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Probing catecholamine neurotransmitters based on iron-coordination surface-enhanced resonance Raman spectroscopy label

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ABSTRACT

Catecholamine (CA) is neurotransmitters of the biological amines class which play an important role in organism. However, it is quite difficult to realize sensitive and selective detection of CA in complex system. Here, we employ surface-enhanced resonance Raman spectroscopy (SERRS) strategy, iron-nitrilotriacetic acid functionalized PVP-Au NPs (Au-Fe(NTA)) as Raman label for rapid and sensitive detection of CA containing dopamine (DA), norepinephrine (NE) or epinephrine (EP) in complex serum. The Au NPs is sufficient to provide Raman enhancement and Fe-NTA label can rapidly trap CA molecules adjoining gold core to form NTA-Fe-CA resonant structure, which can amplify the signals of CA. More important, we successfully distinguish these three CA molecules in serum since surface-enhanced Raman spectroscopy (SERS) technique can provide fingerprint identification. Furthermore, the SERS signals of Au-O band from PVP stabilized Au NPs can be utilized as a stable internal calibration standard for quantitative detection of target. Additionally, we continue to investigate the binding constants between different CA molecules and functionalized substrate to evaluate the corresponding adsorption property. This SERRS strategy is not only capable to offer exciting opportunities to selectively trap the analyte, but also strongly amplify the Raman signals of CA as well as achieve quantitative measurement.

1. Introduction

Neurotransmitters are of vital importance to both the central and peripheral nervous system for transmission of information. Catecholamine (CA) with the structure of amino and catechol is one of the most significant biological amine neurotransmitters, which contains dopamine (DA), norepinephrine (NE) and epinephrine (EP). As a kind of important neurotransmitter, CA not only directly takes part in behavioral activities, but also relates to some functional diseases like disorder, Parkinson's disease and depression [1–3]. There is increasing demand to concern and monitor the level of CA in the human body fluids such as serum and urine due to the special pharmacological property and physiological function [4]. Consequently, developing the sensitive strategy for the study of CA in complex system is of great significance. Typically, the detection of CA molecules (DA, NE or EP) in the complex is achieved through the methods of electrochemical detection [5,6], colorimetric biosensors [7], immunoassays [8,9] and HPLC [10]. Although some progress have been made, there still exists some disadvantages. An example is several techniques are time-consuming and require long pretreatment steps to enrich the sample. Moreover, the major problem of electrochemical detection is the coexistence of interferences, especially ascorbic acid (AA) [11]. Because the voltammetric responses of DA and AA with nearly same oxidation potential are overlapping, so that the analytes cannot be clearly distinguished [12]. These drawbacks can be acted as the driving force to propose the rapid and sensitive analytical method for detection of CA in complex biological fluids.

In recent years, surface-enhanced Raman spectroscopy (SERS) as a promising technology [13], has been widely applied in various fields involving living cells [14,15], food safety [16] and organic pollutants [17] for its intrinsic advantages of providing fingerprint identification and high sensitivity, requiring less volume of sample and less time-consuming [18,19]. More important, SERS is considered to have exceptional potential for employing in complex bio-fluids detection [20] for a number of reasons, one of which is

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that water has a very weak Raman scatter. However, in terms of CA neurotransmitters, the two main limitations of SERS are that the Raman activity of CA is relatively low and measurement of CA is quite complicated with low basal concentration (0.01–1 μM) and coexistent interferences, which cannot be overcome only by modifying substrates. Surface-enhanced resonance Raman spectroscopy (SERRS) strategy is capable to offer exciting opportunities to selectively trap the analyte and strongly amplify the Raman signals by modifying a chromophore on the surface of SERS substrate [21,22]. The chromophore coupled with the localized surface plasmon of active nanostructure leads to spectral resonant and surface enhancements for overcoming above mentioned limitation.

On the other hand, it is worth noting CA with low level plays an important role in various physiological activities, thus the precise determination of analyte concentration is critical for biological sensing applications. Nonetheless, there are only a few reports focus on quantitative detection of CA [23–25]. To realize sensitive and reliable SERS quantitative detection, the two issues need to be addressed: firstly, a uniform SERS substrate is necessary to ensure the stability and reproducibility of the signal. Only on the basis of uniformity can achieve effective control of hotspots. Gwo and co-workers [26] designed self-assembled Ag NPs super-lattices to realize quantitative detection. The second issue of quantitative analysis is related to the measurement of SERS signal. In addition to the intrinsic properties, the intensity of SERS signal is always affected by external conditions such as laser power and resolution of the instrument, etc. As a result, it is hard to reproduce SERS signal even the same sample, which brings a great challenge to quantitative detection. A common solution for this difficulty is to normalized relative intensity of analyte by using an internal reference [27] or internal standard [28].

Herein, by taking the advantage of chromophore feature amplifying the Raman signals of small molecules with weak Raman activity, we employ the SERRS strategy to realize the rapid and high sensitive detection of CA molecules as well as distinction in complex serum specimen. In this report, the iron-nitrilotriacetic acid (Fe-NTA) as a Raman label is modified on the surface of PVP stabilized Au NPs (PVP-Au). We reason that, upon addition of analytes (taking the DA as an example), DA molecule will transform from a non-resonant state to an electronic state because of the formation of NTA-Fe-DA chelate structure. The Au NPs can provide sufficient enhancement for Raman signal, and then Fe-NTA structures can rapidly trap the analytes adjoining the gold core to form the complex of NTA-Fe-DA resonant structure to realize highly sensitive and selective detection for CA molecules by using 633 nm laser. More important, due to the advantage of fingerprint identification of SERS, the spectra of CA molecules in serum can be differentiated successfully. Furthermore, the independent Raman signals of Au-O band of PVP stabilized Au NPs can be used as the internal reference for quantitative SERS detection of target molecules. In view of these three substances of CA molecules, all the normalized relative intensity of analyte-sensitive band versus the band of internal reference exhibits good linear response to the negative logarithm of the concentration. In short, this reported SERRS strategy not only realizes the high sensitive and selective detection, but also obtains the quantitative measurement for CA molecules. Additionally, we study the adsorption constants about three kinds of analytes by means of this quantitative method.

2. Experimental section

2.1. Materials

Hydrogen tetrachloroaurate ($HAuCl_4{\cdot}4H_2O$), iron(III) nitrate nonahydrate ($Fe(NO_3)_3{\cdot}9H_2O$), sodium citrate, crystal violet (CV) were purchased from Shanghai Chemical Reagent Company. Dopamine hydrochloride and α, β-Nitriloacetic acid (NTA) were obtained from Sigma-Aldrich, polyvinylpyrrolidone (PVP), epinephrine bitartrate and noradrenaline bitartrate monohydrate were supplied from Aladdin Company. Millipore water purification was used to produce ultrapure water (18.2 MΩ cm).

2.2. Instruments

Transmission electron microscopy images were collected on a FEI Tecnai G2 F20 S-TWIN high resolution transmission electron microscopy. The scanning electron microscopy images were obtained by a field-emission scanning electron microscope (Quanta 200FEG). Ultraviolet–visible (UV–vis) absorption spectra were taken on a Shimadzu UV-2550 spectrophotometer (Japan), and the background spectrum was deducted. Fourier transform infrared (FT-IR) spectra were performed on a Nexus-870 spectrophotometer. X-ray Photoelectron Spectroscopy (XPS) measurements were carried out by Thermo ESCALAB 250Xi (with a monochromatic Al Kα (1486.6 eV) excitation source). The zeta potentials were measured by Zeta-check, Microtrac (Germany). Raman spectra were recorded by LabRAM HR800 confocal microscope Raman system (Horiba JobinYvon) with a 633 nm He–Ne laser source.

2.3. Synthesis of PVP stabilized Au NPs

The synthesis of PVP stabilized Au NPs by seed growth method [29]. The preparation of Au seed nanoparticles were made by the citrate reduction of $HAuCl_4{\cdot}4H_2O$ [30]. Briefly, Adding 1 mL of $HAuCl_4{\cdot}4H_2O$ (1% wt) to the rounded bottom flask of 250 mL, which injected into 99 mL deionized water, and then the solution was heated to boiling during vigorous stirring, adding into sodium citrate (1% wt) at the moment. The boiling solution was keep heating for 30 min continuously, and then let it cool.

The general procedure for seed growth process was as follows: putting 25 mL seed solution into 250 mL three-necked round bottomed flask, and then adding 1 mL sodium citrate (1% wt), 1 mL PVP solution (1% wt) and 20 mL 2.5 mM $NH_2OH{\cdot}HCl$ into the solution, successively. Under the condition of stirring, 20 mL $HAuCl_4$ (1% wt) was injected into solution at the speed of 1 mL min^{-1} by a peristaltic pump. The reaction was carried out at room temperature.

2.4. Preparation of Au-Fe(NTA) SERRS substrate

The process of Fe-NTA modified on the surface of Au NPs on a basis of an approach which reported by Kayat [21]. Briefly, the formation of Fe-NTA was mixed with $Fe(NO_3)_3{\cdot}9H_2O$ (10^{-3} M) and NTA (10^{-3} M) at the ratio of 1:1, and then 0.1 M NaOH was added to adjust the pH to 7, the solution of Fe-NTA was standing for 15 min. 1 mL PVP stabilized Au NPs was centrifuged and dispersed in 1 mL ultrapure water. Then the prepared Fe-NTA was mixed with redispersed PVP stabilized Au NPs at the volume ratio of 1:1. After centrifugation, discarding the excess Fe-NTA, and the sol precipitation in the bottom was left to use.

2.5. Samples preparation and SERS measurements

2.5.1. Samples preparation

In SERRS detection of these three CA molecules, 3 μL sol of Au-Fe(NTA) prepared above was dropped on the clean Si wafer, and then the SERRS functionalized substrate are dried in incubator at the temperature of 30 °C. To achieve detection of CA molecules in serum (the serum were obtained from CAS Hefei Cancer Hospital), a certain pretreatment method was prepared to process the serum sample. Briefly, 10 μM 10^{-5} M DA (NE or EP) was adding into 100 μM serum sample, and then mixed with 300 μM CH_3OH. The