Microchemical Journal 130 (2017) 40–46

Contents lists available at ScienceDirect

Microchemical Journal

journal homepage: www.elsevier.com/locate/microc

Quantification of neurotransmitters and metabolically related compounds at glassy carbon electrodes modified with bamboo-like carbon nanotubes dispersed in double stranded DNA☆,☆☆

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ARTICLE INFO

Article history:
Received 31 March 2016
Received in revised form 5 August 2016
Accepted 5 August 2016
Available online 6 August 2016

Keywords:
Bamboo carbon nanotubes
Dopac
Dopamine
Normetanephrine
Norepinephrine
Electrochemical (bio)sensor
dsDNA

ABSTRACT

This work reports the application of glassy carbon electrodes (GCE) modified with bamboo-like carbon nanotubes (bCNT) dispersed in calf-thymus double-stranded DNA (dsDNA) (GCE/bCNT-dsDNA) for the highly sensitive and selective quantification of neurotransmitters and metabolically related compounds by Adsorptive Stripping. Dopamine (Do) was quantified in the presence of its most important metabolite, 3,4-dihydroxyphenylacetic acid (dopac), while normetanephrine (NM) was determined in the presence of its precursor norepinephrine (NE). The accumulation of the analytes was performed at open circuit potential and the quantification was carried out, after medium exchange, in a 0.200 M acetate buffer solution pH 5.0 using Differential Pulse Voltammetry. The sensitivity for Do in the presence of 1.0×10^{-5} M dopac was $(7.1 \pm 0.2) \times 10^{5}$ μAM^{-1}, (just 7.0% higher than the one obtained for Do alone), the detection limit was 68 nM, and the linear range 5.0×10^{-7} M-7.0×10^{-6} M. The sensitivities for NM in the absence and presence of NE were $(2.8 \pm 0.1) \times 10^{4}$ μAM^{-1} and $(2.6 \pm 0.2) \times 10^{4}$ μAM^{-1}, with a linear range between 1.0×10^{-6} and 2.0×10^{-5} M, and a detection limit of 0.5 μM. The platform was successfully used for the quantification of Do and NM in enriched human urine samples.

1. Introduction

The knowledge generated in recent years regarding the synthesis and handling of nanoscale materials has made possible a spectacular growth of Nanoscience [1]. In particular, carbon nanotubes (CNTs) have received enormous attention due to their fascinating properties [2–4]. However, in spite of their formidable properties, the use of CNTs for the development of electrochemical sensors presents the problem of their insolubility in common solvents [5–8]. Therefore, several strategies have been proposed for the immobilization of CNTs on electrochemical transducers [9–17].

We have reported the efficient non-covalent functionalization of bamboo-type multi-walled carbon nanotubes (bCNT) with calf-thymus double stranded DNA (dsDNA) [18] and the analytical usefulness of glassy carbon electrodes (GCE) modified with these modified nanostructures (GCE/bCNT-dsDNA) for the sensitive detection of the intercalator promethazine [19] and for the sensitive and selective quantification of glucose by self-assembling of glucose oxidase and poly(diallyldimethyl)ammonium [20].

In this work we report another interesting and original analytical application of GCE/bCNT-dsDNA for the highly sensitive quantification of dopamine (Do) in the presence of 3,4-dihydroxyphenylacetic acid (dopac), and normetanephrine (NM) in the presence of norepinephrine (NE) using Adsorptive Stripping with medium exchange and Differential Pulse Voltammetry for the transduction.

Do is a catecholaminergic neurotransmitter present in mammalian that is converted by the action of monoamino-oxidase into dopac [21,22,23]. Low levels of Do have been associated with disorders like Schizophrenia and Parkinson's disease, Alzheimer disease, depression and anorexia [24–26], while high levels have been associated with pathologies like pheochromocytoma [27,28]. Several analytical techniques have been proposed for the quantification of Do [29–32]. The electrochemical ones have demonstrated to be an important alternative due to their known advantages [32]. However, the development of highly sensitive and selective strategies for the electrochemical sensing of Do is not an easy task due to the presence of other metabolically related compounds which are oxidized at very close potentials [33,34]. Quan et al. [24] have reported the micromolar detection of Do in the presence of ascorbic and

☆ This manuscript is submitted for considering publication in the special issue dedicated to the 8th Argentinean Meeting on Analytical Chemistry.
☆☆ Selected research paper presented at the biannual Argentine Analytical Chemistry meeting held in Argentina, AAQA-2015.

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http://dx.doi.org/10.1016/j.microc.2016.08.001
0026-265X/

uric acids using a GCE modified with Nafion/single wall carbon nanotube/poly(3-methylthiophene). Oko et al. [35] have proposed the use of electrodes containing different amounts of PtAu alloy nanoparticles for the detection of Do in the presence of ascorbic acid. Miękus et al. [36] have reported the use of capillary electrophoresis with spectrophotometric detection for the quantification of catecholamines in the presence of various biogenic amines in urine with a detection limit of 5 μg mL^{-1}. Seo et al. [37] have proposed the electrochemical quantification of Do using inlaid electrodes located along the high performance liquid chromatography (HPLC) column. Erro et al. [38] have demonstrated the use of capillary electrophoresis with a hybrid microchip polydimethylsiloxane (PDMS)/glass and carbon fiber electrode using triple pulse amperometric detection, to separate Do and dopac at milimolar levels. Recently, Fajarmi et al. [39] have demonstrated the efficient biosensing of μM levels of Do in the presence of other neurotransmitters using an electrochemical aptamer-based biosensor.

Metanephrines (metanephrine (M) and normetanephrine (NM)) are the metabolites of epinephrine and NE, respectively released from sympathetic nerves or adrenal medulla [40,41]. NM, the *O*-methylated metabolite of NE, is produced by the action of catechol-*O*-methyltransferase [28,42]. The measurement of urinary metanephrines has been used as one of the foremost screening test for unexplained hypertension or the diagnostic of pheochromocytoma [42–44]. Several procedures have been reported for the determination of metanephrines in plasma and urine samples including gas chromatography–mass spectrometry (GC–MS) [45,46], HPLC with electrochemical detection [47–51], solid-phase extraction using molecularly imprinted polymer [52], and liquid chromatography electrospray ionization in tandem with mass spectroscopy (LC-MS/MS) [28,53–56]. However, even when these techniques have allowed the highly sensitive and selective quantification of NM, they require laborious extraction procedures and well-trained personnel. Therefore, is very important to develop strategies that make possible the quantification of low levels of NM in the presence of NE in a more simple way.

In the following sections we discuss the influence of bCNT-dsDNA immobilized at GCE on the electrochemical behavior of Do, dopac, NE and MM, and we propose new electrochemical strategies based on the use of Differential Pulse Voltammetry (DPV)-Adsorptive stripping with medium exchange for the sensitive quantification of Do in the presence of dopac and NM in the presence of NE. The application of the resulting analytical platforms for the detection of Do and NM in enriched urine samples of human volunteers is also presented.

2. Experimental

2.1. Materials and reagents

Dopamine (Do); 3,4 dihydroxyphenylacetic acid (dopac); norepinephrine (NE); normetanephrine (NM) and calf-thymus double stranded DNA (dsDNA, Catalog number D-4522) were purchased from Sigma. Bamboo-like multiwalled carbon nanotubes (bCNT, diameter (30 ± 10) nm, length 1–5 μm, 98.92% purity) were obtained from NanoLab (U.S.A.). Other chemicals were reagent grade and were used without further purification. Ultrapure water (ρ = 18.2 MΩ cm) from a Millipore-MilliQ system was used for preparing all the solutions. The supporting electrolyte was 0.200 M acetate buffer solution pH 5.00.

2.2. Apparatus

Electrochemical experiments were performed with an Epsilon (BAS) potentiostat. A platinum wire and Ag/AgCl, 3 M NaCl (BAS, Model RE-5B) were used as counter and reference electrodes, respectively. All potentials are referred to the latter. Bare glassy carbon (GCE) and GCE modified with bCNT-dsDNA (GCE/bCNT-dsDNA) were used as working electrodes. A magnetic stirrer (BASi Cell stand) and a stirring bar provided the convective transport during the amperometric measurements (at 800 rpm).

2.3. Preparation of the sensor (GCE/bCNT-dsDNA)

2.3.1. Preparation of bCNT-dsDNA dispersion

The dispersion was obtained by mixing 1.0 mg of bCNT with 1.0 mL of 100 ppm dsDNA solution (prepared in 50% (v/v) ethanol/water) followed by sonication for 45 min in ultrasonic bath. After this treatment, the samples were centrifuged at 9000 rpm for 15 min (twice). The supernatant was used for further modification of the electrodes (Scheme 1).

2.3.2. Modification of GCE with bCNT-dsDNA (GCE/bCNT-dsDNA)

GCEs were polished with alumina slurries of 1.0, 0.30, and 0.05 μm for 2 min each. Before modification with bCNT-dsDNA, the electrodes were cycled in a 0.050 M phosphate buffer solution pH 7.40 for ten times between −0.300 V and 0.800 V at 0.050 V s^{-1}. The modification was performed by depositing an aliquot of 20 μL of b-CNT-dsDNA on top of the GCEs followed by the evaporation of the solvent at room temperature.

2.4. Quantification of Do and NM

The quantification of Do and NM was performed by Adsorptive stripping analysis with medium exchange and Differential Pulse Voltammetry (DPV) transduction according to the following procedure:

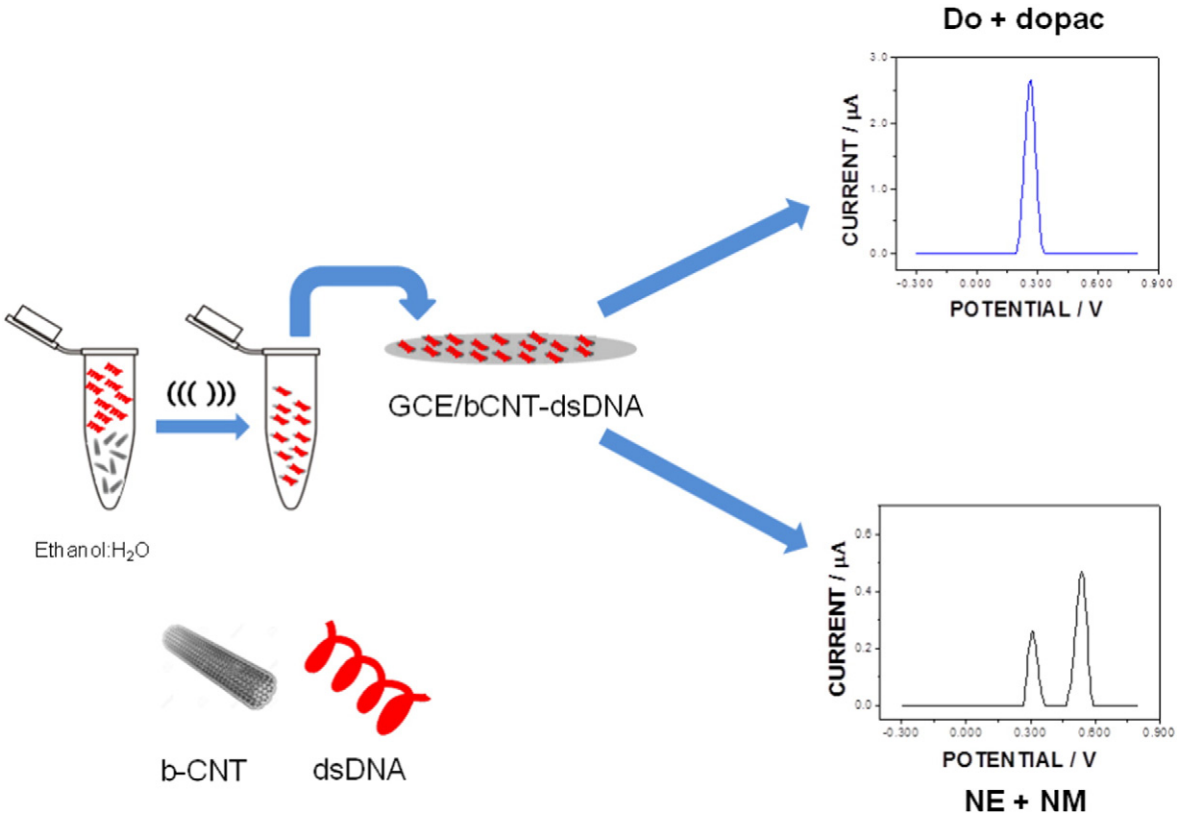
(I) *Preconcentration:* performed at open circuit potential by immersion of GCE/bCNT-dsDNA in the Do or NM solution for a given time under stirring conditions.
(II) *Washing:* the electrodes containing the accumulated material according to I) were washed with a 0.200 M acetate buffer solution pH 5.00 for 10 s and then transferred to a fresh acetate buffer solution.
(III) *Transduction:* The anodic stripping was performed in a 0.200 M acetate buffer solution pH 5.00 by scanning the potential between −0.300 V and 1.500 V at 0.050 V s^{-1} using DPV. The analytical signals were obtained from the oxidation peak currents of the corresponding analyte after subtracting the background currents.

All measurements were performed at room temperature.

3. Results and discussion

3.1. Electrochemical quantification of dopamine

Fig. 1 shows cyclic voltammograms for 5.0×10^{-4} M Do (A), 5.0×10^{-4} M dopac (B) and 5.0×10^{-4} M Do + 5.0×10^{-4} M dopac (C) at GCE (dashed line) and GCE/bCNT-dsDNA (solid line). In the case of Do, a drastic change in the voltammetric profiles is observed at GCE/bCNT-dsDNA. In fact, the peak potential (E_{pa}) for the oxidation of Do to dopaminequinone (DoQ) decreases 166 mV, the peak potential separation (ΔE_p) goes from 0.230 to 0.065 V, and the associated currents show important enhancements (i_{pa} increases in a factor of 4.5). These results clearly demonstrate that the presence of the carbon nanostructures supported by dsDNA largely facilitates the interaction of the positively charged Do with GCE/bCNT-dsDNA. Cyclic voltammograms for Do obtained at GCE modified by deposition of dsDNA (GCE/dsDNA) or bCNT dispersed in ethanol/water (GCE/bCNT) are similar to those obtained at GCE, indicating that the efficient dispersion of bCNTs with dsDNA and the characteristics of negatively charged polyelectrolyte of dsDNA, greatly facilitates the electrooxidation of Do. If the same electrode used to perform one cyclic voltammogram in the presence of Do is used to obtain a new voltammogram in a Do-free acetate buffer solution, a well-defined redox couple is obtained at the potentials for the system Do/DoQ, evidencing a strong adsorption of Do at GCE/bCNT-dsDNA.



Scheme 1. Scheme for the preparation of the bCNT dispersion and the analytical platform.

In the case of dopac (Fig. 1B), the behavior is similar to the one observed for Do, with a decrease of 129 mV in the peak potential separation and a clear enhancement in the oxidation and reduction currents compared to GCE (2.4 and 3.6 times for i_{pa} and i_{pc}, respectively). Control experiments using GCE/dsDNA demonstrated that at GCE/dsDNA there is a small shifting of the peak potential in the positive direction due to the unfavorable electrostatic interaction between dopac and dsDNA (not shown). These results indicate that, even when there is a repulsive effect of dsDNA towards dopac, when GCE is modified with bCNT-dsDNA, the most important effect is the catalytic activity of CNTs, as it was already demonstrated in the case of other compounds [13].

The cyclic voltammograms for the mixture of dopac and Do obtained at the GCE and GCE/bCNT-dsDNA are shown in Fig. 1(C). The resolution of the contribution of Do and dopac was not possible neither at bare GCE nor at GCE/bCNT-dsDNA since both compounds are oxidized at very close potentials.

Therefore, taking into account the advantages obtained for Do electrooxidation at GCE/bCNT-dsDNA and the strong adsorption of Do, we evaluate the adsorptive behavior of Do, dopac and a mixture of Do and dopac at GCE/bCNT-dsDNA using Adsorptive Stripping with medium exchange and DPV transduction. Fig. 2 displays differential pulse voltammograms obtained in a 0.200 M acetate buffer solution pH 5.00 after 1.0 min accumulation of 2.0×10^{-6} M dopamine (solid line), 1.0×10^{-5} M dopac (dotted line) and 2.0×10^{-6} M Do + 1.0×10^{-5} M dopac (dashed line) at GCE/bCNT-dsDNA. The differential pulse voltammograms obtained after the adsorption of Do show a clear oxidation signal at 0.268 V ($i_p = 1.50$) μA, demonstrating the advantages of the adsorption of Do at GCE/bCNT-dsDNA since, even at this micromolar level, there is an excellent definition of the oxidation signal. It is important to remark that no response was obtained at bare GCE under these experimental conditions (not shown). In the case of dopac (dotted line), the response is very small ($i_p = 0.05$ μA) at 0.244 V, due to a non-favorable interaction with the negatively charged electrode surface and a poor adsorption. The voltammetric profiles after the adsorption of the mixture Do + dopac presents a current that is just 6.7% higher than the one obtained for Do alone (1.5 versus 1.6 for Do alone and Do in the mixture). Therefore, the presence of bCNT-dsDNA at GCE largely facilitates the selective adsorption of Do and makes possible a most efficient charge transfer, demonstrating that is possible to quantify Do even in the presence of dopac due to their different adsorptive behavior at GCE/bCNT-dsDNA. The adsorption of Do at GCE/bCNT-dsDNA was fast since after 1.0 min accumulation in a Do solution, the stripping signal reached the maximum value (not shown). Therefore, 1.0 min adsorption of Do was selected for further work.

Fig. 3 displays the calibration plot for Do after 1.0 min adsorption at open circuit potential and stripping with medium exchange (calibration 1). There is a linear relationship between the oxidation peak current and Do concentration between 5.0×10^{-7} M and 7.0×10^{-6} M; with a sensitivity of $(6.6 \pm 0.2) \times 10^5$ μAM^{-1}, and a detection limit, of 74 nM (taken as $3.3 \times \sigma / s$ where σ is the standard deviation of the blank signal and s the sensitivity) [57]. The calibration plot 2 was obtained for Do in the presence of 1.0×10^{-5} M dopac. The linear range is the same as the one obtained in the absence of dopac. The sensitivity is $(7.1 \pm 0.2) \times 10^5$ μAM^{-1}, that is, just 7.0% higher than the one obtained in the presence of Do alone, and the detection limit is 68 nM, demonstrating the usefulness of the sensor for the quantification of Do in the presence of its most important metabolite. Each measurement was obtained with a new electrode and the experimental points represent the average of the currents obtained with three electrodes. The R.S.D. for the determination of 2.0×10^{-6} M Do using six different electrodes modified with the same dispersion was 1.6%. The R.S.D. for the determination of 2.0×10^{-6} M Do using ten different dispersions was 2.6%.

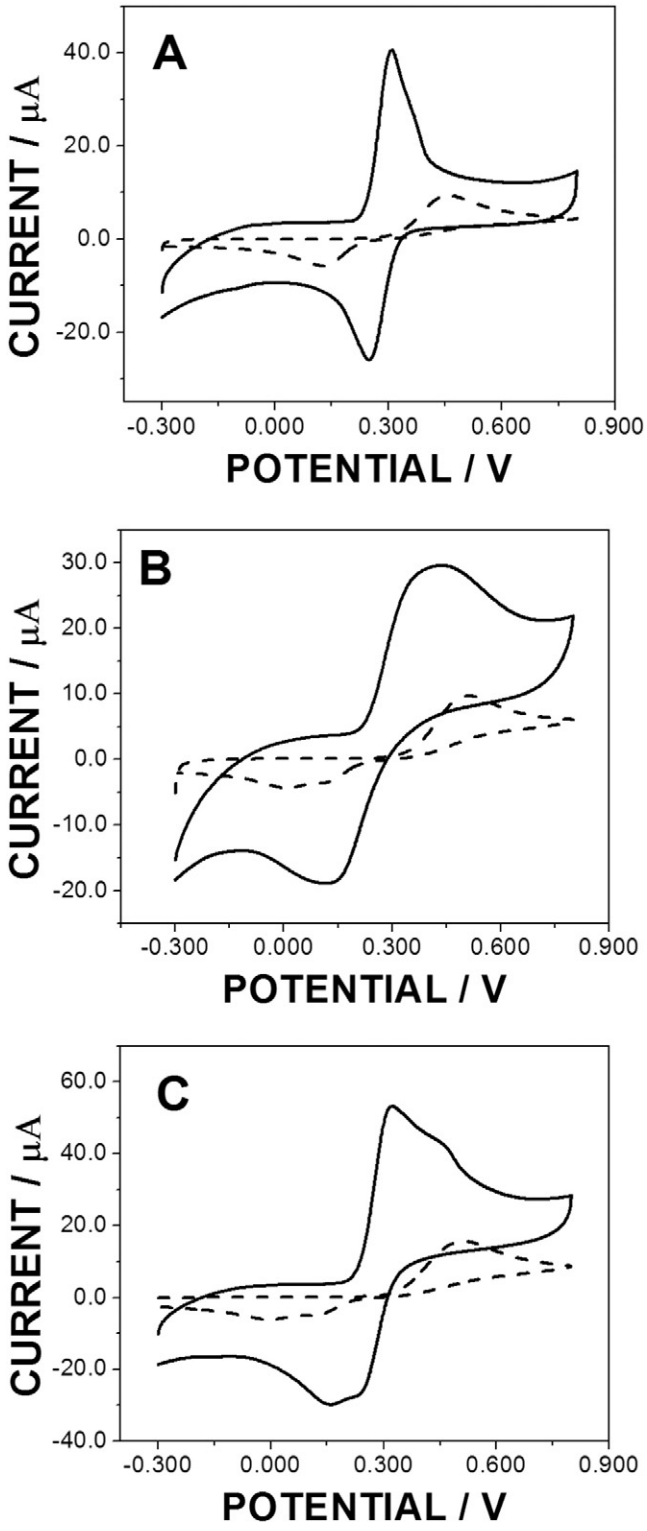


Fig. 1. Cyclic voltammograms for 5.0×10^{-4} M Do (A), 5.0×10^{-4} M dopac (B) and 5.0×10^{-4} M Do + 5.0×10^{-4} M dopac (C) at different electrodes: GCE (dashed line) and GCE/bCNT-dsDNA (solid line) (1.0 mg/mL bCNT/mL of 100 ppm dsDNA). Scan rate: 0.050 V s^{-1}. Supporting electrolyte: 0.200 M acetate buffer solution pH 5.00.

3.2. Electrochemical sensing of NM

Fig. 4A shows differential pulse voltammograms obtained in a 0.200 M acetate buffer solution pH 5.00 after 3.0 min adsorption of 2.0×10^{-5} M NM (dotted line), 5.0×10^{-6} M NE (dashed line) and

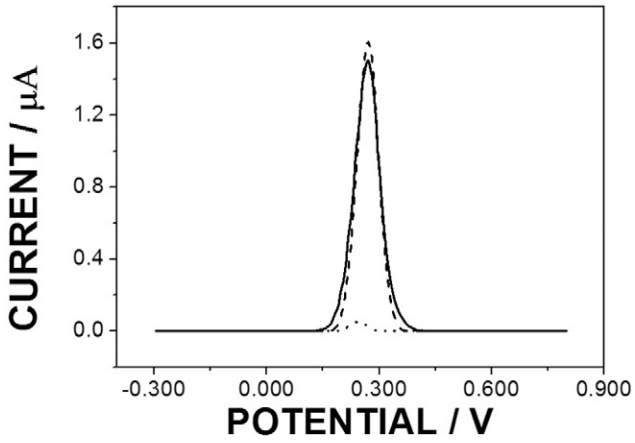


Fig. 2. Differential pulse voltammograms for 2.0×10^{-6} M Do (solid line), 1.0×10^{-5} M dopac (dotted line) and 2.0×10^{-6} M Do + 1.0×10^{-5} M dopac (dashed line) at GCE/bCNT-dsDNA. Accumulation time: 1.0 min; scan rate: 0.020 V s^{-1}, potential increment 0.004 V, pulse amplitude 0.050 V, pulse width 0.050 and pulse period 0.2 s. Supporting electrolyte: 0.200 M acetate buffer solution pH 5.00. Other conditions as in Fig. 1.

2.0×10^{-5} M NM in the presence of 1.0×10^{-5} M NE (solid line). In the case of NM, there is an oxidation current peak at 0.540 V due to the oxidation of the phenolic residue [58]. The oxidation of NE displays the typical signal at 0.300 V due to the oxidation of the catechol group [59]. The mixture of NM and NE, shows the expected oxidation current peaks at 0.300 V and 0.544 V due to the oxidation of NE and at 0.544 V due to the oxidation of NM, respectively. The oxidation currents for NM in the absence and presence of NE were 0.52 and 0.48 μA, indicating that there is almost no influence of NE in the oxidation of NM, opening the doors for the sensitive quantification of NM in the presence of NE.

Fig. 4B displays the effect of the accumulation time of 1.0×10^{-5} M NM at GCE/bCNT-dsDNA at open circuit potential on the oxidation peak current. The signal increases up to 3.0 min accumulation, to keep almost constant thereafter. The best compromise between the sensitivity and the time required for the analysis was obtained with 3.0 min accumulation.

Fig. 4C displays the calibration plot for NM in the presence (calibration 1, solid line) and in the absence (calibration 2, dotted line) of 5.0×10^{-6} M NE. The sensitivity for NM in the absence of NE was $(2.8 \pm 0.1) \times 10^4$ μAM^{-1} ($r = 0.999$), with a linear range between 1.0×10^{-6} and 2.0×10^{-5} M, and a detection limit of 0.5 μM, calculated as it was previously indicated. In the presence of 5.0×10^{-6} M NE, the sensitivity was $(2.6 \pm 0.2) \times 10^4$ μAM^{-1}, ($r = 0.992$), demonstrating

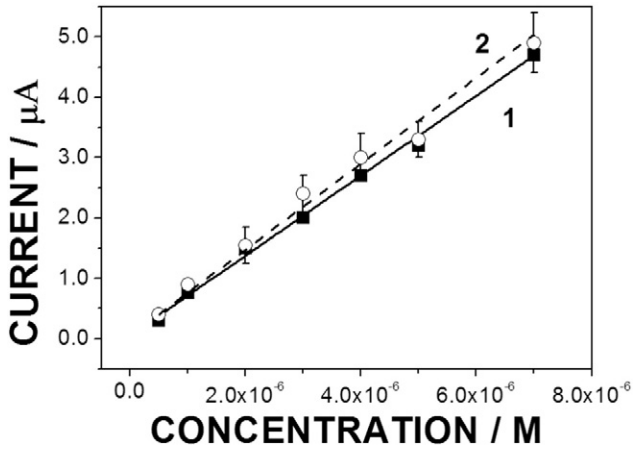


Fig. 3. Current versus Do concentration plots for Do in the absence (curve 1) and presence (curve 2) of 1.0×10^{-5} M dopac. Other conditions as in Fig. 2.

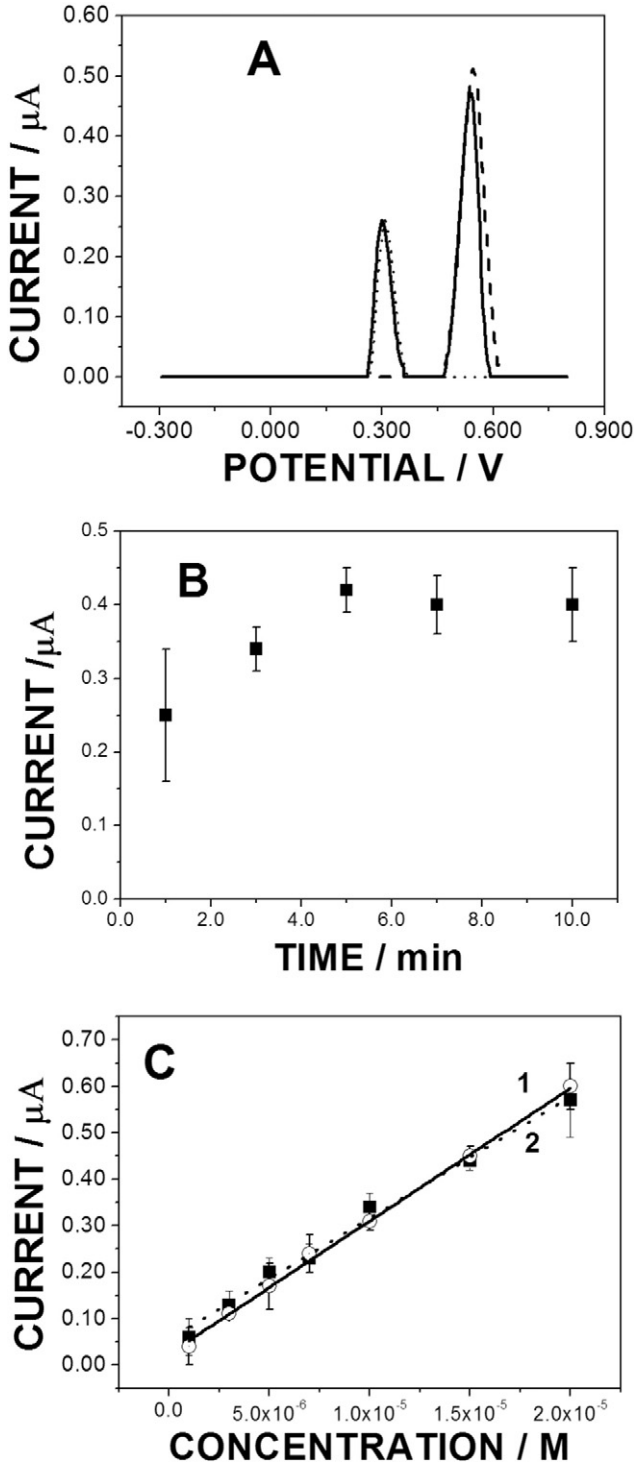


Fig. 4. (A) Differential pulse voltammograms obtained for 2.0×10^{-5} M NM (dotted line), 5.0×10^{-6} M NE (dashed line) and 2.0×10^{-5} M NM in the presence of 1.0×10^{-5} M NE (solid line) at GCE/bCNT-dsDNA. (B). Effect of the accumulation time at open circuit potential of 1.0×10^{-5} M NM on the oxidation peak current.(C) Current versus NM concentration plots for NM in the presence (curve 1) and absence (curve 2) of 5.0×10^{-6} M NE. All of them obtained at GCE/bCNT-dsDNA, 3.0 min. accumulation. Other conditions as Fig. 1.

an excellent correlation between the sensitivities of both calibration plots. Each experimental point represents the average of three determinations performed with three different electrodes. The R.S.D. for the determination of 1.0×10^{-5} M NM using six different electrodes modified with the same dispersion was 2.0%. The R.S.D. for the determination of 1.0×10^{-5} M NM using ten different dispersions was 3.1%.

3.3. Determination of Do and NM in urine samples

We evaluated the usefulness of the proposed sensors for the quantification of Do and NM in diluted human urine samples. Fig. 5 displays differential pulse voltammograms obtained in a 0.200 M acetate buffer solution after the adsorption for 1.0 min at open circuit potential in a urine sample of a human volunteer enriched with 2.0×10^{-6} M Do (dotted line). The differential pulse voltamogram obtained in the acetate buffer solution after adsorption of 2.0×10^{-6} M Do (solid line) at GCE/bCNT-dsDNA under identical experimental conditions was also included for comparison. The enriched urine sample shows two peaks, one at 0.284 V due to the oxidation of Do and the other one due to the oxidation of the uric acid present in the urine sample [12]. The analysis of the peak potentials and the oxidation peak currents (2.0 μA vs 1.9 μA for urine + Do and Do alone, respectively) indicate that it is possible to determine Do in urine without appreciable matrix effects. The recovery percentages obtained adding different concentrations of Do to the urine sample gave recoveries between 99 and 101%. Similar experiments were performed to evaluate the detection of NM in diluted urine samples of another human volunteer enriched with 1.0×10^{-5} M NM with a recovery of 95% (not shown).

In general, the quantification of Do or NM in plasma and urine samples was performed by HPLC associated with different schemes of transduction [29–33,36,37,42,47–52,59,60], GC–MS [45,46], liquid chromatography electrospray ionization in tandem with mass spectroscopy [28,53–56]. Even when they offer better detection limits than our sensor, the alternative proposed here made possible the sensitive detection of Do and NM using a simple, fast, low-cost and friendly strategy.

4. Conclusions

In summary, the combination of the electrocatalytic activity of bCNTs, the efficiency of dsDNA as dispersing agent, and the negative charge of the dsDNA made possible the highly sensitive and selective quantification of Do in the presence of its most important metabolite, dopac; and NM in the presence of it precursor, NE, in a very fast, simple and low-cost way. The electrode was successfully used for the determination of Do and NM in urine samples without appreciable matrix effects. These characteristics make GCE/bCNT-dsDNA an interesting analytical tool for the quantification of neurotransmitters and related compounds and open the doors to new challenges in the electroanalytical determination of other bioanalytes.

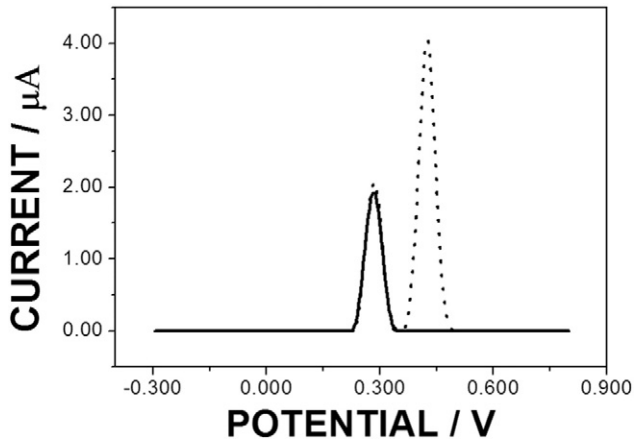


Fig. 5. Differential pulse voltammograms for: human urine sample enriched with 2.0×10^{-6} M Do (dotted line) and Do 2.0×10^{-6} M (solid line). Other conditions as Fig. 2.

Acknowledgements

The authors thank CONICET (PIP2012, PIP2015), SECyT-UNC (2014-2015,2016-2017), ANPCyT (PICT 2013 and PICT MICINN 2011-2748), MINCyT-Córdoba (PID 2013) for the financial support. AG, EP and ME thanks CONICET for the fellowships.

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