New trends in the electrochemical sensing of dopamine

Krystyna Jackowska · Pawel Krysinski

Received: 25 September 2012 / Revised: 12 November 2012 / Accepted: 13 November 2012 / Published online: 16 December 2012
© The Author(s) 2012 This article is published with open access at Springerlink.com

Abstract Since the early 70s electrochemistry has been used as a powerful analytical technique for monitoring electroactive species in living organisms. In particular, after extremely rapid evolution of new micro and nanotechnology it has been established as an invaluable technique ranging from experiments in vivo to measurement of exocytosis during communication between cells under in vitro conditions. This review highlights recent advances in the development of electrochemical sensors for selective sensing of one of the most important neurotransmitters—dopamine. Dopamine is an electroactive catecholamine neurotransmitter, abundant in the mammalian central nervous system, affecting both cognitive and behavioral functions of living organisms. We have not attempted to cover a large time-span nor to be comprehensive in presenting the vast literature devoted to electrochemical dopamine sensing. Instead, we have focused on the last five years, describing recent progress as well as showing some problems and directions for future development.

Keywords Dopamine · Biosensors · Sensors · In vivo detection · Implantable sensors

Introduction

Dopamine (DA), which belongs to the catecholamine family of neurotransmitters, is crucially important in humans. It is produced in adrenal glands and several areas of the brain, and is the most abundant of the catecholamines involved in brain–body integration (Fig. 1).

Dopamine is formed by decarboxylation of DOPA and is a precursor of two other neurotransmitters—adrenaline and noradrenalin (Scheme 1).

Under physiological conditions in the nervous tissues and body fluids, dopamine occurs in the form of large organic cations.

As a potent neuromodulator, it affects many aspects of brain circuitry, neuronal plasticity, and the organization and control of stress responses; it is also of crucial importance in the attention span, learning, and memory [1–4]. Dopamine also affects the cardiovascular and renal systems [5–7] and a variety of motivated behavior (e.g., perceiving rewards and pleasure). Low levels or practically complete depletion of dopamine in the central nervous system is implicated as a major cause of several neurological diseases, for example schizophrenia, Parkinson’s disease, and ADHD/ADD [8–11]. In the neurotransmission process, dopamine acts as an extrasynaptic messenger molecule via volume transmission across the synaptic cleft to bind to extrasynaptic receptors (G protein-coupled receptors) and transporters [12–16] (Fig. 2).

Because all drugs of abuse affect the dopaminergic pathways, much study of addiction focuses on dopamine [17].

Given the wide range of physiological and pathophysiological implications, the development of a sensor for precise and selective measurement of dopamine (and/or its metabolites) at the low levels characteristic of living system (26–40 nmol L⁻¹ [18, 19] and below) can make a great contribution to disease diagnosis.

Many recently published papers have been devoted to detection of dopamine. Sampling and separation techniques for cell or tissue homogenates (microdialysis, low-flow push–pull perfusion) coupled to analytical techniques such as enzyme assays, liquid chromatography, mass spectrometry, capillary electrophoresis, with optical or electrochemical
detection (e.g., biosensors) are the main techniques used for measurement of dopamine (and neurotransmitters in general). However, the most straightforward, rapid, and cost-effective is the use of electrochemical sensing techniques for detection of electroactive neurotransmitters, including dopamine.

Recent developments in electrochemical sensors focus on improvement of their sensitivity, selectivity, and biocompatibility. Miniaturization of such sensors has also been attempted, with the objective of achieving better spatial and temporal resolution, and effective multi-analyte detection. It is beyond the scope of this brief review to cover all these topics. The interested reader is referred to the paper by Kennedy [20], and references cited therein. In this paper we focus solely on amperometric sensors for dopamine.

The 2e/2H⁺ redox reactions of dopamine under physiological conditions constitute the basis of electrochemical detection (e.g., amperometric, differential pulse voltammetry, cyclic voltammetry) of this neurotransmitter. Currents generated in these reactions may be linearly dependent on the concentration of the electroactive molecules in the extracellular medium, enabling quantification of these compounds.

Appropriate design of a sensor system should enable numerous limitations of direct electrochemical detection of catecholamines to be overcome. Electrochemical methods have been widely used for direct measurement for dopamine, with several advantages, for example as rapid response with high accuracy and relatively easy operation. However, early work by Hubbard and coworkers revealed the effects of adsorption, orientation of adsorbed molecules, concentration, supporting electrolyte, etc., on the electrochemistry of dopamine [21, 22]. Other limitations include the relatively large oxidation potential of direct oxidative detection on the electrode and formation of phenoxy radicals with subsequent coupling and formation of passivating polymeric film on the electrode [23–25], consecutive reactions of dopaminoquinone (DOQ), a product of electrochemical DA oxidation, resulting in aminochrome formation and electrode passivation [26]. The other problem which must be solved in the electrochemical detection of dopamine is the co-existence of many interfering compounds in biological systems. Among these interfering compounds, ascorbic acid (AA), epinephrine (EP), and uric acid (UA) are particularly important because they can all be oxidized at similar potentials resulting in overlap of voltammetric responses [27–29]. It is, therefore, important to develop an electrochemical method for selective determination of dopamine with high sensitivity and a low detection limit (LOD).

In recent years, numerous attempts have been made to develop such a method. Among these, different electrode materials have been tested, including metal, carbon, and boron-doped diamond electrodes [30, 31], and different electrolytes, including ionic liquids [32]. Modified electrodes with self-assembled monolayers [33, 34], covalent modification [31, 35], nanotubes, nanowires, nanoparticles [36–42], permselective membranes [43], and conducting polymer films have
been reported to have favorable effects on detection of DA in the presence of AA, UA, or both AA and UA [38, 44–47]. Conducting polymers have several advantages in the sensor preparation for DA detection. Some of these have pendant groups (amine or carboxylic) which interact (e.g., electrostatically) with the analyte or interferent molecules, which results in better separation of the redox signals of DA, AA, and UA [44, 46, 48, 49]. Another approach is to modify the electrode surface for immobilization of enzymes (e.g., tyrosinase), selective toward DA molecules [49–55].

Electrochemical sensors

Electrochemical sensors can be broadly divided in two classes—biosensors and chemical sensors. According to the IUPAC definition [56]: “the electrochemical biosensor is a self-contained integrated device, which is capable of providing specific quantitative or semi quantitative analytical information using a biological recognition element (biochemical receptor) which is retained in direct spatial contact with an electrochemical transduction element”. In the literature, however, many authors use a wider definition of biosensors, focused not on the indispensability of a biological recognition element but on the type of analyte. Throughout this review, we will use the term “biosensor” according to the IUPAC convention.

In contrast with biosensors, chemical sensors contain non-biologically active elements, improving their sensitivity and selectivity in analyte detection. In electrochemical sensors, modified electrodes are widely used as sensing elements. These modified electrodes can be formed on the basis of different inorganic or organic materials characterized by good electrical conductivity and catalytic properties.

Biosensors in dopamine detection

In recent years, much effort has been devoted to improving the catalytic properties, sensitivity, and selectivity of electrochemical sensors, either by application of nanoscale materials (nanoparticles, nanowires, nanotubes) [57–62] or by use of advanced membrane materials (sol–gel composites, hydrogels, lipid membranes) for biomolecule (enzyme) immobilization [63]. Many of the electrochemical biosensors tested for dopamine detection utilize tyrosinase (Tyr), the enzyme also known as polyphenol oxidase (PPO), as recognition element. Tyrosinase is a multifunctional copper-containing oxidoreductase with two types of catalytic activity in the presence of oxygen:

1. hydroxylation of monophenols to o-diphenols by cresolase activity; and
2. oxidation of diphenols to o-quinones by catecholase activity [64, 65].

The resulting quinones can be further reduced electrochemically on the electrode without any mediator, reforming the original o-diphenol. This reaction constitutes the basis of amperometric detection at negative potentials and quantification of phenolic compounds. By the same principle, dopamine, a catechol-like phenolic compound, can be detected by amperometry with an electrode modified with tyrosinase. Application of tyrosinase to electrochemical sensing of dopamine eliminates several problems connected with consecutive reactions of DA oxidation products resulting in the formation of aminochrome [26]. Application of tyrosinase, which is sensitive to some classes of reagent only, can also reduce the problem of many interfering compounds in biological systems, for example ascorbic acid (AA), uric acid (UA), and other neurotransmitters.

The crucial issue in the development of electrochemical biosensors is immobilization of the enzyme on a conductive
surface (electrochemical transducer). Some prerequisites should be fulfilled by the enzyme after immobilization:

- it must be efficiently immobilized on the surface, so loss of enzyme does not occur during measurement;
- it must retain its biological activity;
- it should be compatible with and chemically inert toward the host structure; and
- it should be accessible to the analyte;

There are also requirements of the matrices used for enzyme immobilization:

- the procedure for matrix formation should be simple, reproducible, and inexpensive;
- the matrix should be chemically stable in the analytical environment and inert to the enzyme and detected analytes;
- if the matrix works as a mediator in an electron-transfer process, its properties should be reversible; and
- the conductivity of the matrix should be high, especially when used in an electrochemical biosensor.

The procedures used for immobilization of enzymes on different substrates, and their advantages and disadvantages, have been widely discussed in many reviews of nanoscale materials [57, 58, 62] and conducting polymers [66–69]. A review has been devoted to immobilization of laccase (Lac) and tyrosinase (Tyr) on different substrates [70]. Data were reported for application of biosensors to detection of phenolic compounds; there were no data on dopamine detection, however.

Methods of enzyme immobilization can be divided into two main groups—entrapment in the bulk of the matrix and entrapment on the matrix surface. Entrapment in the bulk is expected when the active layer of the biosensor is formed by mixing the enzyme with the compound used for matrix formation, e.g., carbon paste, or monomers for chemical or electrochemical polymerization of polymers. When sensor active layers are formed by the sol–gel or layer-by-layer techniques, the bulk entrapment is, again, expected to be dominant. Of course, some of the enzyme is also bonded to the matrix surface, but most is trapped within the bulk. In surface-entrapment processes, physical or chemical adsorption are used, or the enzymes are immobilized by covalent bonding to appropriately functionalized matrices. The localization and distribution of the enzyme within the matrix is crucial and can determine the characteristics and performance of the biosensor. For instance, diffusion of analyte to enzyme trapped in the bulk of the matrix is limited; physical adsorption, however, the weakness of the physical interaction and the susceptibility of the binding energy to the environment (pH, ionic strength, type of ions) can result in enzyme losses and instability during practical application. In comparison, covalent linking of the enzyme to the matrix seems to be the most effective means of immobilization and formation of stable biosensors. However, when surface attachment is used for biosensor formation, the main problem is insufficient enzyme (a monolayer on a surface matrix) resulting in reduced biosensor sensitivity. Another limitation is proper orientation of covalently bound enzyme; this also should be taken into account for biosensors based on the so-called direct electron transfer (DET) mechanism. It is beyond the scope of this review to discuss this type of sensor, which has already been thoroughly discussed in an excellent review by Armstrong [71].

Many efforts have been made to improve the properties of the active layer of biosensors, for example accessibility to dopamine and loading capacity, by use of conducting porous and mesoporous materials. Similarly, increased surface active site density for enzyme immobilization can be achieved by constructing the matrix with nano-scale materials, for example metal or oxide nanoparticles, carbon nanowires, nanotubes, etc. These not only increase the amount of enzyme attached to the matrix but can also catalyze the enzymatic reaction, affecting kinetic data, sensitivity, and response time of biosensors. Such an approach has also been used for formation of Tyr biosensors for dopamine detection [49–55, 72–78]. Information about different types of matrix for tyrosinase immobilization, type of entrapment, analytical data (sensitivity, detection limit, linear range), and interferences are collected in Table 1. All the experimental results presented in this table were recalculated to present them in the same units for comparison purposes.

The best characteristics for dopamine biosensors were obtained by Njagi et al. [55] and Wang et al. [78]. They achieved a single-figure nanomole level detection limit for dopamine. However, it is very difficult to compare the results, because tyrosinase activity is very rarely determined after its entrapment in the matrix (in the bulk or attached to the surface). Also the enzyme loading is generally unknown and uncontrolled. Such data are given in a few publications only [55, 76, 77].

Response time is another important analytical property describing Tyr biosensor performance [50, 51, 54, 55, 75, 76]. The lowest response time (<5 s) for DA detection has been obtained with biosensors containing SWNT-PPy (single-wall carbon nanotubes–polypyrrole) as matrix with tyrosinase covalently bound to nanotubes functionalized with carboxyl groups [54]. The effect of matrix composition on response time was tested by Njagi et al. [55]. They obtained the lowest response times (<8 s) for biosensors with a relatively complex matrix consisting of Tyr-Chit/CF and Tyr/TiO2/CeO2/Chit/CF, where CF and Chit denote carbon fiber and chitosan, respectively. Replacement of chitosan in such a matrix by a sol–gel system resulted in a three or
were made by Njagi et al. [55] for tyrosinase biosensors containing mixed oxides (TiO₂, CeO₂). It was shown that the presence of oxides improved biosensor stability; this can be attributed to strong adsorption of the enzyme on the metal oxides.

For practical purposes dopamine biosensors should be tested using real biological systems, and several papers report testing of Tyr biosensors in real biological (in vivo) measurements [55, 74, 77]. In another strategy, detection of dopamine was performed in the presence of different interferents, usually ascorbic acid (AA) [49, 50, 53–55, 72, 73] but also uric acid [49, 55], L-DOPA, DOPAC [55, 72], and even the presence of another catecholamines—serotonin (SE), norepinephrine (NorEP), and epinephrine (EP) [55]. It is generally accepted that Tyr biosensors can be used for selective detection of dopamine in the presence of AA, UA, and SE.

As already mentioned, in practical use all of the properties of dopamine biosensors discussed above are very important. However, to understand the mechanism of the response of the biosensor, why interferents affects its analytical performance, analytical performance, for example

| Table 1 Analytical characteristics for electrochemical detection of dopamine by use of different tyrosinase biosensors |
|--------------------------------------------------|------------------|------------------|------------------|
| Layer description (immobilization matrix)         | Interferents      | Linearity (mL⁻¹) | Sensitivity (mAMol⁻¹L) | Detection limit (mL⁻¹) |
| C paste, b.entrp                                  | AA, DOPA, DOPAC  | 1.5×10⁻³–2.5×10⁻⁴ | 6.3               | 1.5×10⁻⁵          |
| Polyanalogue gel, b.entrp                         | Without AA        | 5×10⁻⁶–1×10⁻⁴    | 5×10⁻⁶            | 5×10⁻⁶            |
| Polyanalogue gel, b.entrp                         | AA                | 3×10⁻⁸–1×10⁻⁶    | 3×10⁻⁸            | 3×10⁻⁸            |
| Polyphosphate, b.entrp                            | AA                | 5×10⁻⁸–8×10⁻⁵    | 5×10⁻⁸            | 5×10⁻⁸            |
| Poly(vinyl alcohol) ferrocene-Pd-sol-gel, b.entrp  |                   | Up to 2×10⁻⁴     | 133               | 1×10⁻⁷            |
| Biocomposite gel (agar, guar gum), b.entrp        |                   | 2×10⁻⁶–1×10⁻⁵    | 9×10⁻⁷            | 9×10⁻⁷            |
| Amine-terminated BDD, surf., cov. bond.           | AA                | 5×10⁻⁶–1.2×10⁻⁴ | 68.6              | 5×10⁻⁷            |
| MWNT/Nafion, b. surf. entrp                       | AA                | 5×10⁻⁶–2.3×10⁻⁵ | 12                | 5×10⁻⁷            |
| Eggshell membrane, GA, surf., phys. ads           |                   | 5×10⁻⁷–2.5×10⁻⁴ | 2.5×10⁻⁶          | 2.5×10⁻⁶          |
| Chit/GC                                          | AA                | 9.7              | 1.9×10⁻⁶          | 1.9×10⁻⁶          |
| TiO₂/CeO₂/Chit/GC, b. surf. entrp                 |                   | 14.9             | 2.4×10⁻⁸          | 2.4×10⁻⁸          |
| SWNT/Ppy, surf. cov. bond                         | AA                | 5×10⁻⁶–5×10⁻⁵    | 467               | 5×10⁻⁶            |
| Fe₂O₃/Chit, b. surf. entrp                        | AA                | 2×10⁻⁷–7.5×10⁻⁵ | 46                | 6×10⁻⁹            |
| TiO₂/CeO₂/Chit/CF                                | AA, UA, DOPA, DOPAC, Chit/CF | 1×10⁻⁸–2.2×10⁻⁴ | 14.2              | 1×10⁻⁹            |
| Chit/CF                                          | SE, EP, NorEP     | 5×10⁻⁸–1.2×10⁻⁴ | 7.3               | 4×10⁻⁷            |
| TiO₂/CeO₂/sol-gel/CF                             |                   | 1×10⁻⁷–1.8×10⁻⁴ | 33.4              | 4×10⁻⁸            |
| sol-gel/CF                                       |                   | 2×10⁻⁷–2.6×10⁻⁴ | 6.4               | 8×10⁻⁸            |
| PIn5COOH surf. cov. bond                         | AA <1×10⁻⁴mL⁻¹    | 5×10⁻⁷–2×10⁻⁵    | 2.200             | 2×10⁻⁷            |
|                                                   | UA <1×10⁻⁴mL⁻¹    |                   | 6,200             |                   |
|                                                   | AA/UA 12.5        |                   | 1,290             |                   |

b.entrp., entrapment of tyrosinase in matrix; surf. entrp., entrapment of tyrosinase on matrix surface; surf., cov. bond, entrapment of tyrosinase on surface, physical adsorption; Chit, chitosan; CF, carbon fiber; PIn5COOH, poly(indolo-5-carboxylic acid); SWNT, single walled carbon nanotube; MWNT, multi walled carbon nanotube; BDD, boron-doped diamond; GC, glassy carbon; GA, glutaraldehyde; AA, ascorbic acid; UA, uric acid; DOPA, 3,4-dihydroxy-L-phenylalanine; DOPAC, dihydroxyphenylacetic acid; SE, serotonin; EP, epinephrine; NorEP, norepinephrine

fourfold increase of response time. This was ascribed to the diffusion barrier imposed by this matrix.

The important features for practical use of biosensors are:

1. sensor stability;
2. reproducibility of sensor readout; and
3. life-time.

These properties depend very much on biosensor construction and its working environment (pH, ions, interferents, inhibitors). The reproducibility, determined in several cases [54, 55, 78], has been found to be in the range 2.2–2.5 %. The stability varied from a week to a few months [52, 55, 75, 77, 78]. The biosensors usually retained approximately 90–95 % of their original response after one week under the same experimental conditions. In the long-term the stability gradually decreased to 70 % or less. The best results were obtained by Pandey et al. [75]. They found their biosensor was stable over three months, retaining 95 % reproducibility when stored at 4 °C. However, the procedure used to evaluate stability was not described precisely. The most complex measurements of stability and reproducibility...
Chemical sensors in dopamine detection

As remarked above, biosensors based on the enzyme tyrosinase have been successfully used for selective determination of dopamine in the presence of ascorbic and uric acids in a biological environment. The main problem in the practical application of such biosensors is their poor long-term stability and reproducibility. One strategy used to overcome problems with DA detection is the development chemical sensors, usually chemically modified electrodes. In the last decade many of different materials have been tested to improve catalytic affinity, to enlarge the reaction space, and to eliminate the effect of interferents. A huge amount of research has resulted in more than hundred publications in the last three years. In 2010, Compton et al. [79] reviewed the literature on amperometric detection of DA in presence of interferents, for example AA, UA, and serotonin. They provided a brief description of modifying layers: polymers, carbon nanotubes, and other types of surface modification. In this section we focus on some new materials used for electrode modification, for example graphene [80–90], ionic liquids [91–98], and nanoparticles [99–119]. We mostly discuss articles published within the last three years. The linear range of DA detection, sensitivity, detection limit, and short descriptions of electrode composition are presented in Tables 3–6.

Graphene

Data for selective determination of DA by use of electrodes modified with graphene (GR) are listed in Table 3 [81–89]. An excellent, short review on the applications of graphene for electrochemical sensing and biosensing was recently published by Pumera et al. [80]. Graphene is a very promising material for electrochemical applications because of its very large electrical conductivity, large surface area, and relatively low cost of preparation. Electrodes can be modified with graphene suspension [81], powder [87], and graphene composites [86]. Graphene sheets [88] can also be used as electrodes. Use of reduced graphene oxide (rGO) for DA detection has recently been studied [82–86, 88]. It is accepted that the reduced GO enhanced the electrochemical response as a result of the presence of oxygen-containing groups on the reduced GO surface [80]. In many articles the rGO is also called reduced graphene (rGR), but this is not correct. The DA sensors with the best detection limit (1–10 nmol L\(^{-1}\)) and linear range were obtained by use of electrodes modified with graphene prepared by GO reduction [82–86, 88]. It is difficult to compare the results because of lack of information about the surface properties of the graphene-modified electrodes. Some FTIR and Raman spectra can be found for graphene electrodes modified with organic compounds [82, 84, 88], and XRD and TEM have been used for their characterization [89]. There are no kinetic data for DA oxidation. The stability and reproducibility of electrodes modified with quercetin (Qu)/GR [82] and PPy/GR [84] have been investigated. The relative standard deviation was found to be lower than 2 % [82] or 3 % [84] and stability was approximately two months for Qu/GR. Graphene-based electrodes have been used to monitor DA in biological samples, for example rat striatum [82], mouse...
liquids have been used to form composite IL electrodes to achieve high conductivity and large electrochemical windows, and can act as electrolytes near room temperature, they have a high ionic conductivity. Ionic liquids (IL) in electrochemical sensors. Wai and Ivaska [96] recently reviewed the applications of ionic liquids (IL) in electrochemical sensors. The ionic liquids (IL) in electrochemical sensors. They have also been used for simultaneous determination of DA, AA, and UA [90].

 Ionic liquid composite electrodes

Wai and Ivaska [96] recently reviewed the applications of ionic liquids (IL) in electrochemical sensors. The ionic liquids have unique properties—they are salts with melting points near room temperature, they have a high ionic conductivity and large electrochemical windows, and can accelerate electron transfer in several reactions. Different ionic liquids have been used to form composite IL electrodes—OPPPF₆−N-octylpyridinium hexafluorophosphat [91, 92], BMIMPF₆−1-butyl-3-methylimidazoliumhexafluorophosphate [93, 95], and PMIMCH₃COO−1-(3-chlorine-2-hydroxypropyl)-3-methylimidazolium acetate [94]. The worst detection limit (LOD) was obtained for carbon paste containing PMIMCH₃COO [94]. The low LOD of this electrode could, however, result not only from the type of IL but also from application of Ni/Al hydroxide layers. The kinetic data for the sensor developed in this work, for example the electron-transfer rate constant, kₑ, and the charge transfer coefficient, α, were 1.66 s⁻¹ and 0.43, respectively. These data are somewhat lower than those obtained for functionalized ordered mesoporous carbon/ionic liquid gel/glassy carbon (f-OMC/ILgel/GC) electrodes [95], for which the detection limit was 4.1×10⁻⁹molL⁻¹, kₑ=2.5 s⁻¹, and α=0.55. For the f-OMC/GC electrode, but without IL, these authors obtained the lower value of kₑ=0.97 s⁻¹, indicating that the presence of IL facilitates electron transfer between dopamine and the electrode surface [95]. The stability and reproducibility of such electrodes modified with IL were also examined. The RSD was in the range 1.5–3 % [91, 92, 94] and stability was ca 1 month for the Ni/Al-layered double hydroxide/carbon ionic liquid electrode (Ni/Al-LDH/CILE, ca 10 % response decrease). The molecular sieve/carbon ionic liquid electrode (MS/CILE) was used for monitoring DA levels in human serum [91]. Analytical data for electrodes containing ionic liquids (IL) are listed in Table 4.

### Metal and semiconductor nanoparticles

Substantial growth of applications of metal and semiconductor nanoparticles for electroanalysis has recently been

---

**Table 2** Kinetic data for tyrosinase biosensors for dopamine

| Layer description (immobilization) | Kₐ (molL⁻¹) | Vₘₐₓ or Iₘₐₓ | Ref. |
|-----------------------------------|-------------|---------------|-----|
| C paste, b,entrp                   | 1.1−2.3×10⁻⁴ | 0.342 μA      | [72]|
| Biocomposite gel (agar, guar gum), b,entrp | 5×10⁻⁶ | –             | [77]|
| MWNT/Nafion, b, surf. entrp        | 6×10⁻⁵     | –             | [51]|
| Chitosan, b, surf. entrp, TiO₂/CeO₂/Chit/GC, b, surf. entrp | 7.99×10⁻⁴ | –             | [53]|
| Eggsheel membrane, GA, surf. phys. ads | 6.7×10⁻⁴ | 0.08 mmolL⁻¹min⁻¹ | [52]|
| PIn5COOH surf. attach, cov. bond   | 1.2×10⁻⁶   | 5.5 µAcm⁻²    | [49]|
| (AA, UA>100 µmolL⁻¹)               | 1.33×10⁻⁶  | 16.5 µAcm⁻²   |     |

The abbreviations are explained in the footnote to Table 1

---

**Table 3** Analytical data for electrooxidation of dopamine at graphene-modified electrodes

| Electrode       | Method | Interferents | Linearity (molL⁻¹) | Sensitivity (mA mol⁻¹ L⁻¹) | Detection limit (molL⁻¹) | Ref. |
|-----------------|--------|--------------|--------------------|---------------------------|----------------------------|-----|
| PPy/GR/GC       | CV     | AA           | 5×10⁻²−1×10⁻⁵      | 94                        | 1×10⁻⁷                     | [81]|
| Qu/GR/GC        | DPV    | AA, UA, others | 3×10⁻⁷−4×10⁻⁴     | –                         | 1×10⁻⁸                     | [82]|
| GR/CFE          | CV     | AA, UA       | 1×10⁻⁸−1×10⁻⁴      | –                         | 1×10⁻⁸                     | [83]|
| PPy/rGO/GC      | DPV    | AA, UA       | 1×10⁻⁷−1.5×10⁻⁴    | –                         | 2.3×10⁻⁸                   | [84]|
| TCP/GR/GC       | DPV    | AA, UA       | 1×10⁻⁷−1×10⁻⁶      | –                         | 2.2×10⁻⁸                   | [85]|
| EDTA/GR/Nafion/GC silanized | DPV     | AA           | 2×10⁻⁷−2.5×10⁻⁶    | –                         | 1×10⁻⁸                     | [86]|
| GR/GC           | DPV    | AA           | 4×10⁻⁷−1×10⁻⁴      | –                         | 2.64×10⁻⁶                  | [87]|
| β-CDOGR/GC sheet| CV     | AA           | 9×10⁻⁷−1.3×10⁻⁵    | –                         | 5×10⁻⁷                     | [88]|
| GR-Chit/GC      | CV     | AA, UA       | 5×10⁻⁸−2×10⁻⁴      | –                         | –                          | [89]|

Gr, graphene; rGO, reduced graphene oxide; GC, glassy carbon; CF, carbon fiber; PPy, polypyrrole; β-CDO, β-cyclooctatetraen; Chit, chitosan; Qu, quercetin; TCP, meso-tetra(4-N,N,N,N-trimethylanilinium)porphyrin
observed [62, 118, 119]. These nanoparticles perform several important functions, including an increase of the sensing surface and facilitation of electron transfer. They also facilitate electrical contact between the redox center of a biomolecule and the electrode surface. They can also be modified further. Analytical data obtained from use of electrodes modified with nanoparticles to detect DA in the presence of AA and UA are listed in Table 5. Data for simultaneous determination of DA, AA, and UA are listed in Table 6.

Comparing of detection limits showed the best result for selective determination of DA in the presence of AA was obtained by use of a sensor containing conducting polymer (PEDOT) and inorganic Cu crystals of appropriate size [110]. It was demonstrated that optimization of the thickness of PEDOT, surface coverage of PEDOT by Cu nanocrystals, and their diameter, resulted in a sensor operating in the nanomolar concentration range. This high sensitivity was related to formation of a Cu(II)–o-quinolate complex and its promotion of subsequent DA oxidation [110]. There is insufficient data describing the properties of the surface of electrodes modified with nano-scale materials and used for DA monitoring. Some information on surface coverage, morphology, and loading can be found for PNPy/Pd(nanoclusters) [112] and Au(nanoparticles)/PANI [111] composites. We were impressed by the publication describing an electrode with methylene blue adsorbed on a phosphorylated zirconia–silica (MB)SZP for which surface properties and electrode composition, for example amount of zirconia, phosphorus content, surface area, the type of surface bond, were determined [116]. Analytical data for electrodes used for simultaneous determination of DA and other analytes show the best results for simultaneous determination of DA and UA were obtained by use of an electrode modified with polypyrrole and Cu nanoparticles, CuNP/Ppy [113]; for detection of DA in the presence of AA,

| Electrode Method | Interferents | Linearity (mol L⁻¹) | Detection limit (mol L⁻¹) | Ref. |
|-----------------|--------------|---------------------|---------------------------|------|
| MS/CILE SWV     | AA           | 5 × 10⁻⁸–8 × 10⁻⁴   | 1 × 10⁻⁸                  | [91] |
| Pglycine/CILE SWV | AA         | 1 × 10⁻⁷–3 × 10⁻⁴   | 5 × 10⁻⁹                  | [92] |
| SCP/CILE SWV    | AA           | to 1 × 10⁻⁴         | 2.6 × 10⁻⁷                | [93] |
| Ni/Al-LDH/CILE  | AA, UA, others | 1 × 10⁻⁵–1.1 × 10⁻³ | 5 × 10⁻⁶                  | [94] |
| f-OMC/ILgel/GC DPV | AA, UA    | 1 × 10⁻⁷–5 × 10⁻⁴   | 4.1 × 10⁻⁹                | [95] |

| Electrode Method | Interferents | Linearity (mol L⁻¹) | Sensitivity (mAMol⁻¹L) | Detection limit (mol L⁻¹) | Ref. |
|-----------------|--------------|---------------------|------------------------|---------------------------|------|
| CD-MWCNT Plu/AuNP/GC DPV | AA, UA, other | 1 × 10⁻⁶–5 × 10⁻⁵   | –                      | 1.9 × 10⁻⁷                 | [99] |
| Pt-DEN/GC FIA   | AA           | –                   | 19 ppb                 | –                         | [100] |
| AuNP UV-visible | AA, DOPA, other | 5.4 × 10⁻⁷–5.4 × 10⁻⁶ | –                      | 3.6 × 10⁻⁷                 | [101] |
| Au/Pt/Pd/TiO₂NT/Ti DPV | AA, UA    | 5 × 10⁻⁸–3 × 10⁻⁵   | –                      | 3 × 10⁻⁸                  | [102] |
| AuNP/TiO₂NT/Ti CV | AA           | 5 × 10⁻⁴–2.5 × 10⁻³ | –                      | –                         | [103] |
| DHBPD/TiO₂NP/CP DPV          | AA         | 8 × 10⁻⁸–2 × 10⁻⁵   | –                      | 3.14 × 10⁻⁸                | [104] |
| CNP/ß-silicate particles/ITO DPV | AA, UA, NADH, other | 3 × 10⁻⁷–1.8 × 10⁻⁵ | –                      | 3.6 × 10⁻⁷                 | [105] |
| Cu nanostructured DPV         | AA           | 1 × 10⁻⁶–1 × 10⁻⁴   | 139                    | 5 × 10⁻⁶                  | [106] |
| a) CuONP/CP DPV               | AA           | 3 × 10⁻⁷            | –                      | 1.8 × 10⁻⁷                | [107] |
| b) CuONP/CP DPV               | AA           | 2 × 10⁻⁵            | –                      | 5.5 × 10⁻⁸                | [108] |
| nanoZnO/GC DPV | AA           | 1.1 × 10⁻⁷–8 × 10⁻⁴ | –                      | 6 × 10⁻⁸                  | [109] |
| Fe₃O₄-SWCNT/PGE SWV DPV       | AA           | 3.2 × 10⁻⁶–3.1 × 10⁻⁵ | –                      | 3.7 × 10⁻⁷                | [109] |
| Cu(CR)-PEDOT/Pt DPV | AA          | 1.2 × 10⁻⁸–6.9 × 10⁻⁸ | 9000                  | 4 × 10⁻⁹                 | [110] |

β-CD, β-cycloextrin; MWCNT, multi-walled carbon nanotubes; SWCNT, single-walled carbon nanotubes; Plu, poly(luminal); NP, nanoparticles; NT, nanotubes; DEN, dendrimers; f, functionalized; CP, carbon paste; PGE, pyrolytic graphite electrode; DHBPD, N,N-(2,3-dioxxybenzylidine)-1,4-phenyldenediamine; CR, crystals; PEDOT, poly(3,4-ethylenedioxythiophene); a) rod-shaped CuO nanoparticles; b) flake-shaped CuO nanoparticles.
and UA the best results were obtained by use of electrodes containing poly(N-methylpyrrole) and Pd clusters [112]. Interesting results were also obtained for simultaneous detection of DA, UA, and AC on a PdNP/PFu/Pt electrode [115]. It is, however, very difficult to compare results obtained with nanoparticles and clusters because the amount used is usually uncontrolled and, therefore, unknown. There are also insufficient data to enable comparison of kinetic data, for example electron-transfer rate constant for DA electrooxidation. Some data are given for nanoparticles of CuO/CP and Fe₂O₃-SWCNT/PGE electrodes [107, 109], and it was pointed out that particle shape (CuO) and electrode composition (Fe₂O₃-SWCNT) affect \( k_s \) values. What can be compared for NP-modified electrodes, however, is separation of anodic peaks for the AA–DA and DA–UA pairs. The best separation results were obtained by use of Pd nanoparticle-modified electrodes—PdNP/CNF (0.244 V, 0.148 V) and PdNC/PMPy/Pt (0.205 V, 0.201 V) [112, 117]. The reproducibility and stability of such electrodes has also been monitored by several workers. RSD, when determined, was found to be in the range 2–5%. The electrodes retained 90–92% of their initial response after storage for 7–14 days [99, 105, 112, 113]. The electrodes were tested with real biological samples (human urine or human serum) [102, 112, 113, 117] and with pharmacological dopamine injections [99, 104, 108, 109, 114].

Taking all these data into account it is clearly apparent that the best results for selective, simultaneous determination of DA can be obtained by use of electrodes modified with conducting polymers and nanoclusters, and/or nanoparticles of selected metals (Pd, Cu). However, the properties of the surface active layer should be optimized. In our opinion, there is no need to prepare sophisticated composites or materials that are not carefully chosen and properly characterized; such an approach will not improve sensor performance and is more expensive.

Finally, comparison of biosensors with chemical sensors reveals it is possible to obtain comparable detection limits. However, the advantage of chemical sensors is the possibility of simultaneous detection of DA, AA, and UA. Most result also show that the long-term stability of chemical sensors is higher than that of biosensors. However, their stability also decreases over longer time periods, most probably as a result of adsorption of oxidation products, formed during successive measurements, on the electrode surface. Investigation of surface properties after such measurements has not been conducted.

### Table 6 Analytical data for electrooxidation of dopamine on electrodes modified with nanoscale materials (simultaneous detection)

| Electrode | Method | Compound | Linearity (molL⁻¹) | Sensitivity (mAMol⁻¹L) | Detection limit (molL⁻¹) | Ref. |
|-----------|--------|----------|-------------------|-------------------------|--------------------------|-----|
| Chit/GR/GC | DPV | DA | \( \times 10^{-5} \) - 2.4 \times 10^{-5} | 6 \times 10^{-8} | 2 \times 10^{-5} | [90] |
| | | UA | \( \times 10^{-6} \) - 4.5 \times 10^{-5} | | | |
| | | AA | \( \times 10^{-3} \) - 1.2 \times 10^{-3} | | | |
| MWNT/IL/GC | DPV | DA | \( \times 10^{-7} \) - 1.2 \times 10^{-5} | 6 \times 10^{-8} | 8 \times 10^{-9} | [97] |
| | | SE | \( \times 10^{-8} \) - 7 \times 10^{-6} | | | |
| CILE/CP | DPV | DA | \( \times 10^{-6} \) - 1.5 \times 10^{-3} | 1 \times 10^{-6} | | [98] |
| | | UA | \( \times 10^{-6} \) - 2.2 \times 10^{-4} | 1 \times 10^{-6} | | |
| | | AA | \( \times 10^{-7} \) - 7.4 \times 10^{-3} | 2 \times 10^{-5} | | |
| AuNP-PANI/GC | DPV | DA | \( \times 10^{-6} \) - 1.4 \times 10^{-4} | 3 \times 10^{-6} | 2 \times 10^{-5} | [111] |
| | | UA | \( \times 10^{-5} \) - 7.2 \times 10^{-4} | 6 \times 10^{-6} | 2 \times 10^{-5} | |
| PdNC/PMPy/Pt | DPV | DA | \( \times 10^{-7} \) - 1 \times 10^{-5} | 710 | 1.2 \times 10^{-8} | [112] |
| | | UA | \( \times 10^{-7} \) - 2 \times 10^{-5} | 2.7 \times 10^{-8} | | |
| | | AA | \( \times 10^{-7} \) - 1 \times 10^{-3} | 5.6 | 7 \times 10^{-9} | |
| CuNP/PPy/GC | DPV | DA | \( \times 10^{-6} \) - 1 \times 10^{-7} | 8.5 \times 10^{-10} | 8 \times 10^{-10} | [113] |
| | | UA | \( \times 10^{-6} \) - 1 \times 10^{-5} | | | |
| HBNBH/ TiO₂NP/ CP | SWV | DA | \( \times 10^{-6} \) - 1.4 \times 10^{-3} | 43.9 | 8.4 \times 10^{-7} | [114] |
| | | UA | \( \times 10^{-6} \) - 6 \times 10^{-4} | 42 | | |
| PdNC/PFu/Pt | DPV | DA | \( \times 10^{-7} \) - 1 \times 10^{-4} | 478.4 | 4.8 \times 10^{-8} | [115] |
| | | AA | \( \times 10^{-7} \) - 1 \times 10^{-3} | 21.3 | 7.1 \times 10^{-6} | |
| (MB)SZP/C | DPV | DA | \( \times 10^{-6} \) - 1 \times 10^{-4} | 623.7 | 7.64 \times 10^{-8} | [116] |
| | | UA | \( \times 10^{-7} \) - 3.5 \times 10^{-4} | 3.7 \times 10^{-6} | | |
| | | AA | \( \times 10^{-7} \) - 1.6 \times 10^{-3} | 8.3 \times 10^{-9} | | |
| PdNP/CNF/C | DPV | DA | \( \times 10^{-7} \) - 1.6 \times 10^{-4} | 2 \times 10^{-7} | 7 \times 10^{-7} | [117] |
| | | UA | \( \times 10^{-6} \) - 2 \times 10^{-4} | | | |
| | | AA | \( \times 10^{-7} \) - 4 \times 10^{-3} | 1.5 \times 10^{-5} | | |
In-vivo and in-vitro sensing—miniaturization

Use of the sensors and biosensors described above for real time in vivo and/or in vitro monitoring of clinically relevant physiological analytes, for example dopamine and other neurotransmitters has, with few exceptions, been restricted to laboratory use. This is primarily because they suffer from poor selectivity and sensitivity when used in a biological or biomimicking environment. Other factors that restrict their application include:

1. most of the sensors developed in laboratories on the bench are too large to be used for implantation because of extensive tissue or cell damage; the same restriction applies to in-vitro extracellular measurements;
2. bio-incompatibility of materials used in their development;
3. long term stability;
4. frequent fouling compromising their sensitivity; and/or
5. concern about selectivity to the analyte of interest.

Recent developments in nano and microtechnology have enabled the manufacture of electrochemical sensors (electrodes) in the range 1–30 μm in diameter. These are now available with different geometry (disc, rod, band, etc.) and materials (C, Au, Pt, Ag) [120, 121] and are expected to take full advantage of the results described in the previous sections of this brief review. With use of appropriate electrochemical techniques (e.g., fast scan cyclic voltammetry, FSCV), micro-electrochemistry has enabled the real-time, in-vivo and/or in-vitro measurements with high spatial and temporal resolution of fluctuations of the neurotransmitter concentration because of its transient release and uptake by living cells. The advantages of miniaturized electrodes (whether implantable or not) for electrochemical sensing of redox neurotransmitters, for example dopamine, can be briefly summarized as follows:

1. they have improved signal-to-noise ratios, because analytical Faraday currents are substantially increased by the higher rates of mass transfer of hemispherical diffusion of the electroactive compounds;
2. their response times are much faster because of the small double-layer capacitance charging currents and time constants, resulting in the capability of high temporal resolution of neurotransmitter fluctuations; and
3. the so-called $iR$ drop is of less concern because the total analytical currents measured by such electrodes are much smaller than those measured with typical large-scale electrodes.

Nevertheless, for such a small dimensions, the major issue, relatively easily resolved for laboratory bench sensors, is the design and fabrication of the sensor–solution interface and its effect on sensitivity and selectivity toward the target dopamine and interfering agents.

Relatively few papers have addressed design of the sensor–solution interface for miniaturized implantable electrodes; most research has focused on development of the electrochemical methods. However, for clarity it is necessary to state that not all state-of-the-art electrochemical techniques, for example scanning electrochemical microscopy, SECM, can be applied to in-vivo measurements for awake, moving animals, for obvious “geometric” reasons. Until now SECM has been restricted to cell cultures or (at most) to small anaesthetized animals [122, 147]. Nevertheless, use of micro or ultramicroelectrodes (UMEs) and microfabricated electrode arrays (MEAs) is not restricted by any particular electrochemical technique and can be used both in vivo and in vitro. Here, we will summarize the state-of-the-art of electrochemical methods used for in-vivo detection of dopamine, mostly for awake, mobile animals. This will be followed by an overview of surface modification of implantable electrodes to improve biocompatibility and selectivity for dopamine, with the proviso that although such modifications can be effective at reducing interferences, they may also reduce the efficiency of the electron transfer kinetics, reducing sensor sensitivity.

Electrochemical techniques for detection of dopamine with implantable electrodes

Since the early work of Adams and colleagues [123, 124] which introduced electrochemistry to the neurosciences, numerous electrochemical techniques and electrode materials have been used to identify and resolve catecholamines. In direct electrochemical detection of in vivo and in vitro dopamine, potentiostats with a three or two-electrode configurations have been used. The two-electrode configuration, consisting of a working electrode (microelectrode or UME) and a reference electrode, is usually preferred, because the measured currents are sufficiently small to preclude polarization of the reference electrode at ca 150 mmolL$^{-1}$ chloride concentrations in physiological electrolytes. The reference electrode is typically a micrometer diameter silver wire coated with a silver chloride layer, positioned next to the working electrode. The techniques most commonly used for direct detection of dopamine (or other electroactive neurotransmitters) are constant-potential amperometry (DC amperometry), differential-pulse voltammetry (DPV), and fast-scan cyclic voltammetry (FSCV), the last being a so-called “dynamic” technique.

In DC amperometry, a constant potential is applied which is sufficient to oxidize dopamine (or reduce dopaquinone) and the current, related to the amount of dopamine by Faraday’s law, is recorded as a function of time. With current sampling rates in the kHz range, this technique can resolve signals on time scales below milliseconds. This technique has been successfully used for studies of catecholamine concentrations in the brain and in brain slices [125, 126],...
exocytosis of the small synaptic vesicles [127], neuroblastosoma, and other cells [128, 129]; it has the best temporal resolution because of sampling rates down to 1 ms. However, the disadvantage of DC amperometry is that it is essentially nonselective, because all electroactive compounds that oxidize (or reduce) at the applied potential will produce a faradaic response at the electrode. Moreover, much amplification is required so the technique is susceptible to noise artifacts arising as a result of animal movement. In a variant of DC amperometry, chronoamperometry, the potential is stepped from its initial value, where no redox reaction occurs, toward a potential at which an oxidation or reduction of the analyte molecules proceeds. Then, after a given holding time, the potential is stepped back to its initial value. This variant has been applied to real-time measurement of dopamine concentrations in the cerebral fluid of the brain [130, 131]. Yet again, it suffers from limited chemical selectivity. Nevertheless, both techniques can be successfully used to measure dopamine dynamics evoked by an electric stimulus (for example deep-brain stimulus, DBS) [132] or reward-induced firing of dopaminergic neurons [133].

Differential pulse voltammetry (DPV) is more sensitive and selective. It uses square potential pulses of constant height superimposed over a linearly increasing potential from the initial to a final value. The potential pulse of constant frequency is typically ca 25 mV. Response currents are sampled before the potential pulse and at the end of the potential pulse. The difference between these current responses is plotted against the potential of the linear ramp. Because DPV is a differential technique, the response is a current peak of amplitude proportional to analyte (dopamine) concentration and its position shows the half-wave potential (for reversible systems). By excluding the first few milliseconds of each pulse (usually lasting tens of milliseconds), the effect of the capacitative current arising as a result of charging and/or discharging of the electrical double layer at the electrode interface is typically minimized. Although differential pulse voltammetry is more sensitive than the previous techniques [133–135], it has limited time resolution, because one full scan can take longer than seconds.

Finally, perhaps the most frequently used technique for in vivo detection of neurotransmitter trafficking is fast-scan cyclic voltammetry (FSCV). This technique provides high temporal resolution without compromising very good selectivity. Since its early application by Whitman’s group [136, 137], this technique has proved effective for multi-analyte detection of catecholamines with chemical selectivity [2]. In FSCV, the voltage applied to the microelectrode is rapidly cycled in a triangular fashion at a rate higher than 100 V s⁻¹. The limits of the triangular wave are chosen so that oxidation and reduction of, e.g., dopamine, lie within this potential window and the current (both faradaic and capacitive) resulting from the process is monitored. FSCV is usually performed with bare electrodes, for which rates of electron transfer are much faster than for modified electrodes. When used with appropriate ultramicroelectrodes (UMEs), FSCV can provide high spatial resolution [2, 138] and time resolution. This fast scanning limits diffusion distance to the electrode and minimizes electrode fouling [20, 139, 140]. To eliminate the capacitative contribution that scales linearly with the scan rate (high-frequency cycling), careful and precise background subtraction is necessary to eliminate the signal from capacitance build-up at the electrode interface [139]. This is usually achieved by analog background subtraction, use of the Hilbert transform, or by principal-components analysis; it is beyond the scope of this work to analyze the advantages and drawbacks of each method. The interested reader is referred to Refs. [20, 139, 140] and references cited therein for more detailed description.

The experimental techniques and approach used for in-vivo experiments with awake Japanese monkeys (Macaca fuscata) during cue–reward trials are summarized in Figs. 3 and 4 [133]. Lee et al. recently introduced pair–pulse voltammetry (PPV) in which a selected binary waveform with a defined time lapse is applied to an electrode which is held at a negative potential between each of two pulses [141]. This enables recording of two simultaneous, yet different, voltammograms, and enables discrimination of analytes on the basis of their adsorption behavior on the electrode [141]. More detailed information about electrochemical techniques as bioanalytical tools for in-vivo and in-vitro experiments can be found in several excellent recent reviews [142–148]. Here we briefly summarize the three techniques most commonly used for monitoring catecholamines in vivo by use of implanted (ultra)microelectrodes.

**Electrode materials, surface functionalization and coatings**

Electrode materials and the components of electrodes are selected carefully to improve sensor sensitivity, selectivity, reproducibility, robustness, and long-term stability and/or resistance to fouling in the biological environment. As already stated, a variety of noble metals have been used for microelectrode fabrication, because of the relative ease preparation and subsequent modifications, yet most research on dopamine release and uptake in vivo cited in this review relies on fiber microelectrodes fabricated from carbon, because of the apparent biocompatibility of this material. However, irrespective of electrode material, relatively few papers address the design of the sensor–solution interface for miniaturized implantable electrodes. Below we discuss some recent approaches to this problem.

Carbon and carbon-derived ultramicroelectrodes

Carbon fiber (CF) microelectrodes are the basis of a vast amount of experimental work in neuroscience. Electrochemical characterization of dopamine oxidation on these
Fig. 3 Applied waveforms and current recordings for fast-scan cyclic voltammetry (FSCV; top row), square-wave differential pulse voltammetry (SW; middle row), and constant-potential amperometry (bottom row). The left column shows the potential applied to the Ag/AgCl reference electrode. The middle column shows the actual current measured for each waveform at the carbon fiber. For square-wave, only one pulse is indicated. The right column shows the current measured at the diamond microelectrode. Typical recorded currents in PBS (black) and in high (10 and 100 nmol L\(^{-1}\)) concentrations of dopamine (green). (Adapted, with permission, from Ref. [133])

electrodes has been well described and optimized [2, 140, 146]. These microelectrodes have been shown to be relatively unsusceptible to fouling by products of dopamine electrooxidation and much superior to other types of material for in-vivo electrochemical experiments [120]. It has been suggested that electrochemical detection of dopamine and other cationic neurotransmitters depends on their adsorption by the CF microelectrode. Therefore, to improve sensitivity and selectivity, carbon fiber microelectrodes have undergone many treatments, for example overoxidation to develop the surface area and/or to control the surface chemistry [149–152]. Other approaches include modification of CF electrodes with carbon nanotubes, either adsorbed [152, 153] or self-assembled on the surface of a functionalized microelectrode [154]. Also, by use of appropriate surface polar functional groups to modify the CNTs used on CNT-modified carbon-based electrodes, the
electron-transfer kinetics have been adjusted to enhance the sensitivity to cationic neurotransmitters (dopamine and serotonin). However, an unexpected result was obtained for negatively charged CNTs (carboxyl groups)—an equivalent signal increase for negatively charged ascorbic acid, a well-known interferent, was also observed, suggesting that for this particular molecule, electrostatic interactions are of secondary importance [152]. A procedure for renewing the surface of a carbon microelectrode, by regenerating its electrochemically active surface while simultaneously reducing or removing fouling problems and improving electron-transfer kinetics, has recently been reported [155].

To summarize, use of carbon fiber microelectrodes seems to enable control of surface functional groups to satisfy most of the criteria for ideal implantable electrodes for dopamine detection: they are easily and reproducibly fabricated and small enough to be located in specific areas with minimal tissue damage. It has also been suggested that carbon electrodes modified with graphene perform better than multi-walled carbon nanotube-modified electrodes in selective detection of DA because of π–π stacking interactions between dopamine and the graphene surface. Apparently, these interactions accelerate electron transfer for DA but hinder oxidation of ascorbic acid on the graphene-modified electrode, completely eliminating the interfering signal from ascorbic acid [89]. Another material recently considered for in-vivo electrochemical detection of dopamine is boron doped diamond (BDD). BDD is known to be a robust, durable, biocompatible electrode material with low charging (capacitive) background currents and a wide range of potential [156]. It is also highly resistant to biological fouling of its surface [133, 147]. It has been found that extensive anodic polarization before in-vivo use improved the selectivity of such electrodes for dopamine, most probably because of the formation of a carboxyl or hydroxyl-terminated surface. Such electrodes were found to be less sensitive to dopamine than CF electrodes, however.

Metal electrodes

Metal electrodes, usually Pt and Au, enable both versatile surface modification and microfabrication of electrode arrays for multi-analyte monitoring and multiplexing, particularly for “lab-on-a-chip” (LOC) monitoring, differentiation, and reporting of catecholamines [121, 157–160]. Gold has the beneficial properties of adsorbing and preconcentrating catecholamines on its surface, thus increasing the sensitivity of gold electrodes to these compounds. The gold surface can, moreover, be easily modified by covalent bonding with thiol groups, enabling formation of self-assembled monolayers (SAMs) with different functionality facing the external solution [161]. Miniature gold electrodes prepared in this way have been used to characterize a variety of neurotransmitters (including dopamine) and interfering agents, and the results have been compared with analogous results obtained by use of carbon fiber microelectrodes [120].

Miniaturized enzymatic electrodes; biosensors

As already mentioned, there are relatively few reports of fabrication and use of miniaturized enzymatic biosensors for in-vivo experiments. Early reports describe ceramic-based lithographically prepared electrode arrays for electrochemical measurement of neurotransmitters [162]. These arrays were coated with glutamate oxidase crosslinked with bovine serum albumin via glutaraldehyde treatment. Their
voltammetric performance was characterized in the presence of dopamine and hydrogen peroxide yet they were not used for in-vivo dopamine measurements. A polyphenol oxidase has also been used to prepare electrochemical microsensors for detection of dopamine and glutamate [74]. However, this enzyme was not selective for dopamine. Catalytic complexes that mimic the active site of catecholases have also been used in sensors of phenolic substrates [163–165].

Despite the innovative technology used in the nanosensing devices discussed above, as far as we are aware only one in-vivo enzymatic microbiosensor for dopamine detection has been reported [55]. This biosensor was fabricated by immobilizing tyrosinase in a matrix consisting of chitosan and ceria-based metal oxides (CeO2 and TiO2) deposited on a carbon-fiber microelectrode. The chitosan coating resulted in a biocompatible sensor and, after optimization, the biosensor was reported to have an extremely large linear range, between 10 nmoL−1 and 220 μmoL−1 dopamine, and sensitivity of ca 14 nA μmol−1L. Sensor selectivity against ascorbic acid (AA), uric acid (UA), serotonin, norepinephrine, epinephrine, and L-DOPA was also tested. Lack of responsive to AA and UA was attributed to the low operating potential of the sensor, and insensitivity/low sensitivity to serotonin, L-DOPA, norepinephrine, and epinephrine was attributed to the bulkier structure of these compounds, which cannot reach the active site of tyrosinase [55].

Conclusions and perspectives

In this brief review we have discussed recent achievements in the development of dopamine sensing. Many advances have been made in the construction of sensors in laboratories, on the bench, leading to a wealth of information on the production of DA electrochemical sensors with detection limits in the picomolar range, selective and specific toward DA, yet easy to operate and reusable or single-use but cost-effective. The biosensors described above are based on tyrosinase attached to different types of immobilizing and signal-transducing substrates, which enable electroanalytical detection. However, the analytical performance of some of these biosensors, for example low detection limit and low linear range of sensor response, clearly indicate that, in the presence of dominant interferents, determination of dopamine at the nanomolar levels characteristic of living system is rarely possible. The situation is very similar for the chemical sensors used for dopamine detection. Many new materials, for example carbon materials (carbon fibers, carbon nanotubes, graphene), nanoparticles, clusters (Au, Ag, Pd, Cu, semiconducting oxides, magnetic oxides, among others), conducting polymers, and ionic liquids, have been used for sensor construction to improve their performance. However, the desired nanomolar limit of detection has been obtained in a few cases only, when electrodes modified with conducting polymers and metal (Pd, Cu) nanoclusters and/or nanoparticles have been used for selective, simultaneous determination of DA in the presence of a variety of interfering agents.

Rapid progress in the use of these new materials for sensor construction has not been accompanied by appropriate characterization of the sensors. For biosensors, tyrosinase activity is very rarely determined after its entrapment in the matrix (in the bulk or attached to the surface). Enzyme loading also is usually unknown and uncontrolled. The situation is similar for chemical sensors also—surface properties and nanoparticle load are rarely controlled.

To our surprise, few kinetic data have been reported for enzymatic reactions of tyrosinase in the presence of dopamine, so it is impossible to compare kinetic data for DA electrooxidation, for example electron-transfer rate constant, or to relate these to the surface properties and analytical performance of such sensors.

To summarize, proper characterization of sensors, i.e. determination of kinetics and analytical performance, then correlation of these with material properties is more important than relentless application of increasingly sophisticated composites or new materials to sensor construction. Currently available methodology for miniaturization could take advantage of developments in real-time mapping of neurotransmitter release zones on cell surfaces, with high spatial and temporal resolution both in vitro and in vivo, e.g., for monitoring of dopamine synaptic trafficking. Although technology, including sensor arrays, is available for combined monitoring of multiple catecholamines, design of sensor–solution interfaces for determination of the selectivity and sensitivity of sensors awaits further improvement.

Acknowledgments This work was supported by Project PSPB-079/2010 supported by a grant from Switzerland through the Swiss Contribution to the enlarged European Union.

Open Access This article is distributed under the terms of the Creative Commons Attribution License which permits any use, distribution, and reproduction in any medium, provided the original author(s) and the source are credited.

References

1. Mora F, Segovia G, del Arco A, de Blas M, Garrido P (2012) Stress, neurotransmitters, corticosterone and body-brain integration. Brain Res. doi:10.1016/j.brainres.2011.12.049
2. Robinson DL, Venton BJ, Heien MLAV, Wightman RM (2003) Detecting subsecond dopamine release with fast-scan cyclic voltammetry in vivo. Clin Chem 49:1763–1773
3. Hefco V, Yamada K, Hefco A, Hrticu L, Tiron A, Nabeshima T (2003) Role of the mesotelencephalic dopamine system in learning and memory processes in the rat. Eur J Pharmacol 475:55–60
4. Swamy BEK, Venton BJ (2007) Carbon nanotube-modified microelectrodes for simultaneous detection of dopamine and serotonin in vivo. Analyst 132:876–884
New trends in the electrochemical sensing of dopamine 3767

5. Lupu S, Lete C, Marin M, Totir N, Balaure PC (2009) Electrochemical sensors based on platinum electrodes modified with hybrid inorganic–organic coatings for determination of 4-nitrophenol and dopamine. Electrochim Acta 54:1932–1938

6. Zhao Y, Gao Y, Zhan D, Liu H, Zhao Q, Kou Y, Shao Y, Li M, Zhuang Q, Zhu Z (2005) Selective detection of dopamine in the presence of ascorbic acid and uric acid by a carbon nanotubes–ionic liquid gel modified electrode. Talanta 66:51–57

7. Chernyshov DV, Shvedene NV, Antiova ER, Pletnev IV (2008) Ionic liquid-based miniature electrochemical sensors for the voltammetric determination of catecholamines. Anal Chim Acta 621:178–184

8. Galvan A, Wichmann T (2008) Pathophysiology of parkinsonism. Clin Neurophysiol 119:1459–1474

9. Swanson JM, Volkov ND (2009) Psychopharmacology: concepts and opinions about the use of stimulant medications. J Child Psychol Psychiatry 50:180–193

10. Kollins SH, March JS (2007) Advances in the pharmacotherapy of attention-deficit/hyperactivity disorder. Biol Psychiatry 62:951–953

11. Dalley JW, Roiser JP (2012) Dopamine, serotonin and impulsivity. Neuroscience 215:42–58

12. Smeets WJ, Gonzalez A (2000) Catecholamine systems in the brain of vertebrates: new perspectives through a comparative approach. Brain Res Brain Res Rev 33:308–379

13. Miller MG (2011) The emerging role of trace amine-associated receptor 1 in the functional regulation of monoamine transporters and dopaminergic activity. J Neurochem 116:164–176

14. Neve KA, Seamans JK, Trantham-Davidson H (2004) Dopamine receptor signaling. J Recept Signal Transduct 24:165–205

15. Neve KA, Jeremy K, Seamans JK, Trantham-Davidson H (2004) Dopamine receptor signaling. J Recept Signal Transduct 24:165–205

16. Wightman RM, May LJ, Michael AC (1988) Detection of dopamine dynamics. Anal Chem 80:769A–776A

17. Sofiougli M, Sewell RA (2009) Norepinephrine and stimulant addiction. Addict Biol 14:119–129

18. Shou M, Ferrario CR, Schultz KN, Robinson TE, Kennedy RT (2006) Monitoring dopamine in vivo by microdialysis sampling and on-line CE-laser induced fluorescence. Anal Chem 78:6717–6725

19. Wang D, Zhu W, An Y, Zheng J, Zhang W, Jin L, Gao H, Lin L (2008) LC with novel electrochemical detection for analysis of monoamine neurotransmitters in rat brain after administration of (R)-salsolinol and (R)-N-methylsalsolinol. Chromatographia 67:369–374

20. Perry M, Li Q, Kennedy RT (2009) Review of recent advances in analytical techniques for the determination of neurotransmitters. Anal Chim Acta 653:1–22

21. Hubbard AT, Stickney JI, Soriaga MP, Chia VKF, Rosasco SD, Schardt BS, Solomun T, Song D, White JH, Wieckowski A (1988) Electrochemical processes at well-defined surfaces. J Electroanal Chem 168:43–66

22. Salata GN, Laguren-Davidson L, Lu F, Walton N, Wellner E, Stern DA, Batina N, Frank DG, Lin C-H, Benton CS, Hubbard AT (1988) Electrochemical reactivity of 2,2′,5,5′-tetrahydroxybiphenyl and related compounds adsorbed at Pt (111) surfaces; studies by EELS, LEED, Auger spectroscopy and cyclic voltammetry. J Electroanal Chem Interf Electrochem 245:253–273

23. Tenreiro AM, Nabais C, Correia JP, Fernandes FMSS, Romero JR, Abrantes LM (2007) Progress in the understanding of tyramine electropolymerisation mechanism. J Solid State Electrochem 11:1059–1069

24. Cooper SE, Venton BJ (2009) Fast-scan cyclic voltammetry for the detection of tyramine and octopamine. Anal Bioanal Chem 394:329–336

25. Sanchez-Cortes S, Francisco O, Garcia-Ramos JV, Ciavatta C, Gessa C (2001) Catechol polymerization in the presence of silver surface. Colloids Surf A 176:177–184

26. Majewska UE, Chmurski K, Biesaga K, Olsyna AR, Bilewicz R (2006) Dopamine oxidation at pert-(6-deoxy-6-thio)-α-cyclohexedrin monolayer modified gold electrodes. Electroanalysis 18:1463–1470

27. Ernst H, Knoll M (2001) Electrochemical characterisation of uric acid and ascorbic acid at a platinum electrode. Anal Chim Acta 449:129–134

28. Zhu L, Tian C, Zhai J, Yang R (2007) Sol–gel derived carbon nanotubes ceramic composite electrodes for electrochemical sensing. Sensors Actuators B Chem 125:254–261

29. Huffman ML, Venton BJ (2008) Electrochemical properties of different carbon-fiber microelectrodes using fast-scan cyclic voltammetry. Electroanalysis 20:2422–2428

30. Fujishima A, Rao TN, Popa E, Sarada BV, Yagi I, Tryk DA (1999) Electroanalysis of dopamine and NADH at conductive diamond electrodes. J Electroanal Chem 473:179–185

31. Roy PR, Saha MS, Okajima T, Park S-G, Fujishima A, Ohsaka T (2004) Selective detection of dopamine and its metabolite, DOPAC, in the presence of ascorbic acid using diamond electrode modified by the polymer film. Electroanalysis 16:1777–1784

32. Barnes EO, O’Mahony AM, Aldous L, Hardacre C, Compton RG (2010) The electrochemical oxidation of catechol and dopamine on platinum in 1-ethyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide ([C2mim][NTf2]) and 1-butyl-3-methylimidazolium tetrafluoroborate ([C4mim][BF4]): adsorption effects in ionic liquid voltammetry. J Electroanal Chem 646:11–17

33. Raj CR, Okajima T, Ohsaka T (2003) Gold nanoparticle arrays for the voltammetric sensing of dopamine. J Electroanal Chem 543:127–133

34. Cabrita JF, Abrantes LM, Viana AS (2005) N-Hydroxyxysuccinimide-terminised self-assembled monolayers on gold for biomolecules immobilization. Electrochim Acta 50:2117–2124

35. Zhao H, Zhang YZ, Yuan ZB (2002) Determination of dopamine in the presence of ascorbic acid using poly(hippuric acid) modified glassy carbon electrode. Electroanalysis 14:1031–1034

36. Liu A, Wei M, Homma I, Zhou H (2006) Biosensing properties of titanate nanotube films: selective detection of dopamine in the presence of ascorbate and uric acid. Adv Funct Mater 16:371–376

37. Yan W, Feng X, Chen X, Li X, Zhu J-J (2008) A selective dopamine biosensor based on AgCl@polyaniline core–shell nanocomposites. Bioelectrochemistry 72:21–27

38. Lange U, Roznyatowska NV, Mirsky VM (2008) Conducting polymers in chemical sensors and arrays. Anal Chim Acta 8:1–25

39. Zheng M, Zhou Y, Chen Y, Tang Y, Lu T (2010) Electrochemical behavior of dopamine in the presence of phosphate and the determination of dopamine at phosphate modified zirconia films electrode with highly antifoiling capability. Electrochim Acta 55:4789–4798

40. Tyagi P, Postetter D, Saragnese DL, Randall CL, Mirski MA, Gracias DH (2009) Patternable nanowire sensors for electrochemical recording of dopamine. Anal Chem 81:9979–9984
44. Li NB, Ren W, Luo HQ (2008) Simultaneous voltammetric measurement of ascorbic acid and dopamine on poly(caffeic acid)-modified glassy carbon electrode. J Solid State Electrochem 12:693–699
45. Kumar SS, Mathiyarasu J, Phani KLN, Yegnaraman V (2006) Simultaneous determination of dopamine and ascorbic acid on poly (3,4-ethylenedioxythiophene) modified glassy carbon electrode. J Solid State Electrochem 10:905–913
46. Balamurugan A, Chen SM (2007) Poly(3,4-ethylenedioxythiophene-co-(5-amino-2-naphthalenesulfonic acid)) (PEDOT-PANS) film modified glassy carbon electrode for selective detection of dopamine in the presence of ascorbic acid and uric acid. Anal Chim Acta 596:92–98
47. Vasanth VS, Chen SM (2006) Electrocatalysis and simultaneous detection of dopamine and ascorbic acid using poly(3,4-ethylenedioxythiophene) film modified electrodes. J Electroanal Chem 592:77–87
48. Lin X, Zhang Y, Chen W, Wu P (2007) Electrocatalytic oxidation and determination of dopamine in the presence of ascorbic acid and uric acid at a poly (p-nitrobenzenazo resorcinol) modified glassy carbon electrode. Sens Actuators B 122:309–314
49. Maciejewska J, Pisarek K, Bartosiewicz J, Krysinski P, Jackowska K, Biegunski AT (2011) Selective detection of dopamine on poly(indole-5-carboxylic acid)/tyrosinase electrode. Electrochim Acta 56:3700–3706
50. Zhou YL, Tian RH, Zhi JF (2007) Enzyme -nanobiosensors. Sens Actuators B 123:1195–1209
51. Njagi J, Ispas C, Andreescu S (2008) Mixed ceria-based metal oxides biosensor for operation in oxygen restictive enviroments. Analyst 133:2016–2022
52. Tembe S, Kubal BS, Karve M, Souza SF (2008) Glutaraldehyde activated eggshell membrane for immobilization of tyrosinase from Amorphophallus companulatus: application in construction of electrochemical biosensor for dopamine. Anal Chim Acta 612:212–217
53. Njagi J, Ispas C, Andreescu S (2008) Mixed ceria-based metal oxides biosensor for operation in oxygen restrictive environments. Anal Chem 80:7266–7244
54. Min K, Yoo YJ (2009) Amperometric detection of dopamine based on tyrosinase-SWNTs-Ppy composite electrode. Talanta 80:1007–1011
55. Njagi J, Chernov MM, Leiter JC, Andreescu S (2010) Amperometric detection of dopamine in vivo with an enzyme based carbon fiber microbiosensor. Anal Chem 82:989–996
56. Thivenot DR, Toth K, Durst RA, Wilson GS (2001) Electrochemical biosensors: recommended definitions and classification. Biosens Bioelectron 16:121–131
57. Pumera M, Sanchez S, Ichinose I, Tang J (2007) Electrochemical nanobiosensors. Sens Actuators B 123:1195–1205
58. Yogeswaran U, Chen S-M (2008) A review on the electrochemical sensors and biosensors composed of nanowires as sensing materials. Sensors 8:290–313
59. Wang J, Lin Y (2008) Functionalized carbon nanotubes and nanofibers for biosensing applications. Trends Anal Chem 27:619–626
60. Balasubramanian K, Burghard M (2006) Biosensors based on carbon nanotubes. Anal Bioanal Chem 385:452–468
61. Lu Y, Yang M, Qu F, Shen G, Yu R (2007) Enzyme-functionalized gold nanowires for the fabrication of biosensors. Bioelectrochemistry 71:211–216
62. Pingarron JM, Yanez Sadeno P, Gonzalez-Cortes A (2008) Gold nanoparticle-based electrochemical biosensors. Electrochim Acta 53:5848–5866
63. Xu Z, Chen X, Dong S (2006) Electrochemical biosensors based on advanced immobilization matrices. Trends Anal Chem 9:899–907
64. Solomon El, Sundaram UM, Machonkin TE (1996) Multicopper oxidases and oxygenases. Chem Rev 96:2563–2605
65. Shleev SS, Tkac J, Christenson A, Ruzgas T, Yaropolov AI, Whitaker JW, Gorton L (2005) Direct electron transfer between copper-containing proteins and electrodes. Biosens Bioelectron 20:2517–2554
66. Cosnier S (1999) Biomolecule immobilization on electrode surfaces by entrapment or attachment to electrochemically polymerized films. A review. Biosens Bioelectron 14:443–456
67. Gerard M, Chaubey A, Malhotra RD (2002) Application of conducting polymers to biosensors. Biosens Bioelectron 17:345–359
68. Cosnier S (2003) Biosensors based on electropolymerized films: new trends. Anal Bioanal Chem 377:507–520
69. Ahuja T, Mir IA, Kumar D, Rajesh (2007) Biomolecular immobilization on conducting polymers for biosensing applications. Biomaterials 28:791–805
70. Duran N, Rosa MA, D’Annibale A, Gianfreda L (2002) Application of laccase and tyrosinases (phenoloxidases) immobilized on different supports: a review. Enzym Microb Technol 31:907–931
71. Cracknell JA, Vincent KA, Armstrong FA (2008) Enzymes as working or inspirational electrocatalysts for fuel cells and electrolysis. Chem Rev 108:2439–2461
72. Forzani ES, Rivas GA, Solis VM (1995) Amperometric detection of dopamine on an enzymatically modified carbon paste electrodes. J Electroanal Chem 382:33–40
73. Hasebe Y, Hirano T, Uchiyama S (1995) Determination of catecholamines and uric acid in biological fluids without pretreatment, using chemically amplified biosensors. Sens Actuators B 24–25:94–97
74. Cosnier S, Innocent C, Allien L, Poitry S, Tsacopoulos M (1997) An electrochemical method for making enzyme microsensors. Application of the detection to the detection of dopamine and glutamate. Anal Chem 89:968–971
75. Pandey PC, Upadhy S, Tiwari I, Singh G, Tripathi VS (2001) A novel ferrocene encapsulated palladium-linked ormosil-based electrocatalytic dopamine biosensor. Sens Actuators B 75:48–55
76. Vedrine C, Fabiano S, Tran-Minh C (2003) Amperometric tyrosinase based biosensor using an electrogenerated polythiophene film as an entrapment support. Talanta 59:535–544
77. Tembe S, Karve M, Inamdar S, Haram S, Melo J, D’Souza SF (2006) Development of electrochemical biosensor based on tyrosinase immobilized in composite biopolimeric film. Anal Biochem 349:72–77
78. Wang Y, Zhang X, Chen Y, Xu H, Tan Y, Wang S (2010) Detection of dopamine based tyrosinase-Fe3O4 nanoparticlchothosan nanocomposite biosensor. Am J Biomed Sci 2:209–216
79. Henstridge MC, Dickinson EIF, Aslanoglu M, Batchelor-McAuley C, Compton RG (2010) Voltammetric selectivity conferred by the modification of electrodes using conductive porous layers or films: the oxidation of dopamine on glassy carbon electrodes modified with multiwalled carbon nanotubes. Sensors Actuators B Chem 145:417–427
80. Pumera M, Ambrosi A, Bonnani A, Chng EL, Poh HL (2010) Graphene for electrochemical sensing and biosensing. Trends Anal Chem 29:954–965
81. Zhuang Z, Li J, Xu R, Xiao D (2011) Electrochemical detection of dopamine in the presence of ascorbic acid using overoxidized polypyrole/graphene modified electrode. Int J Electrochem Sci 6:2149–2161
82. Wang Z, Xia J, Zhu L, Chen X, Zhang F, Yao S, Li Y, Xia Y (2011) A selective voltammetric method for detecting dopamine at quercetin modified electrode incorporating graphene. Electroanalysis 23:2463–2471
83. Zhu M, Zeng C, Ye J (2011) Graphene-modified carbon fiber microelectrode for the detection of dopamine in mice hippocampus tissue. Electroanalysis 23:907–914
New trends in the electrochemical sensing of dopamine

84. Si P, Chen H, Kannan P, Kim D-H (2011) Selective and sensitive determination of dopamine by composites of polypyrrole and graphene modified electrodes. Analyst 136:5134–5138

85. Wu L, Feng L, Ren J, Qu X (2012) Electrochemical detection of dopamine using porphyrin-functionalized graphene. Biosens Bioelectron 34:57–62

86. Hon S, Kasmer ML, Su S, Patel K, Cuellar R (2010) Highly sensitive and selective dopamine biosensor fabricated with silanized graphene. J Phys Chem C 114:14915–14921

87. Kim Y-R, Bong S, Kang Y-J, Yang Y, Mahajan RK, Kim JS, Kim H (2010) Electrochemical detection of dopamine in the presence of ascorbic acid using graphene modified electrodes. Biosens Bioelectron 25:2366–2369

88. Tan L, Zhou K-G, Zhang Y-H, Wang H-X, Wang X-D, Guo Y-F, Zhang H-L (2010) Nanomol detection of dopamine in the presence of ascorbic acid at β-cyclodextrin/graphene nanocomposite platform. Electrochem Commun 12:557–560

89. Wang Y, Li Y, Tang L, Lu J, Li J (2009) Application of grapheme-modified electrode for selective detection of dopamine. Electrochem Commun 11:889–892

90. Han D, Han T, Shan C, Ivaska A, Niu L (2010) Simultaneous determination of ascorbic acid, dopamine, uric acid with chitosan-graphene modified electrode. Electroanalysis 22:2001–2008

91. Li Y, Liu X, Zeng X, Liu X, Kong B, Wei W, Luo S (2011) Selective and sensitive detection of dopamine in the presence of ascorbic acid by molecular sieve/ionic liquids composite electrode. Electrochim Acta 56:2730–2734

92. Li Y, Liu X, Wei W (2011) Square wave voltammetry for selective detection of dopamine using polyglycine modified carbon ionic liquid electrode. Electroanalysis 23:2832–2838

93. Chang J-L, Wei G-T, Zen J-M (2011) Screen-printed ionic liquid/preanodized carbon electrode: effective detection of dopamine in the presence of high concentration of ascorbic acid. Electrochem Commun 13:174–177

94. Zhu Z, Qu L, Guo Y, Zeng Y, Sun W, Huang X (2011) Electrochemical detection of dopamine on a Ni/Al layered double hydroxide modified carbon ionic liquid electrode. Sens Actuators B 151:146–152

95. Dong J, Hu Y, Zhu S, Xu J, Xu Y (2010) A highly selective and sensitive dopamine and uric acid biosensor fabricated with functionalized ordered mesoporous carbon and hydrophobic ionic liquid. Anal Chim Acta 676:1755–1762

96. Wai G, Ivaska A (2008) Application of ionic liquids in electrochemical sensors. Anal Chim Acta 607:126–135

97. Sun Y, Fei J, Hou J, Qin Z, Liu Y, Hu B (2009) Simultaneous determination of dopamine and serotonin using a carbon nanotubes-ionic liquid gel modified glassy carbon electrode. Microchim Acta 165:373–379

98. Safavi A, Maleki N, Moradlou O, Tajabadi F (2006) Simultaneous determination of dopamine, ascorbic acid and uric acid using carbon ionic liquids. Anal Biochem 359:224–229

99. Jia D, Dai J, Yuan H, Lei L, Xiao D (2011) Selective detection of dopamine in the presence of uric acid using a gold nanoparticles–poly(lumino) hybrid film and multi-walled carbon nanotubes with incorporated β-cyclodextrin modified glassy carbon electrode. Talanta 85:2344–2351

100. Garcia MG, Armendariz GME, Godinez LA, Torres J, Sepulveda-Guzman S, Bustos E (2011) Detection of dopamine in non-treated urine samples using glassy carbon electrodes modified with PAMAM dendrimer–Pt composites. Electrochim Acta 56:7712–7717

101. Zheng Y, Wang Y, Yang X (2011) Aptamer-based colorimetric biosensing of dopamine using unmodified nanoparticles. Sens Actuators B 156:95–99

102. Mahshid S, Li C, Mahshid SS, Askari M, Dolati A, Yang L, Luo S, Cai Q (2011) Sensitive determination of dopamine in the presence TiO2 nanoparticles modified with Pd, Pt and Au nanoparticles. Analyst 136:2322–2329

103. Hosseini M, Momeni MM, Faraji M (2010) An innovative approach to electro-oxidation of dopamine on titanium dioxide nanotubes electrode modified by gold particles. J Appl Electrochem 40:1421–1427

104. Ardkani-Mozloum M, Rajabi H, Beitollahi H, Mirjalili BBF, Akbari A, Taghavinia N (2010) Voltammetric determination of dopamine at the surface of TiO2 nanoparticles modified carbon paste electrode. Int J Electrochem Sci 5:147–157

105. Celebańska A, Tomaszewska D, Lesniewski A, Opallo M (2011) Film electrode prepared from oppositely charged silicate submicroparticles and carbon nanoparticles for selective dopamine sensing. Biosens Bioelectron 26:4417–4422

106. Plowman BJ, Mahajan M, O’Mullane AP, Bhargava SK (2010) Electrochemical detection of dopamine and cytochrome c at a nanostructured gold electrode. Electrochim Acta 55:8953–8959

107. Reddy S, Swamy BEK, Jayadevappa H (2012) CuO nanoparticle sensor for the electrochemical determination of dopamine. Electrochem Acta 61:78–86

108. Xia C, Ning W, Long W, Lin G (2010) Synthesis of nanochain-assembled ZnO flowers and their application to dopamine sensing. Sens Actuators B 147:629–634

109. Adekunle AS, Agbola BO, Pillay J, Ozoemenka KJ (2010) Electrocatalytical detection of dopamine at single-wall carbon nanotubes-iron(II)oxide nanoparticles platform. Sens Actuators B 148:93–102

110. Stoyanova A, Tsakova V (2010) Copper-modified poly (3,4-ethylenedioxythiophene) layers for selective determination of dopamine in the presence of ascorbic acid: II role of the characteristics of the metal deposition. J Solid State Electrochem 14:1957–1965

111. Stoyanova A, Ivanov S, Tsakova V, Bund A (2011) Au nanoparticle–polyaniline nanocomposite layers obtained through layer-by-layer adsorption for the simultaneous determination of dopamine and uric acid. Electrochim Acta 56:3693–3699

112. Atta NF, El-Kady MF, Galal A (2010) Simultaneous determination of catecholamines, uric acid and ascorbic acid at physiological levels using poly(N-methylpyrrole)/Pd clusters sensor. Anal Biochem 400:78–88

113. Ulubay S, Dursun Z (2010) Cu nanoparticles incorporated poly-pyrrole modified GCE for sensitive simultaneous determination of dopamine and uric acid. Talanta 80:1467–1466

114. Ardkani MM, Talebi A, Nacimi H, Barzoky MN, Taghavinia N (2009) Fabrication of modified TiO2 nanoparticle carbon paste electrode for simultaneous determination of dopamine, uric acid and L-cysteine. J Solid State Electrochem 13:1433–1440

115. Atta NF, El-Kady MF, Galal A (2009) Palladium nanoclusters-coated polyfuran as a novel sensor for catecholamine neurotransmitters and paracetamol. Sens Actuators B 141:566–574

116. Arguello J, Leidens VL, Magosso HA, Ramos RR, Gushiken Y (2008) Simultaneous voltammetric determination of ascorbic acid, dopamine and uric acid by methylene blue adsorbed on phosphorylated zirconia–silica composite electrode. Electrochim Acta 54:560–565

117. Huang J, Liu Y, Hou H, You T (2008) Simultaneous electrochemical determination of dopamine, uric acid and ascorbic acid using palladium nanoparticle-loaded carbon nanofibers modified electrode. Biosens Bioelectron 24:632–637

118. Katz E, Willner I, Wang J (2003) Electroanalytical and bioelectroanalytical system based on metal and semiconductor nanoparticles. Electroanalysis 15:19–44

119. Hernandez-Santos D, Gonzalez-Garcia MB, Garcia CA (2002) Metal nanoparticles based electroanalysis. Electroanalysis 14:1225–1235

120. Zachek MK, Hermans A, Wightman RM, McCarty GS (2007) Electrochemical dopamine detection: comparing gold and carbon...
fibers on the surface of carbon microelectrodes using background subtracted fast scan cyclic voltammetry. J Electroanal Chem 614:113–120.

121. Zhao Y, Li S-H, Chu J, Chen Y-P, Li W-W, Yu H-Q, Liu G, Tian Y-C, Xiong Y (2012) A nano-sized Au electrode fabricated using lithographic technology for electrochemical detection of dopamine. Biosens Bioelectron 35:115–122.

122. Zachek MK, Park J, Takmakov P, Wightman RM, McCarty GS (2010) Microfabricated FSCV-compatible microelectrode array for real-time monitoring of heterogeneous dopamine release. Analyst 135:1556–1563.

123. Blank CL, Adams RN, Murrill E (1972) Central nervous-system effects of 6-aminoadopine and 6-hydroxydopamine. Brain Res 45:635–637.

124. Adams RN, Murrill E, McCreery R, Blank L, Karolczak M (1972) 6-Hydroxydopamine, a new oxidation mechanism. Eur J Pharmacol 17:287–292.

125. Troyer KP, Heien MLAV, Venton BJ, Wightman RM (2002) Neurochemistry and electroanalytical probes. Curr Opin Chem Biol 6:696–703.

126. Venton BJ, Troyer KP, Wightman RM (2002) Response times of carbon microelectrodes to dynamic changes in catecholamine concentration. Anal Chem 74:539–546.

127. Chen P, Xu B, Tokranova N, Feng X, Castracane J, Gillis KD (2003) Amperometric detection of quantal catecholamine secretion from individual cells on micromachined silicon chips. Anal Chem 75:518–524.

128. Dong Y, Helen ML, Maxson MM, Ewing AG (2008) Amperometric measurements of catecholamine release from single vesicles in MN9D cells. J Neurochem 107:1589–1595.

129. Li Z-Y, Zhou W, Wu Z-X, Zhang R-Y, Xu T (2009) Fabrication of size-controllable ultrasmall-disk electrode: monitoring single vesicle release kinetics at tiny structures with high spatio-temporal resolution. Biosens Bioelectron 24:1358–1364.

130. Miller AD, Forster GL, Yeomans JS, Blaha CD (2005) Midbrain masculinergic receptors modulate morphine-induced accumbal and striatal dopamine efflux in the rat. Neuroscience 136:531–538.

131. Unger EL, Eve DJ, Perez XA, Forster GL, Yeomans JS, Blaha CD (2005) Monitoring of vesicular exocytosis from single cells using micrometer and nanometer-sized electrochemical sensors. Anal Bioanal Chem 394:17–32.

132. Robinson DL, Herrmans A, Seipel AT, Wightman RM (2008) Monitoring rapid communication in the Brain. Chem Rev 108:2554–2584.

133. Jang DP, Kim I, Chang SY, Min HK, Arora K, Marsh MP, Wang SC, Kimble CJ, Bennett KE, Lee KH (2012) Paired pulse voltammetry for differentiating complex analytes. Analyst 137:1428–1435.

134. Lin Y, Trouillon R, Safina G, Ewing AG (2011) Chemical analysis of single cells. Anal Chem 83:4369–4392.

135. Amatore C, Arblaut S, Guille M, Lemaître F (2008) Electrochemical monitoring of single cell secretion: vesicular exocytosis and oxidative stress. Chem Rev 108:2585–2621.

136. Adams KL, Puchades M, Ewing AG (2008) In vitro electrochemistry of biological systems. Annu Rev Anal Chem 1:329–355.

137. Wang W, Zhang S-H, Li L-M, Wang Z-L, Cheng J-K, Huang W-H (2009) Monitoring of vesicular exocytosis from single cells using micrometer and nanometer-sized electrochemical sensors. Anal Bioanal Chem 394:17–32.

138. Duvall SH, McCreery RL (2000) Self-catalysis by catechols and quinones during heterogeneous electron transfer at carbon electrodes. J Am Chem Soc 122:6759–6764.

139. Bath BD, Martin HB, Wightman RM, Anderson MR (2001) Dopamine adsorption at surface modified carbon-fiber electrodes. Langmuir 17:7032–7039.

140. Jacobs CB, Vickers TL, Venton BJ (2011) Functional groups modulate the sensitivity and electron transfer kinetics of neurotransmitters at carbon nanotube modified microelectrodes. Analyst 136:3557–3565.

141. Ewing AG, White CA, Park J, Wightman RM (2011) Comparison of Nafion- and oxidized poly(pyrolane) carbon nanotubes electrodes for neurotransmitter detection. Anal Chem 3:2379–2386.

142. Xiao N, Venton BJ (2012) Rapid, sensitive detection of neurotransmitters at microelectrodes modified with self assembled SWCNT forests. Anal Chem. doi:10.1021/ac301445a.

143. Pears MJ, Ross AE, Venton BJ (2011) Comparison of Nafion- and oxidized polypyrrole-carbon nanotubes electrodes for neurotransmitter detection. Anal Chem 3:2379–2386.

144. Hutton L, Newton ME, Unwin PR, Macpherson JV (2009) Amperometric oxygen sensor based on a platinum nanoparticle-modified polycrystalline boron doped diamond disk electrode. Anal Chem 81:1023–1032.

145. Johnson MD, Franklin RK, Gibson MD, Brown RB, Kipke DR (2008) Implantable microelectrode arrays for simultaneous electrophysiological and neurochemical recordings. J Neurosci Methods 174:62–70.

146. Day BK, Pomerleau F, Burmeister JJ, Huetttl P, Gerhardt GA (2006) J Neurochem 96:1626–1635.
detection: wireless instantaneous neurochemical concentration sensor for deep brain stimulation feedback. Neurosurg Focus 29:E6

160. Chan F-L, Chang W-Y, Kuo L-M, Lin C-H, Wang S-W, Yang Y-S, Lu MS-C (2008) An electrochemical dopamine sensor with a CMOS detection circuit. J Micromech Microeng 18:075028

161. Tsai T-C, Guo C-X, Han H-Z, Li Y-T, Huang Y-Z, Li C-M, Chen J-J J (2012) Microelectrodes with gold nanoparticles and self-assembled monolayers for in vivo recording of striatal dopamine. Analyst 137:2813–2820

162. Burmeister JJ, Moxon K, Gerhardt GA (2000) Ceramic-based multisite microelectrodes for electrochemical recordings. Anal Chem 72:187–192

163. Fernandes SC, Osorio RE-HMB, dos Anjos A, Neves A, Micke GA, Vieira IC (2008) Determination of catechin in green tea using catechol oxidase biomimetic sensor. J Braz Chem Soc 19:1215–1223

164. Oliveita IRWZ, Osorio RE-HMB, Neves A, Vieira IC (2007) Biomimetic sensor based on a novel copper complexes for the determination of hydroquinone in cosmetics. Sens Actuators B 122:89–94

165. Fernandes SC, Vieira IC, Peralta RA, Neves A (2010) Development of a biomimetic chitosan film-coated gold electrode for determination of dopamine in the presence of ascorbic acid and uric acid. Electrochim Acta 55:7152–7157