

# Carbon nanomaterial based electrochemical sensors for biogenic amines

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**Abstract** This review describes recent advances in the use of carbon nanomaterials for electroanalytical detection of biogenic amines (BAs). It starts with a short introduction into carbon nanomaterials such as carbon nanotubes, graphene, nanodiamonds, carbon nanofibers, fullerenes, and their composites. Next, electrochemical sensing schemes are discussed for various BAs including dopamine, serotonin, epinephrine, norepinephrine, tyramine, histamine and putrescine. Examples are then given for methods for simultaneous detection of various BAs. Finally, we discuss the current and future challenges of carbon nanomaterial-based electrochemical sensors for BAs. The review contains 175 references.

**Keywords** Biogenic amines · Carbon nanomaterials · Electrochemical sensors · Review

## Introduction

Biogenic amines (BA) are low-molecular-mass biogenic substances with one or more amine groups, which display important biological activities. They exist in many foods, in

which they are mainly produced by microbial decarboxylation of amino acids or by animation and transamination of aldehydes and ketones [1, 2]. Generally, BA are classified into two distinctive categories: endogenous and exogenous BA. Endogenous amines are produced in many different tissues (for example: adrenaline in adrenal medulla, dopamine in head issuing grave and the pituitary gland and histamine in mast cells and liver). These amines are transmitted locally or via the blood system. The exogenous amines are directly absorbed from food in the intestine. They can be found at low concentrations in non-fermented food such as fruits, vegetables, meat, fish, chocolate, milk and at high concentrations in fermented foods as a result of a contaminating microflora exhibiting amino acid decarboxylase activity. BA are of concern in relation to food hygiene. High amounts of certain amines may be found in food as a consequence of the use of poor quality raw materials, contamination and inappropriate conditions during food processing and storage [3, 7]. BA are potentially toxic organic compounds, trace BA are normal active ingredient in the human body and play important physiological functions in human cells, but excessive intake of BA (especially at the same time intake of a variety of BA) will cause a series of allergic reactions, such as headache, nausea, palpitations, hypertension, and respiratory disorders even life-threatening conditions. Therefore, the importance of the estimation of the levels of BA in food and beverage is linked with their impact on food quality and human health.

Several authors reviewed the occurrence of BA in food [4–6] and as well as their analytical methods [7]. Until now, BA has been determined by several techniques such as thin-layer chromatography (TLC) [8, 9], gas chromatography (GC) [10, 11], high performance liquid chromatography (HPLC) [12, 13], ion chromatography (IC) [14, 15], capillary electrophoresis (CE) [16, 17]. Although these methods can offer good selectivity and low limit of detection (LOD), they often

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require complex pretreatment steps and expensive instrumentations. Thus, alternative approaches for BA detection are necessary. Electrochemical sensors provide a crucial analytical tool as demand for sensitive, rapid, and selective determination of analytes increases. Unlike spectroscopic and chromatographic instruments, electrochemical sensors can be easily adapted for detecting a wide range of analytes, while remaining inexpensive. Additionally, these sensors are capable of being incorporated into robust, portable, or miniaturized devices, enabling tailoring for particular applications. So it will be promising to apply electrochemical technology and develop novel sensors for the fast and sensitive determination of BA.

Nanomaterials with sizes or features ranging from 1 to 100 nm in one or more dimensions [18, 19] have attracted strong scientific and technological interests in recent years. They have shown great promise in many applications of analytical chemistry, such as in sample preparation [20, 21], separation [22, 23], and sensing [24–26] because of the unusual mechanical, electrical, electronic, optical, magnetic, surface and biological properties not found in conventional materials. In the analytical chemistry field, the huge interests in nanomaterials are driven by their exceptional properties. Apart from high mechanical strength, low weight, unique size and structure, their surface properties (area, roughness, energetics, and electron distributions) [27], which enable improved interactions with many biological entities [28], offer excellent prospects for designing novel sensing systems and for enhancing the performance of bioanalytical assays.

The discoveries of carbon nanomaterials (CNs), such as zero-dimensional (0D) fullerenes, one-dimensional (1D) carbon nanotubes (CNTs), two-dimensional (2D) graphene and three-dimensional (3D) nanodiamond substantially contributed to the fast development of nanoscience. Due to their unique properties (almost taking full advantage of nanomaterials), CNs have attracted considerable interests in many fields of research, including materials sciences, microelectronics, biomedicine and analytical electrochemistry [29]. A series of excellent properties of CNs such as chemical stability, high surface area, wide potential window, biocompatibility, enhanced electronic properties, and electrocatalytic activity for a variety of redox reactions make CNs appealing for sensing applications. In most cases, the CNs can increase the electrode area, enhance the electron transfer between the electrode and analytes, and/or act as catalysts to increase the efficiency of electrochemical reactions [34]. Therefore, CNs-based sensors generally have higher sensitivities, lower LOD, and faster electron transfer kinetics than traditional detection electrodes.

It is worth mentioning recent reviews that focus on different aspects of the application of various nanomaterials to analytical chemistry [30–33] and some reviews that focus CNs and their applications [34–37]. However, to the best of

our knowledge, reviews on determination of BA with CNs are quite few up to now. Hence it is the aim of this article to summarize recent advances towards the use of CNs based electrochemical sensors for the detection of BA.

## Carbon nanomaterials

Carbon is the earliest element discovered and used by human. Classical allotropes of carbon are known to be graphite, diamond, and amorphous carbon for a few thousand years. Several new allotropes of carbon (eg. nanodiamond, fullerenes, carbon nanofibers, CNTs, graphene and their derivatives) have been discovered in the past 30 years. These allotropes of carbon called as CNs, which have attracted considerable interests among nanostructured materials for their unique mechanical, thermal and electrical properties as well as for their biocompatibility [38]. Recently, CNs including CNTs, graphene, and their derivatives have been acknowledged to possess great potential to develop materials for a variety of applications such as adsorbent [34, 36], catalyst [39], batteries [35], capacitors [35], electrochemical sensors [37, 40], supports for biomacromolecules immobilization [41] and drug carrier [42] due to their unique properties (mainly displaying in their large surface areas and excellent mechanical and electronic properties).

The physical, chemical, and electronic properties of CNs are strongly coupled to carbon's structural conformation and its hybridization state [43]. According to orbital hybridization theory, this promotion allows carbon to hybridize into a  $sp$ ,  $sp^2$ , or  $sp^3$  configuration based on bonding relationships. These mutable hybridization states account for the diversity among carbon's bulk configuration (Fig. 1). The following contents of this sub-section focus on two kinds of CNs (CNTs and graphene). Their structures, basic properties, preparing methods and electrochemical applications are discussed briefly.

### Carbon nanotubes

Since the discovery of CNTs in 1991 [44], researches on CNTs have progressed rapidly and become one of the most attractive part of nanotechnology. Generally, CNTs can be divided into two types (Fig. 2): single-walled CNTs (SWCNTs) which consist of a single tube of graphite and multi-walled CNTs (MWCNTs) which consist of several concentric tubes of graphite fitted one inside the other. SWCNTs are  $sp^2$  hybridized carbon in a hexagonal honeycomb structure that is rolled into hollow tube morphology. MWCNTs have a complex structure with each carbon layer having different chirality and electronic properties. The diameters of CNTs can range from just a few nanometers in the case of SWCNTs to several tens of nanometers for

MWCNTs. The lengths of the tubes are usually in the micrometer range. Detailed information of the CNTs structures, dimensions and properties can be found in the many published articles [45–47].

CNTs are primarily synthesized by three main techniques: arc discharge, laser ablation /vaporization, and chemical vapor deposition (CVD). Most commercially available CNTs are formed by CVD. Regardless of the method of synthesis, metal impurities remain the sample and affect the CNTs properties, even after some purification processes. The electrocatalytic behaviors of CNTs are unclear and somewhat controversial. Bank et al. [48, 49] think electrocatalysis of CNTs is attributed to edge-plane like sites, occurring at the nanotube open ends. However, subsequent researches pointed out that metal impurities arising from the CVD carbon nanotubes fabrication process might play an important role in the electrocatalytic property of CNTs [50–52].

Due to their large surface area, good conductive ability, excellent electrocatalytic ability, high surface activity and good biocompatibility, the CNTs have been widely used in sensing applications [53–56]. CNT-based sensors generally possess higher sensitivities, lower LODs, and faster electron transfer kinetics. Electrode performances depend on the synthesis method of the nanotubes, modification of CNTs surface, the method of electrode attachment, and the addition of electron mediators. Especially, the functionalization of CNTs surface, which can not only preserve their original properties but also bring in new properties, will broaden the applications of CNTs in electroanalysis. Generally, CNTs can be functionalized by covalent and non-covalent methods. Covalent functionalization of CNTs is to convert the CNTs sidewalls to nanotube-bound carboxylic acids upon oxidation and then functionalized with a range of groups such as amides, thiols, or others. The CNTs sidewalls functionalized noncovalently by, for example, aromatic compounds, surfactants, polymers, and DNA employing  $\pi$ - $\pi$  stacking or hydrophobic interactions for the most part can also alter the electrochemical properties of the material. Some recent reviews have introduced the functionalization strategies and the research carried out using functionalized CNTs for electroanalytical and bioanalytical applications [57–59].

## Graphene

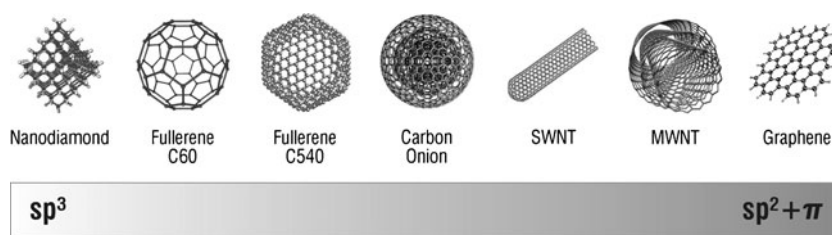
Graphene has emerged as a rapidly rising star on the horizon of materials science and condensed-matter physics in recent years [60, 61]. It has attracted appreciable attentions to be used as a next generation CNs and shown great promise in many applications, such as electronics, energy storage and conversion, and bioscience /biotechnologies due to its exceptional physicochemical properties including high surface area, excellent thermal conductivity and electric conductivity, and strong mechanical strength [62].

Graphene is a 2D sheet of carbon atoms in a hexagonal configuration with atoms bonded by  $sp^2$  bonds. It is the thinnest known and the strongest ever measured material in the universe [63]. Graphene can be considered as a basic building block for CNs of all other dimensionality (Fig. 3). It can be stacked to form 3D graphite, rolled to form 1D nanotubes, and wrapped to form 0D fullerenes. Electrons can move freely in the crystal of graphene owing to the existences of  $\pi$ -orbitals in the graphene plane, which makes graphene show superior electronic transmission performances [64]. On the other hand, every carbon atom is linked with adjacent carbon atom under the action of strong  $\sigma$  bonds and weak  $\pi$  bonds, which make graphene, possess excellent mechanical properties [65].

Up to now, several physical and chemical methods have been proposed to produce individual graphene or its derivatives, for example, mechanical exfoliation of bulk graphite, epitaxial growth on SiC, epitaxial growth by CVD of hydrocarbons on metal substrates, unzipping of CNTs, and chemical reduction of graphite oxide. Among these methods, mechanical exfoliation of highly oriented pyrolytic graphite remains to be the most popular and successful in producing single or few layers of graphene [64]. However, it is not suitable for mass production. Other methods, such as epitaxial growth on SiC and the metal-supported epitaxial growth of graphene via CVD, will be potential mass-production methods with the aim of producing graphene for electronics applications [66, 67]. Another mass-production method is chemical reduction of graphite oxide. Most of graphene used in electrochemistry applications are produced with this method. Graphene obtained from this method usually has abundant structural defects and functional groups which are advantageous for electrochemical applications [62].

In comparison with CNTs, graphene exhibits potential advantages of low cost and high purity (graphene does not contain metallic impurities as CNTs do) [68]. Some reviews summarize the electrochemical applications and advancements of graphene recently [69–71]. In particular it is worth mentioning two reviews that focus on recent advances in graphene-based electrochemical sensors and biosensors [62, 68]. Generally, remarkable properties of graphene for electrochemical sensing and biosensing are mainly manifested in two aspects: (1) The specific electronic structure of graphene, which contributes to its high electrical conductivity and uniform electroactive site distribution and density [68], leads to excellent catalytic behaviors and increase of electrochemical responses toward small biomolecules; (2) Due to large surface area, biocompatibility and high conductivity, graphene is expected to immobilize enzymes and promote the electron transfer between electrode and enzymes. As a novel CNs, graphene and its derivatives have exhibited excellent electrochemical properties for the

**Fig. 1** Hybridization states of CNs. Many chemical and electronic properties of CNs are determined by the dominant hybridization state of the carbon-carbon bonds. Reprinted from [36]



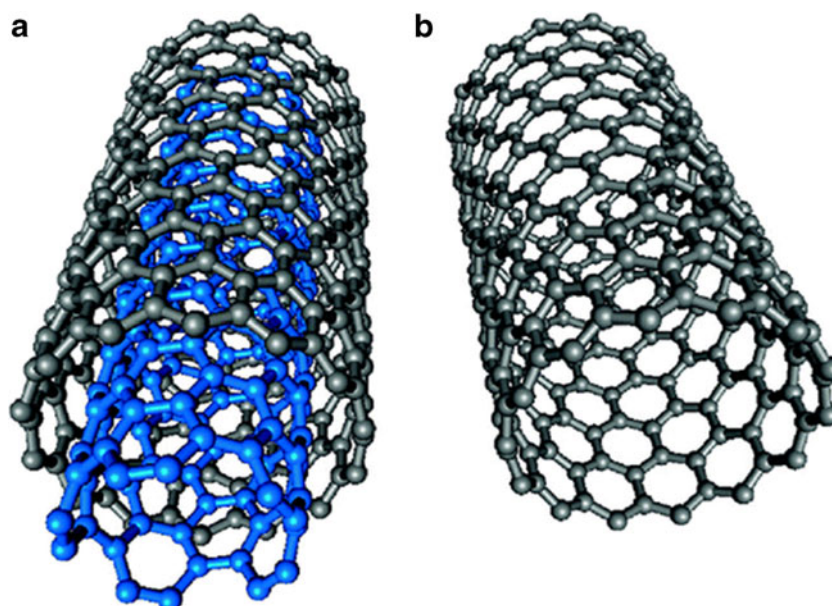
direct electrochemistry of enzymes [72, 73], electrochemical detection of biological small molecules [74, 75] and electrochemical sensor for heavy metal ions [76, 77].

### CNs-based electrochemical sensors for biogenic amine neurotransmitters

During the long-term evolution of creatures on earth, kinds of neurotransmitters emerged. Neurotransmitters are endogenous chemicals that transmit signals from a neuron to a target cell across a synapse. In the brain, neurotransmitters are released into the cerebrospinal fluid via exocytosis and cleared by transporters or metabolism. Extracellular neurotransmitter concentrations can change rapidly and understanding the dynamics of neurotransmission is important for clinical research. There are many different ways to classify neurotransmitters. According to their chemical properties, neurotransmitters can be divided into amino acids, peptides, and biogenic amines (monoamines). Biogenic amine neurotransmitters, mainly including dopamine (DA), epinephrine (EP), norepinephrine (NE), serotonin (5-hydroxytryptamine, 5-HT) (Fig. 4), are compounds of great biomedical interest, playing significant roles in the functioning of the human metabolism, central nervous. DA is well known

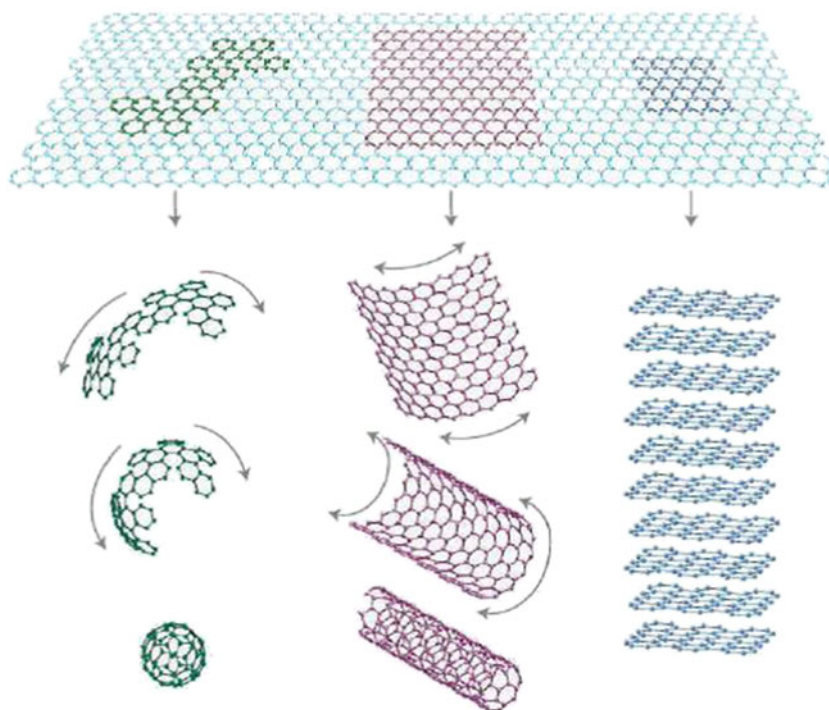
as one of the important neurotransmitters, which is released from brain neurons to extracellular fluids and plays a significant role in the central nervous, renal, hormonal, and cardiovascular systems [78]. Extreme abnormalities in DA levels are symptoms of several disease states such as schizophrenia, parkinson's and alzheimer's diseases [79, 80]. 5-HT is a monoamine neurotransmitter of enormous biological importance widely distributed in the central nervous system, which plays an important role in a number of fundamental biological processes, including a variety of physiological functions (sleep regulation) and pathological states (psychiatric disorders, depression, mental retardation, infantile autism, etc.) [81]. EP known as the "fight or flight" hormone, energizes and speeds up the various systems within the body and plays an important role during the times of physical or mental stress [82]. Medically, EP has been used as a common emergency healthcare medicine. Studies show that extreme abnormalities of EP levels in nervous tissues and body fluids are symptoms of several diseases. The quantitative determination of EP concentration is quite helpful for developing nerve physiology, clinical diagnosis of some diseases and controlling medicine in pharmacological research [83]. NE is one of the derivatives of catecholamines secreted in the adrenal medulla and plays important physiological roles in the central nervous system. It increases the conversion of glycogen to

**Fig. 2** (Super)structure representations of **a** a MWCNT and **b** a SWCNT. Reprinted from [58]





**Fig. 3** Graphene as the basic unit of 0D fullerene, 1D carbon nanotubes, and 3D graphite. Reprinted from [61]



glucose in the liver, helps in converting fats into fatty acids, and relaxing the bronchial muscles [84]. It is also critical in mental disease, heart failure, DNA breaks in cardiac myoblast cells, and diabetes that both catecholamines have complementary actions in human body [85].

As their impacts on human health and diagnosis of some diseases, it is worthwhile to develop a quantitative method for studying concentration of biogenic amine neurotransmitters. Because of the simple procedure and high sensitivity of electroanalysis and the electroactivity of biogenic amine neurotransmitters, studying and measuring of these compounds with electrochemical methods were carried out. CNs are widely used as sensing platform for biogenic amine neurotransmitters due to their unique physical and chemical properties. Adding CNs to electrodes for neurotransmitter sensing might facilitate higher sensitivity and improve the electron transfer kinetics. Most CNs based electrochemical sensors for neurotransmitters do not incorporate a specific molecular recognition element, but the electrochemical techniques offer some selectivity and chemical identification of the species being detected. Cyclic voltammetry (CV) and differential pulse voltammetry (DPV) are the most common electrochemical techniques employed. The DPV method is usually used in studies to discriminate multiple compounds and improve sensitivity because it produces less background current, leading to low LODs. Electrochemical sensors for the detection of biogenic amines neurotransmitters are mainly based on the modification of CNTs and graphene onto the electrodes, which are summarized in Tables 1 and 2, respectively.

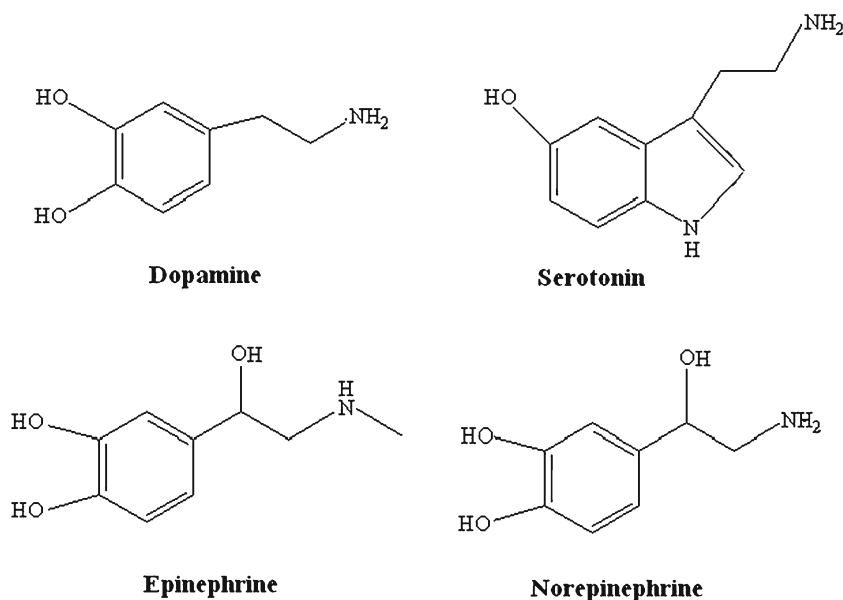
### Dopamine

Electrochemical methods have proven to be rapid, simple and sensitive in the determination of neurotransmitters. However, at traditional solid electrodes, DA and its coexisting species ascorbic acid (AA) and uric acid (UA) have an overlapping voltammetric responses, resulting in rather poor selectivity and sensitivity for the detect of DA. Thus, it is a challenge to separate the oxidation peaks of AA, DA and UA from each other in electrochemical analysis.

#### *Nanodiamond, carbon nanofibers and fullerene modified electrodes for dopamine analysis*

An electrode for biosensing applications should have several material properties such as a wide working potential window, a low and stable background current, high resistance to deactivation due to surface adsorption, biocompatibility, good sensitivity and selectivity for detection of target analytes and a fast response time. Nanodiamond and fullerene have emerged as important materials which meet most of these criteria. Until now, there are only few reports about these materials modified electrodes being applied as sensors for DA. Raina et al. [86] reported a ultra-microelectrode array (UMEA) fabricated with nitrogen-incorporated nanodiamond. The nanodiamond UMEA was fabricated using conventional silicon microfabrication processes and plasma enhanced CVD nanodiamond growth. Without any surface functionalization of the nanodiamond surface, the sensor shows a steady state response and a linear relationship between the limiting current

**Fig. 4** Chemical structures of biogenic amine neurotransmitters



and DA concentration. Breczko et al. reported a carbon nanoion (CNO) and poly (diallyldimethyl- ammoniumchloride) (PDDA) composite modified glass carbon electrode (GCE) to detect DA for the first time [87]. The resulting CNO/PDDA composites film possessed faster adsorption dynamics and higher selectivity for DA than the non-modified GCE. The DPV method exhibits a lower LOD for DA and a sensitivity equal to 0.1  $\mu\text{M}$  and 0.0175  $\mu\text{A} (\mu\text{M})^{-1}$ , respectively. A gold electrode modified with partially reduced fullerene- $\text{C}_{60}$  was developed by Goyal et al. [88]. The modified electrode not only showed strong electrocatalytic activity toward the oxidation of DA and AA, but also resolved the overlapped anodic peak of the analytes into two distinct peaks, and thus DA can be detected selectively in the presence of excess of AA. In their study by square wave voltammetry (SWV), the electrode exhibited substantially enhanced electrochemical signals for DA sensing with linear range of 1 nM–5.0  $\mu\text{M}$  and low LOD of 0.26 nM. The  $\text{C}_{60}/\text{Au}$  electrode was further applied to the determination of DA in DA hydrochloride injection and human blood serum and urine samples with satisfactory results. Carbon fiber microelectrodes (CFMEs) are commonly employed to quantify rapid DA fluctuations both in vitro and in vivo. These electrodes have proven to be particularly useful in biological applications because of their biocompatibility, high tensile strength, low cost, wide potential window, and inert nature [89]. Ates et al. [90] reported a CFME modified with polycarbazole and poly (carbazole-co-p-tolylsulfonyle pyrrole) films by electrochemical deposition technique. This sensor displayed significantly increased currents for the detection of DA in comparison an uncoated CFME, which is attributed to the significant increasing of surface area after polymer modification. Njagi et al. [91] developed a novel implantable enzyme-based carbon fiber biosensor for in vivo monitoring of

DA. The biosensor is fabricated by immobilizing tyrosinase in a biocompatible matrix consisting of a biopolymer, chitosan (CS) and ceria-based metal oxides, deposited onto the surface of a CFME with a diameter of 100  $\mu\text{m}$ . This biosensor demonstrated a LOD of 1 nM DA, a linear range of 5 orders of magnitude between 10 nM and 220  $\mu\text{M}$ , a sensitivity of 14.2 nA  $\mu\text{M}^{-1}$ , and good selectivity against AA, UA, 5-HT, NE, EP, and 3,4-dihydroxy-L-phenylalanine. Importantly, the biosensor provides an alternative to fast scan CV for in vivo monitoring of DA release in the brain of an anesthetized rat. A carbon nanofiber electrode (CNFE) array integrated with the wireless instantaneous neurotransmitter concentration sensor system (WINCS) was used for electrochemical detection of DA by fast scan CV [92]. Compared to the traditional CFME for the detection of DA, the novel CNFE array is expected to facilitate the detection of neurochemical release over a large area of interrogation, yet with high spatial resolution.

#### *Carbon nanotubes modified electrodes for dopamine analysis*

Significant developments have taken place in the field of CNTs based electrochemical sensors for the detection of neurotransmitters. Recently, electrodes modified with CNTs and their composites for the detection of DA were categorized into four types: CNT paste electrodes, CNTs directly deposited or grown on electrodes, polymer coatings on electrodes, functionalized nanotubes modified electrodes.

The first paper that demonstrated the use of CNTs for the detection of DA was published by Britto et al. [93] in 1996. The CNT modified paste electrode increased sensitivity for the determination of DA and showed nearly ideal, reversible kinetics, which is unusual for DA at carbon electrodes. This study paved

**Table 1** Carbon nanotubes based electrochemical sensors for biogenic amines neurotransmitters

Sensors	Analytes	$E_{pa}$	Linear range	LOD	Ref.
CNTs-IL gel modified electrode, DPV	DA	N.M.*	1–100 $\mu$ M	0.1 $\mu$ M	[94]
CPE prepared by incorporating thionine-nafion supported on MWCNTs, DPV	DA	393 mV ( $\Delta E_{pa}$ )	0.1–80 $\mu$ M	0.08 $\mu$ M	[95]
	AA		0.1–80 $\mu$ M		
Modified CNT paste electrode of EBNBH, DPV	DA	N.M.*	0.1–900 $\mu$ M	0.087 $\mu$ M	[96]
	UA		20–650 $\mu$ M	15 $\mu$ M	
HDS/SDS film modified CPE, DPV	DA	0.133 V	N.M.*	0.1 $\mu$ M	[97]
LBL assembled MWCNTs modified GCE, SWV	DA	0.2 V	0–32 $\mu$ M	N.M.*	[98]
GCE modified with negatively charged SWCNTs and positively charged CPB using LBL technique, DPV	DA	0.169 V	4–120 $\mu$ M	0.6 $\mu$ M	[99]
	UA	0.292 V	2–90 $\mu$ M	7 $\mu$ M	
PSS wrapped MWCNTs bound to graphite electrode through LBL technique, amperometry	AA	0.1 V	50–1000 $\mu$ M	0.5 $\mu$ M	[100]
	DA	0.25 V	50–350 $\mu$ M	0.15 $\mu$ M	
	UA	0.35 V	50–800 $\mu$ M	0.8 $\mu$ M	
SDS functionalized MWCNTs grown on Ta, DPV	DA	0.16 V	N.M.*	3.75 $\mu$ M	[101]
SWCNT mat grown on Si, CV	DA	N.M.*	1 $\mu$ M–1 mM	1 $\mu$ M	[102]
GCE modified with both PANI film and MWCNTs with incorporated $\beta$ -CD, CV	DA	N.M.*	0.1–1000 $\mu$ M	0.12 nM	[103]
Overoxidized PPY-MWCNTs composite modified gold electrode, DPV	DA	N.M.*	0.04–1.4 $\mu$ M	1.7 nM	[104]
CFME electrochemically deposited by a film containing OPPY and MWCNTs, DPV	DA	0.221 V	5.0 nM–10 $\mu$ M	0.5 nM	[105]
Poly(acrylic acid)-MWCNTs composite coated GCE, LSV	DA	0.18 V	40 nM–3 $\mu$ M	20 nM	[106]
	UA	0.35 V	0.3–10 $\mu$ M	110 nM	
GCE modified with redox polymer-CNT composite film LSV, amperometry	DA	N.M.*	0.2–1.4 $\mu$ M (LSV)	0.1 $\mu$ M	[107]
	AA		1–56 $\mu$ M (amperometry)	0.2 $\mu$ M	
Poly(orthanilic acid)-MWCNTs composite film modified GCE, DPV	DA	160 ( $\Delta E_{pa}$ )	9–48 $\mu$ M	0.21 $\mu$ M	[108]
	UA		6–55 $\mu$ M	0.44 $\mu$ M	
MWCNTs-CS/poly(amidoamine)/DNA nanocomposite modified gold electrode, DPV	DA	0.17 <sup>a</sup> V	10–100 $\mu$ M	0.03 $\mu$ M	[109]
	UA	0.279 <sup>a</sup> V	0.5–100 $\mu$ M	0.07 $\mu$ M	
PSS/ SWCNTs modified GCE, DPV	DA	0.485 V	0.016–600 $\mu$ M	8.0 nM	[110]
P3MT modified GCE coated with Nafion/ SWCNTs, DPV	DA	N.M.*	0.02–0.10 $\mu$ M, 0.10–1.0 $\mu$ M, 1.0–6.0 $\mu$ M	5.0 nM	[111]
MWCNTs and MIPs modified GCE, chronoamperometry	DA	N.M.*	0.5–200 $\mu$ M	N.M.*	[112]
MWCNTs modified screen-printed electrode, AdSV	DA	0.15 <sup>a</sup> V	0.05–1 $\mu$ M	15 nM	[113]
PtNPs decorated MWCNTs modified GCE, DPV	AA	0.01 V	N.M.*	20 $\mu$ M	[114]
	DA	0.176 V		0.0483 $\mu$ M	
	UA	0.296 V		0.35 $\mu$ M	
EPPGEs modified with SWCNTs-Fe <sub>2</sub> O <sub>3</sub> nanoparticles, SWV	DA	N.M.*	0–31.8 $\mu$ M	0.36 $\mu$ M	[115]
GCE modified with AuNPs-Plu hybrid film and MWCNTs with incorporated $\beta$ -CD, amperometry	DA	0.161 V	1–56 $\mu$ M	0.19 $\mu$ M	[116]
CNTs incorporated with sol-gel derived La(OH) <sub>3</sub> nanorods on GCE, CV	AA	0.02 V	0.5 $\mu$ M–1.46 mM	1.67 $\mu$ M	[117]
	DA	0.24 V	50 nM–35.36 $\mu$ M	1.67 nM	
	UA	0.39 V	50 nM–0.79 mM	1.67 nM	
PDOP functionalized MWCNTs decorated with PtNPs on GCE, DPV	NO <sub>2</sub> <sup>-</sup>	0.77 V	0.55 $\mu$ M–0.72 mM	0.18 $\mu$ M	[118]
	DA	0.310 <sup>a</sup> V	0.25–20 $\mu$ M	0.08 $\mu$ M	
Boron-doped CNTs on GCE, DPV	UA	0.468 <sup>a</sup> V	0.3–13 $\mu$ M	0.12 $\mu$ M	[121]
	DA	N.M.*	0.02–75 $\mu$ M	1.4 nM	
GCEs modified with boronic acid functionalized MWCNTs, DPV	DA	N.M.*	N.M.*	0.5 $\mu$ M	[122]
Self-doped PANI/SWCNTs composite modified electrode, CV	DA	N.M.*	1–10 nM	0.6 nM	[123]
MWNTs-IL gel modified GCE, DPV	5-HT	0.22 <sup>a</sup> V	20 nM–7 $\mu$ M	8 nM	[81]
	DA	0.38 <sup>a</sup> V	0.1–12 $\mu$ M	60 nM	
CFME coated with nafion-SWCNTs, CV	5-HT	N.M.*	N.M.*	N.M.*	[143]
	DA				

**Table 1** (continued)

Sensors	Analytes	$E_{pa}$	Linear range	LOD	Ref.
CFME modified with nafion-CNTs, DPV	5-HT	0.36 V	5–200 nM	1 nM	[144]
Pyrolytic graphite electrode modified with nano-diamond/graphite film, LSV	EP	0.147 V	0.01–10 $\mu$ M	3 nM	[145]
	UA	0.316 V	0.01–60 $\mu$ M	3 nM	
MWCNTs functioned with nafion, nano platinum, and nano gold on GCE, CV, DPV	AA	0.07 <sup>a</sup> V	N.M.*	N.M.*	[146]
	EP	0.29 <sup>a</sup> V			
	UA	0.42 <sup>a</sup> V			
Stainless steel wire coated with SWCNTs by electrodeposition, DPV	EP	0.319 <sup>a</sup> V	2–100 $\mu$ M	2 $\mu$ M	[147]
EBNBH modified CNT paste electrode, DPV	UA	0.065 V	25–750 $\mu$ M	8.8 $\mu$ M	[148]
	EP	0.280 V	0.7–1200 $\mu$ M	0.22 $\mu$ M	
	FA	0.625 V	15–800 $\mu$ M	11.0 $\mu$ M	
In situ electropolymerization of BCB-MWCNTs on GCE, LSV	EP	N.M.*	50 nM–10 $\mu$ M	10 nM	[149]
MWCNTs, CoPc and paraffin composite electrode, DPV	EP	0.175 V	1.33–5.50 $\mu$ M	15.6 nM	[150]
Over-oxidized PPY and MWCNTs composite on GCE, DPV	EP	N.M.*	0.1–8 $\mu$ M, 10–100 $\mu$ M	40 nM	[151]
EPPGE modified with MWCNTs, SWV	EP	0.150 V	0.5 nM–0.1 $\mu$ M	0.15 nM	[83]
CNT paste electrode modified with 2PHC, SWV	EP	240 mV ( $\Delta E_{pa}$ )	50 nM–0.55 mM	9.4 nM	[85]
MWCNTs-PNDGACHi on gold electrodes, CV	EP	0.172 V	N.M.*	30 $\mu$ M	[154]
	NE	0.244 V		780 $\mu$ M	
EPPGE modified with MWCNTs, SWV	EP	0.150 V	0.5–100 nM	0.15 nM	[84]
	NE	0.215 V	0.5–100 nM	0.09 nM	

N.M.\*—Not Mentioned,  $E_{pa}$ —Anodic Peak potential,  $\Delta E_{pa}$ —Anodic Peak separation, a—Studied by CV

a way for the use of CNTs in neurotransmitter sensing. Then Zhao et al. [94] reported a carbon nanotubes-ionic liquid (CNTs-IL) gel modified electrode for DA detection. The anodic peaks of DA, UA and AA were well-distinguished and DA can be detected selectively. Shahrokhian et al. [95] reported a modified carbon paste electrode (CPE) which was prepared by incorporating thionine-nafion supported on MWCNTs. The modified CPE possessed an efficient electrocatalytic activity for the electrochemical oxidation of DA and AA and the peak potential separation of nearly 393 mV is achieved for two compounds. Beitollahi et al. [96] utilized a 2,2'-[1,2-ethanediylbis (nitriloethylidene)]-bis-hydroquinone (EBNBH) modified CNT paste electrode to determine DA and UA. The electrocatalytic currents increased linearly with the DA and UA concentrations in the ranges of 0.1–900  $\mu$ M and 20–650  $\mu$ M, and the LODs for DA and UA were 0.087  $\mu$ M and 15  $\mu$ M, respectively. Sathisha et al. [97] reported a hydroxy double salt (HDS)/sodiumdodecyl sulfate (SDS) film modified CPE, which was developed for the sensitive and selective determination of DA in the presence of large excess of AA and UA. The LOD for DA was 0.1  $\mu$ M.

CNTs can be functionalized with strong acid and then deposited on electrodes using layer-by-layer (LBL) technique. Also CNTs can be grown on different substrates and then used directly as electrodes. For example, Mao et al. [98] prepared a homogeneously and stably assembled CNT multilayer film

modified GCE using LBL method based on electrostatic interaction between the positively charged PDDA and negatively charged shortened CNTs and studied electrochemical catalytic activity of the assembled MWCNTs toward DA in the presence of AA. Zhang et al. assembled functionalized SWCNT multilayer films on GCE by alternately assembling positively charged cetylpyridinium bromide (CPB) and negatively charged SWCNTs based on electrostatic interaction [99]. The DA, AA and UA can be well-separation on multilayer film modified electrode on CVs. The multi-layer films show remarkable selectivity and high sensitivity for DA and UA, which eliminate interference from high concentrations of AA. The LODs for DA and UA were 0.6  $\mu$ M and 7.0  $\mu$ M, respectively. Manjunatha et al. [100] used LBL technique to form multilayer films consisting of PDDA and MWCNTs wrapped with polystyrene sulfonate (PSS). The sensor was applied for the simultaneous detect of DA, AA and UA with the LODs of 0.5  $\mu$ M, 0.15  $\mu$ M and 0.8  $\mu$ M, respectively. Zheng et al. [101] grew MWCNT on a Ta substrate and then functionalized them with SDS to detect DA in the presence of AA. In their DPV studies, they obtained a LOD of 3.75  $\mu$ M for DA in the presence of AA ranging from 0.02  $\mu$ M to 0.2 mM. Macpherson's group has grown ultrathin CNT mat microelectrodes on insulating Si surfaces by CVD [102]. The CNT networks retained a low capacitance and background signal and exhibited less retardation of electron transfer for



**Table 2** Graphene based electrochemical sensors for biogenic amines neurotransmitters

Sensors	Analytes	$E_{pa}$	Linear range	LOD	Ref.
Multilayer graphene nanoflake films electrode, DPV	DA	N.M.*	1–50 $\mu$ M, 50–100 $\mu$ M	0.17 $\mu$ M	[78]
CS–graphene on GCE, DPV	DA	N.M.*	5–200 $\mu$ M	N.M.*	[124]
$\beta$ -CD graphene sheet on GCE, CV, amperometry	DA	N.M.*	9.0 nM–12.7 $\mu$ M (CV) 0.9–200 $\mu$ M (amperometry)	5.0 nM (CV)	[125]
Graphene modified GCE, DPV	DA	N.M.*	4–100 $\mu$ M	2.64 $\mu$ M	[126]
PVP/graphene modified GCE, amperometry	DA	0.4 V	0.5 nM–1.13 mM	0.2 nM	[127]
CS–graphene on GCE, DPV	DA	0.02 V	1.0–24 $\mu$ M	1 $\mu$ M	[128]
	AA	0.185 V	50–1200 $\mu$ M	50 $\mu$ M	
	UA	0.275 V	2.0–45 $\mu$ M	2 $\mu$ M	
EDTA–modified reduced graphene–Nafion on GCE, DPV	DA	0.2 <sup>a</sup> V	0.20–25 $\mu$ M	0.01 $\mu$ M	[129]
Nitrogen doped graphene on GCE, DPV	AA	N.M.*	5–1300 $\mu$ M	2.2 $\mu$ M	[130]
	DA		0.5–170 $\mu$ M	0.25 $\mu$ M	
	UA		0.1–20 $\mu$ M	0.45 nM	
Porphyrin–functionalized graphene on GCE, DPV	DA	0.192 V	100–1000 nM	22 nM	[131]
PtNPs / PFIL/GS nanocomposite on GCE, DPV	AA	0.13 <sup>a</sup> V	N.M.*	N.M.*	[132]
	DA	0.33 <sup>a</sup> V			
Cu <sub>2</sub> O/graphene nanocomposite modified GCE, CV	DA	0.302 V	0.1–10 $\mu$ M	10 nM	[133]
LBL assembled rGO/AuNPs films on GCE, DPV	DA	0.116 V	1–60 $\mu$ M	0.02 $\mu$ M	[134]
GCE modified with electrochemically rGO and AuNPs, DPV	DA	N.M.*	0.1–10 $\mu$ M	0.04 $\mu$ M	[135]
Graphene/Congo red/MIPs on GCE, chronoamperometry	DA	N.M.*	0.1–830 $\mu$ M	0.1 $\mu$ M	[136]
MIPs–CS– graphene modified GCE, DPV	DA	N.M.*	0.001–0.01 $\mu$ M, 0.1–100 $\mu$ M	0.01 nM	[137]
High–performance screen–printed graphene electrode, DPV	AA	–0.05 V	4.0–4500 $\mu$ M,	0.95 $\mu$ M	[138]
	DA	0.15 V	0.5–2000 $\mu$ M,	0.12 $\mu$ M	
	UA	0.3 V	0.8–2500 $\mu$ M	0.20 $\mu$ M	
Novel label–free electrochemical aptasensor based on graphene–PANI composite film, SWV	DA	N.M.*	0.007–90 nM	1.98 pM	[139]
PTCA–GS/ MWCNTs/IL modified GCE, DPV	DA	0.229 <sup>a</sup> V	0.03 $\mu$ M–3.82 mM	1.2 nM	[140]
various graphene nanomaterials modified GCE, DPV	5–HT	0.31 V	1–100 $\mu$ M	32 nM	[142]
Graphene on GCE, CV	EP	N.M.*	0.385–13.1 $\mu$ M,	89 nM	[152]
			13.1 $\mu$ M–0.109 mM		
GCE modified with graphene/AuNPs, CV	EP	0.163 V	50 nM–8 $\mu$ M	7 nM	[153]

N.M.\*—Not Mentioned,  $E_{pa}$ —Anodic Peak potential, a—Studied by CV

multiple scans for DA. However, the peak potentials of DA also shifted to higher potentials than GCE and the reduction peak was diminished.

Another popular strategy for DA detection with CNT sensors is to immobilize CNTs onto electrodes using polymer coatings. Among various types of conducting polymers, polypyrrole (PPY) and polyaniline (PANI) have been the focus of several recent studies because their high conductivity and good environmental stability. For example, a GCE modified with both PANI film and MWCNTs with incorporated  $\beta$ -cyclodextrin ( $\beta$ -CD) was developed by Yin and co-workers [103]. The modified electrode exhibits substantially electrochemical responses toward DA oxidation with a wide linear range (0.1–1,000  $\mu$ M) and a low LOD of 12 nM (S/N=3). PPY can be overoxidized to create an electrically insulating layer. Overoxidized polypyrrole (OPPY) films are permeable

to cations, like DA, but the films repel anions and neutral compounds, such as AA and 5-HT. Tu et al. modified a gold electrode with the OPPY–MWCNTs nanocomposite using electropolymerization method [104]. The properties of the modified films were studied by the electrochemical quartz crystal impedance method in neutral and alkaline solutions. The modification of the overoxidized nanocomposite film improved substantially the sensitivity for DA assay in a neutral phosphate buffer, as compared with the modification of OPPY or MWCNTs alone. In their DPV studies, they obtained a linear range from 0.04  $\mu$ M to 1.4  $\mu$ M and a limit of detection of 1.7 nM. Lin et al. fabricated a microsensor by electrochemically depositing a film containing OPPY and MWCNTs onto a CFME [105]. The modified electrode showed efficient and selective electrocatalytic oxidation of DA and displayed relatively good stability and lifetime. The oxidation currents for

DA are linear in the concentration range from 5.0 nM to 10  $\mu$ M, and the LOD ( $S/N=3$ ) is 0.5 nM. Besides, the sensor was successfully applied to in-vivo determination of DA in rat striatum of freely moving rats. This paper was proof of concept but more work would be needed to miniaturize the microelectrodes for in vivo applications. Several studies were performed for the detection of DA, UA, and AA simultaneously. Two distinct linear sweep voltammetry (LSV) peaks for DA and UA were observed at a GCE modified with poly (acrylic acid) functionalized MWCNTs [106]. The LODs for UA and DA were 20 nM and 100 nM, respectively. A redox polymer–CNT composite film modified GCE was fabricated by electropolymerization of acid yellow 9(AA)/MWCNTs films in 0.1 M  $H_2SO_4$  solution [107]. The newly synthesized PAY–MWCNTs composite film showed excellent electrocatalytic activity towards oxidation of DA and AA with high sensitivity in physiological pH. LODs were 0.1  $\mu$ M and 0.2  $\mu$ M for DA and AA, respectively. Zhang et al. [108] reported a modified GCE with poly (orthanilic acid) coated MWCNTs composite was applied for the simultaneous detect of DA and UA in the presence of AA. The LODs for UA and DA were 0.44  $\mu$ M and 0.21  $\mu$ M, respectively. A novel biocomposite film containing MWCNTs-CS/poly (amidoamine) nanocomposite along with the incorporation of DNA was used to fabricate a biosensor for determination of DA and UA under coexistence of AA [109]. The sensor exhibited strong catalytic activity toward the oxidation of DA and UA and separated the originally overlapped signals of UA, DA and AA oxidation. In the presence of 1.0 mM AA, LODs for DA and UA were 0.03  $\mu$ M and 0.07  $\mu$ M, respectively.

Several polymer-based methods are approaching basal DA levels, 10 nM, in sensitivity. For example, Zhang developed a PSS/SWCNTs composite by dispersing SWCNTs into PSS chloroform solution and then coated it on GCE [110]. The interference was eliminated due to the interaction between DA cations and the negative PSS film in pH 7.0 PBS solutions. The DPV method exhibited a high sensitivity and a very low LOD of 5.0 nM for DA detection. Wang et al. prepared the hybrid film modified GCE by coating the Nafion/SWCNTs onto the electrochemical poly (3-methylthiophene) (P3MT) surface [111]. This modified electrode combined the advantages of P3MT, CNTs and Nafion, which exhibited dramatic electrocatalytic effect on the electrooxidation of DA. The Nafion discriminates AA and UA, while the P3MT polymer and CNTs shows excellent electrocatalytic effects for DA. The LOD was 5.0 nM, less than basal DA levels. Then the modified electrode was successfully applied to the determination of DA contents in human serum with satisfactory results. Several novel sensor combining molecularly imprinted polymers (MIPs) and CNTs has also been developed. Kan et al. developed a sensor with MWCNTs and MIPs modified GCE [112]. By using a MIPs specifically for DA, the sensor showed both rapid adsorption and selectivity over DA and

AA. Because the method required incubation in DA, it was not particularly fast but concentrations low to 0.1  $\mu$ M were measured. CNTs modified screen-printed electrode was fabricated by Moreno et al. [113]. The sensor shows high sensitivity and selectivity for DA detection with coexistence of AA. The LOD for DA was 15 nM. In short, polymer coated CNT electrodes show good LODs and are promising for detecting low quantities of neurotransmitters. The downside of adding a polymer is that it restricts diffusion and slows the temporal resolution.

Studies combining metal or metallic compounds and CNTs to enhance sensitivity and selectivity for DA have been performed using metal nanoparticles functionalized CNTs-modified electrode or metallic oxide (metal hydroxides) nanoparticles functionalized CNTs-modified electrodes. Dursun et al. fabricated a modified electrode by electrochemically deposition of Pt nanoparticles (PtNPs) on the MWCNTs covered GC electrode [114]. The enhanced peak current and well-defined peak separations toward electrocatalytic oxidation of DA, UA and AA on the modified electrode was obtained compared with both bare and MWCNTs/GCE. In their studies of simultaneous determination by DPV, LODs were calculated for AA, DA, and UA, as of 20  $\mu$ M, 48.3 nM, and 0.35  $\mu$ M, respectively. Adekunle et al. modified edge-plane pyrolytic graphite electrode (EPPGE) with SWCNTs–iron (III) oxide (SWCNT/ $Fe_2O_3$ ) nanoparticles by electrochemical deposition [115]. Compared with the bare electrode or electrodes without the  $Fe_2O_3$  nanoparticles, the EPPGE-SWCNT– $Fe_2O_3$  gave best response (7 times more than bare EPPGE and 2-fold more than EPPGE-SWCNT and EPPGE-SWCNT–Fe) towards the detection of DA. The sensitivity and LOD for DA detection were 3.44  $\mu$ A  $\mu$ M<sup>-1</sup> and 0.36  $\mu$ M, respectively. Jia et al. develop nanoparticles and MWCNTs modified electrode [116], where gold nanoparticles–poly (luminol) hybrid film (AuNPs-Plu) was coated on the surface of a GCE by electro-deposition method and MWCNTs incorporated  $\beta$ -CD was dropped onto the surfaces of Plu-AuNPs/GCE. The porous structure of Plu film allows the AuNPs dispersing into the polymer matrix and generates additional electrocatalytic sites.  $\beta$ -CD is used as a dispersing reagent for CNTs and CNTs increased the sensitivity for oxidation of DA, with an electrocatalytic effect as well. Zhang et al. prepared a novel material, sol–gel driven  $La(OH)_3$  nanorods and designed it to incorporate with CNTs to modify GCE and then applied to simultaneously voltammetric determine AA, DA, UA and  $NO_2^-$  [117]. The modified electrode shows high selectivity and well stability. More importance, this material can be extended to construct other electrochemical sensors by the immobilization of enzymes and antibodies. Lin et al. prepared a polydopamine (PDOP) and PtNPs coated MWCNTs and developed a sensor for simultaneous determination of DA and UA [118]. The sensor shows remarkable sensitivity, reproducibility and stability to the electrocatalysis of DA and UA, with

LODs of 0.08  $\mu\text{M}$  and 0.12  $\mu\text{M}$ , respectively. In recent studies, boron-doped CNTs (BCNTs) or boronic acid functionalized CNTs have been used for constructing sensing platform to enhance sensitivity and selectivity of DA. It has been reported that the physicochemical properties of CNTs could be tailored by doping CNTs with B atom and the electronic, mechanic, conductive properties of CNTs could be improved obviously [119, 120]. BCNTs have been used for determination of DA because of more edge plane sites on the surface of CNTs and more functional groups at the defective sites of BCNTs. A modified GCE with BCNTs was used to discriminate DA and AA and a LOD of 1.4 nM was obtained for DA [121]. This LOD is among the lowest reported for a CNT-based sensor for DA with the only disadvantage being that the BCNTs are not widely available. In a study by Wu et al., GCEs were modified with boronic acid functionalized MWCNTs for the indirect detection of DA [122]. Indirect detection was used, based on selective binding of the cis-diol group of DA with boronic acid to form a boronate ester, which is oxidized at a more positive potential than DA. The modified electrode exhibited a LOD below 0.5  $\mu\text{M}$ , not as good as direct detection. Ali et al. report a nonoxidative sensor to indirectly detect DA with high sensitivity and selectivity [123]. This sensor was fabricated with a thin layer of in situ polymerized poly (anilineboronic acid) (PABA)/CNT composite and a thin layer of the highly permselective Nafion film. PABA also binds with DA to form a boronate ester and complex formation greatly affects the conductivity of the PANI backbone. Therefore, the amount of binding is directly proportional to the amperometric signal. The sensor exhibited a linear range from 1 nM to 10 nM and a low LOD (0.6 nM), indicating it might allow for its potential use in the diagnosis of Parkinson's disease.

Different methods CNT-based sensors for have been developed for the DA detection. Overall, CNT paste electrodes are simple-preparing and low cost. Problems with such electrodes may be their miniaturization for DA analysis in vivo. Electrodes grown directly with CNTs may end up being the easiest to fabricate reproducibly in large quantities which could lead to more widespread implementation. Polymer coated methods are used to improve sensitivity by binding of CNTs with some conducting polymers and/or selectivity by screening out interferents such as AA. CNTs functionalized with metal/metallic oxide nanoparticles have emerged as a popular strategy to fabricate electrochemical sensors for DA detection. Electrodes incorporation of metal nanoparticles and CNTs can facilitate heterogeneous electron transfer and increase analytical sensitivity. Boron/boronic acid functionalized CNT studies show high sensitivity for DA, however, practical biologically relevant experiments are necessary. Future studies may focus on the improvement of sensitivity and selectivity of CNTs modified electrodes and applications of these sensors in biological samples.

### *Graphene modified electrodes for dopamine analysis*

Graphene, a flat monolayer of carbon atoms closely packed into a honeycomb 2D lattice, has attracted tremendous attention from scientific communities in recent years. Comparing to the commonly used CNTs, graphene has higher surface area, more excellent electrical conductivity and electron mobility at room temperature due to their unique 2D nanostructure. The special properties of graphene may provide insight to fabricate novel sensors for virtual applications. Recently, graphene exhibited a significant potential for the electrochemical sensors applications. Graphene based electrochemical sensors have displayed favorable electrochemical catalytic activities towards DA, most of which were fabricated by casting the multilayer films of graphene nanosheets or their based hybrids directly onto the electrode surface. Shang et al. [78] reported an electrochemical method on selective detection of DA by using multilayer graphene nanoflake films which were fabricated via CVD. Geim et al. [124], Tan et al. [125], and Kim et al. [126] reported electrochemical sensors for selective detection of DA by using graphene, which was synthesized by chemical reduction of graphite oxide. In their studies, graphene was dispersed in CS,  $\beta$ -CD or DMF to form a stable suspension and sensors were obtained by modifying GCE with microliters of the suspension via drop-casting method. A polyvinylpyrrolidone (PVP)/graphene modified GCE was prepared and applied for the fabrication of DA sensors without the interference of AA by Liu and coworkers [127]. Graphene was synthesized through electrochemical reduction of graphene oxide (GO) and characterized by spectroscopic and electrochemical techniques. Amperometric response results showed that the PVP/graphene based sensor displayed a wide linear range of 0.5 nM-1.13 mM and a LOD of 0.2 nM. Han et al. [128] reported a CS functionalized graphene based electrode, which was synthesized by a together-blending and in situ chemical reduction method. The electrode exhibited well resolved simultaneous discrimination of AA, DA, and UA, and the LODs were 1  $\mu\text{M}$ , 50  $\mu\text{M}$  and 2  $\mu\text{M}$ , respectively. Hou et al. [129] synthesized EDTA-modified reduced graphene (EDTA-RG) by silanization of graphene with N-(trimethoxysilylpropyl) ethylenediamine triacetic acid (EDTA-silane). The EDTA-RG dispersed in Nafion/ethanol solution was used to construct a DA biosensor. The sensor exhibits highly sensitive and selective electrocatalysis toward DA in the presence of AA. They attributed it to carboxylic groups on the edges of graphene produced by the chemical modification process and Nafion, the ionic selectivity film. Sheng et al. [130] developed an electrochemical sensor based on nitrogen doped graphene (NG), which was prepared by thermally annealing graphite oxide and melamine mixture. The electrochemical sensor shows a wide linear response for AA, DA and UA in the concentration range of 5 to 1,300  $\mu\text{M}$ , 0.5 to 170  $\mu\text{M}$  and 0.1 to 20  $\mu\text{M}$  with LODs of 2.2  $\mu\text{M}$ , 0.25  $\mu\text{M}$  and 0.45 nM. The

superior sensing performance is mainly due to the interactions between nitrogen atoms in NG layers with these molecules via hydrogen bond and the  $\pi$ - $\pi$  interactions between graphene layers and these molecules. A new type of porphyrin-functionalized graphene was synthesized and used for highly selective and sensitive detection of DA by Wu and coworkers [131]. In their studies by DPV, the oxidation peak currents of DA in the presence of AA and UA is increased linearly with the concentrations of DA in the range of 100–1,000 nM and the LOD was 22 nM. They attributed it to the aromatic  $\pi$ - $\pi$  stacking and electrostatic attraction between positively-charged DA and negatively-charged porphyrin-modified graphene which can accelerate the electron transfer whereas weakening AA and UA oxidation.

Some groups reported metal or metallic oxide nanoparticles/graphene nanocomposite for DA sensing. A water-soluble and electroactive composite—PtNPs/polyelectrolyte-functionalized ionic liquid (PFIL)/graphene sheets (GS) nanocomposite was synthesized by Li et al. [132]. The nanocomposite can distinguish AA from DA at two independent peaks with the potentials separation of 200 mV by CV, indicating it can realize simultaneous determination of DA and AA. Zhang et al. [133] reported a nanocomposite composed of cuprous oxide ( $\text{Cu}_2\text{O}$ ) and graphene which were synthesized via reduction of copper (II) in ethylene glycol. GCE was modified with this nanocomposite for the detection of DA. The LOD was 10 nM. A modified GCE with graphene/AuNPs multilayer films was used to detect DA [134]. The modified electrode was fabricated by the electrostatic LBL self-assembly technique between polysodium 4-styrenesulfonate functionalized reduced graphene oxide (rGO) and polyamidoamine (PAMAM) dendrimer stabilized AuNPs. The electrode exhibited a improved electrocatalytic activity towards the oxidation of DA due to the synergistic effect of AuNPs and rGO. Li et al. [135] reported a simple, green and controllable approach for electrochemical synthesis of a nanocomposite made up from electrochemically rGO and AuNPs. The nanocomposite showed an excellent electrocatalytic activity toward DA, with a LOD of 0.04  $\mu\text{M}$  (at  $S/N=3$ ). A novel sensor combining MIPs and graphene/Congo red (GSCR) has also been developed (Fig. 5) [136]. Fig. 6 shows the synthesis route of GSCR-MIPs hybrids. The template molecules (DA) were firstly absorbed at the GSCR surface and then selective copolymerization of methacrylic acid (MAA) and ethylene glycol dimethacrylate (EGDMA) was further achieved at the GSCR surface. By using MIPs specifically for DA, the sensor showed both rapid adsorption and selectivity over DA. Graphene-CS composite, as the functional matrix, has been attempted for detection of DA [137]. The MIPs-graphene sensor was prepared through electrodepositing DA-graphene-CS composited film on the GCE and then removing DA from the film via electrochemical induced elution. The sensor exhibited a low LOD of 0.01 nM. Ping et al. [138] developed a high-performance screen-printed

graphene electrode for the simultaneous determination of DA, AA and UA, with LODs of 0.12  $\mu\text{M}$ , 0.95  $\mu\text{M}$  and 0.20  $\mu\text{M}$ , respectively. This work firstly introduced a sensitive and selective electrochemical sensing device by using the disposable graphene electrode made from graphene-based ink, holding great promise for its wide application in the clinical diagnosis and pharmaceutical analysis. Liu et al. reported a novel label-free electrochemical aptasensor based graphene-polyaniline (GR-PANI) nanocomposite film for DA determination [139]. The GR-PANI nanocomposites were synthesized by in situ polymerization method. The aptamer was directly immobilized on the GR-PANI nanocomposites films modified electrode as a DA capture. The electrochemical aptasensor showed a linear response to DA in the range 0.007–90 nM and a ultra lower LOD of 1.98 pM. An electrochemical sensor for determination of DA based on 3,4,9,10-perylene tetracarboxylic acid functionalized GS, MWCNTs and IL composite was fabricated by Niu et al. [140]. This sensors exhibited excellent sensitivity to DA in the presented of high concentration of AA.

### Serotonin

Research shows that DA and 5-HT influence each other in their respective releasing. Thus, simultaneous determination of DA and 5-HT is important because of their co-existence in biological systems. Both DA and 5-HT are readily oxidized; hence, electrochemical techniques have been explored for their analysis. However, a major obstacle encountered in the simultaneous determination of DA and 5-HT is the co-existence of high concentration of AA and UA in vivo, which can be oxidized at potential close to that of DA and 5-HT at conventional electrodes, resulting in an overlapping voltammetric response. A great deal of efforts has been directed towards overcoming these difficulties for the determination of DA and 5-HT by using chemically modified electrodes. Ionic liquids (ILs), which are comprised entirely of ions and exist in liquid state at ambient temperatures around 298 K and below, have good solvating properties, high conductivity, non-volatility, low toxicity, large potential window and good electrochemical stability. CNTs modified electrodes made by using ILs as a binder for analytical purposes give new capabilities to electrochemical sensors by combining the advantages of both ionic liquids and CNTs. Fukushima et al. firstly reported a thermally stable, highly conductive physical gel, which was formed with imidazolium ions and SWCNTs [141]. Subsequently several reports that simultaneously detects DA and 5-HT by using CNT-ILs gel electrodes have been developed. We also developed a MWCNT-IL composite modified GCE for the simultaneous determination of 5-HT and DA [81]. The CNTs-IL composite modified electrode presents excellent selectivity and sensitivity towards 5-HT and DA and eliminates the interference of AA. As shown in the differential pulse voltammograms in Fig. 6, the



DPV current signal for DA (or 5-HT) in the presence of 5-HT (or DA) and a large excess of AA is well-distinguished. Good linearity was obtained between the anodic differential pulse voltammograms peak currents of DA (or 5-HT) and their concentrations in the mixture. Moreover, it is found that AA and other endogenous substrates such as glucose, NaCl, UA, purine, L-histidine and L-cysteine do not provoke any signal response. Recently, graphene has emerged as a promising candidate material for generating novel electrochemical sensors for simple, fast, and sensitive voltammetric determination of 5-HT. Kim et al. [142] developed sensors for detection of 5-HT based on various graphene nanomaterials. Results obtained in this paper show that graphene reduced by hydrazine and ammonia solution had the lowest LOD, highest sensitivity, best selectivity, widest linear range, fastest response time, and best defined peak of 5-HT.

Another method that simultaneously detects DA and 5-HT are CFMEs. Swamy et al. [143] performed an *in vivo* study by using CFMEs coated with SWCNTs suspended in Nafion and DA and 5-HT were simultaneously detected by using fast-scan cyclic voltammetry. They found that the signals for DA and 5-HT increased two fold and the reduction peaks were separated by 200 mV. This study also showed that the SWCNT-modified CFME was useful for measurement of changes of DA and 5-HT in anesthetized rats. A CFMEs modified with CNTs dispersed in nafion for the detection of 5-HT was developed by Njagi et al. [144]. The electrode showed a LOD of 1 nM, a linear range between 5 and 200 nM, and a sensitivity of  $83.65 \text{ nA } \mu\text{M}^{-1}$ . Importantly, it is the first application of electrochemical microsensors for *in vivo* monitoring of intestinal 5-HT levels in intact zebrafish embryos.

### Epinephrine and norepinephrine

EP is electrochemically active, so it can be detected by electrochemical methods. However, it is difficult to distinguish its response signal on unmodified electrodes, such as GCE, because of the overlapping of oxidation potentials of AA, EP, and UA that often cause a pronounced fouling effect resulting in rather poor selectivity and reproducibility. Numerous attempts were made for the simultaneous determination EP in presence of UA or AA, such as using chemically modified electrodes (CMEs). Shahrokhian et al. [145] modified pyrolytic graphite electrode with nano-diamond/graphite film. EP and UA were simultaneous detected and AA was not interfered. Wide linear ranges of 0.01–10  $\mu\text{M}$  and 0.01–60  $\mu\text{M}$  for EP and UA were obtained, respectively. The LODs for both compounds were 3 nM. The human blood serum, urine and the corresponding injecting samples were determined with very good reproducibility, repeatability and sensitivity. A nanocomposite modified electrode composed of MWCNT-nafion-AuNPs-PtNPs was used to detect AA, EP and UA simultaneously [146]. A stainless steel wire coated with SWCNT by electrodeposition was used to detect EP by

Valentini et al. [147]. This electrode is smaller than most wire electrode, often 300  $\mu\text{m}$  in diameter. But the 2  $\mu\text{M}$  of LOD are high for physiological studies. Beitollahi et al. have studied a CNTs paste electrodes for EP detection [148]. The CNTs paste electrode was modified with EBNBH and had LODs of 0.22  $\mu\text{M}$ , 8.8  $\mu\text{M}$  and 11.0  $\mu\text{M}$  for EP, UA and folic acid, respectively. A sensor employs the *in situ* electropolymerization of brilliant cresyl blue (BCB) with MWCNTs onto GCE was applied for the detection of EP [149]. *In situ* electropolymerization presented several advantages such as reducing usage of modifier and producing a uniform composite, which allows for high signal-to-noise ratio and sensitivity. A very low LOD of 10 nM was observed for EP using LSV. Moraes et al. [150] developed a CNTs-composite electrode for selective determination of EP. The electrode was prepared by mixed paraffin, CNTs and cobalt phthalocyanine (CoPc). EP was detected by DPV method without any previous step of extraction, clean-up, and derivatization and the linear range of EP was from 1.33  $\mu\text{M}$  to 5.50  $\mu\text{M}$  with a LOD of 15.6 nM. Human urine samples without any purification step were successfully analyzed under the standard addition method using this modified electrode. A composite film, constructed of surfactant doped over-oxidized PPY and MWCNTs was modified on GCE by electropolymerization method [151]. The electrode shows a high sensitivity and selectivity toward the electrocatalysis of EP coexistence of AA, UA and human serum interferences, which makes it a sensor suitable for the analysis of trace amounts of EP in pharmaceutical and clinical preparation. A EPPGE modified with MWCNTs was used as a sensor for the detection of EP [83]. A very low LOD of 0.15 nM was obtained for EP using SWV. The modified electrode was successfully applied to determine EP in body fluids of smokers and nonsmokers in resting stage.

Recently there are only few reports related to electrochemical sensors based on graphene and its derivatives for the detection of EP. Li et al. [152] fabricated a graphene-modified GCE via a drop-casting method for selective determination of EP in the presence of AA. A nano-Au decorated graphene nanocomposites was prepared via a chemical co-reduction of Au (III) and GO and used to fabricate an electrochemical sensor for EP [153]. In this paper, the co-reduction graphene/AuNPs were prepared by the reduction of a mixture of Au (III) and GO with sodium citrate. Finally, the reduction of GO and the *in situ* deposition of nano-Au were achieved in a one-pot process. The AuNPs, which were dispersed uniformly on the GS, acted as spacers for inhibiting the aggregation of graphene. The modified electrode exhibited high sensitivity and selectivity in the detection of EP. The LOD for EP was 7 nM and AA was not interfered.

EP and NE are difficult to distinguish using common electrochemical methods owing to their structural and chemical similarity. Nevertheless, it is feasible to fabricate selective sensors for EP and NE using CNT-based electrodes. A

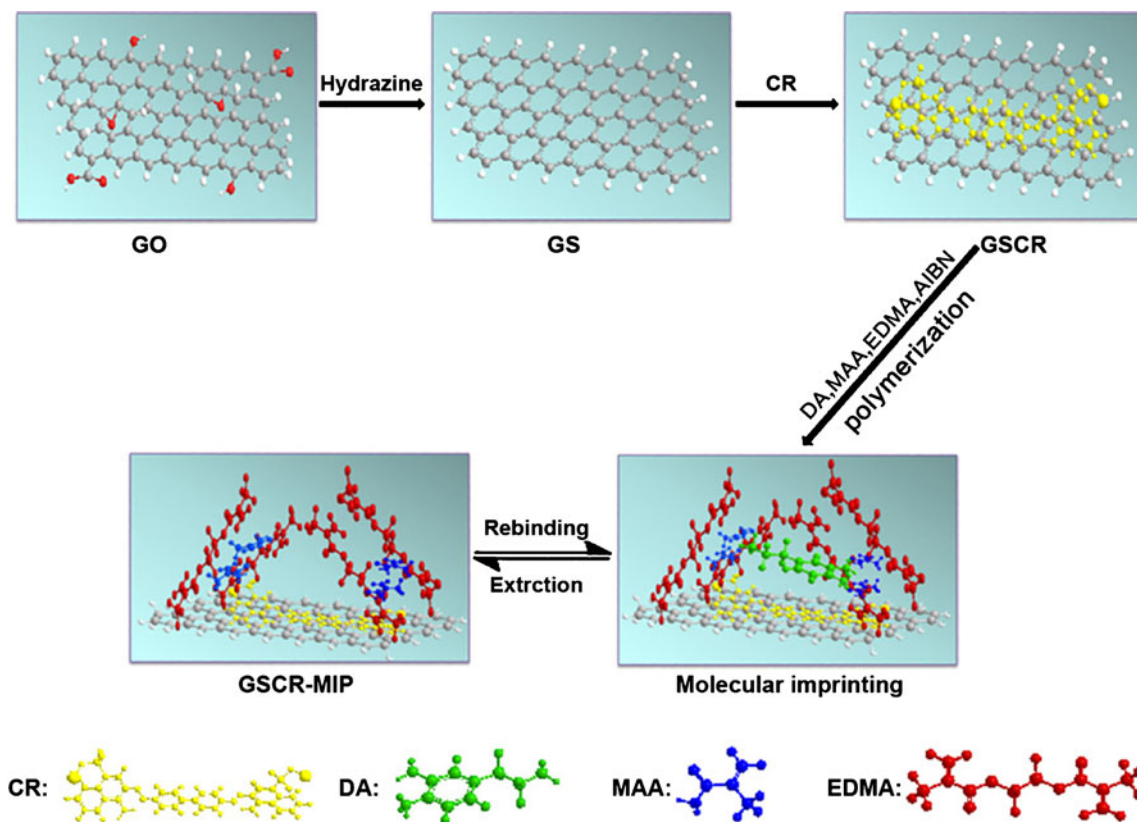


Fig. 5 Illustration of the synthesis route of GSCR-MIPs hybrids. Reprinted from [136]

CNT paste electrode fabricated with a quinazoline derivative, 2-(4-oxo-3-phenyl-3,4-dihydroquinazolinyl)-N'-phenyl-hydrazinocarbothio-amide (2PHC), could detect EP and NE simultaneously [85]. Separate EP and NE peaks (about 240 mV) were observed with SWV (Fig. 7) and the LOD was 9.6 nM for EP. This level is approximately that of basal EP in the brain. Another sensor for the simultaneous determination of EP and NE is based on a MWCNT-poly (nordihydroguaiaretic acid) (PNDGA)-CS copolymer film on gold electrodes or screen-printed carbon electrodes

[154]. MWCNTs enhance PNDGA-CS's surface coverage concentration on the electrode and decreases degradation of PNDGA-CS during cycling. EP and NE were not discriminated and the lowest concentrations studied were 30  $\mu\text{M}$  and 780  $\mu\text{M}$ , respectively. An EPPGE modified with MWCNTs was used as a sensor for the detection of EP and NE [84]. Very low LODs of 0.15 nM and 0.09 nM were obtained for EP and NE using SWV, respectively. The modified electrode was successfully applied to determine EP and NE in blood plasma and urine samples of smokers as well as in athletes.

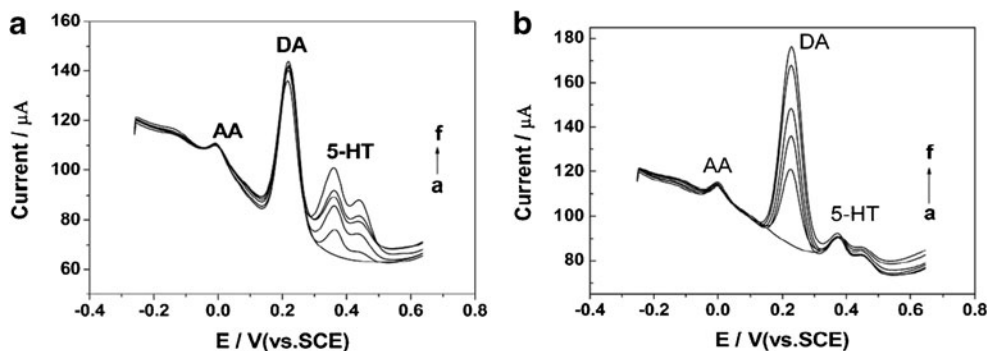


Fig. 6 DPVs of various concentrations of 5-HT (or DA) at MWCNTs-IL-Gel/GCE in pH 7.0 PBS containing 5  $\mu\text{M}$  DA (or 5-HT) and 0.5 mM AA. (A): 5-HT concentration ( $\mu\text{M}$ ): (a) 0, (b) 1, (c) 2.5, (d) 4, (e) 5, (f) 7.5.

(B): DA concentration ( $\mu\text{M}$ ): (a) 0, (b) 2.5, (c) 5, (d) 6, (e) 7.5, (f) 10. Accumulation time=4 min; pulse amplitude=50 mV, scan rate=20 mV/s, pulse width=50 ms. Reprinted with permission from [81]

In general, CNTs, graphene and their derivatives have been widely used as promising nanomaterials for the development of advanced sensors for neurotransmitters owing to their unique structures and properties to decrease overpotential and improve sensitivity. However, only a few studies have used these sensors in a biological system *in vivo* or *in vitro*. For more applied work, efforts would need to be taken on reducing the size of the electrodes, as many are based on large-sized electrodes such as GCE, which are not suitable for real time analysis of neurotransmitters. CFMEs may be one of the candidate electrodes. Future research work can be focused on CNTs or graphene modified CFMEs for *in vivo* monitoring of neurotransmitters in tissues and brain cells. Additionally, DPV method is relatively slow and true measurements of neurotransmitter changes will require subsecond temporal resolution, so methods such as fast-scan cyclic voltammetry and amperometry may become more popular for making real measurements.

### Carbon nanomaterials based electrochemical sensors for biogenic amines in food

BA are organic substances present in foods such as fish, meat, vegetables, fruits, nuts, chocolate, wine and beer. Excessive intake of BA may induce toxicological risks and health troubles. For example, the most frequent foodborne intoxications caused by BA involve histamine. An intake of 5–10 mg of histamine can be considered as defecting to some sensitive people, 10 mg is considered as tolerable limit, 100 mg induce a medium toxicity and 1,000 mg is highly toxic. Therefore, BA in food is commonly used as an indicator for assessing its freshness and quality. Accordingly, there is considerable interest in the determination of BA in foods. The application of electrochemical sensors and biosensors for BA analysis is a good alternative to traditional chromatographic methods due to their low cost, short analysis time, simplicity and possibility to be used outside an organized laboratory.

#### Tyramine

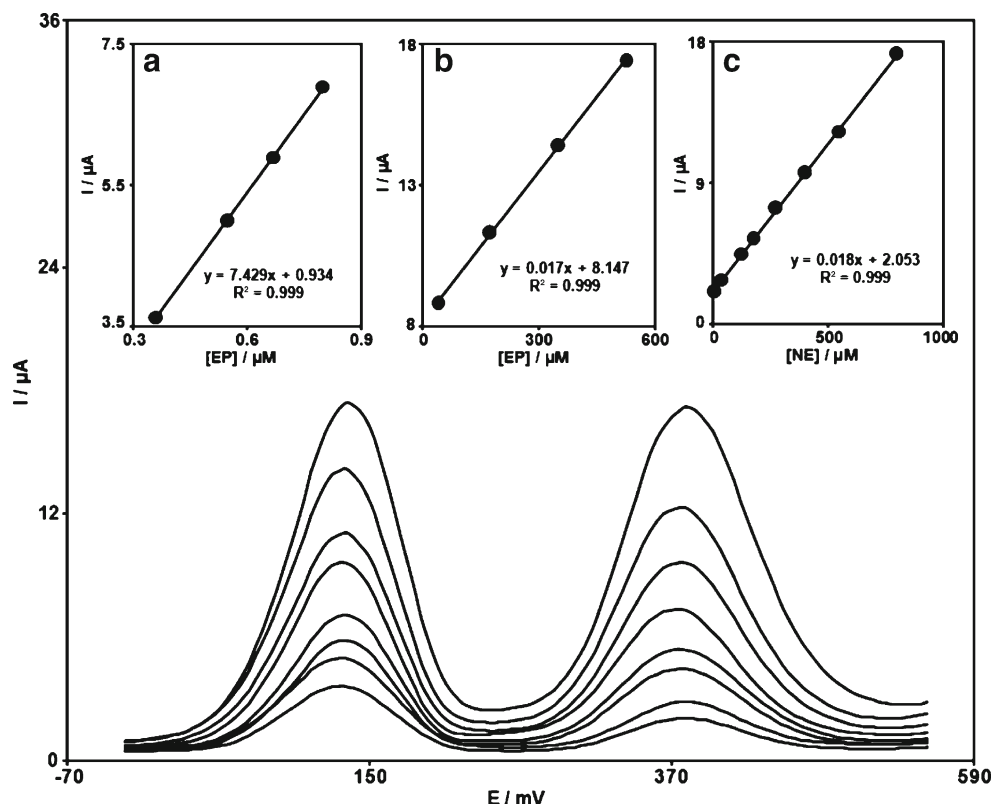
Tyramine, or 4-hydroxyphenethylamine, produced by the decarboxylation of tyrosine, is one of the BA, which are produced as degradation products resulting from microbial activity. Tyramine is found in high amount in certain foods such as chocolates, wine, beer, cheese, beans, banana peel, ketchup's and soya products. It has been reported that tyramine containing foods can cause unnatural and toxic effects when ingested in large quantities. For these reasons, the development of a fast, accurate method to measure tyramine concentrations in foods would be valuable. Electrochemical method may be a better option because of their simplicity, rapidity and high sensitivity. Because

tyramine is known to polymerize and passivate electrode surfaces, detection for tyramine at conventional electrodes is limited. The reported electrochemical biosensors/sensors for tyramine determination have been developed by enzyme-based electrodes or chemically modified electrodes without enzyme.

Cooper et al. [155] developed an electrochemical method to detect fast changes in tyramine and octopamine. They fabricated CFMEs and applied them for the determination of objectives using fast-scan cyclic voltammetry. No fouling was observed for tyramine and octopamine. LODs of 18 nM for tyramine and 30 nM for octopamine were obtained, which were much lower than expected levels in insects and lower than basal levels in some brain regions of mammals. This study showed that the method was useful for measuring tyramine and octopamine changes in insects. A novel sensor combining MIPs, MWCNT-AuNPs composites and CS has been developed [156]. By using MWCNT-AuNPs composites introduced for the enhancement of electronic transmission and a MIP specifically for tyramine, the sensor showed excellent selectivity and sensitivity over tyramine. The linear range using amperometric measurement was 0.108  $\mu\text{M}$  to 10  $\mu\text{M}$ , with a LOD of 57 nM. Determination of tyramine in yoghurt samples showed good recovery. In a study by Raoof et al. [157], a voltammetric sensor was developed to detect levodopa, UA and tyramine for the first time. The sensor was fabricated by the electrodeposition of quercetin on GCE modified with f-MWCNTs (Fig. 8). The prepared sensor showed an excellent electrocatalytic activity for levodopa, UA and tyramine oxidation and the LOD of tyramine reached to 0.647  $\mu\text{M}$ . Moreover, the sensor shows to be promising for the analysis of levodopa, UA and tyramine in real samples without expensive and time-consuming pretreatments.

To the best of our knowledge, there has been no report in the literatures on biosensors for tyramine using CNs. The electrochemical biosensors for tyramine determination have been reported employing either monoamine or tyramine oxidase immobilized on different supports such as gelatin [158], 2-[4,6-bis (aminoethylamine)-1,3,5-triazine]-Silasorb [159], and fluorphore sol-gel containing APTMS [160]. In a recent study by Lata et al., an amperometric biosensor was constructed by covalently immobilizing tyramine oxidase on an epoxy resin membrane [161]. Tyramine was measured specifically and leaching of enzyme was avoided. The LOD for tyramine was 0.24  $\text{mg dL}^{-1}$ , lower than that of tyramine oxidase immobilized on microtiter plate using sol gel fluorophore (6.30  $\text{mg dL}^{-1}$ ) [160] and electrochemical sensor based on MWCNTs-AuNPs composite and CS (0.99  $\text{mg dL}^{-1}$ ) [156]. The biosensor was successfully employed for determination of tyramine in beer and sauce items. Because of the very low LOD, this biosensor may have the sensitivity for future clinical and industrial applications.

**Fig. 7** SWVs of 2PHCMCNPE in 0.1 M PBS (pH 7.0) containing different concentrations of EP and NE: (from inner to outer) mixed solutions of 0.36+10, 0.55+40, 0.67+125, 0.80+175, 40+275, 175+400, 350+550, and 525+800, respectively, in which the first value is concentration of EP in micromolar and the second value is concentration of NE in micromolar. **a** and **b** Plots of the peak currents as a function of EP concentration and **c** plot of the peak currents as a function of NE. Reprinted with permission from [85]



## Histamine

Histamine [1H-imidazole-4-ethanamine], is the most important biogenic amine present in many food products and acts as chemical messengers in biological systems. Histamine is a neurohormone synthesized in mast cells and a product in food synthesized by the microbial degradation of the amino acid histidine. Histamine is naturally present in many vegetables and fruits in amounts below toxic levels. The formation of high levels of histamine correlates strongly with the number of microorganisms present in histidine rich foods (vegetables, fermented foods and certain fish). The presence of histamine in foods is commonly used as an indicator of the state of deterioration of the product and frequently regarded as one of the biomarkers in quality control monitoring during the food production, storage and transportation [162, 163]. Traditionally, histamine has been determined by use of chromatographic and spectrographic techniques. Although electrochemical detection methods are inexpensive and can provide high sensitivity, not many works have been reported on this type of detection, probably due to the high oxidation potential ( $\sim 1.2$  V vs SCE) of histamine, at which conventional electrodes such as GCE exhibit high background currents due to oxidation of the solvent water or of the electrode material itself [164]. The reported electrochemical biosensors

/sensors for histamine determination were mainly focused on boron-doped diamond electrode [164], nickel-film GCE [162], methylamine dehydrogenase immobilized in PPY film modified electrode [165], diamine oxidase screen-printed CPE [166] in the past few years. However, to the best of our knowledge, until now, there are no reports on electrochemical sensors/biosensors based on CNs for the detection of histamine.

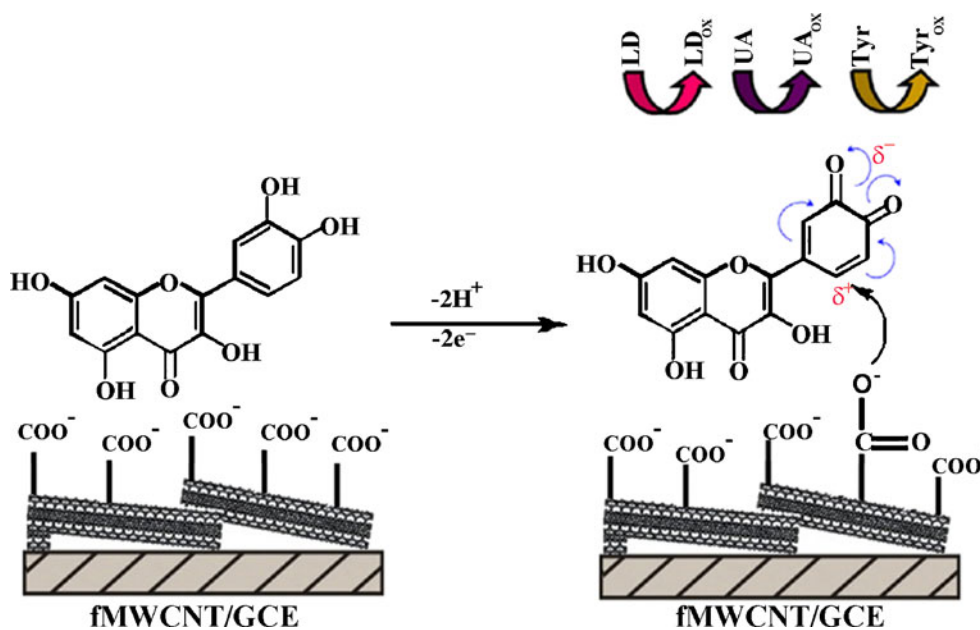
## Putrescine

Putrescine, also 1,4-diaminobutane, is one of important BA present in foods either as natural products or after fermentation, decomposition or putrefaction processes [167]. Putrescine has been implicated for the foul odour of putrefying flesh, bad breath and bacterial vaginosis. It has been used for various analytical and clinical purposes—plant stress markers, food spoilage and cancer markers [168]. Since putrescine plays a very important role in the metabolism of various biological tissues, its detection even at very low concentrations is critical.

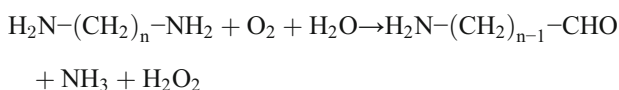
Generally, the basic principle in the electrochemical detection of putrescine is its conversion to hydrogen peroxide by oxidase such as amino oxidase (AO), EC 1.4.3.4 [169], diamine oxidase (DAO), EC 1.4.3.6 [170] and putrescine oxidase (PUO), EC 1.4.3.10 [171]. For both DAOs and



**Fig. 8** Schematic representation of the proposed mechanism for electrodeposition of quercetin at the surface of MWCNT/GCE and the electrooxidation of levodopa, UA and tyramine at the surface of final modified electrode. Reprinted with permission from [157]



PUOs, the enzymatic reaction of the diamines involves an oxidative deamination step with the liberation of ammonia and hydrogen peroxide:



Shanmugam et al. developed a highly sensitive rapid biosensor for detection of putrescine [170]. DAO, which was covalently linked to the iron oxide nanoparticles, was coated on GCE and a modified electrode referred to as DAO/nano-Fe<sub>3</sub>O<sub>4</sub>/GCE was used to sense putrescine by detecting the hydrogen peroxide released in the reaction. The LOD was 0.65 nM and 0.3 seconds was found to be as the response time. The ultrafast detection of low amounts of putrescine indicates that this biosensor may be used for clinical and analytical purposes.

Direct electron transfer between enzymes and the electrode was advantageous because of the potentially fast time response and lack of intermediate reactions that could cause interference. PUO is a rather big molecule (>200 kDa) with the redox center deeply inlaid in its structure. Hence, it is very difficult for the enzyme to directly exchange electrons with the electrode. CNTs are electrically conductive, it may pierce the glycoprotein shell and effectively reduce the distance between the redox site and the electrode surface, increasing sensitivity and decreasing response time. Luong and coworkers reported two MWCNTs based electrochemical biosensors for mediatorless detection of putrescine [168, 172]. GCE, coated with a mixture of MWCNTs, PDDA, APTES, and PUO, displayed oxidation/reduction peaks for FAD/FADH<sub>2</sub> in the CV but an electrode lacking CNTs did not [168]. Mouse plasma was analyzed with good

results compared to HPLC method, indicating that putrescine detection is also possible in mammalian plasma.

Sensors for the simultaneous determination of various biogenic amines

BA are synthesized and degraded during normal metabolism of animals, plants and microorganisms. Histamine, putrescine, cadaverine, tyramine, tryptamine, spermine and spermidine are considered to be some of the most important BA in food and in human body. BA detection has been shown to be a valuable tool for different analytical purposes, such as cancer markers or for assessing the freshness and quality of a wide variety of foodstuffs. Various methods have been developed for separation and quantification of BA and among them all, electrochemical detection has been considered to be a quick, efficient, sensitive, rapid and cheap alternative for the traditional ones. In this way, AOs based biosensors, which combine biological recognition through enzyme specificity with construction simplicity, have been reported in the literature [159, 169, 173–175]. Biosensors, especially the amperometric ones, have been the most successful and still have the most promising future for practical application. However, in the case of BA, there are few reports on biosensors employed by CNs for BA detection.

## Conclusions

This review has offered an overview of the electrochemical sensors of BA using CNs. The incorporation of CNs into electrochemical sensors provided a means for increasing the sensitivity and selectivity of detection of BA because of their interesting designs, comprehensive and detailed study.

Meanwhile, only few sensors are applicable to in vivo measurements in mammals or humans. In addition, the reports about simultaneous detection of different BA were also limited. Thus, considerable time and efforts are required to acquire further improvements.

Whereas, achieving higher sensitivity, selectivity, speediness, stability and reliability accuracy, automation have always been the driving forces in developing new electrochemical sensors for BA. We predict a bright future for CNs as sensing materials in fabricating of electrochemical sensors for BA. The recent Nobel Prize for graphene has sparked investigations of this new material in a variety of applications, including electrochemical sensors. Compared with other CNs, graphene and its derivatives are biocompatibility, lack of metallic impurities (which are a major obstacle in electrochemical sensing research with CNTs), high conductivity and abundance of inexpensive source material, which will play more important role. Moreover, functionalization of graphene and the combination of various other nanomaterials into graphene composites in order to explore their synergistic effects has become an interesting area of research.

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