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ORIGINAL ARTICLE

Analysis of L-tyrosine based on electrocatalytic oxidative reactions via screen-printed electrodes modified with multi-walled carbon nanotubes and nanosized titanium oxide (TiO_2)

Victoria Shumyantseva[1,2] · Tatiana Bulko[1] · Alexey Kuzikov[1,2] · Rami Masamrekh[1,2] · Alexander Archakov[1,2]

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Abstract
Method for electrochemical determination of L-tyrosine with screen-printed electrodes (SPE) modified with multi-walled CNT or CNT/TiO_2 as sensing elements was used for the electroanalysis of L-tyrosine (Tyr). It was demonstrated that SPE/CNT and SPE/CNT/TiO_2 exhibited high electrocatalytic activity and good analytical performance towards oxidation of L-tyrosine. The linear range of Tyr in human serum was 0.025 ÷ 1 mM with the correlation coefficient $R^2 = 0.97$. Direct electrochemistry (without any mediator) of co-factor-free bovine serum albumin (BSA) and human serum albumin (HSA) was investigated by use of modified electrodes. Protein–ligand interactions based on the electrocatalytic oxidation of L-tyrosine during HSA interaction with hemin were analyzed by the change of peak height and oxidation peak area, corresponding to tyrosine oxidation accessibility.

Keywords L-Tyrosine · Electrocatalytic oxidation · TiO_2 · Protein electrochemistry · Multi-walled carbon nanotubes · Modified electrodes

Introduction

It was shown that the increasing content of aromatic amino acids such as tyrosine, phenylalanine and tryptophan in urine or plasma might be dealing with the growth of cancer cells, caused by rearrangement of protein metabolism in cancer patients (An et al. 2010; Moein et al. 2014). Tyrosine is well known as essential amino acid in human. Tyrosine is the precursor of DOPA (dihydroxyphenylalanine), dopamine, thyroxin and neurotransmitters (Huang et al. 2008). Tyrosine was found to be a lung cancer biomarker (An et al. 2010; Moein et al. 2014), the absence of tyrosine could cause albinism and alkaptonuria (Huang et al. 2008); the control of tyrosine level in plasma is important for the study of the mechanism of Parkinson's disease (Xie et al. 2015). Thus, effective and robust methods for Tyr determination are of great importance.

Electrochemical methods are very promising for biotechnological and bioanalytical application and for the fabrication of biosensor devices in the field of applied and analytical biochemistry. Electrochemical activity of proteins depends on two main structural characteristics: (1) availability of redox-active co-factors (cytochrome *c*, cytochrome b_5, cytochrome P450 family, blue-copper proteins, iron–sulfur proteins and flavodoxins) (Shumyantseva et al. 2011, 2012, 2014a; Suprun et al. 2013) and (2) presence of electrochemically active amino acid residues on the surface (Swetha and Kumar 2013; Brabec and Mornstein 1980a; Malfoy and Reynaud 1980; Reynaud et al. 1980a). In 1980 Brabec's and Reynaud's groups discovered that tyrosine, tryptophan, histidine, cysteine, cystine and methionine yielded oxidation peaks at solid electrodes (Brabec and Mornstein 1980b; Malfoy and Reynaud 1980; Reynaud et al. 1980b). Electroactivity of amino acids is a valuable tool for analysis and effective detection of protein post-translational modifications

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✉ Victoria Shumyantseva
v_shumyantseva@mail.ru

[1] Institute of Biomedical Chemistry, Pogodinskaya Street, 10, Moscow 119121, Russia

[2] Pirogov Russian National Research Medical University, Ostrovityanova Street, 1, Moscow 117997, Russia

or "modificomics" (Reinders and Sickmann 2007), protein-function analysis, and detection of conformational changes (Wei et al. 2012).

Amino acid oxidation is an irreversible electrochemical process. From electrochemical viewpoint, L-tyrosine (Tyr) has received the most attention. Scheme of electrochemical oxidation reaction for tyrosine is presented in Fig. 1 (Wei et al. 2012).

Oxidation of proteins (due to electroactivity of amino acid residues) upon applied potential was shown on the surface of carbon paste electrodes (Reynaud et al. 1980a), paraffin-wax impregnated spectroscopic graphite electrodes (Brabec and Mornstein 1980a), conductive diamond electrodes (Chiku et al. 2008), boron-doped diamond (BDD) electrodes (Wei et al. 2012).

Chemically modified electrodes are extensively studied in recent years for electrocatalytic oxidation of amino acids or proteins (Huang et al. 2008; Swetha and Kumar 2013; Yu et al. 2008; Sharifi et al. 2012; Hasanzadeh et al. 2009; Saghatforoush et al. 2011; Hosseini et al. 2014; Sandoval et al. 2013; Beitollahi et al. 2013). Nanomaterial-based electrodes have great application in amino acid label-free electrochemical analysis. Such types of electrodes have demonstrated excellent electron transfer properties, large electroactive surface area and stability. Among the great variety of nanomaterials, multi-walled carbon nanotubes and nanosized titanium oxide (TiO_2) have found the most widespread application in electrode modification approaches (Li et al. 2001).

Electrocatalytic oxidation of tyrosine is the basis of label-free protein biosensors for the monitoring and the detection of protein-conformational change, studying of ligand/protein binding, protein oxidative damage and protein phosphorylation as an example of post-translational modification (Wei et al. 2012). The process of β-amyloid peptides' aggregation was found to be accompanied by conformational changes affecting the degree of exposure of tyrosine to the surface of the peptides (Suprun et al. 2015, 2016a, b).

The present study was undertaken to investigate the electrochemical oxidation of L-tyrosine (Tyr), bovine serum albumin (BSA) and human serum albumin (HSA) using screen-printed graphite electrodes modified with nanosized TiO_2 film and multi-walled carbon nanotubes.

Materials and methods

Apparatus and electrochemical measurements

Electrochemical studies (cyclic voltammetry (CV) and differential pulse voltammetry (DPV)) were performed using an AUTOLAB 12 potentiostat/galvanostat (Metrohm Autolab, the Netherlands) with GPES software (version 4.9.7). Electrochemical studies were conducted in 0.1 M potassium-phosphate buffer, containing 0.05 M NaCl, pH 7.4 (PBS). In this work, three-pronged screen-printed electrodes (SPE) were used (ColorElectronics, Russia; http://www.colorel.ru) with working and auxiliary graphite electrodes (graphite paste was from Acheson) and Ag/AgCl reference electrode. The working electrode diameter was 2 mm. All potentials are referred to the Ag/AgCl reference electrode.

All electrochemical experiments were carried out at room temperature (23 ± 3 °C) in a 60-µl drop put onto the SPE to cover the surface of all three electrodes. The DPV method was used with the following parameters: the pulse amplitude 25 mV, potential step 1 mV, the pulse duration 50 ms.

Chemicals and proteins

All reagents were of analytical grade. For all solutions, distilled water was used. The following reagents were used in the study: titanium oxide(IV) < 100 nm, multi-walled carbon nanotube [Carbon nanotube, multi-walled OD 10–15 nm, ID 2–6 nm, length 0.1–10 µm > 90% as MWCNT, Arkema Inc. Sigma-Aldrich (USA)], human serum myoglobin free (US Biological). The human serum samples were diluted 100 times in PBS for electrochemical experiments. L-Tyrosine and hemin chloride were from Sigma-Aldrich. The proteins used: bovine serum albumin (BSA, Merck); human serum albumin (HSA, Sigma-Aldrich).

Electrode preparation

Electrodes modified with carbon nanotubes (SPE/CNT) were prepared using the CNT suspension in chloroform (1 mg/ml), which was sonicated for 5 min and applied onto the surface of a working graphite electrode (2 µl). After the evaporation of chloroform (10 min), 60 µl of the investigated amino acid or protein solution was applied. For electrode

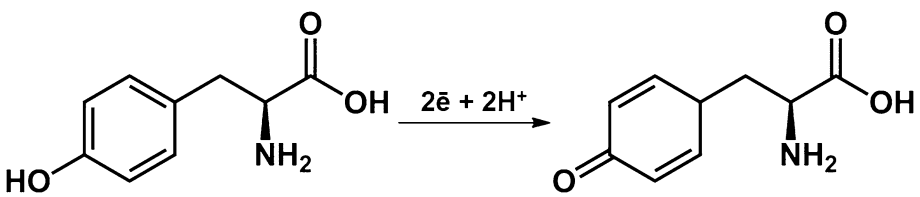

Fig. 1 Scheme of the electrochemical oxidation reaction for L-tyrosine

surface modification with titanium oxide the TiO_2 suspension (1 mg in 0.5 ml of H_2O:C_2H_5OH, 1:1 mixture) was sonicated for 1 h and a 2 µl aliquot of the suspension was sequentially applied onto the electrode surface (SPE/TiO_2). SPE/CNT/TiO_2 was prepared by drop casting of 2 µl CNT and then 2 µl TiO_2 suspensions (Shumyantseva et al. 2014b). 1 mM stock Tyr solution prepared in PBS was used for the modification of SPE/CNT or SPE/CNT/TiO_2 electrode. SPE/CNT or SPE/CNT/TiO_2 modified by Tyr or proteins were prepared by drop casting of 60 µl of sample of appropriate concentration onto the surface of screen-printed electrode. The sensitivity was calculated as the slope of the calibration curve (Carrara et al. 2014). Stock 50 mM hemin solution in DMSO was used. The HSA/hemin complexes were prepared via mixing 1 mM HSA and hemin at the ratio of 1:2, 1:2.5.

Results

We have shown that modification of screen-printed electrodes (SPE) with carbon nanotubes (SPE/CNT) or carbon nanotubes and nanosized TiO_2 suspensions (SPE/CNT/TiO_2) permits to detect L-tyrosine electrochemically. The morphology of SPE—modified electrodes was studied by means of scanning electron microscopy. SEM images confirmed the modification of electrodes with TiO_2 nanoparticles and with CNT/TiO_2 nanocomposite (Supplement Data). The electrooxidation of L-tyrosine was registered as one oxidation peak at three types of electrodes: bare SPE, SPE/CNT and SPE/CNT/TiO_2 with oxidation peak potential at + 0.74, + 0.53 and + 0.62 V, respectively (Fig. 2a). Both modifications lead to negative shift of the oxidation peak potential in comparison with bare SPE. Calibration curve for SPE/CNT was generated by plotting the Faradaic current for DPV vs. log [Tyr] concentration (Fig. 2b). A wide linear Tyr range from 1 nM to 100 µM was obtained. The detection limit corresponded to 1 nM (S/N = 3). The sensitivity was calculated as the slope of the calibration curve and corresponded to 2.7 nA/µM. SPE/CNT/TiO_2 demonstrated approximately the same linear Tyr range. Multi-walled CNT possess the unique properties to stack with aromatic ring by means of π–π interactions (Carrara et al. 2014). This phenomenon can dominate upon Tyr binding on the surface of modified electrode in comparison with Ti ions' interaction with carboxylic groups. Earlier we have shown that with CV at low scan rates (5–100 mV/s) Tyr peak currents increased linearly with the $\nu^{1/2}$, indicating diffusion controlled mechanisms of electrochemical reactions (Suprun et al. 2013).

To demonstrate the applicability of the proposed method in biological samples, the direct determination of Tyr was performed in human serum. As SPE/CNT demonstrated easier electrooxidation of Tyr in comparison with SPE/CNT/TiO_2, for the determination of tyrosine in human serum, SPE

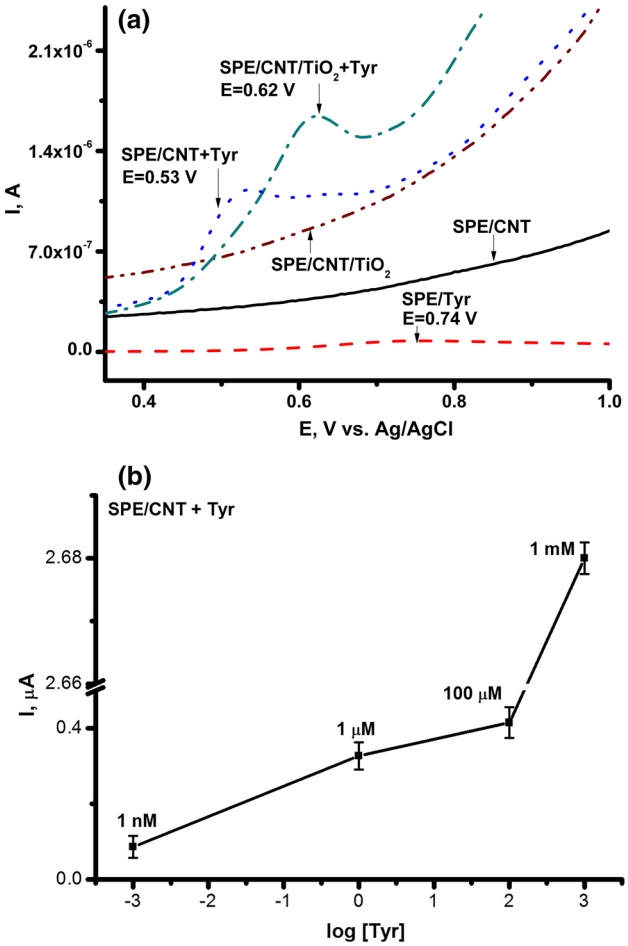

Fig. 2 **a** DPVs (the oxidation curve) of SPE + Tyr (red dashed line), SPE/CNT (straight line), SPE/CNT + Tyr (blue dots), SPE/CNT/TiO_2 (brown dot dashed lines), SPE/CNT/TiO_2 + Tyr (green dot dashed lines) in 0.1 M potassium-phosphate buffer, containing 0.05 M NaCl, pH 7.4 (PBS). **b** The plot of oxidation peak current vs. log [Tyr] concentration on SPE/CNT (color figure online)

modified with CNT as the most effective nanomodifier was used. Standard addition method was used to determine Tyr with DPV technique. Recovery results are shown in Fig. 3a. These results were obtained by three repeatable determinations on each sample and were acceptable, demonstrating the applicability of this method for the Tyr determination in human serum samples using disposable screen-printed electrodes (SPE/CNT). The actual concentration of Tyr in human plasma was identified as 8.80 ± 0.54 µg/ml (0.06 mM) (Xie et al. 2015), so the calibration curve obtained with DPV technique and SPE/CNT is sensitive enough for serum sample manipulation (Fig. 3b). The results showed that the dynamic linear range of the experimentally useful working concentrations for Tyr in human serum was 0.025–1 mM, with the correlation coefficient $R^2 = 0.97$ and the sensitivity of 0.9 ± 0.1 nA/µM. The detection limit of Tyr in the human serum was 0.025 mM (S/N = 3), which is within the

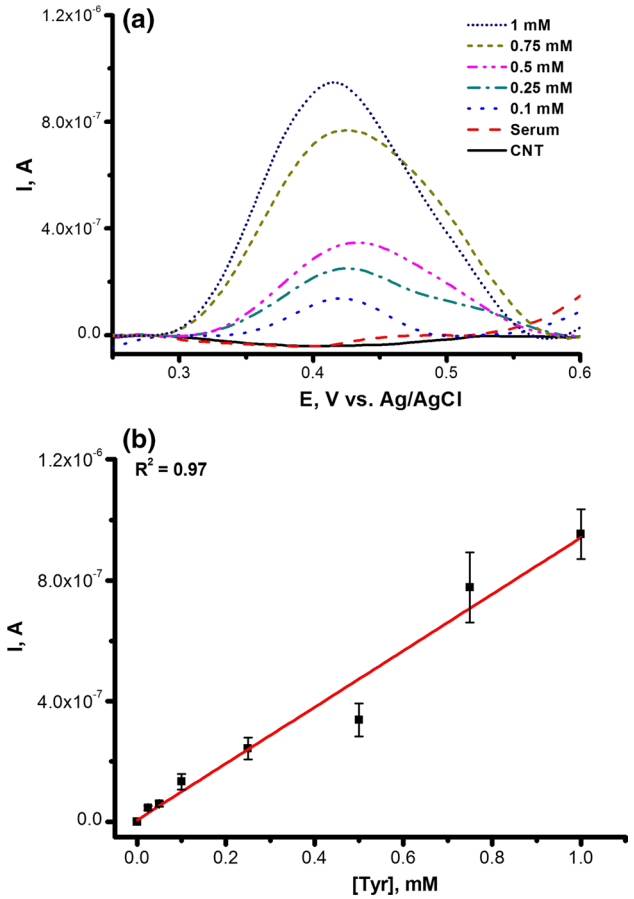

Fig. 3 **a** DPV voltammograms (the oxidation curve) of SPE/CNT with varied L-tyrosine concentration (0.1 mM ÷ 1 mM) in human serum. The voltammograms were corrected for the baseline. **b** The dependence of DPV oxidation current intensity of SPE/CNT on the L-tyrosine concentration in human serum

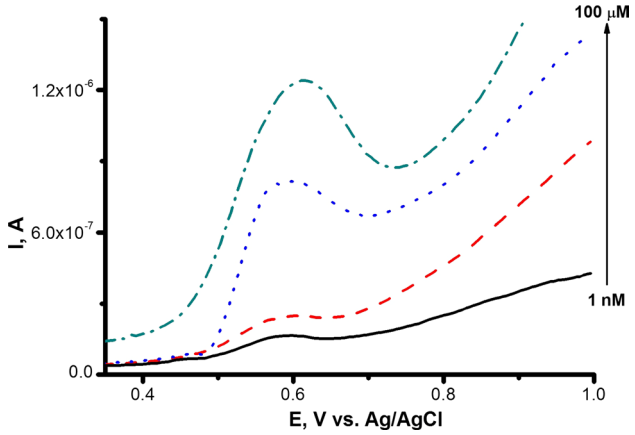

Fig. 4 DPV voltammograms (the oxidation curve) of varied BSA concentration (1 nM straight line; 1 μM red dashed line; 10 μM blue dots; 100 μM green dot dashed line) on screen-printed graphite electrode modified with CNT (SPE/CNT) (color figure online)

concentration range determined in plasma and urine (Xie et al. 2015).

The SPE/CNT/TiO_2 and SPE/CNT modified electrodes possessed good stability and reproducibility, which would provide a potential biosensing platform in the electroanalysis of proteins via registration of amino acid electrooxidation. The proposed approach was used for the detection of bovine serum albumin (BSA) in the concentration range 1 nM–100 μM (Fig. 4). Oxidative peaks of BSA represent the electrochemical signature of this protein reflecting oxidation of Tyr, Cys, and Trp amino acids as we have shown earlier (Suprun et al. 2013).

Human serum albumin (HSA), the most abundant protein in plasma, is a monomeric multidomain macromolecule. HSA is known as a protein carrier for many endogenous and exogenous compounds (Elsadek and Kratz 2012). HSA displays an extraordinary ligand binding capacity and can target the drug to the pathogenic site. The fraction of peptides and proteins bound to HSA is defined as ''albuminome'' (Gundry et al. 2007). HSA is a valuable biomarker of many diseases, including cancer, rheumatoid arthritis, ischemia, post-menopausal obesity, severe acute graft-versus-host disease, and diseases that need monitoring of the glycemic control (Fanali et al. 2012). HSA effectively binds fatty acids, and this type of interaction was studied by electrochemical technique, utilizing electrocatalytic oxidation of Tyr (Wei et al. 2012). Electrochemical detection of HSA and BSA may proceed not only through Tyr electrocatalytic oxidation, but also with participation of Cys and Trp amino acids (Suprun et al. 2013).

Earlier we have investigated the binding of hemin to HSA by registering of complex formation with spectrophotometry. Such artificial hemoalbumin possessed the cytochrome P450-like activity and catalyzed aniline hydroxylation, dimethylaniline and aminopyrine *N*-demethylation (Shumyantseva et al. 1996). Our experiments demonstrate that artificial hemoprotein (with hemin/HSA 1:2 ratio) and HSA possessed very close electrochemical parameters. In the case of enhanced hemin ratio (hemin/HSA ratio 2.5:1 in the complex), electrochemical parameters such as the current intensity and the anodic peak area demonstrated more pronounced changes. Upon HSA interaction with hemin at the hemin/HSA ratio 2.5:1 the tendency to the positive shift of HSA electrocatalytic oxidation, as well as the decrease of peak height and oxidation peak area, was observed (Table 1). Electrochemical oxidation of amino acids can reflect the interaction of protein chain with ligands and serve as intrinsic sensor for such binding (Fig. 5).

The anodic oxidation of drugs, such as *R*,*S*-warfarin, sulfaphenazole, acetaminophen, ibuprofen, diclofenac usually occurs at the positive potential window (Gupta et al. 2011; Carrara et al. 2011). This phenomenon shields and complicates the monitoring of protein-conformation change based

Table 1 Electrochemical parameters of HSA and HSA/hemin complex

SPE/CNT	Oxidation potential (E_{ox}), V	Peak height, A	Oxidation peak area
HSA[a]	0.591 ± 0.012	$(3.71 \pm 1.16) \times 10^{-6}$	$(6.08 \pm 2.10) \times 10^{-7}$
HSA + hemin (1:2.5)	0.598 ± 0.005	$(3.10 \pm 0.87) \times 10^{-6}$	$(4.70 \pm 1.61) \times 10^{-7}$

[a]In 0.1 M KH_2PO_4 + 50 mM NaCl, pH 7.4 with 5% DMSO

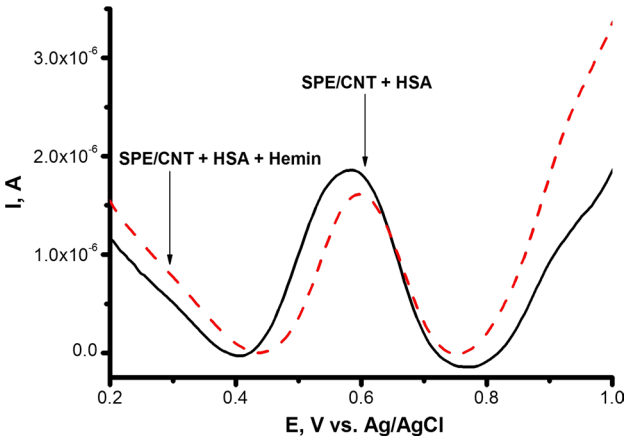

Fig. 5 DPV voltammograms (the oxidation curve) of HSA (60 µl of 1 mM HSA + 5% DMSO straight line) and complex of HSA + hemin (60 µl of 1 mM HSA + 2.5 mM hemin in 5% DMSO red dashed line) on screen-printed graphite electrode modified with CNT (SPE/CNT) (color figure online)

on tyrosine, tryptophan and cysteine oxidation upon pharmaceuticals binding registered by means of electrochemical technique.

Discussion

The main purpose of a modern analytical method and/or the diagnostic device is the increase in sensitivity. In electrochemistry the "dimensional" effects using physical and chemical properties of nanodimensional particles of metals, oxides of metals and nonmetals, conducting polymers are applied for this purpose. Modification of the surface of an electrochemical sensor with nanocomposite material increases an active surface area and leads to the transition of sensor mode to the nanosensor mode that enhances and improves analytical characteristics. Nanostructured materials and nanocomposites based on nanoparticles, nanowires, nanobands and carbon nanotubes (CNT) have been intensively investigated especially in electroanalysis due to their fantastic 'size effect' and superior chemical and physical properties and functions (Xiao and Li 2008).

The role of L-tyrosine as a biomarker was discussed from different viewpoints. Tyrosine is one of the essential amino acids in human, it is added to dietary and pharmaceutical formulations. Tyrosine was found to be the lung cancer biomarker (An et al. 2010; Moein et al. 2014). Thus, effective, sensitive and robust methods for Tyr determination in biological fluids and clinical preparations are of great importance.

Earlier, we have reported direct unmediated electron transfer between the hemoprotein myoglobin and screen-printed electrodes (SPE) modified with hybrid nanocomposites based on nanosized titanium oxide(IV) (TiO_2, particle size < 100 nm) and multi-walled carbon nanotubes (CNT, outer diameter of 10–15 nm, inner diameter of 2–6 nm and length of 0.1–10 µm). The midpoint potential of the Fe^{3+}/Fe^{2+} pair of myoglobin corresponded to $E_{1/2} = -0.263 \pm 0.08$ V for CNT film, and $E_{1/2} = -0.468 \pm 0.09$ V for TiO_2 nanocomposite (vs. Ag/AgCl reference electrode) (Shumyantseva et al. 2014b). Screen-printed electrodes are cheap and effective basic elements for electrochemical analysis of biomolecules in biological liquids, such as blood, serum, plasma, urine. They are suitable for modification with a variety of nanomaterials and are perspective as personalized health care sensors and as the main sensor element in clinical analysis (Carrara et al. 2014).

TiO_2 nanoparticles possess such properties as large surface area, optical transparency and good biocompatibility, so TiO_2 nanoparticles are applied to immobilize proteins on electrode surface for the fabrication of electrochemical biosensors (Shumyantseva et al. 2014b). Besides, Ti ions on the TiO_2 particles' surface were reported to interact with carboxylic groups (Li et al. 2001). Based on this feature of TiO_2 films, good interaction of amino acids or proteins with the surface of TiO_2/electrode could be predicted.

From a variety of several different approaches for depositing carbon nanotubes, such as microspotting, electrodeposition, the direct growth and others (Carrara et al. 2014), we have chosen drop casting (Shumyantseva et al. 2014b) for SPE/TiO_2, SPE/CNT and SPE/CNT/TiO_2 as the most simple and robust technique.

In our earlier paper, the direct redox activity of proteins and amino acids on the surface of unmodified carbon screen-printed electrodes was reported (Suprun et al. 2013). The signal attributed to electrochemical oxidation of three amino acid residues (cysteine, tryptophan and tyrosine) was observed at E_{max} of 0.6 ÷ 0.7 V (vs. Ag/AgCl). Based on the difference in redox behavior of L-tyrosine and

3-nitro-L-tyrosine, the selective electrochemical detection of normal and nitrated albumins was demonstrated. For signal enhancement in label free electroanalysis of amino acids, the modification of screen-printed graphite electrode with promoters—such as a solid matrix of nanosized titanium oxide(IV) (TiO_2)—was performed. However, the electrocatalytic oxidation of tyrosine using SPE/TiO_2 was not effective. The reason for this may be the insufficient electroactive surface area of TiO_2 coverage (Shumyantseva et al. 2014b) and low conductivity of such nanosized coverage.

In conclusion, we have demonstrated that screen-printed electrodes modified with CNT or CNT/TiO_2 exhibited good promotion for electrocatalytic oxidation of Tyr in buffer solutions, Tyr in human serum, and proteins such as BSA and HSA. The peak current of Tyr is linear to its concentration in the range of 1 nM ÷ 100 μM in PBS, and 0.025 ÷ 1 mM range in human serum. The ability of HSA to bind biologically active compounds can be detected by means of electrochemical technique based on electrocatalytic oxidation of its tyrosines. Therefore, label-free electroanalysis of proteins has a great application potential in the investigation of ''albuminome'', protein–ligand interactions (registered through Tyr oxidation), and Tyr determination in human serum with the help of modified with carbon nanotubes SPE.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest in this work.

Research involving human participants and/or animals No human participants and/or animals were involved in this research.

Informed consent No informed consent is required for this research.

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