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Conformational switch for cisplatin with hemin/G-quadruplex DNAzyme supersandwich structure

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ABSTRACT

Cisplatin is a representative of cytotoxic and antineoplastic metallodrugs used for the treatment of various malignancies. In this paper, an enzyme-free amplification platform involving an autonomous target triggered process that yields the formation of the hemin/G-quadruplex DNAzyme wires was designed for the detection of cisplatin. Given the virtue of hemin/G-quadruplex DNAzyme wires (supersandwich DNAzyme structure) containing many units of hemin/G-quadruplex DNAzyme, an amplified electrochemical signal was achieved. Based on the combination of cisplatin with the guanine of the designed hemin/G-quadruplex DNAzyme supersandwich DNA structure, changing this structure and decreasing its catalytic effect on H_2O_2, it was used for the study on the analysis of cisplatin. With the concentration of the cisplatin increasing, the conformational change of the supersandwich DNA structure changed gradually. Then a relationship between the concentration of the cisplatin and the obtained electrochemical signal can be established. The detection concentration range of cisplatin was from 0.05 to 5 μM with a low detection limit of 20 nM using a signal three-fold the background noise and the correlation coefficient is 0.9993. The proposed approach is able to provide unique opportunities as simplicity in design and easy operations. Therefore, the proposed sensor presents remarkably high sensitivity and selectivity.

1. Introduction

Cisplatin [*cis*-diamminedichloroplatinum (II)] has been employed as an anticancer drug since 1969, when Rosenberg et al. (1969) discovered its chemotherapeutic properties. It is a representative of cytotoxic and antineoplastic metallodrugs used for the treatment of various malignancies or being developed for such purpose (Palecek et al., 2009, 1992; Jelen et al., 1991; Trefulka et al., 2007; Kasparkova et al., 2004; Marini et al., 2002). When cisplatin enters into the cells, it coordinates to different molecules, such as enzymes (affinity for sulfur groups), RNA or DNA, being responsible of the therapeutic action. The drug binds covalently to DNA, forming several kinds of adducts. It can coordinate to N7 of two neighboring guanine and/or adenine bases, as this nitrogen does not form H bonds with other bases, in the same or in opposite DNA strands. In double-stranded chromosomal DNA, the most frequent of them are intra-strand cross-links (IAC) between neighboring purine residues: 65% of 1, 2-GG IAC and 25% of 1, 2-AG IAC. Another 6–10% belongs to 1, 3-GNG IAC and interstrand cross-links and 2–3% of various monofunctional adducts.

So far, the employment of cisplatin (apart of being an anti-cancer drug) is mainly to act as linker between a biomolecule and a label (mainly enzymes or fluorochromes). Since cisplatin is able to bind to DNA and other biomolecules, thus, if cisplatin (or a similar Pt complex) could be detected, the other labels (enzymes, fluorochromes) used for the detection of the biomolecule would not be necessary. That is, detection of cisplatin would allow the detection of biomolecules labeled with cisplatin. Thus it became necessary to detect the cisplatin in biological samples (Marsh et al., 1984; Elferink et al., 1986; Khuhawar et al., 1997; Hanada et al., 1995; O'Dea et al., 1988; Digua et al., 1992; Zhao et al., 1993; Vr´ana and Brabec, 1984; Wong and Justin Gooding, 2007; Pil and Lippard, 1992). The most employed technique has been High Performance Liquid Chromatography (HPLC) coupled to different kinds of detection (electrochemical, spectrophotometric), but the electrochemical detection of cisplatin, by differential pulse voltammertry, without previous separation has also been described (Vr´ana and Brabec, 1984). Moreover, Sadik and co-workers (Yan and Sadik, 2001a, 2001b; K'Owino et al., 2003) have described that some silver (electrochemically deposited) and avidin covered gold electrodes modified with biotinylated double stranded DNA for the electrochemical sensitive detection of cisplatin in which

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K'Owino showed an excellent sensor with an analysis time of 30 min and detection limit of 10 pM. However, these methods have their limits, such as the requirements of expensive apparatus, complicated preparation process, without study of the interference, or without amplifying the signal.

Since the first discovery of a DNAzyme (also called deoxyribozyme) through in vitro selection in the 1990s, DNA is no longer considered as only a genetic material; it is now recognized as also being capable of catalyzing many reactions (Robertson and Joyce, 1990; Breaker and Joyce, 1994; Schlosser and Li, 2009; Lu, 2002; Deuss et al., 2011; Breaker, 2004). They have been used increasingly in sensor design in the past decade, such as sensor of Pb(II) (Liu and Lu, 2003; Li and Lu, 2000; Xiao et al., 2007; Li et al., 2010; Xiang et al., 2009, 2010), UO2(II) (Liu et al., 2007; Breon et al., 2009; Xiang and Lu, 2011), Cu(II) (Liu and Lu, 2007a, 2007b), Hg(II) (Liu and Lu 2007c; Hollenstein et al., 2008), histidine (Liang et al., 2011), DNA (Wang et al., 2011a) and aptamers (Ali et al., 2011; Vinkenborg et al., 2011; Famulok et al., 2007). The hemin/G-quadruplex horseradish peroxidase-mimicking DNAzyme (HRP-DNAzyme) is, probably, the most frequently used biocatalytic DNAzyme label for amplified biosensing (Pelossof et al., 2010). G-quadruplex DNAzymes are peroxidase-like G-quadruplex–hemin complexes, which are able to catalyze the H_2O_2-mediated oxidation of 2,2-azinobis (3-ethylbenzothiazoline)-6-sulfonic acid (ABTS), producing a free-radical cation $ABTS^{\bullet+}$ with a maximal absorption signal at a wavelength of ~419 nm (Zhang et al., 2012). A variety of enzyme-based biosensors (Shlyahovsky et al., 2007), DNA sensors (Xiao et al., 2004; Weiamann et al., 2006), or aptasensors (Li et al., 2007) using the HRP-DNAzyme amplifying label were reported in recent years. Also, different biocatalytic cascades that synthesize the HRP-DNAzyme were used to develop ultrasensitive biosensing platforms (Weiamann et al., 2006, Zhu et al., 2009, Li et al., 2008). Recently, target triggered autonomous cross-opening process for DNAzyme wires was reported for its signal amplification in the detection of DNA by Willner's group (Wang et al., 2011b; Shimron et al., 2012). The target triggered process for DNA wires, also named supersandwich structure was studied first by Stefan Matile et al. (Takeuchi and Matil, 2009). By using signal probes that hybridize to two regions of a target DNA in such a manner that a single signal probe hybridizes more readily to complementary regions on each of two target molecules than to two regions on a single target molecule, long concatamers containing multiple target molecules and signal probes are created which may have an amplification of signal without the preparation of complicated nanoparticles or other enzymes. It was then developed to detect DNA (Xia et al., 2010; Yin et al., 2012; Chen et al. 2012a, 2012b), cancer cell (Zhong et al., 2012), antigen (Tang et al., 2012; Wang et al., 2012a; Zhou et al., 2013), protein (Li et al., 2013a), methylation (Li et al.,2013b) and metal ion (Wang et al., 2012b).

In this paper, we described the detection of cisplatin by the hemin/G-quadruplex DNAzyme–H_2O_2 bioelectrocatalytic system. An enzyme-free amplification platform involving an autonomous target triggered process that yields the formation of the hemin/G-quadruplex DNAzyme wires was designed for the sensor. The resulting DNAzyme wires enable the electrochemical readout of the sensing process. With the addition of the cisplatin and its reaction with guanine, the conformation of hemin/G-quadruplex DNAzyme was changed and its catalytic effect on H_2O_2 was affected, which is the base to detect the cisplatin.

2. Experimental part

2.1. Materials

HPLC-purified oligonucleotides (S0: SH-$(CH_2)_6$-ATGCTC AGTCAGTTCA; S1: ACTTGACTGGTTGGGCGGGTTGGTGAACTGACTGA; S2: AGTCAAGTTCAGTCAGTTCA; and S3: AGTCAAGTATGC) were obtained from Sangon Biotechnology Co. Ltd. (Shanghai, China). Hemin and DNA were used without any further purification. Tris (hydroxymethyl) aminomethane (Tris), HEPES (amino acid 4-(2-hydroxyethyl)-1-piperazineëthanesulfonic acid) and other reagents were obtained from the Sinopharm Chemical Reagent Co. Ltd. (Shanghai, China). Human blood serum samples are from Wuhu infectious hospital. Double distilled water was used throughout the experiments. The chemotherapeutic drug of cisplatin was synthesized and provided by Pliva-Lachema (Brno, Czech Republic). Stock standard solutions of cisplatin (10 μg ml^{-1}) were prepared in 0.5 M NaCl (0.5 M, pH 6.4) and stored in the dark at the temperature of −20 °C.

2.2. Capture probe S0 self-assembled on gold electrode

Before use, oligonucleotides were dissolved in 0.05 M Tris–HCl buffer (pH 7.4) and stored at 4 °C for one night. The DNA solution was heated to 90 °C for 5 min to remove aggregates, and then cooled slowly to 30 °C (Wang et al., 2011; Schaffitzel et al., 2010). Prior to the modification, the gold working electrode (2 mm diameter) was first polished sequentially with 0.1 and 0.05 μm alumina powder followed by ultrasonic cleaning with ethanol and ultrapure water for 3 min each. Then the electrode was scanned in 0.1 M H_2SO_4 between −0.2 and 1.55 V at 100 mV/s until a steady-state redox wave was observed. The immobilization of the capture probe (S0) was performed by dropping 30 μL of 10 mM Tris–HCl buffer (pH 7.4) containing 1.0 μM S0 probe and 0.4 M NaCl on the cleaned gold electrode in a humidified chamber. The self-assembly through the thiol of S0 and Au atom was proceeded for 10 h. Then the gold electrode was rinsed with water and incubated in 2 mM 6-mercaptohexanol in Tris–HCl buffer for 2 h to eliminate the nonspecific-bonded DNA. Then the S0 probe modified gold electrode (S0/GE) was stored at 4 °C in HEPES (pH 7.4) buffer for further use.

2.3. Preparation of supersandwich hemin/G-quadruplex DNAzyme structure

The S0/GE electrodes were then incubated in the hybridization buffer 0.05 M Tris–HCl buffer (pH 7.4) and 0.2 mM hemin solution containing 3 μM S1 and S2 probes at 37 °C to form the supersandwich structure modified electrode (S2/S1/S0/GE) containing multiple units of hemin/G-quadruplex DNAzyme. When finishing assembly, the modified electrode was thoroughly rinsed, dried with N_2 before electrochemical measurements. Under the same conditions, S3 substituting S2 was prepared for traditional sandwich DNA structure modified gold electrode (S3/S1/S0/GE) containing one unit of hemin/G-quadruplex DNAzyme.

2.4. Detection of cisplatin with supersandwich hemin/G-quadruplex DNAzyme structure

The cisplatin solutions used in this work were prepared at low illumination intensity and stored in darkness at 28 °C. The cisplatin was allowed to react with S2/S1/S0/GE in 10 mM $NaClO_4$ (Legendre et al., 2000; Halamikova et al., 2007), pH 5.6 about 5 h. The mixtures of cisplatin and DNA were incubated in darkness and stated at 28 °C. Moreover, the test solutions were always deoxygenated by purging with N_2 for ca. 10 min and N_2 atmosphere was maintained in the cell throughout the experiments.

2.5. Measurement procedure

Electrochemical measurements were carried out using a CHI 660B electrochemistry workstation (Shanghai CH Instruments Co., China) at ambient temperature (22 ± 2 °C). All electrochemical

experiments were carried out in a conventional electrochemical cell containing a three-electrode, a modified gold electrode (GE, $d=2$ mm) as working electrode, a platinum wire as auxiliary electrode and a saturated calomel electrode (SCE) as a reference electrode. All potentials were measured and reported versus the SCE. Cyclic voltammetry (CV) and differential pulse voltammertry (DPV) were performed in 0.1 M PBS containing 1 μM H_2O_2. Electrochemical impedance spectroscopy (EIS) measurements were performed in the presence of a 5 mM $K_3[Fe(CN)_6]/K_4[Fe(CN)_6]$ (1:1) mixture as redox probe in 0.1 M phosphate buffer solution (PBS, pH 7.4) containing 0.1 M KCl at a bias potential of 0.18 V. The alternative voltage was 5 mV and the frequency range was 0.1–10 KHz.

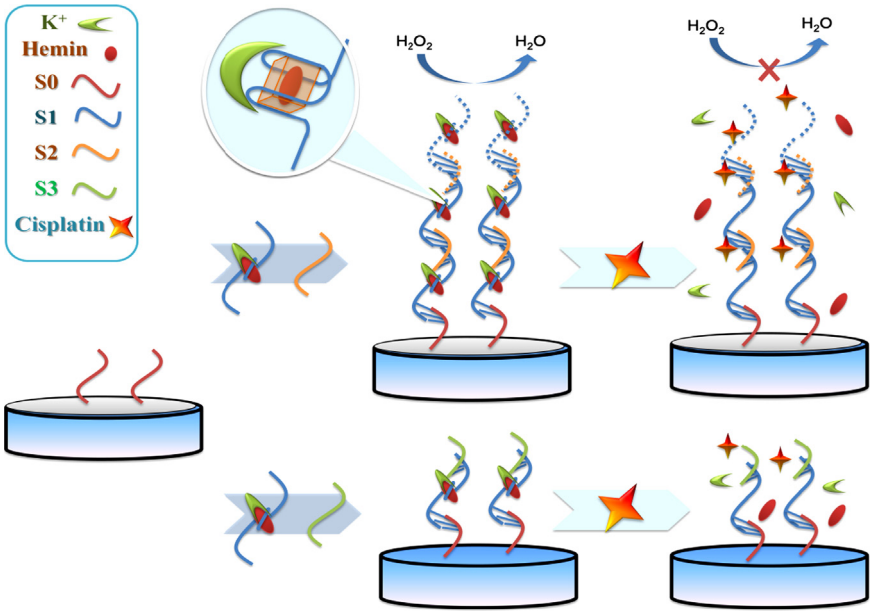
3. Results and discussion

3.1. Design of the sensor

Scheme 1 depicts electrochemical sensor for the detection of cisplatin based on supersandwich hemin/G-quadruplex DNAzyme structure. First, the thiolated ssDNA (S0) is assembled on the electrode surface based on Au–S chemistry band. Upon interacting with the modified electrode with K^+ and hemin, the hemin/G-quadruplex DNAzyme is fabricated. Subsequently, with the modified electrode hybridizing with hemin/G-quadruplex DNAzyme and S2, because the remaining part of S1 can hybridize to two complementary regions on 3′ end of S0 and 5′ end of S2, hemin/G-quadruplex DNAzyme supersandwich structure was formed, resulting in the increasing numbers of HRP-DNAzyme modified on gold electrode (S2/S1/S0/GE). Because the electrochemical signal is originated from the electroreduction of HRP-DNAzyme towards the H_2O_2, more units of HRP-DNAzyme will amplify the electrochemical signals. In the system, as cisplatin is added, it will combine with the guanine of G-quadruplex, thus breaks the electrocatalysis of the HRP-DNAzyme to H_2O_2, and the obtained electrochemical signals are inclined to decrease. With the introduction of more cisplatin, the signal will decrease more obviously. However, in the traditional sandwich HRP-DNAzyme structure only one unit of HRP-DNAzyme was contained in which the signal molecules are much less than those in the supersandwich HRP-DNAzyme structure. And thus the traditional sandwich HRP-DNAzyme structure will bring low electrochemical response.

3.2. Electrochemical characterization

The fabrication process of the cisplatin biosensor was characterized by CV and EIS. The resulting voltammograms are displayed in Fig. 1A. The redox couple of $[Fe(CN)_6]^{3-/4-}$, which is sensitive to surface chemistry, was engaged here to indicate the electrochemical behaviors of the sensor at different stages. A couple of quasi-reversible, well defined redox peaks of $[Fe(CN)_6]^{3-/4-}$ was observed on the pretreated bare gold electrode (curve a). After the immobilization of the capture DNA probes S0 and surface blocking with MCH, the current responses (curve b) of $[Fe(CN)_6]^{3-/4-}$ on the modified electrode were smaller than that of the bare electrode because the negative charges on the DNA backbone and MCH repelled $[Fe(CN)_6]^{3-/4-}$ from the electrode. In addition, the redox peaks also became irreversible, suggesting successful formation of the self-assembled layer on the gold electrode. As expected, the current response decreased, after binding with S1 and S3 (for control experiments) to form the traditional sandwich structure (curve c). And the current further decreased when S0 binding with S1 and S2 to form supersandwich structure (curve d) due to introduction of more negative charges on the gold surface upon formation of more dsDNA polymers and more proteins on the modified electrode. And the EIS result is the same with that of CV. As shown in Fig. 2B (curve a), the impedance spectrum of the bare GE showed almost no semicircle domain. After the immobilization of S1, a semicircle can be observed due to the formation of a negatively charged interface, which may electrostatically repel the same negatively charged redox species $[Fe(CN)_6]^{3-/4-}$ (curve b). When the electrode was modified with hemin/G-quadruplex DNAzyme supersandwich structure, the Ret is almost 10^4 Ω owing to which the formed hemin/G-quadruplex DNAzyme makes the negative charge more orderly and densely on the surface of electrode. Compared with curves c and d, the Ret in supersandwich structure is much larger than that in traditional sandwich structure, implying that S2 and S3 were modified on the electrode successfully. All these impedance spectra are coherent as predicted.



Scheme 1. The schematic representation of electrochemical sensor for detection of cisplatin based on hemin/G-quadruplex DNAzyme supersandwich structure.

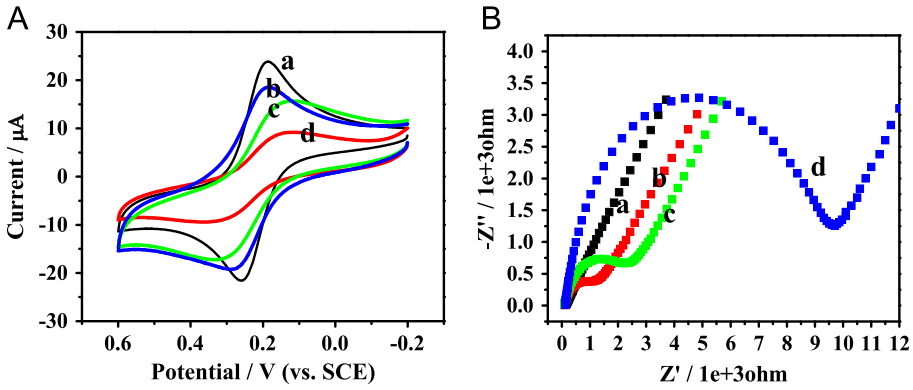


Fig. 1. Cyclic voltammograms by scanning the potential from −0.2 to 0.6 V at a scan rate of 50 mV s^{-1} (A) and electrochemical impedance spectroscopy (B) at the bare GE (a), S0/GE (b), S1/S3/S0/GE (c), S1/S2/S0/GE (d) electrode in $[Fe(CN)_6]^{3-/4-}$ probe solutions.

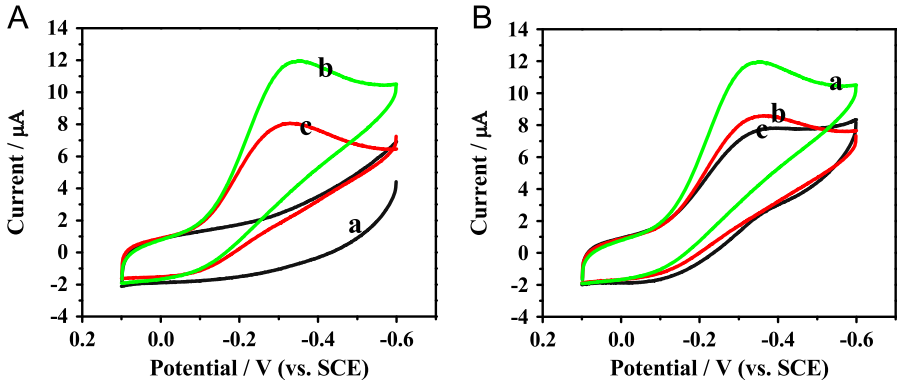


Fig. 2. Cyclic voltammograms by scanning the potential from 0.1 to −0.6 V at a scan rate of 50 mV s^{-1} on bare GE (a) and S2/S1/S0/GE (b, c) in 0.1 M PBS containing 1 μM H_2O_2 with 0 (a, b) and 3 μM (c) cisplatin (A); S2/S1/S0/GE (a) and S3/S1/S0/GE (b, c) in PBS containing H_2O_2 with 0 (a, b) and 3 μM (c) cisplatin (B).

3.3. The response of the modified electrode towards cisplatin

As shown in Fig. 2A, in the absence of cisplatin, the hemin/G-quadruplex DNAzyme supersandwich modified electrode has an obvious response in the PBS containing H_2O_2 (curve b) comparing with that on the bare gold electrode (curve a). But as the cisplatin was added in the system, the catalytic current (curve c) decreased largely indicating that the addition of cisplatin has changed the conformation of the hemin/G-quadruplex DNAzyme supersandwich structure. This interesting phenomenon observed suggested that the proposed method described here may become an efficient way to detect cisplatin. In the control experiment (Fig. 2B), a traditional sandwich DNA structure containing HRP-DNAzyme has also shown the similar CV response. However, according to the comparison with Fig. 2A, the signal of hemin/G-quadruplex DNAzyme supersandwich structure modified electrode (Fig. 2A curve b) is much higher than that of the traditional sandwich structure (Fig. 2B curve c). Meanwhile the traditional sandwich structure shows weaker response change towards the same amount of cisplatin (Fig. 2B curve a) than the supersandwich structure (Fig. 2A curve c). The reason is ascribed to be the fact that in the traditional sandwich HRP-DNAzyme structure only one unit of HRP-DNAzyme was contained in which the signal molecules are much less than those in the supersandwich HRP-DNAzyme structure. And thus the traditional sandwich HRP-DNAzyme structure will bring low electrochemical response. Larger amount of HRP-DNAzyme in supersandwich provides stronger electrochemical responses, which exhibit efficient signal amplification as expected.

3.4. Optimization of the variables of the system.

In order to achieve high sensitivity, experimental conditions were optimized. The optimization of the variables of the system is shown in Fig. 3. Fig. 3A depicts the time-dependent voltammetric waves upon breaking the composition of hemin/G-quadruplex DNAzyme supersandwich structure. As the time of interaction is prolonged, the currents decreased. When incubation time is more than 5 h, the signal of current shows a level, indicating that the reaction may complete in 5 h. Therefore, 5 h was chosen as optimization of incubation time used in the experiments. Furthermore, Fig. 3B and C depicts the electrocatalytic currents of hemin/G-quadruplex DNAzyme supersandwich structure, resulting upon the analysis of different temperatures and the effect of pH, the highest sensitivity was obtained at 35 °C under pH 7.4, which is consensus with human body (Jiang et al., 2013; Sanson et al., 2010).

3.5. Determination of cisplatin with the hemin/G-quadruplex DNAzyme supersandwich structure

The quantitative analysis of cisplatin is based on the conformational change of the system. Under the optimal conditions, the sensors are incubated in different concentrations of cisplatin. And DPV was chosen for the study of the concentrations of cisplatin on the system. As shown in Fig. 4A, the reduction current descends proportionally to the concentration of cisplatin within the range from 0.05 to 5 μM (Fig. 4C) with a detection limit of 20 nM using a

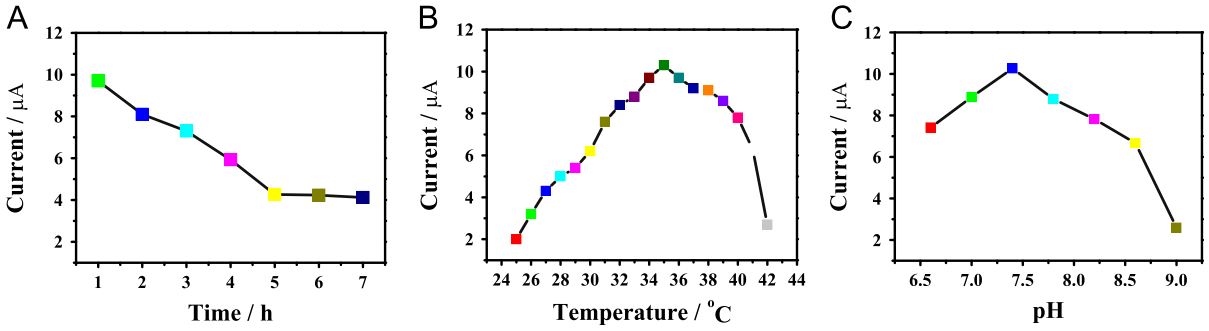


Fig. 3. Optimization of experimental conditions including hybridization time (A), incubation temperature (B) and pH value (C).

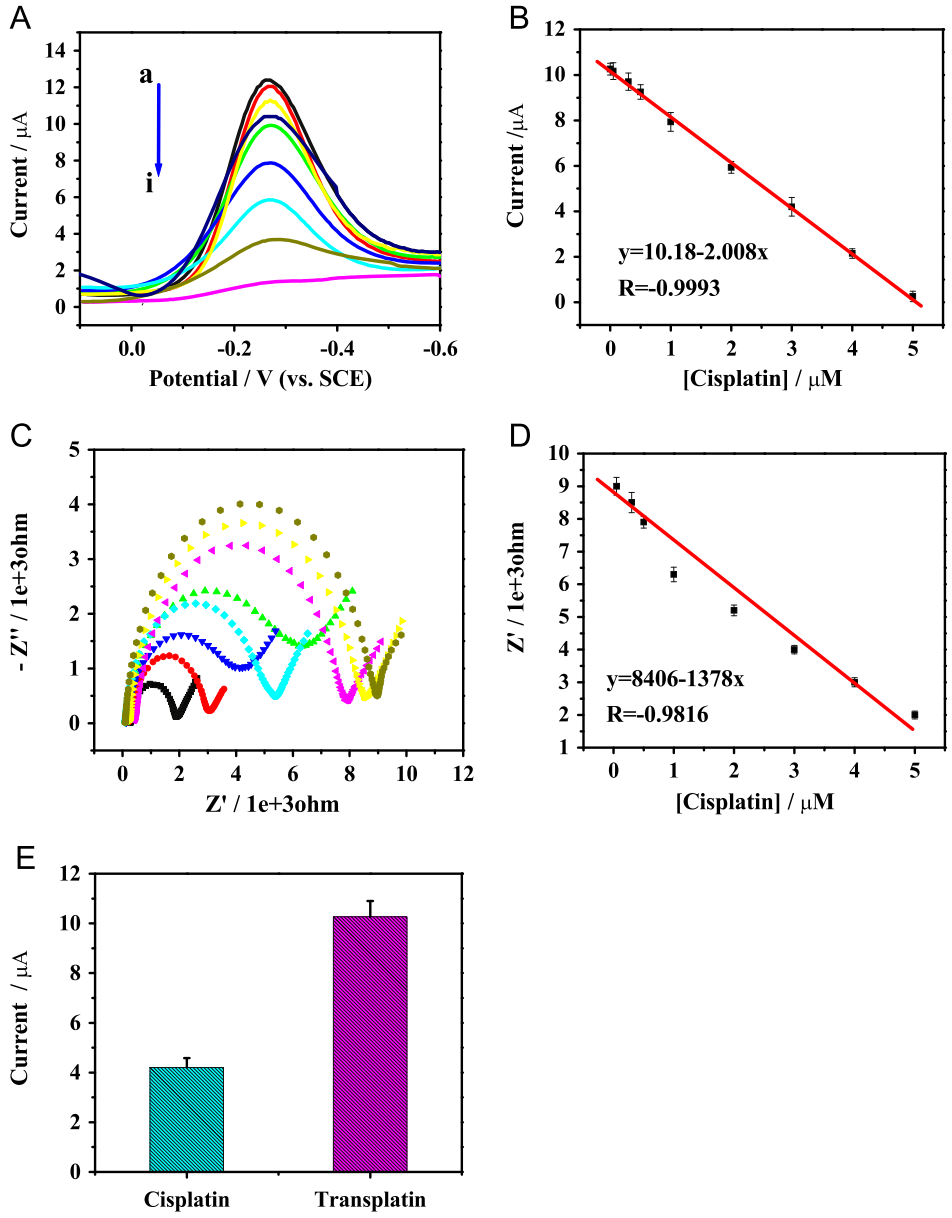


Fig. 4. DPV (A) and EIS (C) on S2/S1/S0/GE in the presence of various concentrations of cisplatin: 0, 0.05, 0.3, 0.5, 1, 2, 3, 4, 5 μM (a–i) in 0.1 M PBS containing 1 μM H_2O_2; the corresponding calibration curve of current (B) and Ret (D) vs. the concentration of cisplatin; and selectivity of the supersandwich assay for cisplatin analysis (E).

signal three-fold the background noise. The linear relationship between the concentration of cisplatin and the electrocatalytic current and the correlation coefficient is 0.9993 as shown in Fig. 4B. These results adequately suggest that the supersandwich structure has greatly improved the sensitivity and detection range. The proposed approach is also able to provide unique opportunities as simplicity in design and easy operations. And the concentration is also shown by EIS change in Fig. 4B showing the same trend with the result of DPV because the number of hemin/G-quadruplex DNAzyme unit decreases, and it also characterized the presented

Table 1
Comparison of our results by the method of proposed method with the standard cisplatin concentrations in serum samples.

Sample (μM)	Current changes in PBS (μA)	Current changes in human serum (μA)	Relative error (%)
1	0.313	0.294	4.9
5	2.278	2.125	4.7

design. The linear relationship is exhibited in Fig. 4D with the correlation coefficient 0.9816.

3.6. Selectivity, stability and application of the sensor

Specificity of the method for cisplatin is shown in Fig. 4E, compared with 3 μM cisplatin by employing its isomeride, 3 μM transplatin. Obviously, no significant effect exists on the electrochemical intensity, revealing the high selectivity of the proposed approach which may be attributed with the special design of the DNA sequence in our system. Therefore, the proposed sensor presents remarkably high sensitivity and selectivity. Considering these merits of this amplified electrochemical sensor, it was supposed to hold great promise in medical technology. Human blood serum is 1000 times diluted with 0.5 M NaCl (pH 6.4) before measurements. Due to the dilution of human blood serum samples and quick analysis of the prepared samples, we assume that the amount of the platinum based cytostatic bound to protein containing blood serum is very low, and do not interfere the analysis. For the sake of veracity of experiments, we did the analysis once the cisplatin was added both in normal human serum and PBS buffer solution. We can get the result in 10 min although the best incubation time is 5 h. The average relative error is less than 5%, comparing the assay results both in PBS and human serum, which is shown in Table 1. In order to detect the stability of this sensor, we also stored the biosensors in refrigerator for a period of two weeks, 93.2% of the initial DPV response for cisplatin (3 μM as an example) is obtained, indicating that the proposed method possesses an acceptable stability. In a word, the suggested approach shows the possible way for simple, sensitive detection of the anti-cancer drug-cisplatin in the human body.

4. Conclusions

In conclusion, this work describes a novel electrochemical biosensor for the detection of cisplatin by hemin/G-quadruplex DNAzyme supersandwich structure with signal amplification. The highlight of this work is to adequately utilize the signal amplification based on one-step supersandwich structure amplification for the determination of cisplatin. Furthermore, this label-free design does not require any chemical modification for DNA or sophisticated equipment, which offers the advantages of simplicity and cost efficiency. Given this method possesses high sensitivity and selectivity it may have good prospects for the detection of cisplatin in biomedical fields.

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