electrode materials and nickel oxide nanoparticles (NiO NPs) which also possess electrocatalytic and conductive properties were combined together to form nanocomposite of structurally uniform and electrocatalytically active material which enhances the surface area for EP determination. In this study, the DPV-based NiONPs sensor detected EP within the range between 1.0 and 1800.0 μM , and the detection limit was 0.42 μM [24]. A nanocomposite of ZnO nanoparticles and graphene has been used in sensing epinephrine due to their low-cost, large specific surface area, being friendly to the environment and high sensitivity on screen-printed electrode acts as an efficient electrocatalyst for the determination of epinephrine, in which EP tends to oxidize electrocatalytically in the presence of ZnO-GO, resulting in the voltammetric detection of EP with the detection limit of 7.0×10^{-7} M [25].

2.2.2. Indolamines

Cobalt hydroxide nanoparticles (CHNPs), which are interconnected nano-flakes with homogeneous average size of about 100 nm and that can be crystallized into a hexagonal layered structure with two polymorphs: α and β , in which α -form have a larger interlayer spacing of about >7 Å are theoretically expected to exhibit superior electro-chemical activity. Multiwalled carbon nanotubes (MWCNTs) which promote electron transfer reactions were used with a carbon ionic liquid electrode (CILE) for the determination of melatonin with a detection limit of 0.004 μM [26]. A composite-coated glassy carbon electrode (GCE), which contained nafion, multiwalled carbon nanotubes (MWCNTs) and $\text{Ni}(\text{OH})_2$ nanoparticles which appears to have a platelet-like shape and with a dimension of 50–80 nm, which could facilitate electron transfer when 5-HT exists in the cationic form, leading to synergistic electrocatalysis effects which result in excellent sensitivity to 5-HT within the range of 0.008–10 $\mu\text{mol L}^{-1}$, with a detection limit of 0.003 $\mu\text{mol L}^{-1}$, along with the simultaneous determination of DA, which is considered to be an added advantage of this approach [27]. Tungsten trioxide nanoparticles (WO_3 NPs) were synthesized by a microwave irradiation method for the sensitive and selective electrochemical detection of 5-HT using gamma-ray. GI- WO_3 NPs show improvement in electroactive surface area of about 0.059 cm^2 and enhanced electron transfer rate of 109 ncm/s when compared to bare GCE of 0.07 cm^2 and 50 ncm/s respectively, allowing 5-HT to be oxidized to form quinone/hydroquinone in the presence of the WO_3 NPs, which results in the sensitive detection of 5-HT over a wide linear range of 0.01–600 μM , with the lowest detection limit of 1.42 nM [28]. A highly selective electrochemical sensor was fabricated based on a modified carbon paste electrode with zinc

ferrite nanoparticles (ZnFe_2O_4 NPs) which provides large effective surface area of about 0.16 cm^2 and increased potential of about 0.26 V with two electron-two proton mechanisms were proposed as the possible mechanism for the oxidation of melatonin, facilitating the chronoamperometric detection of melatonin within the linear range of $6.5\text{--}145 \mu\text{mol L}^{-1}$, with a detection limit of $3 \mu\text{mol L}^{-1}$. This mechanism has been used for the detection of various targets such as epinephrine, acetaminophen and other significant biomolecules [29].

2.2.3. Histamine

Recently, four novel inorganic-organic hybrid nanoparticles (IOH-NPs), $\text{Cu}^{2+}[\text{Calc}]^{2-}$, $\text{Ag}^{2+}[\text{Calc}]^{2-}$ (Calc: calcein, $\text{C}_{30}\text{H}_{24}\text{N}_2\text{O}_{13}$), $\text{Cu}_2^{2+}[\text{PTC}]^{4-}$ and $\text{Ag}_4^{4+}[\text{PTC}]^{4-}$ (PTC: perylenetetracarboxylate, $\text{C}_{24}\text{H}_8\text{O}_8$), which possesses specific advantages like aqueous synthesis method, extraordinarily high dye load of 50–90 wt% and tremendous increase of emission intensity (e.g., 180-times higher emission addition of $100 \mu\text{M}$ of histamine at $510\text{--}520 \text{ nm}$) were synthesized, and the dissolution of the IOH-NPs was directed by histamine, with the release of the respective complexes resulting in the fluorescence detection of histamine within the range of $0\text{--}1000 \mu\text{M}$. In addition to histamine, these IOH-NPs were also used for the fluorescence sensing of other biomolecules such as DA, GABA, adrenaline, heparin, and thyroxine and in allergy diagnostics [30].

2.3. Purinergic neurotransmitter

The existence of purinergic NTs was proposed by Burnstock in 1972, but the concept is still in controversy because it is well known that purines are intracellular constituents, which are effectively involved in various cellular functions. However, several studies on purinergic neurotransmissions initially suggested that purines are released in the extracellular space to act as cotransmitters; subsequent scrutinized studies accepted adenosine triphosphate (ATP) and adenosine as NTs, since they are involved in nerve-mediated functions, neuromodulation and neurodegenerative diseases such as Parkinson's disease [31]. Further consecutive studies on ATP and adenosine ensured its importance, and its detection by a wide assortment of techniques has facilitated the understanding of the pathogenesis of diseases. Among the diverse techniques, nanomaterial-based detection has been receiving attention recently.

2.3.1. Adenosine triphosphate (ATP)

Gold nanoparticles (AuNPs) which have gained much attention because of their high extinction coefficient of about $2.78 \times 10^8 \text{ M}^{-1} \text{ cm}^{-1}$, uniqueness in shape and size ($\sim 10\text{--}20 \text{ nm}$) were coupled with an aptamer and employed as an aptasensor for the calorimetric detection of ATP, in which ATP bound to DNA to form the ATP binding aptamer (ABA)-ATP complex, resulting in different extents of AuNPs aggregation and, thus, color changes from blue to red within the range of $50\text{--}1000 \text{ nM}$. The AuNPs-based aptasensor is novel, simple in design, free from chemical modification & complicated operations and has good sensitivity [32]. A copper nanoparticles (CuNPs) poly T-template with DNA is used as a fluorescent indicator in the label-free aptasensor detection of ATP, in which ABA associated with DNA is folded into the G-quadruplex, resulting in strong red emissions of CuNPs in the presence of ATP. This approach to ATP detection is cost-effective and facile and limits the use of conventional dyes, with a detection limit of 93 nM [33]. The other nanomaterial utilized recently for ATP detection is graphene in the form of foam-collectively called a graphene foam field-effect transistor (GF-FET) biosensor-in which ATP ensures the formation of an ATP-aptamer complex that affects the gate potential of the FET device and alters the drain-source

current, which allows us to detect ATP from the readout of the drain-source current at a certain gate voltage. The major advantage of this technique is that it is label-free, and the detection limit of ATP is 0.5 pM , which is much lower than the levels in previously reported results [34].

2.3.2. Adenosine

Concerning the importance of adenosine in the neurotransmission process, distinct research has been carried out to quantify it. A novel bioassay has emerged based on DNA aptamers and gold nanoparticles (AuNPs), in which the aptamers adhere together in the presence of adenosine, and the subsequent decrease in the surface plasmon resonance of the AuNPs led to a color change from red to purple. The favorable part of this technique is that it takes less than half an hour to finish the whole detection process [35]. The major pitfall to be considered is that its detection limit is in the millimolar range, at 0.25 mM . Silver nanoparticles (AgNPs), which have a higher extinction coefficient than AuNPs, their preparation is economical and also because of its low stability AgNPs been used in few reports together with aptasensor. Recently optical aptasensor based on AgNPs were used for the detection of adenosine which results in the binding of adenosine with AP, and thus, the aggregated AgNPs dispersed in the solution produce color intensity changes, which are monitored accordingly [36]. The AgNPs-based detection of adenosine seems favorable because this method is simple, time-saving, and cost-effective with a detection limit of 21 nM . Since the importance of purinergic NTs has been receiving notice day by day, several approaches have emerged to determine their roles in neurotransmission.

2.4. Acetylcholine

Acetylcholine (ACh) was the first transmitter to be characterized and identified as a neurotransmitter in the peripheral nervous system, and it is associated with attention, learning, memory, consciousness, sleep, and the control of voluntary movements [37]. The disruption of normal ACh signaling is implicated in Huntington's disease, Alzheimer's disease, schizophrenia, and Parkinson's disease. The deposition of tantalum (v) oxide (Ta_2O_5) nanoflakes a high refractive index material ($n \sim 2.2@ 633 \text{ nm}$) functionalized with the acetylcholinesterase (AChE) enzyme over a silver metal coating markedly enhances the electric field intensity at the sensing surface, where ACh interacts with AChE to form choline and acetate, resulting in a surface plasmon resonance (SPR) response, which leads to an increase in the sensitivity to $8.709 \mu\text{M}$ with a detection limit of 38 nM . The ease of handling, compactness and cost efficacy, along with the capability of online monitoring and remote sensing, are the precedented qualities of this biosensor [38]. The co-immobilization of the enzymes AChE and choline oxidase (ChO) onto $\text{Pd}_{\text{nano}}/\text{MoS}_2$ nanocomposites was effectively achieved, and the nanocomposites were electrodeposited onto a gold electrode for the effective sensing of ACh, in which ACh hydrolyzes to choline and acetate in the presence of AChE and choline hydrolyzes to H_2O_2 in the presence of ChO, thus leading to the electrochemical sensing of H_2O_2 and resulting in the linear detection range of $1.0 \text{ nM}\text{--}10 \text{ mM}$, with 1.0 nM as the limit of detection. The supremacy of this approach is that it uses chitosan to enhance the enzyme stability [39].

2.5. Neuropeptides

Neuropeptides (short-chain amino acids) are a type of neurotransmitter produced in the cell body of neurons and released at sites of action different than their origin. Diverse neuropeptides can be prominent, depending on their origin, and they include

somatostatin, β -endorphin, vasopressin, neurotensin, calcitonin, etc. [40]. Concerning the importance of neuropeptides, several quantifying techniques have been developed, noting that nanoparticle-based detection is in the emerging stage.

2.6. Gasotransmitters

Gasotransmitters are endogenously generated molecules of gas. The most common soluble gases identified as gasotransmitters are nitric oxide (NO), carbon monoxide (CO), and hydrogen sulfide (H_2S). They act as signaling molecules for neurotransmission and neuromodulation and play significant roles in learning, memory, nociception and physiological functions [41]. Reduced graphene oxide (RGO) being of active sites and function groups has been widely demonstrated to be able to detect NO_2 , NH_3 , H_2 effectively when compared with graphene. Thus RGO nanosheets were decorated with palladium nanoparticles (Pd-rGO) were used with chemical vapor deposition (CVD)-grown graphene electrodes, wherein NO acts as a donor molecule to increase the conductance of the sensor and thus paves the way its sensing, which ranges from 2 to 420 ppb. The predominant feature of this approach is that comparative study was done using NH_3 , which clearly explained the conductance mechanism [42]. Ultrathin mesoporous In_2O_3 nanosheets were synthesized, which had large surface areas and rich pore channels, and the exposure of NO to In_2O_3 in the nanosheets trapped the free electrons in a process closely related to chemisorption, which facilitated the detection of NO with short response time (ca. 4 s), at a low detection temperature ($120^\circ C$) and with a low detection limit of 10 ppb [43]. Crystalline bismuth ferrite nanoparticles (BFO) because of its lower bandgap (2.2 eV), good thermal stability and long-term reliable properties, it can also be a

suitable material for gas sensing. In this report, facile sol-gel technique based BFO were synthesized for CO detection, where CO creates weak van der Waals bonds with surface-adsorbed oxygen molecules; thus, physisorption will take place. The higher surface-to-volume ratios of BFO were utilized for the efficient sensing of CO, exhibiting rapid response of 25 s and a recovery time of approximately 13 s, with a detection limit of 30 ppm. The superior quality of this approach is that kinetics studies of CO adsorption/desorption were explained effectively [44]. Perovskite oxides are an important group of gas sensing materials owing to its great sensitivity and stability in harsh environments and outstanding affordability of high doping concentration, high temperature and corrosivity. Cerium-doped and Fe_2O_3 -decorated $BaTiO_3$ ($Ba_{0.99}Ce_{0.01}TiO_3$) nanoparticles with sizes of 30–60 nm were prepared by the co-precipitation method for the sensing of H_2S . The mechanism behind this approach is that upon exposure to H_2S , the consumption of electrons occurs, resulting in a thicker electron depletion layer, and thereby, a higher sensor resistance is achieved in the presence of Fe_2O_3 , which shows a fascinating response at low concentrations of 400 ppb, fast response and recovery speeds ($t_{res} = 45$ s and $t_{rec} = 124$ s) and a low working temperature of $150^\circ C$. The most fascinating part of this approach is the utilization of Fe_2O_3 for its catalytic effect, which enhanced the sensing performance [45].

3. Nanomaterials for neurotransmitter sensors

Due to the significant impact of nanomaterials, they have received great attention in biosensing applications, especially in NTs sensor (Fig. 2). The use of such efficient nanomaterials in neurotransmitter sensors has led to a clear enhancement of the

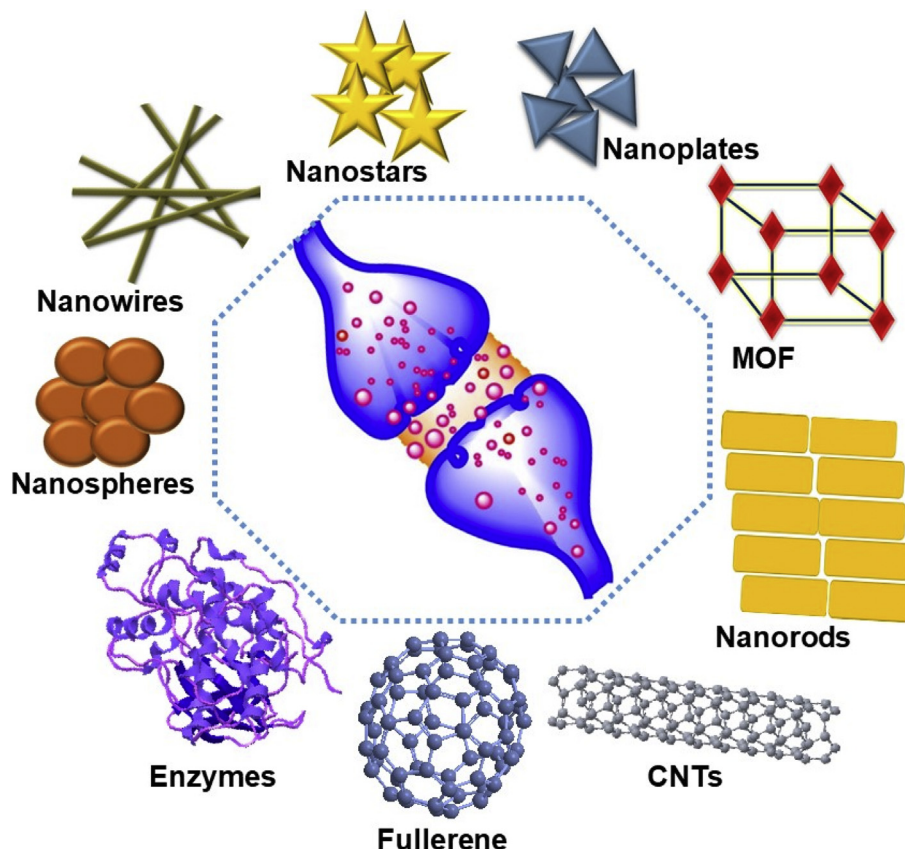


Fig. 2. Various nanomaterials involving in NTs sensor.

detection performance with high sensitivity and selectivity and a lowered detection limit. Different electrode material, analyte and limit of detection in Table 3.

3.1. Carbon-based nanomaterials for NTs sensors

Carbon-based materials are widely used in the biosensor field due to their broad potential range, high surface area, ease of modification, excellent conductivity, low background current, low cost and chemical inertness towards electrolytes. Modified carbon electrodes absorb amines on the surface of the NTs by the quick electron transfer mechanism. A fluorescent-based corona phase molecular recognition (CoPhMoRe) single-walled carbon nanotube (SWCNT) wrapped with thirty different polymers was used for the simultaneous detection of DA, UA, EP leading to quenching or dequenching of fluorescence. The interaction between the nucleic acid-SWCNT and dopamine involves direct physical contact that dopamine is easily oxidized to dopaminoquinone, undergoing further downstream reactions [46]. Graphene oxide reduced electrochemically is made as a composite with carbon dots (CD) through electrochemical deposition on the surface of microelectrode; thereby remarkably providing increased surface area and enhanced electrochemical activity, for selective detection of DA. The presence of CD on GO sheets avoid inter-layer stacking and provide increased surface-area for DA-electrode interaction, additionally increasing the surface charge of the electrode, this enhances the oxidation of DA over a concentration range from 0.1 to 100 μM and a detection limit of 0.02 μM [47]. A novel approach using nano-pipette electrodes (CNPEs) with a diameter of 250 nm were used in the detection of NTs such as dopamine, serotonin, and octopamine. The nano-pipette electrodes are modified with carbon using CVD technique, followed by etching with hydrofluoric acid. Fabricated CNPEs are also compared with carbon fiber microelectrodes (CFMEs) for *in-vivo* detection of DA in *Drosophila* larvae using full-scan cyclic voltammetry (FSCV) over a linear concentration range of 100nM–10 μM with a limit of detection of 25 ± 5 nM [48]. The hydrothermal synthesis of N-rGO/NH₃ from graphene oxide and amitrole (3-amino-1,2,4-triazole) for specific detection of DA over a linear concentration range of 0.5–150 μM with LOD of

410 nM. This lower detection value is because of the higher degree of reduction and improved electrical conductivity. The binding mechanism between the N-rGO/NH₃ is remarkably due to the faradaic process observed at negative potentials related to leuco-dopaminochrome/dopaminochrome redox pair [49].

3.2. Metal-based nanomaterials for biosensors

Metal-based nanoparticles include one-dimensional, two-dimensional (2D) and three-dimensional materials that exhibit high surface areas, good stability, good conductivity, excellent capability, and different morphologies. The properties of a nanomaterial depend on the geometry, oxidation state of metal in the nanoparticles, and physical and chemical environment, which can play the main role in determining the catalytic activity [50]. Metal-based nanoparticles have promising applications in the field of biosensors. In recent years, a different type of metal nanoparticle (Au, Pd, Cu, Ag, Pt, Zn) has been used for electrochemical-based biosensors. Gold and palladium NPs were modified on the nanoporous stainless steel (Au-Pd/NPSS) electrodes for the simultaneous detection of LD and UA. The redox peak for the Au-Pd/NPSS shows 1.4 and it is 1.2 times higher than the other GE modified electrodes, due to the combination of Au/Pd. The underlying mechanism is direct electron transfer kinetics was used for the simultaneous detection of LD and UA within a wide linear range of 5 $\mu\text{mol/L}$ –55 $\mu\text{mol/L}$ and 100–1200 $\mu\text{mol/L}$, with an LOD of 0.2 $\mu\text{mol/L}$ and 15 $\mu\text{mol/L}$ [51]. Gold nanoclusters (AuNCs) immobilized with BSA was used for the detection of EP through fluorescence enhancement. BSA immobilization is attributed for the homogeneous structure of AuNCs. The underlying principle behind the fluorescent enhancement because of the self-polymerization of epinephrine, due to the oxidation of catechol over a linear concentration range of 10–100 μM with a lower detection limit of 587 pM [52]. Core-shell hybrid nanomaterial of MoNPs@f-MWCNTs synthesized via acid condensation method, for electrochemical DA detection. The negatively charged oxygen functionalities of MWCNTs serve as anchoring sites for positively charged MoNPs and binding of DA through electrostatic interactions. The entrapment of f-MWCNTs with MoNPs providing excellent sensing platform through better conductivity and exceptional electron transferability across a wide range of 0.01–1609 μM with a LOD of 1.26 nM [53]. Mesoporous hollow carbon spheres (HCSs) were chosen as a catalyst support, which were produced via SiO₂ as the base template, and AgNPs were decorated on their surface for DA detection. HCSs have abundant mass transport, excellent surface area (568.62 m²/g) and better electrocatalytic activities. Thus, the Ag@HSC composite was used for the detection of DA undergoes ECE mechanism which means electrochemical oxidation of DA to dopaminoquinone over a linear range of 3 μM –7 mM, with an LOD of 0.6 μM [54]. Pyridinium-based task-specific ionic liquid (TSIL) functionalized with hexagonal AgNPs was used for the detection of DA using fluorescence spectroscopy. Herewith, the sensing strategy is based on architectural changes and decreasing size of AgNPs in presence of DA causing a blue shift in localized surface plasma resonance. This study was performed over a wide range of 0.1–7.5 μM , with an LOD of 0.031 μM , and it is applicable for colorimetric real sample analysis [55].

N-doped porous carbon (NC) was formed from the carbonization of ZIF-8 MOF at 800°C under a nitrogen atmosphere. This provides an excellent porosity and large surface area. The FeNPs are evenly distributed in the pores of the NC, producing enhanced detection of DA. The possible reason for the activity enhancement is the presence of radical scavengers such as superoxide (O₂^{•−}) and singlet oxygen (¹O₂) in the colorimetric reaction between TMB and the Fe/NC-800 hybrid. In the presence of DA, the color of the Fe/NC-

Table-3
Different electrode material, analyte, and limit of detection.

Electrode Materials	Analyte	LOD
SWCNT-Polymer	DA	11 nM
rGO/CD	DA	0.02 μM
CNPEs	DA	25 nM
Mesoporous carbon mITO	SE	50 μM
N-rGO	DA	0.25 μM
Cu-MOF	DA	0.092, 0.11 nM
f-CNT/Cu-Mo	DA	5.3 μM
Au-NP/GO	DA, SE	0.56, 7 μM
Au-Pd/NPSS	LD	0.2 μM
Au-NP/HCS	DA	0.6 μM
CuFe ₂ O ₃ /1H3MBr	DXEP	0.09 μM
Co ₃ O ₄ /Fe ₃ O ₄ /mC@g-C ₃ N ₄	DA	0.21 μM
Fe ₃ O ₄ /GRS	DA	0.004 μM
NiO/Ionic liquid	DA	8.613 nM
ZnO-RGO	AA, UA, DA	3.71, 0.33, 1.08 μM
Green-CuO	DA	0.1 μM
N-GE/NiO	LD	17 nM
SnO ₂ /CCY	DA	53 nM
PANI/NiO	DA	0.153 μM
PEDOT/rGO/Fe ₂ O ₃	AChCl	4 nM
OLC-CNF(PAN)	DA	1.42 μM
PPy-MIP	DA, NE, EP	7.972, 3.047, 7.081 μM
Polypyrrole/Cu ₃ O/AgNP	SE	0.0124 μM
MIP/rGO	DA	32.7 nM

800 hybrid decreases over a wide range of concentrations from 0.01 to 40 μM , with a detection limit of 10 nM [56].

A chemical approach was used to detect NTs using graphene oxide (GO) and organometallic complexes. In this study, six amino acids were functionalized with GO, followed by immobilization with seven metal ions, resulting in the production of forty-two different GO nanohybrids. The fluorescence responses of the GO-AA-MI derivatives to DA and NE were modulated by varying the amino acids and metal ions. Tyrosine-modified GO with Fe^{2+} ions (GO-Y-Fe) exhibited fluorescence quenching via electron-hole transfer in valence band selectively for DA, whereas lysine-modified GO with Au^{3+} (GO-K-Au) showed fluorescence enhancement for NE. The developed GO-Y-Fe nanohybrids were able to selectively detect DA with an LOD of 5.5 nM and an assay time of 10 min on respect to other interferents. In addition, GO-Y-Fe was also able to sense DA secreted from PC12 cells in a rapid and simple manner [57].

3.3. Metal oxide-based nanomaterials for biosensors

Transition metal oxides have excellent potential for use with electrochemical NTs because of their excellent catalytic and physicochemical properties (bandgap, stability, nontoxicity and inexpensiveness). Bimetal-based metal oxide nanocomposites were synthesized and used with amorphous carbon nanosheets for the electrochemical oxidation of DA, AA and UA through the high-temperature calcination of Co_3O_4 and Fe_3O_4 to form CoFe-MOFs, showing an intrinsic performance with the addition of mesoporous carbon ($\text{Co}_3\text{O}_4/\text{Fe}_3\text{O}_4/\text{mC}$) to enhance the electrocatalytic activity. The two-dimensional g- C_3N_4 endowed the prepared series of $\text{Co}_3\text{O}_4/\text{Fe}_3\text{O}_4/\text{mC@g-C}_3\text{N}_4$ hybrids with enhanced electro-oxidation activity and high adsorption ability for the detection of DA, AA and UA over a concentration range of 1–70 μM , 500–8000 μM and 5–100 μM with an LOD of 0.69 μM , 24.75 μM and 0.37 μM [58]. The selective detection of DA was achieved based on iron oxide nanoparticle ($\text{Fe}_2\text{O}_3\text{NP}$)-capped graphene sheets (GRS). The $\text{Fe}_2\text{O}_3\text{NPs}$ were synthesized by a pyrophoric technique, and their nanocomposite with GRS was prepared by a sonochemical method. GRS enhances the electro catalytic activity by π - π stacking interaction between the aromatic structure of GRS with DA and $\text{Fe}_2\text{O}_3\text{NPs}$ helps in the sensitive detection of DA through amperometric and DPV over a wide concentration range of 0.006–635 μM , with a detection limit of 0.001 μM [59].

The fabrication of ZnO with reduced graphene oxide was conducted by a one-pot approach at room temperature. This ZnO-rGO composite enhances the electrochemical activity since it has a high surface area and more active sites because of the interfacial interactions between electrode and analyte leading to the simultaneous detection of DA, AA and UA over a linear concentration range of 1–70 μM , 50–2350 μM and 3–330 μM and a detection limit of 0.33 μM , 3.71 μM and 1.08 μM [60]. The UiO-67-bpy composite with electrochemically reduced graphene (ERG) were used to detect the NE. It shows synergistic electro-catalytic effect and lead to enhanced the electrochemical performance towards the NE. Here, UiO-67-bpy and GO-UiO-67-bpy show weak redox activity for NE, due to the weak electron transfer of the MOF and GO. After the addition of ERG to the UiO-67-bpy, it enhances the oxidation state of NE and also used to absorb and activate the analyte for better electron transfer, underlying a mechanism of π - π stacking interaction between the aromatic moieties of ERG-MOF with NE over a concentration range of 0.2–100 μM with a detection limit of 0.026 μM [61]. The green synthesis of CuO nanowires from *Sapindus mukorossi* fruit extract (SMFE) was used for electrochemical DA detection. The interaction between CuO and DA is based on the surface hydroxyl groups ($-\text{OH}$) that undergo chemical bonding

with the positively charged amine group ($-\text{NH}_2$) over a concentration range of 0.1 μM –0.105 mM with a detection limit of 0.1 μM [62]. Nitrogen-doped graphene is formed by the interaction between sp^2 -hybridized carbon atoms and the lone pair electron of a nitrogen atom. N-GE offers many binding sites, as well as improved sensitivity and biocompatibility as an LD sensor. Nickel oxide has good electrical conductivity, low cost, and high stability. N-GE/NiO was prepared for the determination of LD following electro-oxidation mechanism over a concentration range of 0.03–386.3 μM , and the limit of detection was 17 nM [63]. Conductive carbon yarn has excellent intrinsic carrier mobility, electrical conductivity, environmental stability and a low cost of production. The hydrothermal process was used to grow uniform SnO_2 nanosheets on CCY. These nanosheets of SnO_2/CCY could be directly used as the binder-free working electrode for the electrochemical detection of DA underlying a mechanistic approach of DA to dopaminoquinone by exchange of two protons and electrons. The SnO_2/CCY electrode showed a higher sensitivity for DA with a wide linear range of 0.01–150 μM and a detection limit of 53 nM [64].

3.4. Polymer-based nanomaterials for biosensors

Conducting polymers received great attention in 1977 due to the work of MacDiarmid for their potential applications in the fields of batteries, sensors, capacitors, solar cells, electronic devices and electrochromic displays. Intensive studies were devoted to the preparation and characterization of conducting polymers such as polyaniline (PANI), polypyrrole (PPy), polythiophene (PTh), poly(3,4-ethylene dioxythiophene) (PEDOT), diaminonaphthalene (DAN) and their derivatives. Tremendous efforts have been undertaken to combine carbon nanomaterials (CNMs), namely, fullerenes, carbon nanotubes (CNTs), carbon nanofibers (CNFs), graphene and graphene oxide (GO), with polymers because of their superior morphological properties and technological applications [65]. The molecularly imprinted polymer method was used for the selective determination of three NTs DA, NE and EP. Pyrrole (Py) and o-phenylenediamine (o-PD) were used as functional monomers for the synthesis of PPy-MIP to develop an electrochemical sensor. PPy and o-PD were used in an encapsulating polymer because of their packaging density. The MIP polymer, which contains cavities resembling the shape of the target analytes, helps in the specific detection of targets. The detection limits are less than 1.3×10^{-5} M for MIPs [66]. A polyaniline and metal oxide (NiO, ZnO, and Fe_3O_4) nanocomposite showed excellent and fast electron transfer for DA detection. The dynamic range for DA detection was from 2×10^{-5} M to 2.4×10^{-6} M, with detection limits of 0.153×10^{-7} M, 0.166×10^{-7} M, and 0.176×10^{-7} M for the GCE/PANI-NiO, GCE/PANI-ZnO, and GCE/PANI- Fe_3O_4 sensors. The LOD value reveals that GCE/PANI-NiO produces good electrochemical oxidation of DA [67]. The conducting polymer PEDOT with iron oxide nanoparticles ($\text{Fe}_2\text{O}_3\text{NPs}$) and reduced graphene oxide (rGO) was used for the biological sensing of ACh using AChE and ChO. The electrochemical response generated by the oxidation of H_2O_2 is linearly related to Ch and its current is directly proportional to ACh concentration. A fabricated PEDOT/rGO/ Fe_2O_3 nanocomposite was used to modify a fluorine-doped tin oxide (FTO) plate for ACh sensing over a wide linear range of 4 nM–800 μM with a detection limit of 4 nM [68]. Onion-like carbon (OLC) and its carbon nanofiber composites (OLC-CNF), along with the precursor materials polyacrylonitrile (PAN) and OLC-PAN, were synthesized using the electrospinning process for DA detection. The electron transfer properties are in the order of $\text{OLC} > \text{OLC-PAN} > \text{OLC-CNF} > \text{PAN}$, suggesting that OLC is highly conductive, as proven via an EIS study. The reversible electrochemistry of dopamine, are due to the electrocatalytic conversion

of DA to dopaminoquinone via two-electron/proton scheme over a linear range from 3 to 24 μM , with an LOD of 1.24 μM [69]. Polypyrrole was modified with Cu_2O and Ag nanoparticles for 5-HT sensing. Polypyrrole, a conducting polymer, has the ability to oxidize 5-HT chemically with the help of CuO and AgNPs. The sensing strategy underlies an irreversible oxidation of hydroxyl group present in the aromatic ring of 5-HT forming ketone species. The dynamic range of the sensor was from 0.01 $\mu\text{mol/L}$ to 250 $\mu\text{mol/L}$, with low detection limit of 0.0124 $\mu\text{mol/L}$ [70]. A synthesized molecularly imprinted conducting polymer of 5-amino 8-hydroxy quinolone (AHQ) was electrodeposited onto rGO to demonstrate the selective detection of DA. An MIP-modified electrode showed excellent affinity towards DA due to the presence of imprinted sites through hydrogen bonding interactions between DA and the poly AHQ membrane. The detection limit of DA was found to be 32.7 nM over a wide linear range of 0.1–1.4 μM [71].

3.5. Enzyme-based biosensors

Enzymes, which are biological catalysts, paved the way for enzyme-based sensors used to elucidate biological processes, networks, and neurochemicals with predictable substrate selectivity. The sensing of nonelectroactive NTs such as glutamate, ACh, and ATP is discussed because they are hard to detect via standard electrochemical methods [72]. The simple L-glutamate oxidase (GmOx) and chitosan-based amperometric sensing of glutamate was developed, which relies on the electro-oxidation of H_2O_2 produced, which displays a low detection limit of 1.0×10^{-7} M, a linear range from 5.0×10^{-7} M – 2×10^{-4} M, with a sensitivity of $85 \text{ mA M}^{-1} \text{ cm}^{-2}$, and a short response time of 2 s [73]. An enzyme and nanocomposite-based biosensor was fabricated, including GmOx, ceria and titania nanoparticles, in which ceria and titania NPs embedded in the immobilization environment of GmOx minimized the problems associated with low oxygen levels and maintained the proper functioning of the enzyme, which requires oxygen as cosubstrate, enabling the biosensor to work in a hypoxic environment as well as resulting in the active detection of glutamate with detection limits of 0.594 μM and 0.493 μM in oxygenated and deoxygenated conditions, respectively [74]. Screen-printed carbon electrodes have utilized MWCNTs with the integration of the enzyme glutamate dehydrogenase (GLDH) and the cofactor nicotinamide adenine dinucleotide (NAD^+) for the detection of glutamate using the interaction between the enzyme and the electrode surface in the linear range of 7.5–105 μM with a detection limit of 3 μM [75]. A novel amperometric acetylcholine (ACh) biosensor with the immobilization of AChE–ChOx on an electrochemically polymerized PANI–PVS film has been developed for the determination of ACh carried out by the enzymatic oxidation of H_2O_2 in the linear range of 1.0×10^{-7} – 6.0×10^{-7} M [76]. A new approach to covalently immobilize AChE and ChOx on Fe_3O_4 NPs and MWCNTs was used for the amperometric sensing of ACh, in which AChE and ChOx are catalyzed to produce H_2O_2 , resulting in the potential detection of ACh over a linear range of 0.02 $\mu\text{mol/L}$ –1.87 $\mu\text{mol/L}$ with a detection limit of 0.61 nmol L^{-1} [77]. Purinergic NTs (ATP, adenosine) have also been sensed using enzyme-based biosensors with glucose oxidase (GOD) and hexokinase (HEX), which was utilized in an approach for the sensitive detection of ATP based on the simultaneous enzymatic reaction of GOD and HEX in the absence and presence of ATP, respectively, and H_2O_2 oxidation on the working electrode, resulting in the effective determination of ATP with a detection limit of 4–6 μM and a sensitivity of 200–280 nA [78]. The pitfall of this biosensor is that the cost of the enzyme is higher than those of standard reagents, and the sensor also lacks stability due to enzyme denaturation, which has resulted in lesser interest in using enzyme-based sensors

and thus paved the way for the development of simpler nonenzymatic sensors, which have been detailed above.

3.6. Other materials/techniques for NTs detection

A novel biosensor which uses GO, AuNPs and ssDNA along with complementary ssDNA were linked with each other to form dsDNA for the detection of DA and 5-HT using both electrochemical and microdialysis techniques. Initially, for the electrochemical detection of analytes, GCE was modified with GO, followed by the electrodeposition of AuNPs and immobilization with dsDNA for detecting DA and 5-HT over wide linear ranges of 9×10^{-7} M– 7×10^{-5} M and 6×10^{-7} M– 4×10^{-5} M with LODs of 5.6×10^{-8} M and 7×10^{-9} M, respectively. Second, for the microdialysis technique, a microdialysis probe was inserted into blood samples and perfused with a DA and 5-HT mixture at a constant flow rate of 5 $\mu\text{L/min}$ using a perfusion pump for detection over a concentration range from 10 μM to 25 μM , with a recovery rate of 82–118% [79].

Deoxyepinephrine (DXEP), or epinine, is a catecholamine derivative and is detected using copper ferrite nanoparticles (CuFe_2O_4 NPs) and an ionic liquid (1-hexyl-3-methylimidazolium bromide (1H3MBr)). The CuFe_2O_4 was prepared using a sonochemical strategy, and the composite of CuFe_2O_4 /1H3MBr/PE was made as a paste and tightly packed in a glass tube for electrochemical detection. DXEP showed linear proportionality over a wide range of 0.7 μM –300 μM , with an LOD of 0.09 μM [80].

In summary, performance of various nanomaterials has been discussed for detection of neurotransmitters. Among them, carbon and gold based nanomaterials are promising towards NTs detection, due to their important properties such as, controllable and adjustable nature, which includes their size, shape, aspect ratio, and density. It has excellent selective and sensitive property, when they performing individually or composite towards NTs sensor, which ultimately improves the results in the NTs sensing field.

4. Techniques in neurotransmitter sensors

Extracellular NTs concentrations can change rapidly due to the dynamics of neurotransmission in clinical research. The quantitative analysis of NTs plays a front role in keeping ourselves healthy from Parkinson's disease, Alzheimer's disease, etc. To detect and monitor NTs, various techniques such as luminescence, electrochemical, chromatographic detection, microdialysis, and mass spectrometry are available. As an advancement, lab-on-a-chip techniques have proven useful by the combination of biological and analytical systems. Different techniques for NTs sensor were given in Table 4.

4.1. PL-based sensor

Fluorescent biosensors are analytical devices used for the noninvasive detection of biomolecules present in biological samples. The principle behind this study is the fluorescence phenomenon that occurs while electromagnetic radiation is absorbed by fluorophores or fluorescently labeled molecules [81] (Fig. 3).

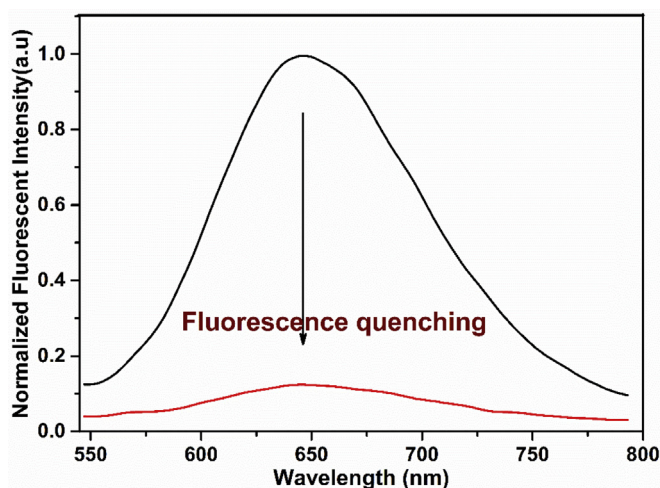
The obtained signal is employed in any of the following techniques:

- FRET (fluorescence resonance energy transfer).
- FLIM (fluorescence lifetime imaging).
- FCS (fluorescence correlation spectroscopy).
- FI (fluorescence intensity).

FRET is a radiation-less energy transfer from the donor to the acceptor fluorophore. The determination is mostly based on

Table 4
Different techniques for NTs sensor.

Nanomaterial	Analyte	Technique	Concentration range	Limit of Detection
SiNPs	DA	Fluorescence Resonance energy Transfer (FRET)	0.005μM–10μM	0.3 nM
BSA-AuNCs	DA	Fluorescence Intensity (FI)	0nM–10nM	0.83 nM
CQDs and CdTe QDs	DA	Fluorescence Intensity (FI)	0μM–2.5 μM	100nM–150nM
H ₂ O ₂ -Cit-AgNPs,	GSH, GSSH,	Chemiluminescence	5μM–800μM	
AgNO ₃ -Cit-AuNPs	Cys		5μM–800μM	
			25μM–100μM	
Met-AuNCs	DA	Electrochemiluminescence	0.1μM–4μM	32 nM
GNS@rGO	GSH	Chemiluminescence	1nM–1μM	0.2 nM
rGO/ILC/CD	EP	Electrochemical	$0.8 \times 10^{-7} \text{ mol L}^{-1}$ – $0.1 \times 10^{-4} \text{ mol L}^{-1}$	$0.0117 \times 10^{-9} \text{ mol L}^{-1}$
Graphene@PBCB	EP	Electrochemical	1μM–1000μM	0.24 μM
AuNPs/MWCNTs	L-Cys	Electrochemical	0.2μM–100μM	0.03 μM
PEDOT/rGO/AgNPs	Ser	Electrochemical	1nM–0.5 mM	0.1 nM
Fe ₂ O ₃ NPs/PEDOT/rGO	ACh	Electrochemical	1μM–120μM	83 nM
CalixareNE	ACh	Electrochemical	1nM–1mM	
TBA/AuNPs	EP	Electrochemical	$9.0 \times 10^{-8} \text{ mol/L}$ – $1.0 \times 10^{-4} \text{ mol/L}$	$7.6 \times 10^{-8} \text{ mol/L}$
PPy/MCM-48	DA	Electrochemical	2μM–250μM	0.7 μM
C18 column	Asp	HPLC		19 μM
	Glu			25 μM
	Gln			116 μM
	GABA			38 μM
DB-5 ms Column	GA	GC-MS/MS	0.5μg/mL–100 μg/mL	100 ng/mL
	GABA			250 ng/mL
BEH amide column	GABA	UHPLC-MS/MS	2.5μg/mL–250 μg/mL	1.82 μg/mL
	Chol		2.5μg/mL–250 μg/mL	0.62 μg/mL
	PyroGlu		0.25μg/mL–25 μg/mL	0.046 μg/mL
	Asn		0.25μg/mL–25 μg/mL	0.088 μg/mL
	Asp		2.5μg/mL–250 μg/mL	1.93 μg/mL
	ACh		0.025μg/mL–2.5 μg/mL	0.012 μg/mL
	Gln		2.5μg/mL–250 μg/mL	1.05 μg/mL
	Glu		2.5μg/mL–250 μg/mL	1.52 μg/mL
	NAA		0.25μg/mL–25 μg/mL	0.25 μg/mL
C18 column	Trp	LC-MS/MS		0.96nmol/L–24.48 nmol/L
	Kyn			
	Kyna			
	3-HK			
	5-HT			
	5-HIAA			
	NE			
	Glu			
	GABA			

**Fig. 3.** Fluorescence quenching based FRET sensor.

quenching of the fluorescence [82]. FLIM is an imaging process applied to living cells, in which a molecule remains excited after absorbing a photon to be detected. This provides information about the fluorophore local environment or energy changes [83]. FCS quantifies the real-time mobility of fluorescently labeled receptors

or ligands within regions of single living cells. It provides information about the kinetics of the thermodynamic processes related to reversible fluorescence changes [84]. FI is a direct measurement of the fluorescence intensity used in investigations of biosensors containing enzyme-bioreceptor complexes [85].

A fluorescence resonance energy transfer (FRET)-based method for detecting DA using silicon nanoparticles (SiNPs) was developed. The possible mechanism of the quenching of fluorescence is that upon exposure to air, DA readily forms dopamine quinone (DA quinone), and the DA molecules get adsorbed onto the SiNP surface due to strong noncovalent interactions (electrostatic and hydrogen bond formation). Here, fluorescence quenching is achieved by the distance between the donor (SiNP) and acceptor (DA quinone) due to the overlap of the emission spectrum of SiNPs with the absorption spectrum of DA quinone, thereby fulfilling the requirement of the FRET process [20]. The DA detection varies over a concentration range from 0.005 to 10 μM, with a detection limit of 0.3 nM.

The progression of DA through different regions of lipid vesicles (1,2-ditetradecanoyl-sn-glycero-3-phospho-(1'-rac-glycerol)) has been studied using 7-nitrobenz-2-oxa-1,3-diazol-4-yl (NBD)-labeled phospholipid molecules tagged to either the head (NBDPE) or acyl region (NBDPG). The DA-induced quenching of NBD fluorescence in lipid vesicles was illustrated by fluorescence lifetime imaging microscopy through the diffusion of DA into the lipid bilayer [86].

The development and use of fluorescence ligand technologies for the binding of GPCR with allosterism and dimerization has recently occurred. The use of a fluorescent ligand is advantageous due to the differences in molecular mass and diffusion characteristics. Fluorescence ligands diffuse freely, with a dwell time of 50–100 μ s upon interaction with membrane-bound receptors. To date, fluorescent ligands have been conjugated with FCS for characterizing adenosine A₁, adenosine A₃, histamine H₁ receptors, β ₂-adrenoreceptors, galani, and somatostatin receptors [87].

A fluorescence intensity-based method for detecting DA was developed using protein-conjugated gold nanoclusters (BSA-AuNCs). The mechanism behind this study is that upon photon emission, BSA-AuNCs electrons were excited to the conduction band from the valence band, thereby forming an exciton (electron-hole pair), which, upon interaction with DA, readily donates protons to BSA-AuNCs to form a stable phenoxide-enolate and form DA quinone (Fig. 4). The fluorescence intensity of BSA-AuNCs was quenched upon the addition of varying concentration of DA via an electron transfer mechanism, showing a linear range from 0 to 10 nM and an LOD of 0.83 nM [88]. A dual-emission molecularly imprinted polymer (DE-MIPs) layer was synthesized using carbon quantum dots (CQDs) and cadmium telluride quantum dots (CdTe QDs) for the variable fluorescence signal and acrylamide (AAM), 4-vinylphenylboronic acid (VPBA) and methyl bisacrylamide (MBAAm) as the backbone monomer, functional monomer, and crosslinker, respectively. In this method, hydrophilic AAM was employed to suppress nonspecific binding in real biofluid samples, and VPBA was used to enhance the specific interaction of DA due to boronate-catechol interaction and B-N coordination between VPBA and DA. Additionally, the carboxyl group of CdTe QDs could electrostatically interact with DA, thus facilitating not only the formation of multiple point interactions but also fluorescence quenching. As expected, the fluorescence spectra of DE-MIPs showed dual color emission at 448 nm and 651 nm, corresponding to CQDs and CdTe QDs, over a varying concentration of DA ranging from 0 to 2.5 μ M with a detection limit of 100–150 nM [89].

4.2. Chemiluminescence

Chemiluminescence involves both luminescence and chemical reactions. The luminescence observed is based on the rate of the chemical reaction, i.e., the number of species excited is proportional to the light emission efficiency. There are two basic approaches

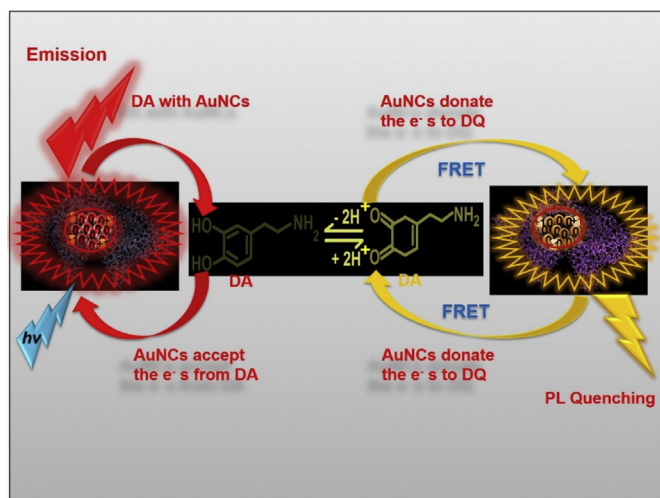


Fig. 4. Fluorescence quenching mechanism for AuNCs with DA.

used to employ chemiluminescence studies for analytical detection: static solutions and flow analysis [90]. The other form of chemiluminescence is electrochemiluminescence (ECL), or electrogenerated chemiluminescence, involving species generation at the electrode surface due to electron-transfer reactions to form excited states that emit light [91].

A chemiluminescence flow analysis-based array was developed for biothiols (glutathione (GSH), glutathione disulfide (GSSG) and cysteine (Cys)) detection using luminol-H₂O₂-Cit-AgNPs and luminol-AgNO₃-Cit-AuNPs. The mechanism behind this detection is that the reducing group (-SH) reacts with active oxygen to form intermediate radicals. The concentration ranges are 5–800 μ M for GSH and GSSG, and 25–100 μ M for Cys [92]. DA detection was achieved using a methionine-gold cluster (Met-Au NCs) nanocomposite, in which methionine acts as a reductant and stabilizer. The ECL property is provided by potassium persulphate (K₂S₂O₈). The ECL intensity is increased by 8-fold after the addition of persulphate. The mechanism behind the system involves Met-AuNCs/S₂O₈²⁻, in which Met-AuNCs shows luminophore activity, while S₂O₈²⁻ acts as a coreactant. The ECL emission mechanism is caused by electron transfer annihilation between the anionic quantum dot radical (R⁻) and the electrogenerated SO₄⁻. The modified GCE shows a linear response from 0.1 to 4 μ M and a detection limit of 32 nM [93]. In addition, this system was also studied for the detection of the analyte released from PC12 cells.

Chemiluminescent flow analysis-based glutathione (GSH) detection was achieved using a gold nanostar@reduced graphene oxide (GNS@rGO) nanocomposite. The chemiluminescence was provided by the luminol-sodium periodate (NaIO₄) system. The mechanism behind the luminescence enhancement is the production of ROS such as the superoxide anion radical (O₂⁻) and OH⁻. The radicals are generated by the reaction between IO₄⁻ ions and O₂ in alkaline solution. The calibration curve exhibits a linear range of 1 nM–1 μ M and a detection limit of 0.2 nM [94].

4.3. Electrochemical sensors

Electrochemical sensors are broadly classified based on the receptor type as bioreceptor- and nonbioreceptor-type. Mostly, bioreceptors are generally preferred due to their high specificity, selectivity and strong interface with the analyte. Electrochemical biosensors are auxiliary divided based on the techniques of study into three types, namely, amperometric, impedimetric and potentiometric, among which amperometric techniques are the most extensively studied. These sensors are further classified based on the bioreceptor type into three categories as enzymes, antibodies, and aptamers. The corresponding initiative in the sensor field was provided by Clark and Lyons in 1962 [95], who developed an enzyme-based glucose sensor. From 1962 until now, remarkable efforts have been made towards the development of new enzyme-based biosensors possessing good chemical and thermal stabilities. A reduced graphene oxide (rGO) composite GCE modified with an ionic liquid crystal (ILC), 1-butyl-1-methylpiperidinium hexafluoro-phosphate and cyclodextrin (GC/ILC/rGO/ILC/CD) was fabricated via mechanical casting. This method provided enhanced conductivity of the composite, since CD provides a unique cavity shape with a hydrophobic inner cavity and a hydrophilic outer surface. This property enables the selective binding of guest molecules into the cavity, forming stable host-guest inclusion complexes. The mechanism behind this complex is the direct interaction with the analyte molecules [96]. The sensor shows good sensitivity for EP determination, with a linear range of 0.8×10^{-7} molL⁻¹– 0.1×10^{-4} molL⁻¹ and an LOD of 0.0117×10^{-9} molL⁻¹.

Graphene modified with polymer poly (brilliant cresyl blue) (PBCB) was fabricated on GCE using the electropolymerization technique, thereby facilitating the detection of EP. In this case, graphene@PBCB promotes direct electron transfer on the electrode surface with a linear range of 1–1000 μM and a detection limit of 0.24 μM using the voltammetry technique [97]. A self-assembled monolayer (SAM) of L-Cysteine modified AuNPs/MWCNTs on a GCE surface shows excellent electrocatalytic activity for the detection of NE in the presence of sodium dodecyl sulfate (SDS). The possible mechanism of the sensor is as follows: (i) the interaction between AuNPs and L-cysteine through the thiol group of L-cysteine forms a strong covalent Au-S bond, and (ii) the interaction between L-cysteine on the AuNPs and NE occurs via electrostatic interaction [98]. The DPV study produced a linear range of 0.2–100 μM and an LOD of 0.03 μM . Nanostructured conducting polymers (PEDOT, polyaniline, polypyrrole) exhibit tunable conductivity, high capacitance, charge carrier mobility, and biological compatibility and are highly stable in aqueous solutions. Therefore, a PEDOT-rGO-AgNPs nanocomposite on a modified GCE acts as a transducer for the detection of 5-HT. The possible mechanistic approach of this sensor was found to be direct electron transfer on the interfacial layer of the electrode [99]. The chronoamperometric study reveals a linear range of 1 nM–0.5 mM and a detection limit of 0.1 nM.

An enzyme-modified detector for acetylcholine (ACh) was produced using Fe₂O₃NPs/PEDOT-rGO nanocomposite-modified fluorine doped tin oxide (FTO). The mechanism behind the ACh biosensing is enzyme-substrate interaction, which is briefly explained as ACh interacts with AChE, thereby producing choline (Ch). The Ch further reacts with choline oxidase (ChO) to form H₂O₂, thereby indicating that the amount of H₂O₂ produced is linearly proportional to the substrate concentration, i.e., ACh [68]. This fabricated biosensor was applied over a wide concentration range of 4 nM–800 μM , with a detection limit of 4 nM. The enzyme-immobilization detection of EP was achieved using GQDs/Lac on GCE. Upon modification with laccase (Lac), cross-linking is formed in such a way that it enhances the electrochemically active surface area of the electrode. The mechanism behind this fabricated biosensor is direct electron transfer between the laccase and the analyte [100]. Here, the voltammetry technique was studied over a wide linear range of 1–120 μM , with an LOD of 83 nM.

A potentiometric sensor for ACh detection with a broad linear range of 1 nM–1 mM was developed using a hydrophilic sulfonate-calixarene in the inner filling solution of an ion selective electrode (ISE) and a hydrophobic calix(4) arene doped into the sensing membrane of the ISE. The developed sensor could provide a new tool for the treatment of neurodegenerative diseases and for studying the enzymatic activity of cholinesterase enzymes in complex matrices [101]. Molecular imprinting polymers (MIP) such as 3-thiophene boronic acid (TBA) have been used as functional monomers for the electrochemical sensing of EP. To enhance the conductivity of the poly(3-TBA) matrix, gold nanoparticles (AuNPs) were also-modified onto a GCE to improve the sensitivity of the sensor. The mechanism behind this study was the covalent interaction between boronic acid and *cis*-diol containing compounds, i.e., EP forming cyclic ester bonds [102]. The modified sensor uses the DPV technique with a linear range of 9.0×10^{-8} mol/L– 1.0×10^{-4} mol/L and a detection limit of 7.6×10^{-8} mol/L.

A gold electrode modified with a polypyrrole-MCM-48 (mesoporous silica molecular sieves) nanocomposite was used for the detection of DA. MCM-48 has a cubic form with a three-dimensional pore structure, exhibiting a high surface area and thermal stability and a large pore volume. The conductivity is also further increased by a conducting polymer, i.e., polypyrrole. Here, DA is determined using cyclic voltammetry (CV) and square-wave

voltammetry (SWV) techniques [103]. SWV shows a linear range of 2–250 μM and a detection limit of 0.7 μM .

4.4. Chromatography-based sensors

Chromatography is a powerful tool for measuring the NTs levels in specific tissue samples and dialysates from patients and animals. High-performance liquid chromatography (HPLC) is the most suitable technology for the simultaneous detection of NTs. Liquid chromatography (LC) with mass spectrometry (MS) has been used to quantify NTs in various biological matrices [104]. However, the derivatization or addition of ion pair reagents was used to achieve good chromatographic separation.

A high-performance liquid chromatography procedure was used for the determination of four different amino acid NTs, namely, aspartate, glutamic acid, glycine, and γ -aminobutyric acid. The samples were derivatized using 2,4-dinitrofluorobenzene, and the amino acids were separated using a C18 column. The LODs were found to be 19 μM , 25 μM , 116 μM and 38 μM , respectively [105]. A rapid and selective method for the quantification of L-glutamic acid (GA) and γ -aminobutyric acid (GABA) was developed using gas chromatography-mass spectrometry (GC-MS/MS). The GC column used for this study was DB-5 ms, and the samples were derivatized with the MethElute reagent under hot conditions. The calibration method was linear from 0.5 $\mu\text{g/mL}$ – 100 $\mu\text{g/mL}$, with limits of detection of 100 ng/mL and 250 ng/mL for GA and GABA, respectively [106].

The simultaneous detection of nine NTs, asparagine (Asn), aspartic acid (Asp), glutamic acid (Glu), glutamine (Gln), γ -aminobutyric acid (GABA), N-acetyl-L-aspartic acid (NAA), pyroglutamic acid (PyroGlu), acetylcholine (ACh) and choline (Ch), was achieved using ultra-high-performance liquid chromatography with tandem mass spectrometry (UHPLC-MS/MS). An ethylene-bridged hybrid inorganic-organic (BEH) amide column and a 50 mM ammonium formate gradient were selected after optimization of the column for further validation [107].

A liquid chromatography-tandem mass spectrometry (LC-MS/MS) method was developed for the detection of Trp, L-kynurenine (Kyn), kynurenic acid (Kyna), 3-hydroxykynurenine (3-HK), 5-HT, 5-hydroxyindoleacetic acid (5-HIAA), NE, L-glutamic acid (Glu), γ -aminobutyric acid (GABA) and ACh. Chromatographic separation was achieved using an ultra-aqueous C18 column in combination with gradient elution within 8 min [108]. This method provided good sensitivity and selectivity for the calibration curves of each analyte, and their correlation coefficients were >0.99. The limit of detection of the various analytes ranged from 0.96 nmol/L – 24.48 nmol/L.

5. Multiple-neurotransmitter sensors

The detection and monitoring of different neurotransmitter analytes in real time is carried out using the next generation of neurotransmitter sensors to cure diseases in the early stage. The detection of multiple NTs helps to understand and produce important insights into the brain chemical behaviors and concentration fluctuations that lead to neurodegenerative diseases. An amperometric detection circuit time-based CMOS potentiostat sensor was developed for the detection of DA and glutamate at different concentrations. The working electrode was functionalized with a chemical coating of CNT for selectivity and sensitivity [109]. A multichannel Cu(II) phenanthroline-modified α HL nanopore was developed for the detection of six important NTs.

The neurotransmitters were distinguished by the dwell times versus the current blocks and by the visual inspection of a current recording. The authors suggest that this sensor has the potential for

ex vivo and *in vivo* use and that it might be combined with the recent technological innovations to produce a key outcome in pharmacology tools [110]. EP and NP sensors were investigated using a different composite of metal oxide nanomaterials with the enhancement of oxidation properties, with the linear ranges of 7.5–56 μM and 7.5–48 μM , respectively. Kinetics limitations play an important role in sensitivity; moreover, high sensitivity is not reliable to the limit of detection, and background noise is also involved in the sensitivity. An interference study was performed with a 30-fold AA concentration containing an excess of EP, and there is no significant interference with the EP [111].

Dopamine and 5-HT are important NTs which play main roles in brain activities. Compared to DA, 5-HT is much more difficult to detect due to the formation of reactive species after oxidation of the electrodes. The co-detection of DA and 5-HT using carbon nanotube-modified electrodes was performed through fast-scan cyclic voltammetry. A carbon nanotube can help reduce fouling by biomolecules. Based on the fast scan rate and potential current, a sensor was developed [112]. A Nafion/ $\text{Ni}(\text{OH})_2$ -multiwalled carbon nanotubes-modified glassy carbon electrode (Nafion/ $\text{Ni}(\text{OH})_2$ -MWNTs/GCE) was fabricated for the detection of DA and 5-HT in the presence of AA with the detection limits of 0.015 $\mu\text{mol L}^{-1}$ and 0.003 $\mu\text{mol L}^{-1}$, respectively. In this method, Nafion helps to attract the cationic species to pass through the electrodes, which is in contrasts to the case for anionic species. In the interference study, AA and UA produced no interference during the detection of DA and ST, because the AA and UA were present in the anionic form and DA and ST were in the cationic form [27].

Molecularly imprinted polymers were anchored to two differently colored quantum dots for the simultaneous detection of NE and EP with detection limits of 9 nm and 12 nm, respectively. The pH, incubation time and concentrations of nanomaterials are the main factors affecting the detection limit. The methyl group is the only difference between NE and EP, and it provides an active site for quantum dots with a polymer to influence the selectivity and sensitivity [113]. Expanded HPLC techniques with an electrochemistry method were developed for the simultaneous detection of glutamate, glutamine (Gln), and γ -aminobutyric acid (GABA), with a detection linear range of 0.1–3.2 ng/ μL in rat brain homogenates. The methanol percentage, pH, temperature, flow rate, and several other parameters were different for those used in previous works to obtain the perfect protocol for amino acid quantification with a low-cost and simple technique [114].

6. Detection of NTs in real samples

The detection of NTs in real samples plays an important role in therapeutic interventions, monitoring of disease states and early diagnoses. Accordingly, most research deals with the CSF, serum samples, urine and medicine samples, and it also focuses mainly on selective NTs such as GABA and catecholamines.

6.1. Serum and urine samples

Simple sensing elements of gold nanorods with silver nitrate were capable of the selective detection of catecholamines in urine samples by a colorimetric sensor. Due to the similar structures of DA, EP, and NE, developing the sensor was more challenging compared to individual sensors. The sensor array was built using binary (DA-EP, DA-NE, and EP-NE) and ternary (DA-EP-NE) mixtures of the analytes at the concentration level of 10 $\mu\text{g mL}^{-1}$. The final result shows completely different patterns from those of their individual structures [115]. Moreover, a DA sensor was developed using porphyrin-functionalized graphene for application in both human urine and serum samples via a hydrochloride injection

method. The electrostatic interaction and π - π staking between DA and the polymer can help enhance the sensitivity, and it also decreases the interference from other molecules [116]. Low-cost resorcinol has been employed to create a fast, simple and sensitive fluorescence-based DA sensor with the LOD of 1.8 nM, and 97–103% recovery was observed. The fluorescence-quenching sensor is based on the photoinduced charge transfer between the DA and fluorescence materials [117].

Ink-type graphene-based screen-printed electrodes have wide potential due to characteristics such as low background currents, fast electron transfers and disposability. This electrode type possesses good conductivity towards AA, DA, and UA in real samples of vitamin C injection, hydrochloride acid, and human urine, respectively. The developed sensor holds great potential for use in clinical applications [118]. Hierarchical carbon-nitrogen nanospheres with nickel oxide echinop flowers (CN@HDN) were used for the detection of EP in human serum at the detection limit of 4 nM. The sensitivity was due to the high surface area pore distribution, unique structure, adsorption, and diffusion of molecular and active sites of the CN@HDN-modified electrodes [119]. PPyNPs and AuNPs (polypyrrole nanoparticles decorated with gold nanoparticles)-based electrochemical methods were developed for the detection of 5-HT in human serum samples [120]. Because the oxidation potential of DA, NE and other molecules are very close to that of 5-HT, it is very difficult to detect the other molecules. The surface area and active site are the two main factors behind the high sensitivity towards NTs.

6.2. Pharmaceutical samples

Epinephrine was detected by a carbon paste electrode modified with graphene and ferrocene derivatives in an EP injection and folic acid tablet with the LOD of 27 nM. The EP was oxidized due to the high surface concentration of the electro catalyst, and the charge transfer was controlled by the different concentration of EP compared to those of the other molecules [121]. The oxidation of the EP sensor was investigated in an EP ampule drug sample using a DDPT/GO/CPE (carbon paste electrode with graphene oxide nanosheets and a hydroquinone derivative) at the detection limit of 0.65 μM . Moreover, the developed sensor was capable of the simultaneous detection of EP, DA, and ACh [122]. The large surface area of the GC/(CNTs-ILC)/Crown (Multi-walled carbon nanotubes-ionic liquid crystals and crown ether on a glassy carbon electrode surface) can produce stable host-guest interaction between the ethers in the crown and NTs. Accordingly, it exhibits the highest potential electrocatalytic activity toward 5-HT with the detection limit of 0.203 nM [123].

6.3. Commercialized application in neurotransmitter sensor

The complicated modification procedure and chemistry have limited the commercialization of the sensor. In 2018, blood based amyloid- β markers in plasma were demonstrated by using mass spectroscopy. Furthermore, individual and composite biomarkers (amyloid- β precursor protein (APP)669-711/amyloid- β (A β)1-42 and A β 1-40/A β 1-42 ratios, and their composites) were used to define the amyloid- β -positive or -negative status by the PET imaging from the two set of human samples. The composite biomarkers provide the standard and high accuracy value towards amyloid- β -PET burden and levels of A β 1-42 in cerebrospinal fluid. However, before the clinical applications several issues like, validation study, standardized operating procedures, evaluation of remains biomarkers tools, and performance for different diagnosis need to be addressed [124]. Recently, Prof. Huilin Shao et al., developed an analytical platform for multi-parametric analysis of

amyloid β proteins-exosomes-bounds vs. unbound directly from blood. Prefibrillar A β aggregates preferentially bind with exosomes. The population of A β bound were measure directly from AD and control blood samples. Compared to the unbound and other circulating A β , the A β bound to the exosome could be better reflect in the PET imaging of brain amyloid plaques and numerous clinical groups. The current invention is expected in market within five years and at present in discussion for commercialize with the industries partners [125].

6.4. Nanoparticles free diagnostic techniques

The other techniques used for reliable determination of neurotransmitters both *in vivo* and *in vitro* are liquid chromatography (LC), capillary electrophoresis (CE), microdialysis, coupled with high performance liquid chromatography (HPLC), fast scan cyclic voltammetry. Some other techniques carried out in real time determination of brain functions since neurotransmitters involve much in brain activity are electroencephalography (EEG), magnetic resonance imaging (MRI), proton nuclear magnetic resonance (PNMR).

Microdialysis is preferred technique to monitor several neurotransmitters, which has gotten a big impact during 1970's because of its accurate determination of neurotransmitters utilizing HPLC. Above all it faced major disadvantages like poor temporal resolution which depends on the speed of sample collection (2 μ l/min) and insertion of the probe itself that causes a local injury. With advancement in HPLC systems, capillary electrophoresis (CE) method has been emerged, it also faced the problem like handling small volumes of sample became an issue and took much time for separation and analysis. Imaging techniques like MRI, PNMR involves patients to be faced with high radio frequency waves, which some way causes a serious problem. To overcome all such problems like separation and the detection, the field of biosensors has been emerged utilizing fluorescent sensors, electrochemical sensors coupled with nanoparticles.

Biosensors have allowed the monitoring of changes in NTs with good temporal and spatial resolution and also allowed the NTs to be studied simultaneously. The use of biosensors with NPs opens the possibility to obtain sufficient sensitivity and selectivity to correlate changes with particular neurotransmitter in real samples including blood, serum, urine, plasma and cerebrospinal fluid [9].

7. Summary and future prospectus

In this review, we have comprehensively discussed various NTs, nanomaterials and detection techniques of NTs in the current research. However, several issues should still be pointed out concerning NT sensors in terms of early detection, sensitivity, and selectivity. The mechanisms behind the sensor interaction with the target, nanomaterials, and sensing techniques are discussed individually. However, the sensing mechanisms for some NTs are still having problems. The analysis of NTs is the main challenge in the rapid and accurate detection of neural disorders. A selective and sensitive method for the monitoring of NTs is in high demand. It can also be used to optimize NTs imbalances in the early stage to prevent severe diseases.

To date, nanomaterials-based analytical techniques have tended to focus on enhancements of sensitivity and selectivity. Robust and easily fabricated nanomaterials-based working systems would able to facilitate a new type of experiments and play a critical role in understanding neurotransmissions and neuromodulators [126]. Various parameters are critical to the performance of a sensor, including high sensitivity and selectivity that are satisfactory for the level of concentration of the NTs in real samples and are high

enough to compensate for the abundant interference presented in real samples. Moreover, many NTs have similar molecular structures and physicochemical properties, which presents the major challenging task in the simultaneous detection of NTs. Many types of nanomaterials are involved in the fast and accurate detection of NTs by various techniques. Current research is focusing on tests that can measure the biological signals of diseases related to NT-deficiency diseases. In the future, these inventions may take NTs research to the next level and may be used for accurate diagnoses before the onset of symptoms.

Acknowledgement

This research was supported by the National Research Foundation of Korea grant funded by the Korea Government (No. 2017R1A2B4004700).

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