

Amplified voltammetric detection of dopamine using ferrocene-capped gold nanoparticle/streptavidin conjugates

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ABSTRACT

Dopamine (DA) is one of the most important neurotransmitters present in brain tissues and body fluids of mammals. The change in the concentration levels has been associated with various diseases and disorders. Thus, sensitive and selective determination of DA is much preferred. In this work, sandwich-type electrochemical biosensor was developed, in which phenylboronic acid immobilized onto gold electrodes was used to capture DA. The anchored DA was then derivatized with biotin for the attachment of ferrocene-capped gold nanoparticle/streptavidin conjugates. The voltammetric responses were found to be proportional to the concentrations of DA ranging from 0.5 to 50 nM. A detection limit of 0.2 nM was achieved, which is 1–2 orders of magnitude lower than those achievable at various chemically modified electrodes. Analytical merits (e.g., dynamic range, reproducibility, detection level, selectivity and interference) were evaluated. The feasibility of the method for analysis of DA in artificial cerebrospinal fluid and dopamine hydrochloride injection has been demonstrated.

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1. Introduction

Dopamine (DA) is an important neurotransmitter compound that has been paid much attention recently. It is widely distributed in the central neural system brain tissues and body fluids of mammals and plays pivotal roles in the function of central nervous, renal, hormonal and cardiovascular system. Trace level measurement of DA has been a long-standing goal since the concentration change has been associated with various diseases and disorders, such as Parkinson's disease, Alzheimer's disease, Huntington's disease, epilepsy, pheochromocytoma and neuroblastoma (Atta et al., 2011; Bruhlmann et al., 2001; Liu et al., 2005; Lunsford et al., 2007; Mo and Ogorevc, 2001; Wightman et al., 1988).

DA can be easily oxidized electrochemically at electrodes. In recent years, the development of voltammetric methods for DA determination in human fluid such as urine and serum has received considerable interest (Jin et al., 2008). However, some biochemical compounds such as ascorbate acid and uric acid, the levels of which are 100–1000 times higher than that of DA, are oxidized at nearly same potential. The overlap of their

voltammetric responses makes the sensitive and selective detection of DA highly difficult. To overcome this problem, various modified electrodes have been constructed, such as carbon nanotube electrodes (Hocevar et al., 2005; Huang et al., 2010; Noroozifar et al., 2011), nanoparticles modified electrodes (Huang et al., 2008; Weng et al., 2005), carbon ceramic electrodes (Salimi et al., 2006), boron-doped diamond electrodes (Siew et al., 2005), organic redox mediators modified electrodes (Zare et al., 2005), polymers modified electrodes (Gao and Huang, 1998; Lin et al., 2010), pyrolytic graphite electrodes (Kachooosangi and Compton, 2007; Silva et al., 2008), screen-printed carbon electrodes (Prasad et al., 2008), carbon ionic liquid electrodes (Safavi et al., 2006) and electrochemically oxidized glass carbon electrodes (Thiagarajan et al., 2009). Although these electrodes have distinguished the overlap peaks to some extent and achieved the selective or simultaneous determination of DA and other biochemical compounds, the detectable concentration is still high for DA in real sample. In addition, the oxidation products of DA can react with ascorbate acid present in sample and regenerate DA that becomes available again for oxidation, which severely limits the accuracy of detection (Ali et al., 2007a; Tse et al., 1976). Therefore, a highly sensitive and selective method is desired for the quantification of DA in the coexistence of other biological species.

Sandwich-type biosensor is one of the major analytical techniques for sensitive and selective detection of biological species and has found wide applications in clinical diagnosis, biomedical research, food quality control and environmental monitoring (Li et al., 2011; Liu and Ju, 2005; Yang et al., 2008; Yuan et al., 2001;

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Zhang et al., 2007). The increasing demand for detection of ultralow amount of analytes is pushing the enhancement of detection sensitivity by selecting different signal amplification strategy. Recently, we have achieved the amplified surface plasmon resonance detection of amyloid- β peptides with streptavidin conjugated to a specific antibody (Xia et al., 2010). Wang et al. (2012, 2008b) achieved amplified voltammetric detection of p53 proteins and miRNA using ferrocene (Fc)-capped gold nanoparticle/streptavidin (SA-AuNPs) conjugates. In this work, we attempted to carry out a sensitive and selective detection of DA in the sandwich format. In this format, the crucial step is the capture and identification of DA. Boronic acids are known to bind with compounds containing diol moieties (Shoji and Freund, 2001; Yoon and Czarnik, 1992). It has been reported that phenylboronic acids can form stable boronate esters with diols, and the resulting complexes were employed to develop optical and electrochemical or electronic sensors for DA (Ali et al., 2007a; Fabre and Taillebois, 2003; Strawbridge et al., 2000; Wu et al., 2007). For example, Strawbridge et al. (2000) reported that the oxidation peak potential of DA shifts positively to 0.619 V after binding to phenylboronic acid; thus, DA can be detected in the presence of 20-fold excess ascorbate acid. Based on this principle, Fabre and Taillebois (2003) developed a poly(aniline boronic acid)(PABA)-based conductimetric sensor of DA using platinum interdigitated microelectrodes and the formation of DA-boronate ester complex greatly decreased the conductivity of the polyaniline backbone. To improve the sensitivity, Wu et al. (2007) prepared boronic acid functionalized multi-walled carbon nanotubes (MWNTs)-modified glass carbon electrode for the detection of DA. At the same time, Ali et al. (2007a) combined the benefits of carbon nanotubes (CNTs) and PABA to develop a sensitive and selective electrochemical DA sensor. They first deposited PABA/ssDNA/single-walled nanotube nanocomposite onto the electrode to improve the sensitivity and then coated a thin layer of perfluorosulfonated ion-exchange polymer Nafion above the composite to eliminate the interference from ascorbate acid. Here, we used phenylboronic acid modified electrodes to capture DA via the interaction of boronic acid and catechol group of DA. The amino group of captured DA could react with biotin *N*-hydroxysuccinimide ester which facilitated the detection of DA with signal amplification by Fc-capped SA-AuNPs conjugates.

2. Experimental

2.1. Reagents and materials

SA-AuNPs conjugates, 4-mercaptophenylboronic acid (MBA), biotin *N*-hydroxysuccinimide ester, 1-ethanethiol (ET), 6-ferrocenyl-1-hexanethiol (Fc(CH₂)₆SH), ascorbate acid, DA hydrochloride, glucose, uric acid, cysteine, tyrosine, adrenaline, noradrenaline, dithiobis(succinylmidylpropionate), K₂HPO₄ and KH₂PO₄ were all purchased from Sigma–Aldrich. *N,N*-dimethylformamide (DMF), hexane, and other reagents were of analytical grade and obtained from Beijing Chemical Reagent Co. (Beijing, China). The preparation of the Fc-capped SA-AuNP conjugates and the determination of the average number of Fc groups per Au nanoparticle followed the methods described in the previous report (Wang et al., 2003). The stock solution of DA was freshly prepared with water and then diluted with phosphate buffer solution (PBS, pH 7.4) to the desired concentrations. The supporting electrolyte was 10 mM PBS containing 0.1 M NaSO₄. All aqueous solutions were prepared with N₂-saturated deionized water treated with a Millipore system (Simplicity Plus, Millipore Corp., Billerica, MA).

Artificial cerebrospinal fluid (aCSF) comprising 150 mM NaCl, 3.0 mM KCl, 1.4 mM CaCl₂, 0.8 mM MgCl₂, and 1.0 mM sodium

phosphate was prepared in-house. Dopamine hydrochloride injection was diluted 10⁷ fold with PBS before assay.

2.2. Instruments

The electrochemical determinations were performed on a DY2013 electrochemical workstation (Digi-Ivy, Inc., Austin, TX) using a homemade plastic electrochemical cell. Gold disk electrodes with a diameter of 2 mm were used as the working electrode. A platinum wire and a Ag/AgCl electrode were used as the auxiliary and the reference electrodes, respectively. Prior to each measurement, the gold disk electrodes were polished with diamond pastes down to 3 μ m and alumina pastes down to 0.3 μ m, and then sonicated in water.

2.3. Procedures

The schematic representation of the amplified voltammetric detection of DA via oxidation of Fc tags on the SA-AuNPs conjugates is illustrated in Fig. 1. The MBA self-assembled monolayers (SAMs) were formed by immersing the cleaned gold substrate in a solution of 10 mM MBA in the darkness for 18 h. This step was followed by washing the electrode thoroughly with ethanol and water and soaking the MBA-modified electrode in an aqueous solution containing 0.1 mM ET for 5 min. After the MBA film had been formed, 10 μ L of PBS buffer comprising a given concentration of DA was cast onto the electrode surface for 10 min. Again, the electrode was rinsed with water to rid any non-specifically adsorbed substance. To attach Fc-capped SA-AuNPs conjugates, the electrode was first allowed to react with 10 μ L of 2.0 mM biotin *N*-hydroxysuccinimide ester for 15 min (Deckert et al., 2004; Kong et al., 2011; Liu et al., 2012). Upon rinsing with a copious amount of 50% ethanol/water, the electrode was exposed to 3 μ L of Fc-capped SA-AuNPs conjugates for 15 min. Fc-capped SA-AuNPs conjugates were attached to the biotin-covered electrode through the strong biotin-streptavidin non-covalent interaction ($K_d = 10^{-15}$ M) (Samanta and Sarkar, 2011). After the electrode had been rinsed with water, voltammetric determination in PBS solution was conducted via scanning the electrode potential within 0–0.6 V.

3. Results and discussion

3.1. Amplified voltammetric determination of DA

In Fig. 1, DA molecules were captured by MBA-modified electrode. The amino groups of DA were then derivatized with biotin *N*-hydroxysuccinimide ester, which was followed by the attachment of Fc-capped SA-AuNPs conjugates through biotin-streptavidin complexation. As a result, facile electron transfer

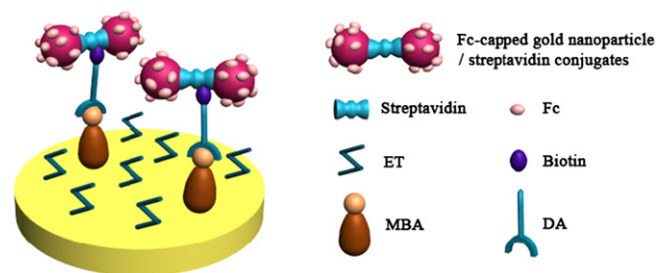


Fig. 1. Schematic representation showing the capture of DA by the immobilized MBA and the detection of DA by attachment of Fc-capped SA-AuNPs conjugates.

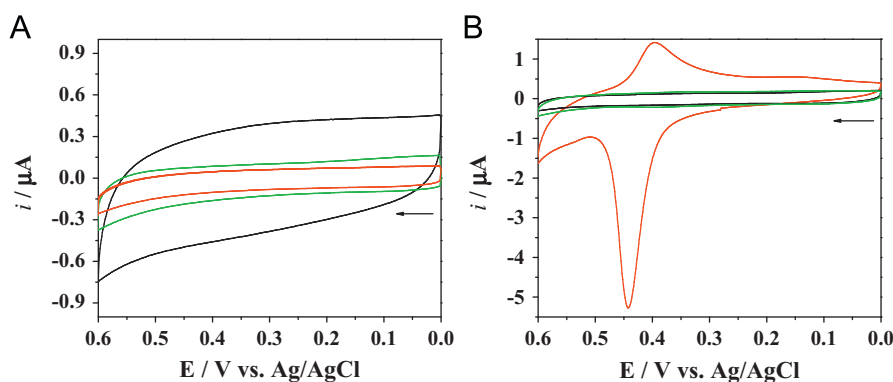


Fig. 2. (A) CVs of bare gold electrode (black line curve) and MBA-covered (green line curve) and MBA/ET-covered (red line curve) gold electrodes in PBS; (B) CVs at electrodes covered with DA (black line curve) and then modified with Fc-capped SA-AuNPs conjugates (red line curve). The electrochemical responses in the absence of DA (green line curve) followed by the attachment of the conjugates were also shown. The concentration of DA is 100 nM. The scan rate was 0.1 V/s, and the arrow indicates the scan direction. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this article.)

reactions between the Fc tags and the electrode could take place. Note that each gold nanoparticle is capped with a large number of Fc molecules (119 ± 12 Fc molecules per gold nanoparticle) and that most of the streptavidin molecules are linked to two gold nanoparticles, greatly amplifying the electrochemical signals (Wang et al., 2008a, 2003, 2012). The peak currents are proportional to the amounts of captured DA molecules.

Fig. 2A shows the cyclic voltammograms (CVs) of the bare gold electrode and MBA- and MBA/ET-covered gold electrodes in PBS. There is no redox peak at the electrodes. However, CV collected at electrode modified with DA and Fc-capped SA-AuNPs conjugates shows a couple of redox waves with high signal intensity (red line curve in Fig. 2B). The redox peaks with $E_{pa}=0.436$ V and $E_{pc}=0.385$ V were attributed to the oxidation/reduction of the Fc moieties because no redox peaks were observed at DA-anchored electrode (black line curve in Fig. 2B). The reduction peak current is apparently lower than the oxidation peak current probably due to the loss of Fc tags caused by the oxidation of DA-boronate ester and the subsequent breakage of diol-boronic acid bond (Strawbridge et al., 2000). In the absence of DA (green line curve), the voltammetric peak currents dropped to a background level, indicating that this method is amenable to the detection of DA in a highly sensitive manner.

3.2. Effect of pH

The binding strength and ionization state of the diol-boronic acid complex are pH-dependent. Several groups have measured the association constants of diol-boronic acid complexes under a variety of conditions, including different pH values and solvents (Springsteen and Wang, 2001, 2002; Tong et al., 2001; Yang et al., 2001). The effect of pH on the assembly of DA on the MBA-modified electrode surface was also carried out. As shown in Fig. 3, the oxidation peak current reaches the maximum at pH 8.0 and slightly decreases at pH above 8.0. This is understandable because the affinity of diol-boronic acid complex is small at low pH and the ionization of DA-boronate ester at high pH can also result in the decrease of the binding affinity. For the quantitative analysis of DA, physiological pH 7.4 was chosen as the reaction media. Moreover, we found that the electrode can be conveniently regenerated by immersing the electrode in 10 mM HCl solution and then rinsing the surface with water/ethanol solvent (i.e., desorbing DA bound to boronic acid and Fc-capped SA-AuNPs conjugates). As can be seen from Fig. 3B, no change in the oxidation peak current of the Fc tags was observed after five regeneration/assay cycles. Thus, multiple samples can be determined using one electrode, dramatically increasing the sample

throughput and reducing the sample analysis time. In addition, we found that the relative standard deviations (RSDs) are all below 7.5% by performing these regeneration/assay cycles at three different electrodes in parallel, indicating that multiple electrodes can be prepared concurrently for the assays of many different samples.

3.3. Sensitivity to DA

With the regeneration of the method established, we assessed other analytical merits, such as reproducibility, sensitivity and the detection limit. The dependence of the oxidation peak currents on the concentrations of DA is presented in Fig. 4. The aforementioned regeneration of the sensor surface contributes to good reproducibility of the method, as the RSDs, shown as the error bars in Fig. 4B, are all less than 10%. The oxidation peak current increases linearly with the concentrations of DA ranging from 0.5 to 50 nM and begin to level off beyond 50 nM. The linear regression equation is expressed as $i_{pa}(\mu A)=0.08+0.11[DA](nM)$ ($R^2=0.99$). The detection limit (3σ) of the method was estimated to be 0.2 nM ($n=11$), which is 1–2 orders of magnitude lower than those achievable using other modified electrodes reported so far (Gao and Huang, 1998; Hocevar et al., 2005; Huang et al., 2008, 2010; Lin et al., 2010; Noroozifar et al., 2011; Weng et al., 2005; Zare et al., 2005). Notice that the slight potential shift of Fc tags in different DA concentrations and the characteristic diffusional “tailing” of the peaks in Fig. 4A were due to the repulsive interaction between the ferrocenium moieties confined to the electrode surface (Wang et al., 2008a, 2003; Ye et al., 1997).

3.4. Selectivity and interference

Boronic acid can also bind to other members of the diol family, such as ascorbate acid, glucose, noradrenaline and adrenaline, producing the diol-boronate ester (Springsteen and Wang, 2002). The selectivity of the present approach was evaluated by testing other biomolecules that may coexist in the body fluids of mammals. As a result, we found that no significant oxidation currents were obtained when the MBA-modified electrodes were incubated in the solution containing each of the interfering agents (black bars in Fig. 5A). For cysteine, tyrosine and uric acid, this result is understandable because they cannot absorb onto the MBA surface via the formation of diol-boronic acid complex. Although ascorbate acid and glucose can react with MBA, the two compounds have no amine groups. Thus, biotin cannot be assembled onto the surface via the amine coupling reaction, making Fc-capped SA-AuNPs conjugates impossible to be captured

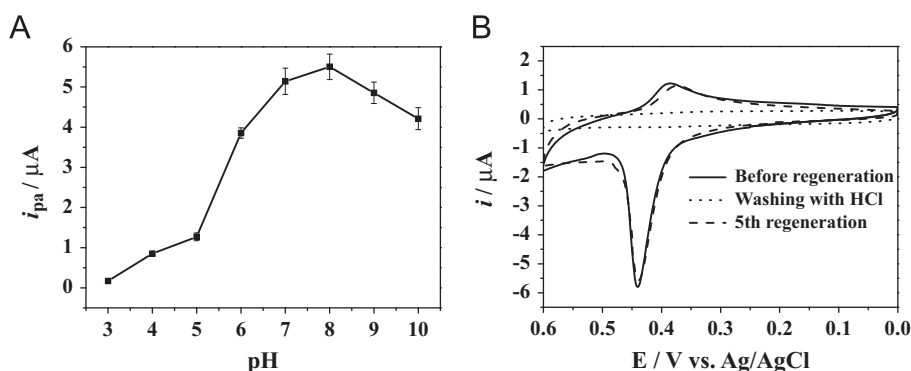


Fig. 3. (A) Effect of pH on the oxidation peak current (i_{pa}). The MBA-modified electrodes were modified with 50 nM DA at different pH. The amino groups of anchored DA were then derivatized with biotin *N*-hydroxysuccinimide ester followed by the attachment of Fc-capped SA-AuNPs conjugates. (B) CVs depicting the regeneration of the electrode for DA assays. The regeneration solution was 10 mM HCl. The regenerated surface was remodified with DA at pH 7.4 and derivatized with biotin *N*-hydroxysuccinimide ester followed by the attachment of Fc-capped SA-AuNPs conjugates.

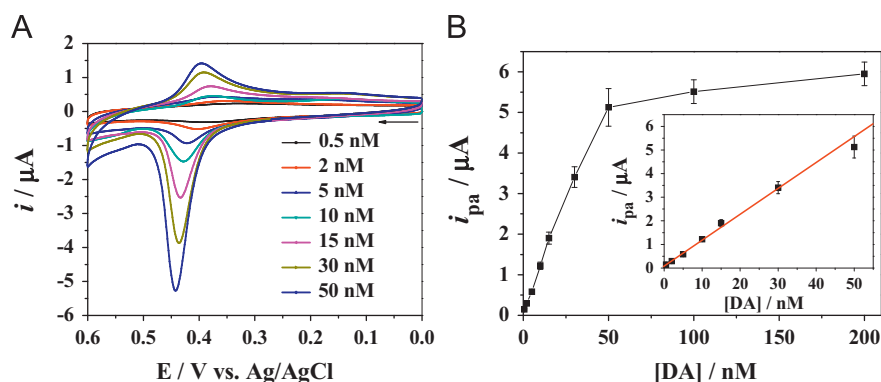


Fig. 4. (A) CVs at electrodes covered with different concentrations of DA and then modified with Fc-capped SA-AuNPs conjugates and (B) dependence of the oxidation peak current on the concentration of DA. Other experimental conditions are the same as those in Fig. 2. The absolute errors were deduced from at least three replicate measurements and are shown as the error bars. The inset shows the linear portion of the curve with DA concentrations ranging from 0.5 to 50 nM.

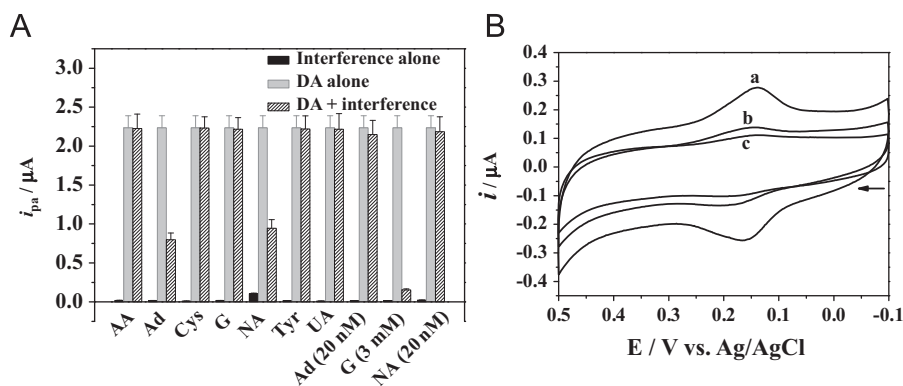


Fig. 5. (A) Selectivity and interference of the sensing protocol. The MBA-modified electrodes were modified with interferences in the absence (gray bars) and presence (hatched bars) of 20 nM DA. Unless otherwise noted, the concentration of interference was 200 nM. Other experimental conditions are the same as those in Fig. 2. AA, ascorbate acid; Ad, adrenaline; Cys, cysteine; G, glucose; NA, noradrenaline; Tyr, tyrosine; UA, uric acid. (B) CVs collected at dithiobis(succini-midylpropionate)-covered electrodes after modification with DA (curve a), noradrenaline (curve b) and adrenaline (curve c) for 15 min. The concentrations of DA, noradrenaline and adrenaline are all 1 mM. The scan rate was 50 mV/s.

through the strong biotin–streptavidin interaction. Interestingly, although noradrenaline and adrenaline have primary and secondary amine groups, respectively, they did not induce significant voltammetric signals. We presume that this behavior is caused by their poor reactivity to biotin *N*-hydroxysuccinimide ester due to the ortho-effect of the hydroxy group (Kong et al., 2011). Dithiobis(succini-midylpropionate), a *N*-hydroxysuccinimide ester, is usually used to immobilize biomolecules through a standard amine coupling reaction. After incubating the dithiobis(succini-midylpropionate)-covered electrodes in DA, noradrenaline and adrenaline

solutions and then collecting the CVs at these electrodes in PBS, we observed marked differences in the oxidation and reduction currents (Fig. 5B). The redox peaks with $E_{pa}=0.164$ V and $E_{pc}=0.136$ V were attributed to the oxidation/reduction of the catechol moieties (Sun et al., 2011). The currents at DA-modified electrode (curve a) are greatly higher than those at the noradrenaline- and adrenaline-modified electrodes (curves b and c, respectively), demonstrating that the reactions of noradrenaline and adrenaline with *N*-hydroxysuccinimide ester on electrode surface are indeed slower than that of DA.

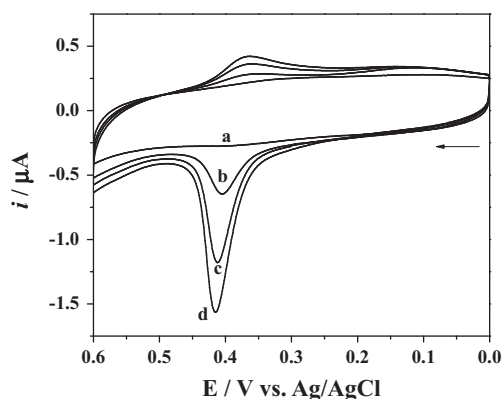


Fig. 6. CVs depicting the detection of DA in aCSF with (curve b) and without (curve a) addition of 2.5 nM DA, and in dopamine hydrochloride injection with (curves d) and without (curves c) addition of 5.0 nM DA. Other experimental conditions are the same as those in Fig. 2.

To further investigate the interference, the MBA-modified electrodes were incubated in 20 nM of DA solution containing 200 nM of different interfering agents. As shown in Fig. 5A, cysteine, tyrosine, uric acid, ascorbate acid and glucose at a concentration of 10 times higher than DA did not cause a significant change in oxidation peak current (hatched bars) in comparison with the result obtained in the presence of DA only (gray bars), indicating that DA was preferred to absorb onto the MBA surface than these biological species. For ascorbate acid and glucose, a reasonable explanation is that the binding affinity between DA and MBA is higher than that of the other two diol-boronate esters (Ali et al., 2007b; Springsteen and Wang, 2002). However, noradrenaline and adrenaline at a concentration 10 times higher than that of DA caused a remarkable decrease in the oxidation peak current. The result is reasonable given that they have a similar catechol group to DA, thus decreasing the amount of DA bound to MBA-modified electrodes. Notice that levels of these two catechol compounds *in vivo* are extremely low and comparable to (or even lower than) that of DA (approximately 10 nM) (Ali et al., 2007a; Kong et al., 2011; Liu et al., 2007; Tsunoda et al., 2011; Vanderas et al., 1999). We found that these two compounds at a concentration of 20 nM did not cause a significant decrease in the oxidation peak current (Fig. 5A). However, real samples, such as blood, urine or cerebrospinal fluid, contain micromolar glucose concentrations, above 10^5 times higher than that of DA. As shown in Fig. 5A, 3 mM glucose caused a significant decrease in the oxidation peak current due to the competition between glucose and DA. Therefore, the proposed method currently cannot directly detect DA in real body fluid samples without pretreatment. To avoid interference from other biological species, new chips (e.g., metal complexes, polymers and nanocomposites) are needed for selective DA capture in a sandwich format.

3.5. Artificial samples detection

To demonstrate the viability of the MBA-modified electrodes for amplified voltammetric analysis of different artificial samples, we carried out the measurement of amounts of DA in aCSF and dopamine hydrochloride injection. As shown in Fig. 6, no DA was found in aCSF (curve a); thus, 2.50 nM of DA was added into the aCSF and then analyzed. The i_{pa} was 0.3862 μ A (curve b) and the content of DA was deduced to be 2.78 nM by the calibration curve. The dopamine hydrochloride injection was disposed as aforementioned procedures. The level of DA in the diluted injection sample was found to be 6.13 nM (curve c), which is close to

the known content of 5.28 nM. To ascertain the correctness of the results, we tested the diluted injection sample spiked with 5 nM of DA and the concentration was determined to be 10.83 nM (curve d). These results confirm that the present method is applicable for DA detection in artificial samples and could offer a useful means for quantifying DA in laboratory studies.

4. Conclusion

In this work, specific binding between DA and boronic acid preimmobilized onto the electrode was used for detecting DA at trace levels. The small number of DA bound to boronic acid was tagged with gold nanoparticles capped with a large number of Fc tags. Well-defined Fc voltammetric peaks, whose currents increase with the DA concentration on the electrode surface, were observed. Analytical merits (e.g., dynamic range, reproducibility, detection level, selectivity and interference) were evaluated through the analysis of different concentrations of DA in the presence and absence of other biological species. We anticipate that the proposed sandwich-type electrochemical biosensor would become a clinical protocol for the detection of DA.

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