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Colorimetry and SERS dual-mode sensing of serotonin based on functionalized gold nanoparticles

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HIGHLIGHTS

- A combined strategy for detecting serotonin is developed using a dual-mode system.
- Two kinds of functionalized AuNPs can specifically recognize 5-HT.
- The dual-mode detection is more sensitive and more accurate.
- The system could be further applied to sense other diseases relating to serotonin level.

GRAPHICAL ABSTRACT
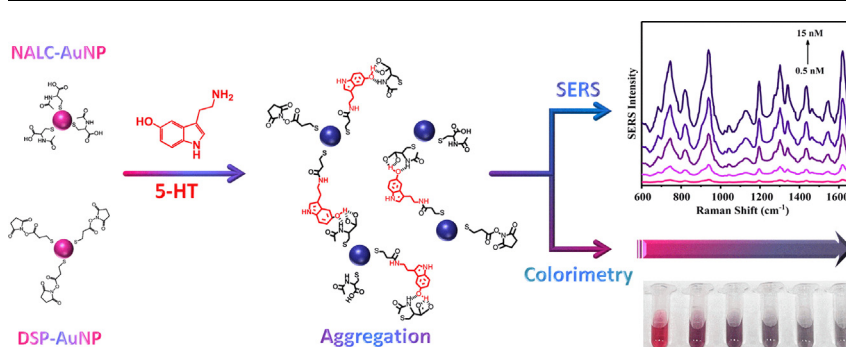
ARTICLE INFO

ABSTRACT

In this study, we reported a colorimetry and SERS dual-mode sensing of serotonin (5-HT) based on functionalized gold nanoparticles (AuNPs). Based on the amino and hydroxyl groups in 5-HT can react with dithiobis succinimidyl propionate (DSP) and N-acetyl-L-cysteine (NALC) respectively, we synthesized two kinds of functionalized AuNPs (DSP-AuNPs and NALC-AuNPs). A double interaction between functionalized nanoparticles and the hydroxyl and the amino group of serotonin led to interparticle-crosslinking aggregation. The aggregation of the two functionalized AuNPs can cause the plasmon coupling of AuNPs resulting in a color change visible to the naked eye and the enlargement of SERS "hot spot" area and the enhancement of SERS signal. Furthermore, two kinds of functionalized AuNPs can specifically recognize 5-HT and effectively reduce the interference of biomolecules with similar structure to 5-HT in the experiment. This dual-mode system has the advantages of low detection limit, high sensitivity and good selectivity, and the detection limit is 0.15 nmol L^{-1}. Besides, the system was applied to the determination of 5-HT content in human serum, and the relative standard deviation (RSD) was lower than 3.75%, which indicated that the system had a good application prospect in the determination of biological samples.

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1. Introduction

Serotonin (5-hydroxytryptamine, 5-HT) is an important neurotransmitter that is produced in the spinal cord, digestive system and central nervous system and circulates in the body [1–4]. It can regulate various cognitive and behavioral functions of the human body, such as sleep [5], mood [6], pain [7], appetite [8], and digestion [9]. Abnormally elevated 5-HT levels are closely linked to many diseases, such as depression [10], migraine [11], high blood pressure [12], vascular problems [13,14], bowel movements [15] and diabetes [16], etc. Abnormally reduced 5-HT levels

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are also associated with many diseases, such as: Alzheimer's disease [17,18], Parkinson's disease [19,20], sleep disorders [21] and mental retardation [22]. Therefore, sensitive determination of 5-HT can play a significant role in the clinical diagnosis of 5-HT-related diseases. A variety of methods for the determination of 5-HT have been developed, such as liquid chromatography [23], capillary electrophoresis [24] and mass spectrometry [25]. These methods have good accuracy and reproducibility in the determination of 5-HT, however these techniques are quite time-consuming, require complex and high-cost equipment and require highly skilled personnel to operate the instrument, which have greatly limited their practical applications in the diagnosis of 5-HT-related diseases. In recent years, fluorescence method [26], electrochemical method [27], enzyme-linked immunosorbent assay (ELISA) [28], colorimetric method [29], SERS method [30] show great advantages in the determination of 5-HT. Fluorescence and electrochemical methods have the advantages of low cost and rapid detection. ELISA has the advantages of better specificity and higher sensitivity. SERS method has the advantages of high sensitivity, multiplexing capability, and applicability in molecular-specific fingerprint spectroscopy. Researchers have designed many probes that combine SERS with other methods for dual-mode or multi-mode detection of the same target [31–34]. The advantages of dual-mode or multi-mode probes are low detection limit, high sensitivity and good selectivity compared with other methods. Colorimetric method is simple to operate, requires simple instruments or does not require instruments at all, and can perform on-site inspections. The development of colorimetric probes is often based on gold nanoparticles (AuNPs) with unique optical properties. When analyte is induced, AuNPs tend to aggregation and cause the plasmon coupling of AuNPs resulting in a color change visible to the naked eye [35–38]. Due to the complexity of the 5-HT molecule and the interference of other neurotransmitters with similar chemical structures (such as dopamine and epinephrine), the determination of 5-HT remains a challenge. Researchers often modify AuNPs with molecules that can specifically react with 5-HT groups by functionalized AuNPs to eliminate the interference of structurally similar substances [39].

Tania et al. reported a colorimetric method for the determination of 5-HT using AuNPs functionalized with dithiobis(succinimidylpropionate) (DSP) and N-acetyl-l-cysteine (NALC) [29]. DSP was chosen to react with the amino group of 5-HT, whereas NALC was chosen to bind the hydroxyl group in 5-HT through hydrogen bonding and electrostatic interactions. We were inspired by the work and designed a colorimetry and SERS dual-readout system for sensitive and selective determination of 5-HT. Based on the fact that the amino and hydroxyl groups in 5-HT can react with DSP and NALC, respectively, the Au-S bond is used to combine DSP with NALC was modified on AuNPs, and two functionalized gold nanoparticles (DSP-AuNPs and NALC-AuNPs) were synthesized. A double reaction between functionalized AuNPs and 5-HT can lead to interparticle-crosslinking aggregation, which not only cause the plasmon coupling of AuNPs, but also increase the SERS "hot spot" area and the SERS signal. Besides, the construction of two functionalized AuNPs can specifically recognize 5-HT and effectively reduce the interference of biomolecules similar to 5-HT in the experiment.

2. Experimental section

2.1. Chemicals and materials

2.1.1. Reagents
Tetrachloroauric acid (HAuCl$_4$) (99.99%, HAuCl$_4$·3H$_2$O), sodium citrate dehydrate (Na$_3$Ct) were purchased from Meilun Biotechnol-

ogy Co., Ltd. Serotonin (5-HT), N-acetyl-L-cysteine (NALC), dithiobis succinimidyl propionate (DSP) was purchased from Sun Chemical Technology (Shanghai) Co., Ltd. Dopamine (DA), epinephrine (Epy), nore-pinephrine (NE), L-tyrosine (L-Tyr), uric acid (UA) were purchased from Shanghai Macklin Biochemical Technology Co., Ltd. L-cysteine (L-Cys), aspartic acid (AA) were purchased from Shanghai yuanye Bio-Technology Co., Ltd. Glutamic acid (GA) was purchased from Beijing Dingguo Changsheng Biotechnology Co., Ltd.

All glassware should be soaked overnight with 1:1 diluted aqua regia before use, and then thoroughly rinsed with ultra-pure water. Serum samples from healthy adult volunteers were provided by China-Japan union hospital of Jilin University (Changchun, China) and were diluted with Tris-HCl buffer (pH = 7.4) solution before analyses. The sample was diluted to ensure that the final 5-HT concentration in the sample remained within the linear detection range.

2.1.2. Instruments
Raman spectra were obtained using a portable Raman spectrometer i-Raman plus (B&W TEK Opto-Electronic. Co., Ltd, USA) with a 785 nm diode laser. The laser power was 100 mW. The exposure time used for data collection was typically 3 s. Absorption spectra were recorded on a Cary 60 UV–Vis spectrometer (Agilent Technologies Inc., USA). Morphologies of AuNPs were investigated by using a JEM2100F transmission electron microscopy (TEM, JEOL. Co., Ltd, Japan).

2.2. Synthesis of DSP-AuNPs and NALC-AuNPs

According to the previous Frens method [36], AuNPs with a particle size of about 26 nm were synthesized. Briefly, 0.1 g mL^{-1} HAuCl$_4$ solution (50 μL) was added to 50 mL of ultrapure water and boiled, and then 820 μL Na$_3$Ct solution (1 wt%) was quickly injected into the boiling HAuCl$_4$ solution, and the solution changed from light yellow to blue-black, and finally to wine red. The mixture was then kept boiling for about 10 min before cooling to room temperature. The obtained AuNPs solution were centrifuged and resuspended in 50 mL of ultrapure water, then stored at 4 °C for the following usage.

Then DSP-AuNPs and NALC-AuNPs were prepared. 100 μL DSP (2 mM) and 100 μL NALC (2 mM) was added to the 500 μL synthesized AuNPs solution respectively and diluted to 1 mL with Tris-HCl buffer (50 mM, pH = 7.4). The synthesized DSP-AuNPs and NALC-AuNPs solution were oscillated at room temperature in darkness for 30 min and stored at 4 °C for later use.

2.3. Colorimetry and SERS system for sensing determination of 5-HT

For the determination of 5-HT, different concentrations of 5-HT (100 μL) were added into the mixed solutions of DSP-AuNPs (500 μL) and NALC-AuNPs (500 μL). The mixed solution was diluted to 2 mL with Tris-HCl buffer (0.1 mol L^{-1}, pH = 7.4) and incubated at room temperature for 10 min. The mixture was transferred to a 1-cm quartz cuvette for analysis. The Raman spectra were acquired with an acquisition time of 3 s and 80% laser power. All SERS measurements were detected via a 785 nm laser. Quantitative analysis was carried out by measuring the change of SERS peak area at 941 cm^{-1}. Five experiments using five replicated samples were conducted in parallel. Besides, the color change and absorbance spectrum of mixed solutions were obtained by a digital camera and UV–vis spectrophotometer.

2.4. Sensing detection of human serum samples

To verify the practicability of our sensing system, the 5-HT of human serum was detected by our dual-mode probe. The detection of 5-HT was carried out according to the procedure described in 2.3, except that the 100 μL 5-HT solution was replaced with 100 μL of human serum sample. The sample was diluted 150 times to ensure that the final 5-HT concentration in the sample remained within the linear detection range of the SERS method. The colorimetry does not require dilution of the human serum sample because the 5-HT content level is within the linear range.

3. Results and discussion

3.1. 5-HT detection principle of the SERS and fluorescence dual-readout system

The principle of colorimetry and SERS dual-mode sensing of 5-HT was based on the double interaction between functionalized nanoparticles and 5-HT to lead to interparticle-crosslinking aggregation, illustrated in Fig. 1.

DSP-AuNPs and NALC-AuNPs were synthesized by modifying AuNPs with DSP and NALC through strong interactions between sulfhydryl groups and AuNPs. DSP can react with the amino group of 5-HT, while NALC can have specific hydrogen bonding and electrostatic interaction with hydroxyl groups of 5-HT. A double reaction between functionalized nanoparticles and 5-HT can lead to interparticle-crosslinking aggregation, which would not only lead to a change in color from red to blue but also cause the enlargement of SERS "hot spot" area and the enhancement of SERS signal. Besides, the double reaction can identify 5-HT specifically, reducing interference from other similar molecular structure.

The average size of monodisperse AuNPs measured by TEM was 26 nm (Fig. 2(A)). It can be seen from Fig. 2(B) that the aqueous suspensions of unfunctionalized AuNPs was red wine-colored and showed a surface plasmon absorption peak at 535 nm. Besides, the surface plasmon absorption peak of the DSP-AuNPs and NALC-AuNPs has no significant change, indicating that the surface plasmon resonance effect of AuNPs both before and after modification was not changed. The red wine-colored aqueous dispersions of functionalized AuNPs remained stable in the refrigerator for more than 1 month, and no changes were observed on the characteristic plasmon absorption band.

After the DSP-AuNPs and NALC-AuNPs solution was incubated with 5-HT, the plasma absorption peak of the mixed solution was redshifted from 535 nm to 750 nm. At the same time, the color

of the solution changed from wine red to blue-purple, indicating that AuNPs aggregated after adding 5-HT. Fig. 3 shows the obvious changes of the nanoparticles before and after 5-HT addition. In absence of 5-HT, functionalized AuNPs showed a dispersed spherical shape. When the DSP-AuNPs and NALC-AuNPs solution was incubated with 5-HT, functionalized AuNPs aggregated significantly, which confirms that the red shift of the surface plasmon absorption peak in the UV–vis spectrum was caused by the interparticle-crosslinking aggregation.

Due to the double reaction between functionalized AuNPs and 5-HT can lead to interparticle-crosslinking, SERS "hot spot" area would increase, and the SERS signal would appear. As shown in Fig. S1, in the absence of 5-HT, DSP-AuNPs solution and NALC-AuNPs solution did not exhibit SERS signals. When the DSP-AuNPs or NALC-AuNPs solution was incubated with 5-HT, the SERS intensity was still weak. After mixed solution of DSP-AuNPs and NALC-AuNPs was incubated with 5-HT, a clear SERS peak appeared. The detailed peak assignment of SERS spectral data is given in Table S1. Therefore, these results prove that the SERS intensity obtain from this system was generated due to the double reaction between 5-HT and functionalized AuNPs.

3.2. Determination of 5-HT by SERS and colorimetry dual-readout system

As designed, A_{750}/A_{535} of UV–vis spectrum and intensity of SERS signal at 941 cm^{-1} gradually increased with the increase of 5-HT concentration, due to the interparticle-crosslinking aggregation of between functionalized nanoparticles and 5-HT by double reaction. Under the optimal experimental conditions, the calibration plots of the assay achieved using both the colorimetry and SERS methods were constructed. The respective text and figures on the optimizations are given in the Electronic Supporting Material.

SERS spectra of various 5-HT concentrations (0.5–15 nmol L^{-1}) added to the mixture of DSP-AuNPs and NALC-AuNPs were illustrated in Fig. 4. As exhibited in Fig. 4 (A), the SERS intensity at 941 cm^{-1} increases with the 5-HT concentration increased. As is displayed in Fig. 4 (B), there was a great linear correlation between the difference of SERS intensity (ΔI_{SERS}) of the mixture and 5-HT concentration (0.5–10 nmol L^{-1}). In addition, a regression equation: y = 0.7796x ± 3.7336 (r = 0.994) was obtained. The limit of detection (LOD) was 0. 15 nmol L^{-1} (as calculated by 3σ/slope, where σ is the standard deviation of the blank samples).

A_{750}/A_{535} of UV–vis spectra of various 5-HT concentrations (10–2500 nmol L^{-1}) added to the mixture of DSP-AuNPs and NALC-AuNPs were illustrated in Fig. 4 (C) and Fig. 4 (D). As seen in
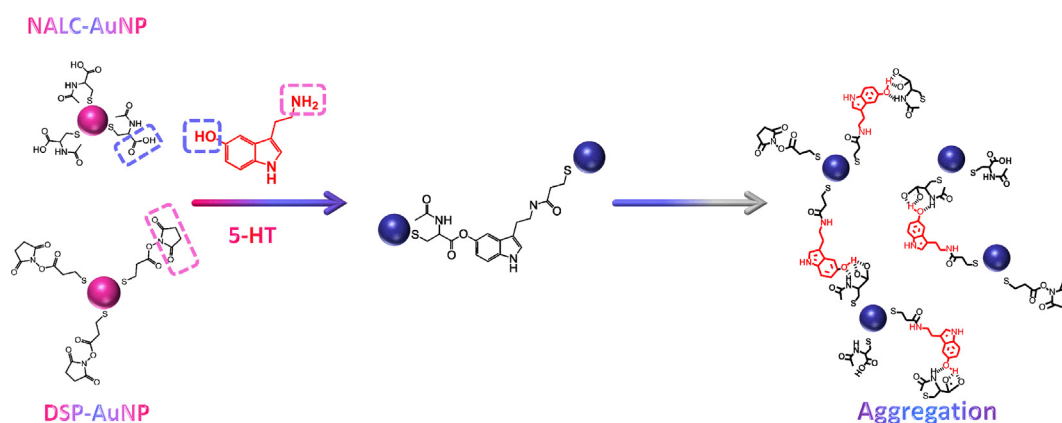

Fig. 1. Principle diagram of the colorimetry and SERS dual-mode system for the determination of 5-HT.
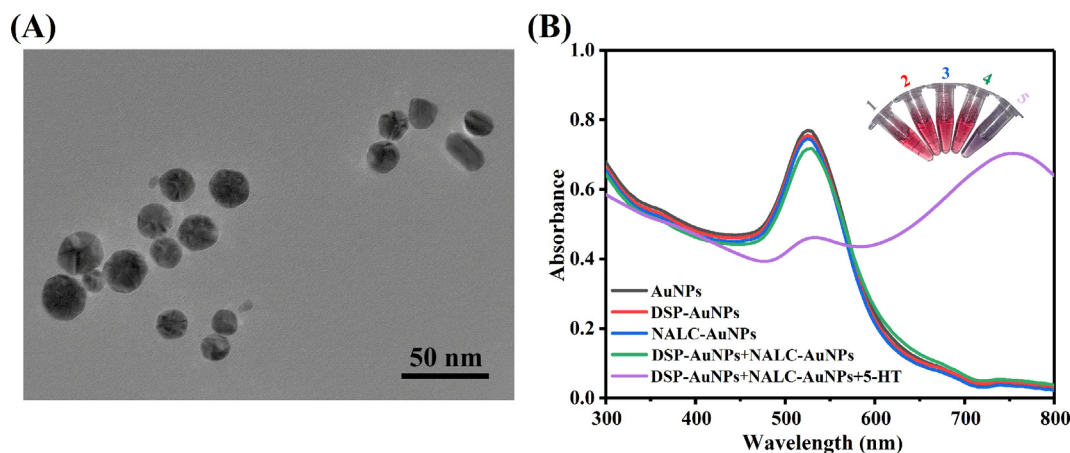
Fig. 2. (A) TEM image of AuNPs. (B) UV–vis spectra and photographic images of AuNPs (1), DSP-AuNPs (2), NALC-AuNPs (3), DSP-AuNPs + NALC-AuNPs (4), DSP-AuNPs + NALC- AuNPs + 5-HT (5).
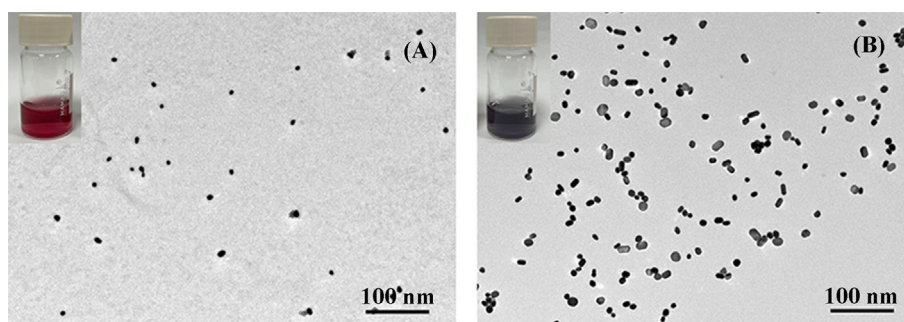

Fig. 3. TEM image of mixture solution before (A) and after (B) adding 5-HT. (Inset: Photographs of mixture solution before and after adding 5-HT.)

Fig. 4 (C), a gradual color change from red wine to purple, which was dependent on the 5-HT concentration, was observed. This change coincides with the proposed sensing protocol that involves the 5-HT-induced aggregation of the functionalized AuNPs. As displayed in Fig. 4 (D), there was a great linear correlation between the A_{750}/A_{535} of the mixture and 5-HT concentration (10–1500 nmol L^{-1}). In addition, a regression equation: y = 0.00071x ± 0.64374 (r = 0.991) was obtained. The limit of detection (LOD) was 3.33 nmol L^{-1} (as calculated by 3σ/slope, where σ is the standard deviation of the blank samples). With the increase of 5-HT concentration, the color of the mixture changes significantly (Fig. 4 (E)).

Therefore, we constructed a combined strategy for detecting 5-HT in human serum in the concentration range of 0.5–1500 nmol L^{-1}. SERS method can be used for quantification in the concentration range of 0.5–10 nmol L^{-1}, and colorimetry can be used for quantification in the concentration range of 10–1500 nmol L^{-1}.

We further compared 5-HT determination capability of our method with that of other reported methods [40–46], and the data are shown in Table 1. Compared with other methods, our method has a lower detection limit, indicating that our method is more sensitive.

3.3. Selectivity of the colorimetry and SERS dual-mode system

In order to verify the selectivity of colorimetry and SERS dual-mode system in the determination of 5-HT, we selected several neurotransmitters commonly found in serum, such as DA, EPY, NE, and some biomolecules with similar structure to 5-HT, such as L-Tyr, L-Cys, AA, GA and UA (Fig. 5(A)). In addition, for the

nanoparticle solution, the existence of high concentration ions may destroy the charge balance on the surface of nanoparticle, which leads to the aggregation of nanoparticles to further change the color and affect the SERS intensity. Therefore, several ions commonly found in serum were additionally detected, including K$^+$, Na$^+$, Ca^{2+}, Mg^{2+}, SO$_4^{2-}$, Cl$^-$, etc. As shown in Fig. 5(B), only 5-HT could generate colorimetry and SERS signals, which proved that the dual-mode system could specifically identify 5-HT by using the dual interaction of two kinds of functionalized AuNPs and 5-HT, reducing the interference of other molecules with similar structure.

3.4. Determination of 5-HT in human serum samples

Abnormal fluctuation of 5-HT concentration in serum can be used as an important criterion for disease diagnosis, and the normal concentration of 5-HT in human serum range from 262 to 1550 nmol L^{-1} [47]. To demonstrate the applicability of the system in assaying real sample, 5-HT concentration in real human serum sample was investigated (Table 2). The human serum samples should be diluted 150 times in SERS method to ensure that the final 5-HT concentration in the sample remained within the linear detection range. The colorimetry does not require dilution of the human serum sample because the 5-HT content level is within the linear range. The correlation coefficient of colorimetry and SERS methods is 0.995. The results of the two methods were not significantly different (Fig. 6), indicating the dual-readout system could reliably assay 5-HT in the serum sample. Thus, it can be inferred that the system developed in this work is highly suitable for assaying 5-HT concentration in clinical diagnosis.
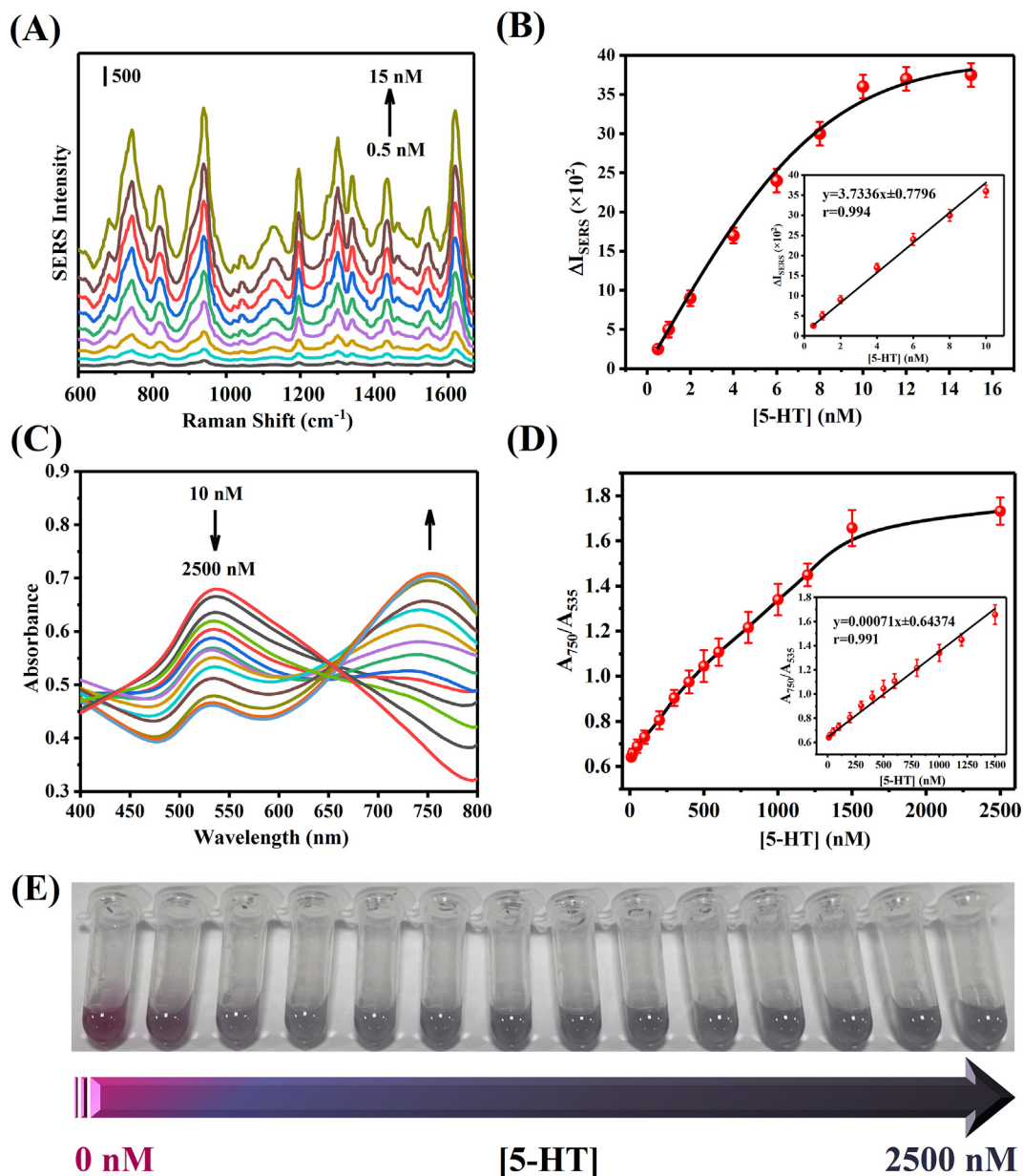
Fig. 4. (A) SERS spectra of DSP-AuNPs and NALC-AuNPs when 5-HT was added at concentrations of 0.5–15 nmol L^{-1}. (B) Calibration plot at 941 cm^{-1} of SERS spectra vs. 5-HT concentrations. (C) Changes in the UV–vis spectra of DSP-AuNPs and NALC-AuNPs when 5-HT was added at concentrations of 10–2500 nmol L^{-1}. (D) Calibration plot of the A$_{750}$/A$_{535}$ vs. 5-HT concentrations. (E) Colorimetric photographs of DSP-AuNPs and NALC-AuNPs when 5-HT was added at concentrations of 0–2500 nmol L^{-1}.

Table 1
Comparison of the developed method for the determination of 5-HT with other reported methods.

| Method	Materials	Determination of 5-HT		Ref.
		Linear range (nmol L^{-1})	Detection Limit (nmol L^{-1})	
Electrometry	GCE/AuNPs/AuNRTs-rGO	3000–100000	387	[46]
Colorimetry	DSP&NALC-AuNPs	0–1000	120	[29]
Simultaneous Voltammetry	glassy carbon electrode	500–10500	97	[45]
HLPC-MS/MS	–	56.70–2837.36	28.37	[44]
LCMS-MS/MS	–	57–2837	18.2	[43]
Amperometry	CNTs-Cu$_2$O-CuO@Pt	10–3000000	3	[42]
Electrometry	Poly(TAPP)-SWNT/GCE	200–10000	1	[41]
SERS	AuNCs/ITO glass	1–10000	1	[40]
Colorimetry/SERS	DSP-AuNPs&NALC-AuNPs	0.5–1500	0.15	This work
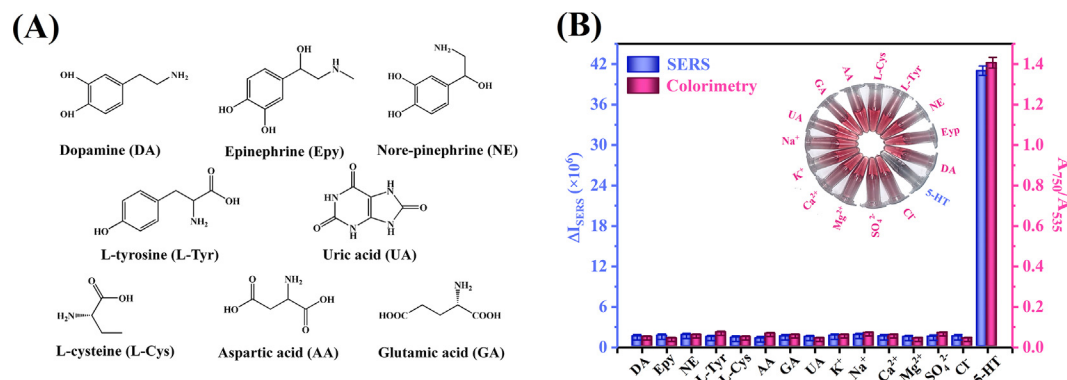
Fig. 5. (A) The structures of interfering substances. (B) ΔI_{SERS} and A_{750}/A_{535} of mixture in the presence of 5-HT (10 nmol L^{-1}) or various other interferences: DA, Epy, NE, L-Tyr, L-Cys, AA, GA, UA, K$^+$, Na$^+$, Ca^{2+}, Mg^{2+}, SO$_4^{2-}$, Cl$^-$ (each at 1 mM) (Inset: the corresponding optical photograph of mixture after incubated with different interferences).

Table 2
Analytical results by this system for in real human serum samples (n = 3).

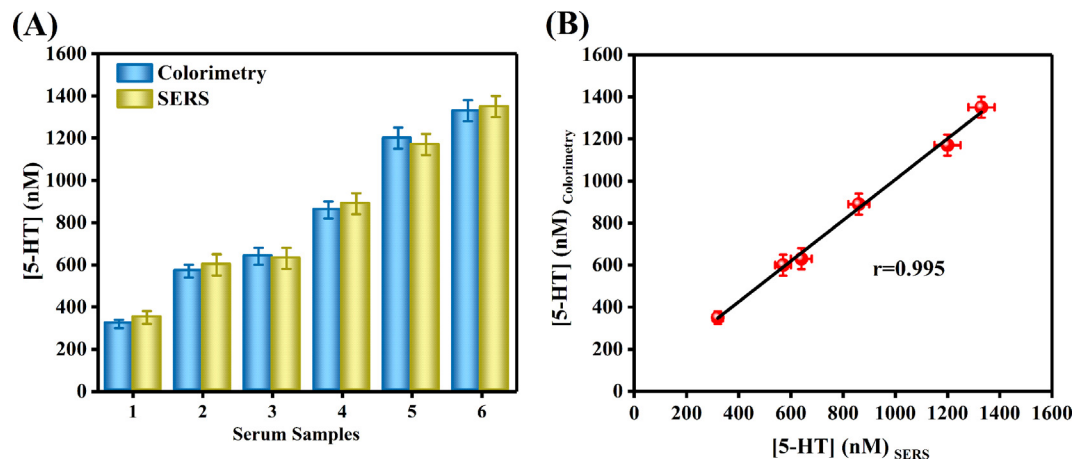| Samples	Colorimetry Result		SERS Result	
	Detection level (nmol L^{-1})	RSD (%)	Detection level (nmol L^{-1})	RSD (%)
1	321	1.25	348	1.57
2	568	2.26	592	2.34
3	643	1.65	637	2.69
4	867	1.84	891	2.61
5	1201	2.81	1170	2.47
6	1330	3.75	1353	2.87

Fig. 6. (A) Comparison and (B) correlation relationship of detection results of 5-HT concentration in real human serum samples obtained by colorimetry and SERS methods.

4. Conclusion

In summary, a colorimetry/SERS dual-readout system for determination of 5-HT concentration was successfully developed. Based on the fact that the amino and hydroxyl groups in 5-HT can react with DSP and NALC, respectively, the double reaction between functionalized AuNPs and 5-HT can lead to interparticle-crosslinking aggregation, which not only cause the plasmon coupling of AuNPs, but also increase the SERS "hot spot" area and the SERS signal. Besides, the construction of two functionalized AuNPs can specifically recognize 5-HT and effectively reduce the interference of biomolecules similar to 5-HT in the experiment. The combined strategy for detecting 5-HT in human serum was constructed in the concentration range of 0.5–1500 nmol L^{-1}, which had high selectivity and sensitivity with remarkable LODs of 0.15 nmol L^{-1} and 3.33 nmol L^{-1}, respectively. Appling the system to the determination of 5-HT in human serum, the system is not only efficient and simple, but also has dual-readout ability and high specificity, thus is a promising tool that should be applied in the diagnosis of various 5-HT-related diseases.

CRediT authorship contribution statement

Wei Wang: Conceptualization, Methodology, Software, Investigation, Validation, Data curation, Writing - original draft. **Bo**

Zhang: Writing - review & editing. **Yue Zhang:** Writing - review & editing. **Pinyi Ma:** Conceptualization, Project administration. **Xinghua Wang:** Investigation, Supervision. **Ying Sun:** Data curation. **Daqian Song:** Resources, Data curation. **Qiang Fei:** Project administration, Funding acquisition, Resources, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.saa.2021.120057.

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