



A Sensitive Quantification of Agmatine Using a Hybrid Electrode Based on Zinc Oxide Nanoparticles

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Abstract: An electrochemical sensor was prepared by modifying a hybrid of multi-walled carbon nanotubes (MWCNTs) and zinc oxide nanoparticles (ZnONPs) to a glassy carbon (GC) electrode surface to accurately determine agmatine. The ZnONPs+MWCNTs/GC electrode surface was characterized using scanning electron microscopy (SEM) and energy dispersive X-ray (XRD). Agmatine did not exhibit any peak on the GC electrode surface, but exhibited a large oxidation peak at 637.9 mV on the MWCNTs/GC electrode surface. Furthermore, it was observed that the electrochemical behavior of agmatine was greatly improved on the MWCNT+ZnONPs/GC electrode surface and that this surface exhibited a well-defined higher current peak at 581.9 mV. The electrochemical responses of agmatine on the MWCNT+ZnONPs/GC electrode surface were performed using square-wave voltammetry (SWV). A linear plot was obtained for the current responses of agmatine against concentrations in the range of 0.1 μ M–5.2 μ M yielding a detection limit of 4.13×10^{-8} M (based on $3S_b/m$). The accurate quantification of agmatine makes the ZnONPs+MWCNTs/GC electrode system of great interest for the treatment of schizophrenia.

Keywords: Agmatine, zinc oxide nanoparticles, hybrid, sensor.

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INTRODUCTION

Agmatine is a cationic polyamine produced naturally by the decarboxylation of L-arginine by arginine decarboxylase enzyme. It is produced in the mammalian brain and is also preserved in nature (1, 2). Agmatine has the properties of a neurotransmitter synthesized in the brain, stored in the vesicles and released from the brain (3-5). Current studies demonstrate that agmatine meets all the necessary criteria for the definition of a neurotransmitter and has been accepted as a new neurotransmitter (6-8). In addition, many studies have shown that agmatine degradation products such as spermidine and spermine are found at high rates in the brains, cerebrospinal fluid, and blood of patients with schizophrenia. The high levels of these metabolites in patients

with schizophrenia have led to the idea that agmatine may be present at high concentrations (9). As a matter of fact, a study published by Uzbay *et al.* found that the levels of agmatine in patients with schizophrenia who did not take any medication for at least 6 months were significantly higher than those of healthy controls (10). There are studies that suggest that there may be a relationship between schizophrenia and increased agmatine concentrations due to excessive release of agmatine and agmatine derivatives in the brain and cerebrospinal fluid (2, 11, 12). For this reason, it is important to determine agmatine levels correctly and quickly. High-performance liquid chromatography methods are generally used for agmatine measurements. However, due to problems such as selectivity and time-consuming steps

for derivatization, these techniques can create problems in conducting correctly analysis of samples. Nevertheless, voltammetric techniques with modified electrodes provide advantages such as high selectivity, speed, and simplicity. Furthermore, voltammetric methods have attracted attention in the analysis of many samples since they have the properties of speed, selectivity, and reproducibility (13, 14). The preparation of electrode surfaces in the nanostructure has also attracted focus, particularly regarding the

design of electrochemical sensing electrodes (15-17). Of these nanostructures, carbon nanotubes (CNTs), which have excellent electrocatalytic activity and sensitivity, are applied to obtain electrochemical sensors and biosensors. In addition, electrodes modified with hybrids of nanoparticles of CNTs and metal oxides offer good performance benefits, such as increased sensitivity, reduced overvoltage, mass transport, catalysis, and a high effective surface area and detection limit (18-19).

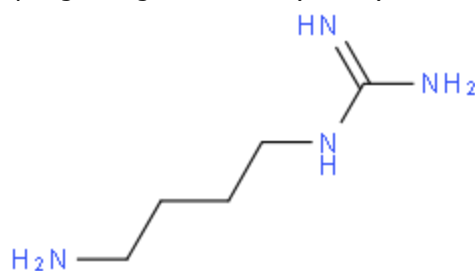


Figure 1. Chemical structure of agmatine.

In this study, a GC electrode surface was modified with a hybrid of MWCNTs and ZnO nanoparticles for agmatine quantification. The modification of the GC electrode surface with this hybrid provided excellent electrocatalytic efficiency, good selectivity and high sensitivity.

EXPERIMENTAL

Chemical reagents

Agmatine, multi-walled carbon nanotubes (MWCNTs), zinc oxide nanoparticles (ZnONPs), sodium hydroxide (NaOH) and disodium phosphate dibasic (Na_2HPO_4) were purchased from Sigma (Missouri, USA). Acetonitrile and chloroform were obtained from VWR International (Radnor, USA). Potassium dihydrogen phosphate (KH_2PO_4) was purchased from Merck (Darmstadt, Germany). The solutions were prepared with ultrapure water.

Instrumentation

A Gamry Interface 1000B Potentiostat/Galvanostat/ZRA was used to apply electrochemical measurements with cyclic voltammetry (CV) and square-wave voltammetry (SWV) techniques. Electrochemical measurements were performed in a three-electrode cell. A glassy carbon (GC) electrode was used as working electrode (MF-2012 BASi, USA), Ag/AgCl/(KCl_{sat.}) was used as the reference electrode (MF-2052 BASi, USA), and Pt wire was used as the counter electrode. All experimental data was plotted with the Origin

8.0 program so that a comparison between the data was made.

Preparation of modified electrodes

GC electrodes were first polished with 0.05 μm and 0.30 μm alumina slurry on a velvet cleaning pad and then the electrodes were sonicated for 5 minutes in pure water and acetonitrile. Then commercial MWCNTs were sonicated in concentrated $\text{HClO}_4 + \text{HNO}_3$ (3:7, v:v) for 5 hours to functionalize the MWCNTs surfaces (20). The functionalized MWCNTs were washed with ultrapure water and dried. MWCNTs, ZnONPs, and ZnONPs+MWCNTs suspensions were then prepared by sonicating 1.0 mg of functionalized MWCNTs, 0.1 mg of ZnONPs and 0.1 mg of ZnONPs plus 1.0 mg of functionalized MWCNTs in 5 mL of chloroform for 50 min. MWCNTs/GC, ZnONPs/GC and ZnONPs+MWCNTs/GC electrode surfaces were prepared by dropping 5 μL of each of the prepared suspensions onto cleaned GC electrode surfaces. Afterward, the surfaces of these electrodes were extensively washed with ultra-pure water.

Optimization of Modified Electrode

The experimental results showed that the best results were obtained by sonicating MWCNTs and ZnONPs mixture in 5 mL chloroform at a 10:1 ratio for 50 minutes. On the other hand, the composite layer on GC electrode surface showed a clear peak formation for agmatine when the amount of ZnONPs/MWCNTs suspension was 5 μL . Besides, a considerable decrease in sensitivity and reproducibility was observed when higher amounts of this

suspension were added to the GC electrode surface.

Voltammetric analysis of agmatine

The prepared ZnONPs+MWCNTs/GC electrode was immersed in a cell containing agmatine with a concentration of 1.0×10^{-7} M dissolved in 50 mM phosphate buffer solution (PBS) (pH 7.0) and the voltammogram was recorded with CV. Under the same conditions, voltammograms of agmatine were taken at the bare/GC and MWCNTs/GC electrode surfaces and compared with the ZnONPs+MWCNTs/GC electrode. Then, voltammograms were taken at different scan rates for the ZnONPs+MWCNTs/GC electrode surface at the maximum voltammetric response to accurately conceptualize the electrochemical process of agmatine. Voltammograms of agmatine at the ZnONPs+MWCNTs/GC electrode surface were then taken at various pH values to determine the pH level at which the best voltammetric response was observed for agmatine

oxidation. Furthermore, square-wave voltammetry was applied to detect the sensitivity to different concentrations of agmatine at the ZnONPs+MWCNTs/GC electrode surface.

RESULTS AND DISCUSSION

Characterization of MWCNTs/GC and ZnONPs+MWCNTs/GC electrode surfaces

The modified electrode surfaces were examined using SEM. The image of the MWCNTs/GC electrode surface in Figure 2A shows that the MWCNTs are homogeneously distributed on the electrode surface and that there is no significant agglutination. In addition, Figure 2B shows the distribution of ZnONPs on the MWCNTs and Figure 2C shows the EDX data for the ZnONPs+MWCNTs/GC electrode surface. C, O, N and Zn were observed in the EDX analysis in Figure 2C.

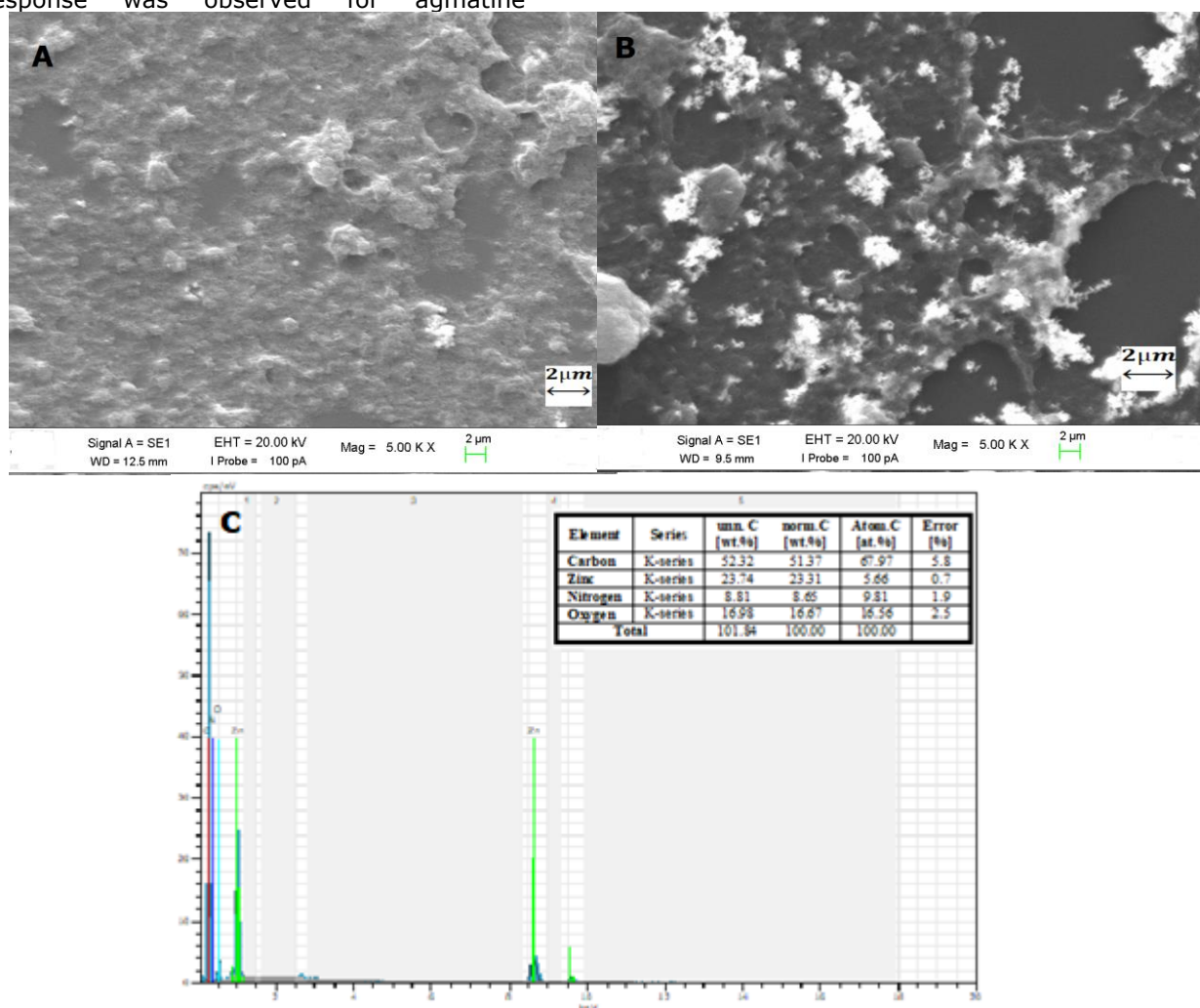


Figure 2. SEM images of **A)** MWCNTs/GC electrode surface, **B)** ZnONPs+MWCNTs/GC electrode surface, **C)** EDX analysis of ZnONPs+MWCNTs/GC electrode surface.

Electrochemical behavior of agmatine at the ZnONPs+MWCNTs/GC electrode surface

Figure 3 shows the cyclic voltammograms of the agmatine molecule on the surface of a) bare/GC, b) MWCNTs/GC, c) ZnONPs/GC and d) ZnONPs+MWCNTs/GC electrodes in PBS with 50 mM at pH 7.0. No peak was observed because no electrochemical response was detected for the agmatine molecule on the surface of the bare GC electrode (a). However, a broad and poor oxidation peak for the agmatine molecule was observed at $E_{pa}=+637.9$ mV on the surface of the GC electrode modified with MWCNTs (b), while a weak and clearly undefined oxidation peak for the agmatine molecule was observed at $E_{pa}=+668.2$ mV on the surface of the GC electrode modified with ZnONPs (c). Additionally, a well-defined peak with a higher current of the agmatine molecule was observed at $E_{pa}=+581.0$ mV on the surface of the GC electrode modified by the hybrid

formation of MWCNTs and ZnONPs (d). Compared to the bare/GC, MWCNTs/GC and ZnONPs/GC electrode surfaces, the voltammetric behavior of agmatine was found to be greatly enhanced on the ZnONPs+MWCNTs/GC electrode surface with a large enhancement in the voltammetric current response. The observation of a higher current response for the agmatine molecule at the ZnONPs+MWCNTs/GC electrode surface is mainly due to the catalytic effect of the ZnO nanoparticles and an increase in the electron transfer rate by providing an active layer on the electrode surface (21-23). There are also studies that claim that the peak potential observed for nanoparticles of metal oxides can be attributed to the oxygen vacancies on the nanoparticles (24, 25). In addition, the voltammetric data indicates that agmatine oxidation is irreversible at the MWCNTs/GC and ZnONPs+MWCNTs/GC electrode surfaces due to the absence of any peak in the cathodic region.

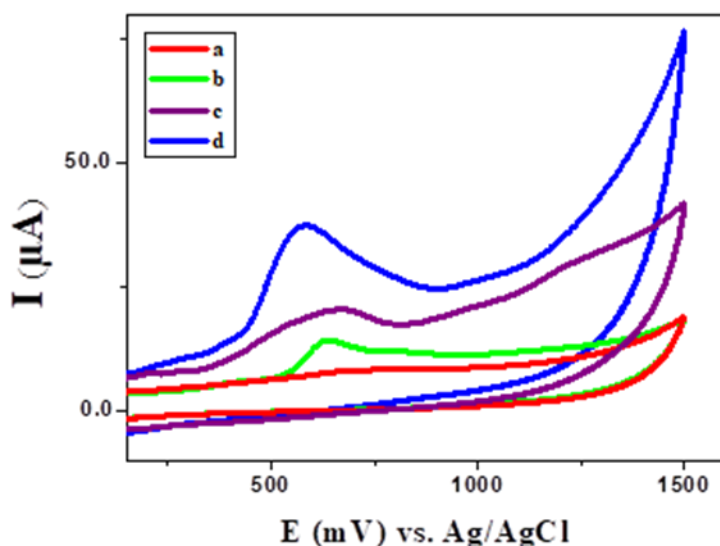


Figure 3. Cyclic voltammograms of 1.0×10^{-7} M agmatine in 50 mM PBS at pH 7.0. at a) bare/GC, b) MWCNTs/GC, c) ZnONPs/GC, d) ZnONPs+MWCNTs/GC electrode surfaces (Scan rate: 50 mV/s).

Figure 4A shows the voltammograms at different scan rates of the agmatine solution at 1.0×10^{-7} M concentration prepared in pH 7.0 PBS buffer, in order to examine the effect of the scan rate on agmatine oxidation at the ZnONPs+MWCNTs/GC electrode surface. A linear curve is obtained by plotting the peak current values against the square root of the scanning speed, indicating that the reaction is diffusion-controlled. The slope of graphic obtained by plotting the logarithm of the peak current

against the logarithm of the scanning rate is close to 0.5, suggesting that electron transfer is diffusion-controlled, while a slope closer to 1.0 indicates adsorption control (26). It was determined that the graph obtained from the plot of the peak currents against the square root of the scan rate is linear ($R^2=0.9988$) in Figure 4B, and therefore, it is thought that a diffusion-controlled reaction occurs at the electrode surface. In Figure 4C, the equation of the graph obtained from the logarithm of the

peak current versus the logarithm of the scanning rate is calculated as being $y=0.4983x-3.538$. The slope of the graph is 0.4983, indicating that the diffusion reaction is controlled. In addition, it has also been observed that agmatine peak potentials are shifted towards more anodic values (higher potentials) due to increased scanning speeds. When the agmatine peak potential shifts towards anodic values and the absence of any reduction peak are assessed together, it can be concluded that the oxidation of agmatine on the ZnONPs+MWCNTs/GC electrode surface is irreversible. Further, the behavior of the oxidation peak potential of the agmatine

molecule at various pH values is given in Figure 5. A shift in the negative direction of the peak potential of the agmatine molecule was observed due to the increase in pH of the solution. This indicates that the proton is transferred during the oxidation of the agmatine molecule. Also, the voltammetric signals at pH 6.0, 7.0 and 8.0 were observed at values close to each other, as shown in Figure 5. However, since the observed voltammetric signal at pH 7.0 has a relatively higher and smoother peak shape, this pH value was chosen for quantification of the agmatine molecule.

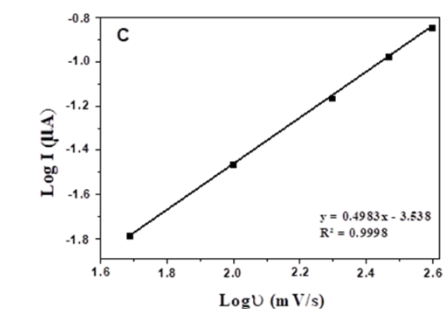
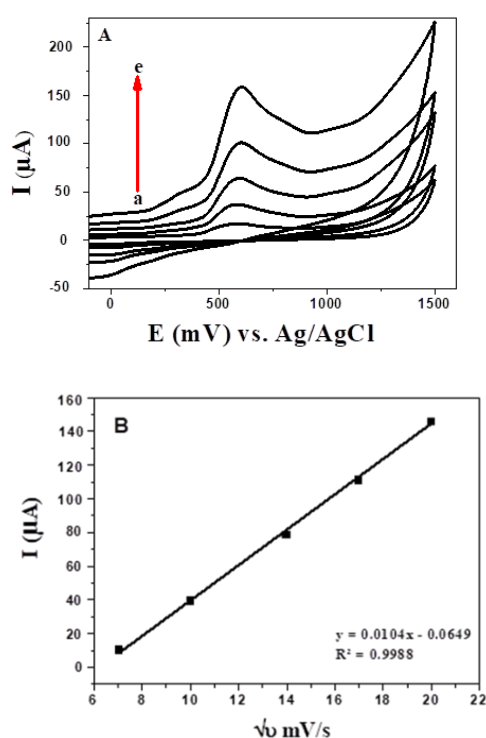


Figure 4. A) Cyclic voltammograms of 1.0×10^{-7} M agmatine at ZnONPs+MWCNTs/GC electrode in 50 mM PBS at pH 7.0. Scan rates: a) 50 mV/s; b) 100 mV/s; c) 200; d) 300 mV/s; e) 400 mV/s (Equilibrium time: 5 s); B) A plot of anodic peak current of agmatine versus the square root of scan rates at ZnONPs+MWCNTs/GC electrode surface; C) A plot of logarithm of anodic peak current of agmatine versus the logarithm of scan rates at ZnONPs+MWCNTs/GC electrode surface.

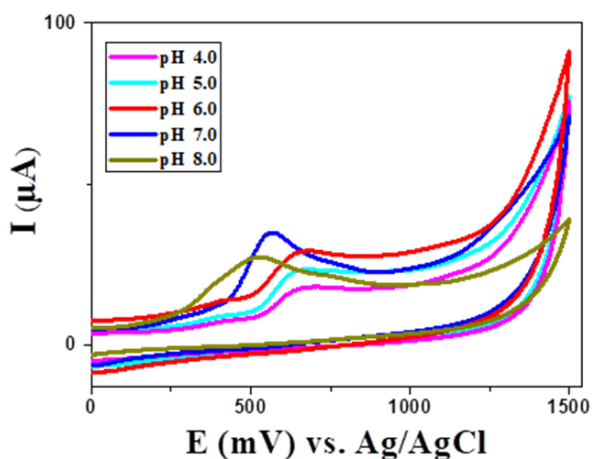


Figure 5. Cyclic voltammograms of 1.0×10^{-7} M agmatine at ZnONPs+MWCNTs/GC electrode in 50 mM PBS at pH=3.0; 4.0; 5.0; 6.0;7.0;8.0 values. (Scan rate: 50 mV/s, Equilibrium time: 5 s).

Quantification of agmatine

The quantification of agmatine was performed using the SWV technique at the ZnONPs+MWCNTs/GC electrode surface. Figure 6A exhibits square-wave voltammograms for different concentrations of agmatine at the ZnONPs+MWCNTs/GC electrode surface in 50 mM PBS at pH 7.0. A linear plot was obtained with measured peak currents versus agmatine concentrations

ranging from 0.1 μM to 5.2 μM . (Figure 6B). The regression equation was calculated as $I_{pa}(\mu\text{A})=0.002C(\mu\text{M})+0.0013$ with a correlation coefficient of 0.9990. In addition, the detection limit (LOD) of the agmatine molecule was calculated as 4.13×10^{-8} M by using $C_m=3S_b/m$ (S_b is the standard deviation of the blank signal and m is the slope of the regression equation).

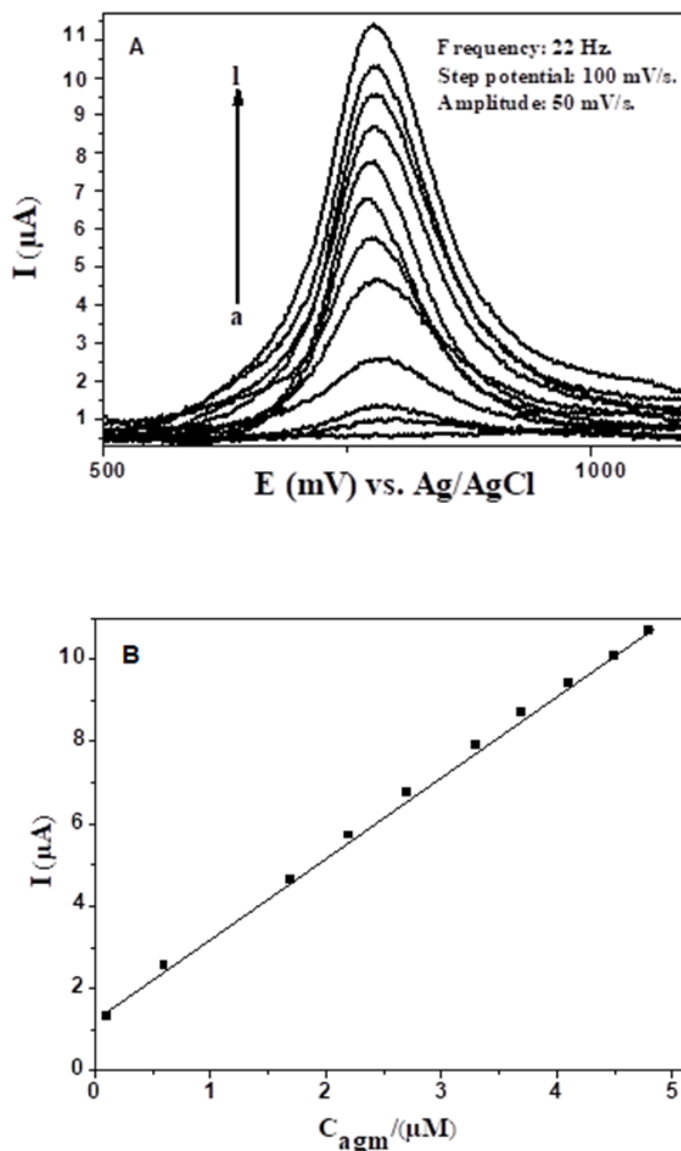


Figure 6. A) Square-wave voltammograms of various agmatine concentrations at ZnONPs+MWCNTs/GC electrode in 50 mM PBS at pH 7.0. Agmatine concentrations: a) 0.0 μM b) 0.1 μM ; c) 0.6 μM ; d) 1.7 μM ; e) 2.2 μM ; f)

2.7 μM ; g) 3.3 μM ; h) 3.7 μM ; i) 4.1 μM ; j) 4.5 μM ; k) 4.8 μM ; l) 5.2 μM . **B)** A plot of peak currents against the concentrations of agmatine.

Stability and reproducibility of the ZnONPs+MWCNTs/GC electrode

The reproducibility of the ZnONPs+MWCNTs/GC electrode was determined by calculating the relative

standard deviation of eight consecutive runs with the electrodes prepared in two different ways. In the first method, the electrode was redeveloped every time and voltammograms were recorded. In the second, eight different electrodes were prepared in the same way and voltammograms were recorded. The RDS of both reproducibilities for 0.2 μM agmatin was calculated to be 1.8% and 1.6%, respectively. This showed that the ZnONPs+MWCNTs/GC electrode had excellent reproducibility. The stability of the ZnONPs+MWCNTs/GC electrode was also examined by incubation in PBS for 40 days. Then, the voltammograms of the incubated modified electrode were recorded in 50 mM PBS at pH 7.0 by CV and compared with the voltammograms taken before incubation. Compared to those obtained before immersing the recorded voltammograms, the change in the peak current was observed to be less than 5%. This slight reduction in current indicated that the ZnONPs+MWCNTs/GC electrode system had good stability.

Interference study

In order to verify the selectivity of the proposed electrode, the effects of some molecules that could make possible interference on the agmatine were also investigated by CV. For this purpose, voltammograms of the mixture containing 30 μM ascorbic acid (AA), 45 μM serotonin

(SE) and 60 μM dopamine (DA) in the presence of 0.3 μM agmatine were taken on bare GC and ZnONPs+MWCNTs/GC electrodes. In Figure 7A, no peak currents of these molecules were observed on the bare GC electrode, whereas a broad and overlapping voltammetric peak current of DA and SE, a small and relatively distinct peak current of AA, and a clearly defined peak current of agmatine molecule were observed on the ZnONPs+MWCNTs/GC electrode. This showed that ZnO nanoparticles did not have a successful effect on the catalysis of AA, SE and DA molecules. Since AA, SE and DA have similar oxidation potentials and overlapping signals, it is already known that the detection of these species separately is a major problem on most solid electrodes (27). However, it was observed that these molecules did not have any interference effect in determining the agmatine molecule. In addition, voltammograms of increased concentrations of agmatine were also taken in the presence of AA, SE and DA. The voltammograms showed that the increased concentration of agmatine exhibited a linear increase in anodic peak currents in Figure 7B. But there was no change in AA, SE and DA peak currents. The results showed that 100-fold AA, 150-fold SE and 200-fold of DA molecules had no effect on the selective determination of the agmatine molecule in the proposed electrode.

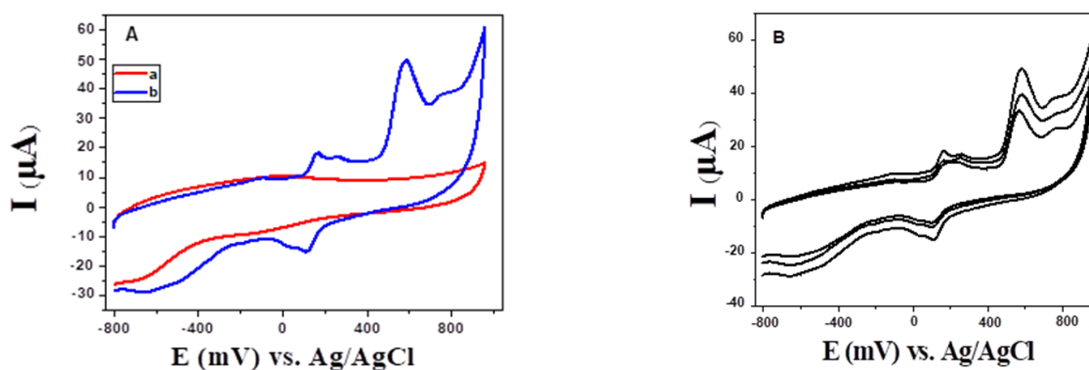


Figure 7. A) Cyclic voltammograms of 30 μM AA, 45 μM SE, 60 μM DA 0.3 μM agmatine in 50 mM PBS at pH 7.0. at a) bare/GC, b) ZnONPs+MWCNTs/GC electrode surfaces (Scan rate: 50 mV/s). **B)** Cyclic voltammograms of increasing concentrations of agmatine in the presence of 30 μM AA, 45 μM SE, 60 μM DA at ZnONPs+MWCNTs/GC in in 50 mM PBS at pH 7.0. (Agmatine concentrations: 0.1 μM , 0.2 μM , 0.3 μM)

CONCLUSIONS

An electrode surface system prepared with a multi-walled carbon nanotubes (MWCNTs) hybrid decorated with ZnOPs was designed to quantify agmatine molecules quickly, economically, and reliably. The

ZnONPs+MWCNTs/GC electrode system was performed to quantifying agmatine using SWV. A linear plot of the current-concentration calibration graph in the range of 0.1 μM to 5.2 μM was obtained with a detection limit of 4.13×10^{-8} M. In accordance with the direction of this data, the rapid and reliable determination of the agmatine molecule,

which causes schizophrenia and is secreted in the brain, makes this electrode system of great interest for drug development studies and clinical use.

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