Conductive Nanodiamond-Based Detection of Neurotransmitters: One Decade, Few Sensors

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ABSTRACT: Nanodiamond (ND) is a class of carbon nanomaterial with covalently connected sp³ carbon atoms in its core and an sp² carbon adorned surface via edge defects or doping. Endogenous chemicals that provoke physiological responses in the human system called neurotransmitters (NTs) have been detected with several sensors with carbon-based nanomaterials. Nanodiamonds (NDs), another class of carbon nanomaterial, have shown the requisite surface area and electrocatalytic activity toward NTs in the past decade. Surprisingly, only a few electrochemical ND based NT sensors are available. This work briefly looked into the performance of the available sensors, NT and ND interactions, and the possible reason for data paucity on the subject matter.

1. INTRODUCTION

The 1963 discovery of nanodiamond synthesis¹ opened a new chapter in the development of nanoscience and has consequently presented the nanotechnology branch of science with yet another tool for state-of-the-art inventions. Pure crystalline nanodiamonds (NDs) are composed of sp³ carbon atoms connected in a tetrahedral fashion. The conducting sp² carbon atoms responsible for the electrical conductivity of NDs emanate from its edge defects or surface modification.²a Arguably, similar architecture has been found in graphite, but the electrical conductivity of graphite is not solely dependent on the edge defect, introduction of dopants or stabilization by surface functional groups like what obtains in NDs. Beyond this, core graphite carbon atoms are not connected in a tetrahedral manner like that of NDs. In certain accounts, NDs have been considered as a nanosized form of bulk diamond with sp³ hybridized diamond and sp² hybridized graphite carbon atoms assembled in a core–shell manner.²b This architecture and the termination of dangling bonds of the shell with various functional groups have contributed to the stability of the metastable ND particles. It is noteworthy that NDs have a much lower bandgap width than natural bulk diamond (~5.6 eV) due to the higher value of sp²:sp³ in NDs.²b,c This property has made it possible to utilize NDs in cases where the delocalization of electrons in the sp² hybridized carbon component and the chemical stability of the diamond core is required. Also, in contrast to the bulk diamond and the confirmation of the presence of sp² hybridization in NDs, there have been pieces of evidence of NDs having absorption in the visible region.²d Essentially, the surface of the diamond core of NDs can be covered with functional groups or witness the conversion of sp³ hybridized carbon atoms to sp² in order to achieve more beneficial stability of the material.²²d NDs of various sizes have been reported but the broad definition of NDs includes diamond materials with sizes less than 100 nm.

The chemical and electronic identity of NDs are affected by the kind of dopant adopted for the improvement of the latter. Heavily boron-doped NDs (BDNs) have electrical conductivity close to that of metals due to the absence of a bandgap which is fairly wide in crystalline diamonds.²²b This architecture of BDNs and the presence of sp² carbon atom impurities have been reported to positively impact the conductivity of BDNs and also reduce the background current in some redox systems.²²a,b,5 Interestingly, the dependence of parameters indicative of good electrochemical behavior of a BDN on its sp² carbon impurity content has been documented.⁰⁴a Nitrogen doping of NDs has also resulted in the production of NDs with improved electrical properties relative to those of BDNs, considering the hydrogen evolution potential of nitrogen-doped NDs (NDN) and that of BDN.⁰⁶ Also, NDs have been terminated by –OH which made the formation of NDs
possible with terminal alkyl groups when the hydroxyl groups react with acid chlorides. The chemical properties of NDs have also been tailored for various applications due to the ability of the graphitic carbons on ND surfaces to form covalent bonds with surface groups such as N, O, and S (Figure 1) and in some cases via more complex reaction such as the Diels–Alder reaction or diazotization. Noteworthy, H-terminated NDs are hydrophobic NDs with much higher electrical conductivity at room temperature than the untreated NDs. The most popular and synthesized NDs are the detonation nanodiamonds (DNs). They were a product of the detonation of explosives which remained relatively unknown until the 1980s. This reaction, which desirably fuels itself by providing energy and a carbon source, often leads to the formation of soot among other materials. The detonation soot contains about 75 wt % diamond, graphitic carbon, and some metal and metal oxide impurities. Apart from DNs, nanodiamonds synthesized through carbon vapor deposition (CVD) and the use of lasers and autoclaves just like some other nanomaterials are also available. ONC, or onion-like carbon (OLC), a highly conducting multishell carbon sphere is a member of the fullerene family that has also been synthesized by annealing DNs in a vacuum. This class of nanomaterials otherwise called carbon nano-onions (CNOs) has gained tremendous attention as an electrochemical sensing material due to their nanoscale size and high conductivity. It is noteworthy that special treatments of OLC have been adopted to mitigate the agglomeration of its particles in an aqueous medium.

The nontoxic nature and the biocompatibility of NDs have been harnessed in their application in drug delivery, gene therapy, antimicrobial agent formulation, and the development of implant coatings. In the same vein, the optical properties of NDs have made them a worthy candidate in the design of bioimaging devices. The mechanical properties of NDs such as the huge hardness and Young’s modulus inherited from bulk diamond have been found useful in nanocomposites containing NDs. In essence, NDs have been incorporated into composites for the corrosion inhibition of metals due to their suitability as fillers. The biocompatibility and low background current of NDs in addition to the electrical conductivity of its derivatives after doping, heat pretreatment, or morphological perturbation of NDs have endeared electrochemists to the adoption of ND variants as one of the components of electrochemical sensors for biomolecules. Nanodiamond remains a nanomaterial whose application in biomedicine is quite pronounced irrespective of the synthetic route. Specifically, doped and heat-treated NDs have been used as a material for the modification of electrodes in electrochemical sensors for the detection of neurotransmitters in vivo and in vitro as a result of their exceptionally low cytotoxicity and good conductivity. The high sensitivity, low background current, and stability of ND based electrodes are enough reasons to expect that electrochemical sensors tailored toward NT detection would be too numerous to count, particularly since the beginning of the past decade. Surprisingly, electrodes of this designation are too few in number.

Neurotransmitters (NTs) are chemical substances that are transmitted between neurons and capable of provoking physiological responses in humans depending on their chemical nature. Dementia, Parkinson disease, anxiety, depression, schizophrenia, myocardial infarction, and Alzheimer’s disease are few of the disorders associated with inappropriate level or imbalance of NTs in the human system. NTs such as dopamine (DA), serotonin (5-HTP), acetylcholine, and glutaraldehyde are a few of the NTs implicated in these ailments. Compared to other analytical means of determination of NTs, electrochemical sensors are much easier to handle and cheaper to fabricate. Considering the merits of this technique and the potentials of NDs, it is expected that over a period of one decade, numerous ND based sensors for NTs would be available. Surprisingly, the data on this subject matter is limited (Figure 2).

This review is a searchlight on the possible reasons for the unexpected dearth of data on ND based electrochemical sensors for NT detection and the possible ways of circumventing the challenges encountered in developing past sensors for the emergence of future sensors with outstanding figures of merit and little or no technical challenges. This review covers the utilization of materials of ND origin such as the OLC and doped NDs in this regard.

2. NDS AND NTS: THE ELECTROCHEMICAL INTERACTION

The chemistry of the electroanalysis of NTs with ND based electrodes would have been a simplified one if the conductivity
of NDs due to the presence of edge defects, nature of surface termination, or the doping with an atom that enhances electron transfer had been completely accepted by material and electroanalytical scientists. Pristine nanodiamonds have undergone modifications such as doping (with atoms such as boron and nitrogen), surface termination, and heat treatment (as seen in CNO) to obtain materials with requisite electrical conductivity for biomolecule detection. This section of the review briefly discussed the electrochemical interactions between these modified NDs and NTs.

Puthongkham and Venton\(^\text{12}\) predicated their study on the detection of DA, SE, NE, and EP using ND based sensors on the morphology of the \(-\text{COOH}\) terminated NDs (ND-COOH). This study revealed that the better electrocatalytic activity of ND-COOH (with large particle size) toward the \([\text{Fe(CN)}_6]^{3-}/4^-\) redox probe compared to the smaller sized particles is due to the sparse coating of the former on the carbon fiber microelectrode (CFME). The significantly better current response to NTs provided by ND-COOH relative to that of H-terminated NDs was ascribed to the decrease in band gap brought about by the presence of sp\(^2\) hybridized carbon which consequently raised the NDs’ density of states (DOS).

Oxidation of BDNs which consequently gave oxygenated groups around the ND edge and resultant attraction for cationic NTs (like DA) at physiological pH as well as the dependence of the electrocatalytic activity of BDNs on film thickness were the explanations given by Qi et al.\(^\text{14}a\) for the selective detection of DA in the presence of AA (ascorbic acid). A similar line of thought was presented by Dincer et al.\(^\text{14}b\) in their investigation of the effect of surface termination of the BDN nanoelectrode array on the detection of DA and AA. In the same vein, the oxygenated functional groups on the carbon nano-onions (CNOs) derived from NDs was reported to be responsible for the superior electrocatalytic activity of the CNO modified electrode over that of electrodes modified with other carbon-based materials. CNOs of the same origin were subjected to different annealing temperatures to investigate the dependence of annealing temperature on the extent of edge defects and electrochemical properties of NDs. The decrease in the central diamond core and the simultaneous increase in the graphitic shell with an increase in annealing temperature which induced a strain in the outer sp\(^2\) hybridized graphitic shell were reported by Ko et al.\(^\text{11}a\) to have led to CNO edge defect generation. This edge defect which reached an optimum level at 1200 °C was ascribed to the superior electrocatalytic activity of the CNOs annealed at 1200 °C. Ko and his group further stated that the edge defect also enhanced the CNOs’ DOS.

In a study that posited differently from the accounts of some authors on the electrocatalytic activity of NDs emanating solely from the conductivity caused by surface sp\(^2\) hybridized carbon atoms or dopants,\(^\text{14}c,d\) Baccarin et al.\(^\text{15}\) concluded their findings on the chemistry of the electrochemical detection of DA by ND based sensors on the premise that NDs are insulators. The authors proposed a mechanism of electrocatalysis based on mass transport redirection induced by the interaction of the NDs with the screen-printed electrode (SPE) due to the formation of an array of graphite microelectrode. This position agrees with the report of Ramos and his group\(^\text{16}\) where untreated NDs were incorporated into a composite with Au nanoparticles, graphite, and casein for glassy carbon electrode (GCE) modification. The synergy between NDs and AuNPs which resulted in the formation of a composite with a large

Figure 3. (a) Fabrication of the NEA. (b) Schematic diagram of NEA sensor fabrication, and cyclic voltammogram of (c) dopamine and (d) ascorbic acid at H and O terminated NEA (Reprinted with permission from ref 14b. Copyright 2015 Elsevier).
surface area was presented as the rationale behind the catalytic effect of the ND based electrode. Ramos and his team did not connect the electrocatalytic activity of their electrode to the conductivity of NDs. Their silence on the impact of NDs in SE detection resonates well with the findings of Baccarin et al. and that of authors that carried out heat treatment, doping, and morphology adjustment on NDs before application as the sensing material. The paucity of data on the application of pure crystalline NDs as a sensing material compared to the heat-sensing material. The paucity of data on the application of pure crystalline NDs as a sensing material compared to the heat-sensing material. The paucity of data on the application of pure crystalline NDs as a sensing material compared to the heat-sensing material. The paucity of data on the application of pure crystalline NDs as a sensing material compared to the heat-sensing material. The paucity of data on the application of pure crystalline NDs as a sensing material compared to the heat-sensing material. The paucity of data on the application of pure crystalline NDs as a sensing material compared to the heat-sensing material. The paucity of data on the application of pure crystalline NDs as a sensing material compared to the heat-sensing material. The paucity of data on the application of pure crystalline NDs as a sensing material compared to the heat-sensing material. The paucity of data on the application of pure crystalline NDs as a sensing material compared to the heat-sensing material. The paucity of data on the application of pure crystalline NDs as a sensing material compared to the heat-sensing material. The paucity of data on the application of pure crystalline NDs as a sensing material compared to the heat-sensing material.

3. NDS AS A COMPONENT OF NTS SENSORS

Over the past decade, nanodiamonds have been included as a modifier for electrochemical sensors in order to achieve a sensing platform capable of NTs and their metabolites detection down to a very low concentration. Dopamine, serotonin, 5-hydroxytryptophan (5-HTP), epinephrine, and norepinephrine are a few of the NTs determined with ND modified electrodes. This section of the review focuses on the role of NDs in electrochemical sensors designed for these NTs.

3.1. Dopamine Detection.

Carbon-based nanomaterials such as carbon nanotubes, graphene, graphene oxide, and carbon quantum dots are often introduced into matrices for electrochemical sensor modification to either act as a support for other conducting materials or the main active electrochemical signal conductor. In the same vein, NDs have been incorporated into sensors for NT detection to take up both responsibilities depending on the design of the electrochemical sensor.

Utilizing BDNs fabricated at a German institute for solid-state physics, Dincer et al. fabricated an ND based electrochemical sensor for DA detection. Specifically, the sensing platform was an array of nanoelectrodes made from the chemical vapor deposition of BDN on a silicon wafer prior to silica deposition, patterning of the nanoelectrode array (NEA), and etching to obtain a chip fixed to the bottom of a measurement cell with a platinum wire providing the mandatory electrical connection (Figure 3a–b). It is noteworthy that the NEA was positioned with a distance of 10 μm between each electrode. Oxygen and hydrogen surface termination of the electrode arrays were carried out to investigate the effect of surface termination on the detection of DA in the presence of AA. The authors confirmed that the oxygen terminated NEA (O-NEA) were more suitable due to the adsorption of ascorbic acid at o-NEA while DA’s adsorption was not significant. The pretreatment of the electrode prior to analyte detection played a significant role on peak resolution. As seen in Figure 3c and d, the O-terminated BDN NEA was able to achieve peak resolution that seems impossible with the H-terminated analogue.

In a comparative study, the influence of the level of boron doping on the electrochemical and structural properties of BDN and its application for DA detection in the presence of AA and uric acid (UA) were investigated by Baluchová et al. Planar BDN was prepared by assembling dilute NDs on silicon prior to the growth of BDN in the presence of methane under optimum temperature, microwave power, and pressure. It is noteworthy that the boron doping was achieved with the incorporation of trimethyl boron using a boron–carbon ratio ranging from 500 to 8000 ppm in the gas phase. These planar BDN were used as the base upon which porous BDN of varying thicknesses were grown at different growth periods. This was achieved by spin-coating silica nanofiber with a nanodiamond seed on the planar BDN base. The prepared BDN was cut into shapes and used in the hydrogen-terminated form as the working electrode for DA detection. Electrochemical characterization of the electrode revealed that porous BDN films with a lower amount of dopant gave background currents that are much higher than that of planar BDN. Also, the porous BDN had a higher effective surface area and lower detection limit for DA detection compared to the planar BDN.

In the same vein, porous BDNs for simultaneous DA and pyridoxine determination were prepared by Li et al. This study was partly done to investigate the contribution of the morphology of BDNs to their electrocatalytic properties. The BDNs in this study were prepared from the methane and hydrogen gas reaction in the presence of trimethyl borate as a boron source and Ni as a catalyst. The resultant BDNs was prepared on a tantalum (Ta) support. The pores on BDNs were introduced by a plasma-induced absorption and release of carbon atoms. Electrochemical characterization of the porous BDNs confirmed the low background current commonly reported for BDNs. Compared to bare GCE, Ta, and BDNs, the porous BDN modified Ta electrode had the lowest charge transfer resistance. The superior electrochemical properties of this electrode are evident in its ability to detect DA and pyridoxine to a very low concentration over a wide linear range in the presence of notable interferents. The plasma etching of the BDN surface made a difference due to the provision of the abundant active site on the BDN surface as well as the H-termination of the BDNs after etching. The surface hydrogen is reported to be susceptible to oxidation to oxygen-containing functionalities that make DA detection easy.

Similarly, BDNs of varying film thickness were prepared and applied for DA detection in the presence of AA in order to investigate the connection between the electrocatalytic activity of BDNs and their film thickness. Qi and his team prepared BDNs via CVD using CH₄ and hydrogen as the gaseous mixture in the presence of B₂H₆ as the boron source on a silicon substrate, following the seeding of the Si substrate with a ND suspension. Varying BDN film deposition times were adopted to prepare four BDN films of different thicknesses (Figure 4). The best voltammogram (with K₃Fe(CN)₆) in terms of reversibility was recorded at the electrode with the

Figure 4. SEM images of BDN films at various deposition times (1−12 h) (Reprinted with permission from ref 14a. Copyright 2016 Elsevier).

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thickest BDN film. Also, the DA oxidation potential shifted to the anodic side with an increase in the film thickness. The ability of the electrode to detect DA in the presence of AA was attributed to the presence of oxygen-containing functionalities on the surface of BDNs as a result of anodic pretreatment in the presence of KOH. These functionalities were believed to be instrumental to the repulsion of anionic AA and the attraction of the cationic DA. Beyond the best AA and DA peak resolution emerging from the thickest BDN electrode, the highest sensitivity was also reported for this electrode. This study clearly showed the significance of BDN film thickness on its catalytic activity toward DA detection.

Inspired by the need to improve the clinical applicability of tetrahedral amorphous carbon (ta-C), Peltola and his group\textsuperscript{174} combined ta-C (prepared on a titanium-coated silicon substrate) with four variants of NDs namely H-terminated, COOH and NH\textsubscript{2} functionalized, COOH functionalized, and NH\textsubscript{2} functionalized NDs. Specifically, a solution of the mixture of each of these NDs was cast and sprayed on separate ta-C substrates to obtain two different types of sensors (drop-casted and spray-coated sensors) worked into a circular Teflon holder. The characterization of the NDs showed that they all contained a lower percentage of O and N compared to C. The charge transfer potential investigated for the individual samples and unmodified ta-C revealed that the H-terminated NDs had the highest rate constant. This result was corroborated by the reversibility of the cyclic voltammogram recorded from spray-coated H-terminated ta-C in 1 mM as opposed to the irreversibility and quasi-reversibility that characterized the other modified ta-C samples. This study concluded that the technique used for the modification of ta-C by the NDs played a significant role in the reaction kinetics of the materials toward DA oxidation and reduction. The spray coating fabricated H-terminated NDs modified ta-C for instance gave CV shifted to the anodic side with a less steep slope compared to the drop-cast electrode. Differences in the voltammogram shape and position were equally observed in other samples on both sides. Possible functional group denaturation on the drop-cast NDs during ta-C modification which consequently reduced the repulsion of DA was ascribed to their better performance.

Another comparative study based on the investigation of the superiority of CNOs of ND origin over other carbon-based materials such as multiwalled carbon nanotubes (MWCNTs), glassy carbon (GC), and graphene nanoflakes (GNFs) was carried out by Yang et al.\textsuperscript{176} CNOs are a type of carbon-based material with an onionlike hollow core encapsulated by an electronically conducting graphene shell. Yang and his group prepared CNOs via the ND thermal annealing prior to GC electrode (GCE) modification and subsequent DA, serotonin (SE), and epinephrine (EP) detection. Before DA, SE, and EP detection, CNOs were treated with oxygen-containing functional groups and poly(diallyl dimethylammonium chloride) (PDDA) to determine their effect on NT detection. PDDA treatment of CNOs showed an improved catalytic effect; therefore, MWCNTs were equally treated with PDDA before GCE modification. Compared to bare GCE, MWCNT/PDDA modified GCE, and GNF film, the CNO/PDDA modified GCE gave the best current response to DA, SE, and EP. DA detection in the presence of AA and UA was achieved with the highest peak difference using the CNO/PDDA modified GCE. CNOs produced through the same synthetic route as the one reported by Yang et al.\textsuperscript{175} were subjected to two different oxidation procedures for a comparative study on H\textsubscript{2}O\textsubscript{2}, DA, AA, and UA. Radiofrequency plasma (CNO-R) and chemical oxidation (CNO-C) procedures were adopted by Zuaznabar-Gardona et al.\textsuperscript{175} for the preparation of two other variants of the pristine CNOs. These CNO variants and the pristine CNOs were used for GCE modification, characterized, and subjected to voltammetric studies. X-ray photoemission spectroscopy data showed that the oxidized CNOs do not have peaks for sp\textsuperscript{3} hybridized carbon as seen in the pristine CNOs. GCE modified with CNO-C showed a tremendous improvement in the current response of the GCE to H\textsubscript{2}O\textsubscript{2} to a degree better than that of the GCE/CNO-R electrode. On the contrary, the GCE/CNO electrode gave the best peak resolution for the detection of DA in the presence of AA and UA while the peaks overlapped with GCE/CNO-C. This was attributed to the hydrogen bonding between CNOs and AA as well as the π–π interaction between CNOs and DA and UA molecules. The electrostatic attraction between DA and CNO-C due to the –COOH group on the CNO-C surface made the detection of DA by GCE/CNO-C more pronounced such that a broad DA peak that overlaps with that of UA emerged, thus preventing the simultaneous detection of the three analytes. This study concluded that the pristine CNO-modified GCE had superior electrocatalytic activity toward simultaneous AA, UA, and DA detection.

CNOs otherwise called onionlike carbon (OLC) by Ko et al.\textsuperscript{174} obtained from vacuum annealing of NDs was applied for DA, UA, and AA detection. In this study, CNOs were prepared through thermal annealing at various temperatures (1000–1400 °C) to obtain CNOs whose surface defects are temperature-dependent in order to study the dependence of the catalytic properties of the CNOs on DA, AA, and UA detection. TEM images revealed that the CNOs at each temperature are composed of a graphitic shell around the diamond core which vanishes at the highest annealing temperature (1400 °C). The particle size of the CNOs also increased with the annealing temperature before saturation at 1200 °C. This was attributed to the interplanar spacing of the graphitic shell (about 50% larger than that of the diamond core) compared to the spacing between diamond core planes. The defects created by the thermal annealing were ascribed to the strain on the outermost graphite as the inner diamond is consumed. The various CNO samples were drop-coated on GCE and applied for the electroanalysis of DA, AA, and UA. The highest current response mostly obtained for each of the analytes both individually and simultaneously was obtained with the CNOs annealed at 1200 °C, thus confirming 1200 °C as the onset of the disappearance of the diamond core. Consequently, the 1200 °C annealed CNOs were adopted for further electroanalysis of DA in the presence of UA and AA. This study confirmed the dependence of the electrocatalytic activity of CNO toward DA on the annealing temperature.

In a project aimed at optimizing NDs for carbon fiber microelectrode (CFME) modification for subsequent NT detection, Puthongkham and Venston\textsuperscript{12} presented sensing platforms based on the electropolymerization of polypyrrole on H-terminated and carboxylated NDs. NDs were procured, and various sizes of the carboxylated NDs were used in a comparative study with 5 nm H-terminated NDs. The SEM micrograph showed that the small-sized carboxylated NDs gave denser and less sparse coatings than that of large-sized COOH-terminated NDs when applied for CFME modification (Figure S). Electrochemical impedance spectroscopy (EIS) revealed
that the more sparse coatings of the large size carboxylated NDs have lower charge transfer resistance compared to those with small size and the H-terminated NDs. This was attributed to the increase in the active site provided by the sparse coating. The authors were also able to establish the fact that the −COOH functional groups supported DA adsorption which eventually contributed immensely to the electrocatalytic activity of the carboxylated NDs. The CFME with carboxylated NDs of 15 nm size gave the best performance for DA, EP, NE, and SE detection in the presence of AA compared to bare NDs of 15 nm size and the H-terminated NDs. This was attributed to the repulsion of the anionic AA by the electrode which contains anionic groups on NDs surface. Antifouling studies show that the anionic nature of the NDs was instrumental to the less fouling of the modified electrode by SE for instance while 5-hydroxyindoleacetic acid (5-HIAA), an SE precursor, shows a similar current response to bare CFME after 1-h exposure to 5-HIAA due to the significant fouling of the electrode by anionic 5-HIAA which also suffered repulsion from the ND-COOH modified electrode. This study is one of the very few instances where a conventional electrode was modified with NDs through drop-casting.

Just like Puthongkham and Venton, NDs procured commercially (without pretreatment) were used for screen-printed electrode (SPE) modification in an attempt to provide a sensing platform for DA in the presence of UA. In this study, Baccarin et al.15 disproved the previous findings on NDs as electrode modifiers that improved the conductivity of the modified electrode as a result of the sp² functionalities on their surface. They attributed the electrocatalytic activity of the ND modified SPE (made via drop-casting) toward DA and not the conductivity of NDs but to the diffusion of the electroactive species. After a series of investigations with ND modification of conventional electrodes such as the carbon paste electrode (CPE), edge plane pyrolytic graphite electrode (EPPGE), and GCE, the authors emphatically concluded that the NDs in their pristine form are nonconductive electrochemically. They further explained the “perceived electrocatalysis” as a case of mass transport change facilitated by the formation of a graphitic microelectrode array as a result of blockage of the surface of the conventional electrode. It is noteworthy that the NDs/SPE gave a better current response to DA than the unmodified SPE.

3.2. Detection of Other NTs. Apart from DA detection, SE, 5-hydroxytryptophan, and EP were also detected with ND based electrodes. As evident in some of our reviews on neurotransmitters, it is not surprising that DA once again took the largest percentage of ND sensors at the expense of other NTs (Table 1, Figure 2). This reality could be connected to the clinical significance of DA.

SE, an NT of the peripheral and central nervous system considered as a mood and sleep regulator among other

Table 1. Figures of Merit for Electrochemical Detection of NTs using ND-Based Electrodes

| NTs  | electrode       | supporting electrolyte | technique | LOD (nM) | LDR (μM) | interferents                                      | real sample | ref |
|------|-----------------|-------------------------|-----------|----------|----------|--------------------------------------------------|-------------|-----|
| DA   | BDN/Si          | 0.1 M PBS (pH 7.4)      | SWV       | 220      | 0.5–10   | AA, UA, caffeine, PAR                              |             | 3   |
|      | BDN             | 0.1 M HClO₃ (pH 3.0)    | DPV       | 1        | 1–20     | AA                                               |             | 14a|
|      | BDN-NEA         | 0.1 M PBS               | DPV       | <100     | 0.1–20   | AA                                               |             | 14b|
|      | PBND/Ta         | 0.1 M PBS (pH 7.0)      | DPV       | 60       | 0.1–600  | AA, UA, SE, glucose                               | human serum | 11b|
|      | CNO/PDDA/GCE    | 0.1 M PBS (pH 7.0)      | AP        | 100      | 0.1–6    | AA, UA                                           |             | 17b|
|      | CN0/GCE         | 0.1 M PBS (pH 7.0)      | DPV       | 450      | 0–800    | AA, UA                                           |             | 17c|
|      | 1200-CN0/GCE    | 0.1 M PBS (pH 7.0)      | DPV       | 11       | 0.1–700  | AA, UA                                           |             | 11a|
|      | ND-COOH/CFME    | PBS (pH 7.4)            | DPV       | 3        | 0.02–5   | EP, SE, NE, AA                                   | rat brain   | 12  |
| ta-C/ND | PBS (pH 7.7) | CV        | 50        | 0.05–1000| AA       |                                                   |             | 17a|
|      | SPE/ND          | Acetate buffer (pH 5.5) | DPV       | 570      | 0.01–10  | UA                                               |             | 15  |
|      | EP              | PGE/ND/Gr               | LSV       | 3        | 0.01–10  | UA                                               | human serum, urine, and DA injection | 20a|
|      | SE              | ND-AuNP-Gr-CS/GCE        | DPV       | 100      | 0.3–3    | urine                                            |             | 16  |
|      | 5-HTP           | PGE/ND-Gr               | LSV       | 6        | 0.1–80   | TRP                                              | human serum | 20  |

*PAR paracetamol; PBS phosphate buffer saline; TRP tryptophan; LSV linear sweep voltammetry; SWV square wave voltammetry; DPV differential pulse voltammetry; CV cyclic voltammetry; AP amperometry.*
physiological functions,\textsuperscript{16,18a,b} has equally been detected by ND based sensors. Aside from the ND modified CFME fabricated by Puthongkham and Venton,\textsuperscript{12} for the detection of monoamine NTs and the CNO/PDDA modified GCE prepared by Yang and his group,\textsuperscript{18c} for DA, SE, and EP detection, another ND based electrode solely for SE detection was prepared by Ramos and his team.\textsuperscript{16} The working electrode was made by immobilizing graphite (Gr), Au nanoparticles (AuNPs), and NDs on casein biopolymer (CS) for GCE modification. This is one of the very few instances in the years under review where NDs were incorporated into a composite with metal nanoparticles for GCE modification just like in other carbon nanomaterials. The electrocatalytic activity of this electrode (ND-Gr-AuNP-CS/GCE) toward SE detection was attributed to the synergistic effect of the materials as well as the presence of AuNP and the NDs in the composite which resulted in an increase in the surface area of the electrode. This was evident from the fact that Gr-CS/GCE gave the lowest result of technicalities might be required for the use of NDs for NT detection.

EP, a catecholamine NT produced by the adrenal gland’s medulla, is known for heart rate and blood pressure regulation as well as the regulation of some metabolic functions of the human system.\textsuperscript{15,16} Just like Ramos et al.\textsuperscript{16} did with the ND based GCE, Shahrokhian and Khafaji\textsuperscript{18a} presented an ND/Gr mixture modified pyrolytic graphite electrode (PGE) as a sensing platform for EP. This electrode was applied for EP detection in the presence of AA. The low LOD and wide linear range obtained for this electrode showed its good electrocatalytic activity which can be connected with the conductivity of the ND/Gr mixture used as a modifier. This electrode was further used for EP detection in human plasma, urine, and SE injection samples. 5-hydroxytryptophan (5-HTP) is a SE precursor and a NTs from the central nervous system and the human liver. Also, 5-HTP has been used as a drug for combating depression.\textsuperscript{20b–d} Considering the importance of this biomolecule, Shahrokhian and Bayat\textsuperscript{18a} used the same electrode applied for EP detection (ND/Gr modified PGE) for the determination of 5-HTP and tryptophan. This electrode was also able to achieve a very low detection limit for 5-HTP over a wide linear range. Apart from the good electrocatalytic activity of the electrode toward 5-HTP, a simple fabrication technique and high stability were equally part of its merits. The electrode was used for 5-HTP detection in a blood sample without interference from amino acids in the blood sample matrix.

4. PROBING THE DEARTH OF ND BASED ELECTROCHEMICAL SENSORS

Compared to other prominent carbon-based nanomaterials like CNT, carbon quantum dots, graphene, and graphene oxide, ND based sensors for NT detection are few in number, especially over the past decade. For electroanalytical scientists with a good knowledge of the interaction between materials and electroactive molecules like NTs, the easiest guess for the reason behind this paucity of data would be the low sensitivity of the ND based electrodes to NTs. However, the figures of merit in Table 1 proved otherwise because a very low limit of detection (LOD) has been achieved with ND based electrodes in various forms. The boron-doped NDs have succeeded in giving very low LOD (1 nM) for DA detection just as conventional electrodes modified with NDs have equally given LOD as low as 3 nM for DA and EP detection. Also, these ND based electrodes have been successfully adopted for NT detection in the presence of interferents. These facts show that the dearth of sensors of this architecture is not a product of the lack of effectiveness of the pre-existing ones. Then what could have held scientists back from fully utilizing the potentials of NDs as sensing materials for NTs?

Considering the articles under review, it is apparent that some of the NDs adopted for sensors fabrication were prepared following some rigorous synthetic route. For instance, the preparation of the NEA by Dincer et al.\textsuperscript{14} required the production of BDNs on a silicon wafer and subsequent etching and fixing to a cell. Surface termination of the NEA was also done to achieve the desired result. In some cases, the annealing temperature, porosity, or film thickness of the carefully synthesized BDNs were optimized to realize the best form of the NDs required for sensing. Electrochemical detection of analytes is known to be a simple and less time-consuming method of analysis, but the time required for the preparation of some NDs for this task shows that longer time and quite a lot of technicalities might be required for the use of NDs for NT detection.

Another possible reason for the few ND-based NT sensors could be the cost of technical inputs required for the production of NDs of desired chemical properties and morphology. A very good instance could be found in the production of porous BDNs from hydrogen and methane gas.\textsuperscript{3,11b,14a} The authors were only able to get the porous BDNs after the use of sophisticated equipment such as a plasma deposition system and magnetron deposition system. The same magnetron deposition sputtering was equally used among other equipment such as the ta-C film deposition system for the preparation of NDs on the ta-C support.

These possible reasons seem very much unlikely to contribute significantly to the limited focus on NDs as sensing materials for NTs because some sensors for NT detection have equally been fabricated with commercialized NDs. The resultant sensors have given very good LODs with selectivity for the analyte of interest in the presence of interferents. On the other hand, sensors with NDs as part of a composite for conventional electrode modification have equally been spotted in the available literature within the years under review.\textsuperscript{15,16} This rules out the possibility of technicalities involved in the design of ND based sensors. Specifically, Ramos et al.\textsuperscript{16} were able to achieve an SE sensing platform by incorporating a commercially procured ND into a composite comprising graphene, AuNP, and casein for the modification of GCEs.

In a manner of reiteration, it is important to emphasize that electrochemical platforms for analyte detection stand to provide an alternative to other expensive analytical means such as high-performance liquid chromatography (HPLC), and as such, it would be expected that materials for sensor fabrication are affordable regardless of the location of the laboratory. This seems to be the case for NDs as about 100 g of the particles barely cost more than CNTs of similar weight.

5. CONCLUSION AND FUTURE PERSPECTIVE

The ND based electrodes designed for NT detection are evidently too few in number for such a wide range of analytes and time frame. This review clearly showed that there is no reason other than some conflicting chemistry of the interaction of NDs with the electroactive biomolecules which disrupts the conductivity of NDs. Regardless of what the actual chemistry is, it is clear that the presence of NDs has significantly

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influenced the sensitivity of conventional electrodes toward NTs. In addition, it has been proven that nanodiamond films are alternatives to graphene and carbon nanotubes which exhibit some level of cytotoxicity, thus raising the level of risk involved in their application for in vivo NT detection. For these reasons, it is pertinent to further harness the potentials of NDs by investigating possible synergistic effects of NDs and various classes of nanomaterials of low cytotoxicity for the safe in vivo and in vitro electrochemical determination of NTs.

The past decade has witnessed several means of treating NDs for enhanced electrocatalytic activity and direct application without treatment or doping in some instances. These NDs have given sensing platforms with high sensitivity toward DA but a lot remains desired to fully harness the potential of this material. It is therefore expected that scientists would see reasons to delve into the combination of NDs with conducting polymers, metal oxide nanoparticles, enzymes, graphene oxide and some other materials capable of improving the performance of NDs as a material for NT detection in the years ahead. It would equally be expected that the use of ND modified electrodes in the detection of other NTs such as NE, acetylcholine, and glutathione would be attempted. By so doing, the academic world would have judiciously tapped into the potential of this nanogem (NDs).

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Prof. Bhekie B. Mamba  He has been the executive dean of the College of Science, Engineering and Technology, University of South Africa since January 2016. He previously served as the director of the Nanotechnology and Water Sustainability (NanoWS) research unit at the University of South Africa. Prof Mamba is a visionary and astounding leader and has occupied a number of leadership positions including being a Professor and Head at the Department of Applied Chemistry at the University of Johannesburg, Executive Dean of the Faculty of Science at the University of Johannesburg, Director of the DST/Mintek Nanotechnology Innovation Centre−Water Research Node, and the Director of the Institute of Nanotechnology and Water Research at the University of Johannesburg. Prof. Mamba has published about 7 book chapters, over 250 journal papers, about 12 technical reports, and over 50 conference proceedings. He has supervised to completion over 60 Master’s and Doctoral students who are now either employed or running businesses in South Africa and other countries in Southern Africa. Besides his established international collaborative research network with other esteemed universities locally and abroad, Prof. Mamba has presented his research work in several local and international conferences. He has reviewed journal articles for at least 20 international journals and has been an external examiner of M.Sc. dissertations and Ph.D. theses from various universities including Wits University, Tshwane University of Technology, University of the Free State, Royal Institute of Science and Technology (Sweden) (Main External Examiner), Rhodes University, University of Western Cape, University of Botswana, and University of Stellenbosch. His general research interest involves developing advanced technologies for water treatment, which include nanotechnology and membrane technology. His main interest is the removal of organic micropollutants in water and improving the efficiency of conventional technologies in dealing with new emerging pollutants through integrating existing technologies with nanotechnology.
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