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A novel portable biosensor based on aptamer functionalized gold nanoparticles for adenosine detection

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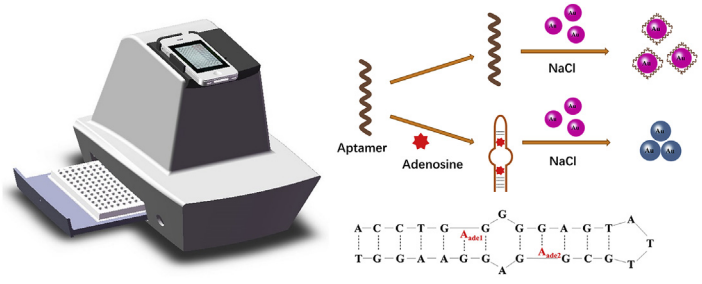
HIGHLIGHTS

- A sensitive, rapid and in-situ colorimetric aptasensor was developed for adenosine detection.
- A home-made bionic electronic-eye system was developed and utilized as a portable in-situ detection platform.
- The performance of adenosine detection with 4 kinds of aptamer was evaluate and the biotin-modified aptamer was selected.

GRAPHICAL ABSTRACT



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ABSTRACT

Adenosine has received great attentions acting as a potential biomarker for monitoring lung cancer. Most of the reported studies for adenosine detection require large instruments and complicated procedures. Herein, a sensitive, rapid and in-situ colorimetric aptasensor was developed for adenosine detection. Moreover, a homemade biomimetic electronic-eye (E-eye) was established and utilized as a portable in-time detection equipment. The entire measurement can be completed within 20 min, including the combination of aptamer with adenosine or AuNPs and the detection of adenosine. Four different kinds of aptamer were compared and the results showed that the AuNPs-aptamer-biotin system was the most stable and with the widest detection range of 5.0 μM–60.0 μM and the lowest LOD of 0.17 μM. Moreover, the artificial urine samples were also tested with a linear range from 5.0 to 50.0 μM and a LOD of 0.48 μM. The results validated that the aptasensor together with the E-eye can be a promising platform for adenosine detection.

1. Introduction

Adenosine is a nucleoside which makes an significant impact in the regulation of physiological activity in human. It is a vital component of many biological cofactors such as ATP [1]. Adenosine would be accumulated by hypoxia and necrosis of cells resulting from rapid proliferation of cancer cells and released through urine

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[1]. Some researches have indicated that adenosine can be a potential biomarker for monitoring lung cancer [2–4], that the level of urinary adenosine in lung cancer patients is about 2 fold higher than healthy people (1800 ng/mL) [2,4,5]. Therefore, it is of great significance to detect adenosine in urine, which can be an effective tool for non-invasive disease diagnosis.

Different methods have been currently reported for the detection of adenosine including surface-enhanced Raman spectroscopy (SERS) [6,7], high performance liquid chromatographic (HPLC) [8] and electrochemical biosensors [9,10] Aptamers are single-stranded oligonucleotides selected from random-sequence DNA or RNA libraries and can specifically bind to target molecules [11,12]. Because of its convenient synthesis, chemical stability and diverse applications, aptamers are becoming increasingly competitive biosensing elements. Szostak [13] first isolated the aptamer of adenosine in 1995 and other researches [14–16] have characterized the binding mechanism, two adenosines can bind with one aptamer through continuous six-base mismatch segment. So far, various detection methods such as electrochemical [17,18], colorimetric [19], and fluorescence [20] have been developed to detect adenosine based on aptamers.

Gold nanoparticles (AuNPs) have a high extinction coefficient and a strong particle-dependent optical property. The AuNPs-based colorimetric detection has a comparable sensitivity and selectivity to conventional fluorescent detection [21] based on the color change from blue to red when AuNPs aggregate. Due to the advantages of simple operation, rapid detection and low cost, the AuNPs-based colorimetric method has been applied to the detection of various substances, including DNA [22], proteins [23], metal ions [24,25] and other organic molecules [26]. Rothberg [27] first discovered that single-stranded DNA can be directly adsorbed on the surface of AuNPs and prevent the AuNPs from aggregation in high concentration salt solutions. As reported in many studies [28–30], the adsorption is based on the coordination and a number of other forces. Based on that, the aptamer can bind with the AuNPs and targets to control the color change of the AuNPs, thus achieving a simple, rapid, sensitive and visual analysis technique.

Most of the previous study for adenosine detection required large instruments with high costs such as microplate readers, spectrophotometers. This study developed a sensitive, rapid and in-situ colorimetric sensor for adenosine detection based on AuNPs and aptamer (Fig. 1). A homemade biomimetic E-eye was established and utilized as a portable in-time detection equipment. The principle of the detection method is showed in Fig. 1 B, in the presence of adenosine and aptamer, two adenosines wound bind one aptamer, which prevents the aptamer being adsorbed on the surface of AuNPs. By adding a high salt solution, the AuNPs would aggregate, and the color change can be detected by the E-eye system for quantitative analysis of adenosine. Aptamers modified with different molecules were selected for optimization, and the biotin-modified-aptamers-AuNPs were observed to be the most stable which reducing the detection limit and expanding the detection range. Moreover, the detection of adenosine was also carried in water and artificial urine to verify the performance of this colorimetric sensor.

2. Materials and methods

2.1. Chemicals and reagents

Adenosine (>99%), guanosine (>99%), cytidine (>99%), uridine (>99%), thymidine (>99%) and uricase were purchased from Sigma (Seelze, Germany). Uric acid, urea, NaCl, KCl, $MgSO_4$, $Na_2C_2O_4$, NaH_2PO_4, $HAuCl_4 \cdot 4H_2O$ and sodium citrate (analytical grade) were purchased from Aladdin (Shanghai, China). Unmodified aptamers and aptamers modified with Amino, Thiol and Biotin (5′-ACCTGGGGGAGTATTGCGGAGGAAGGT-3′) were synthesized by Genscript (Nanjing, China). Pure water (18.2 MΩ cm) was prepared by the Mill-Q water purification system.

2.2. Preparation of AuNPs

150 mL of 0.01% chloroauric acid was added into 250 mL round-bottom flask and heated at 120 °C until the solution was boiling. Then 6 mL of 1% sodium citrate solution was rapidly added to the boiling solution and stirred for 20 min at 120 °C. The color of the solution turned into wine red eventually. The resulting solution was cooled at room temperature and kept at 4 °C in dark for future use. The surface structure was verified through transmission electron microscopy (TEM) and the absorbance of the AuNPs was measured by the spectramax paradigm (molecular devices, USA).

2.3. Preparation of artificial urine

1.20 g of urea, 0.0168 g of uric acid, 0.0944 g of trisodium citrate dihydrate, 0.6119 g of NaCl, 0.4713 g of KCl, 0.0462 g of $MgSO_4$, 0.03 g of $CaCl_2$, 0.092 g of Na_2SO_4, 3.23 g of NaH_2PO_4 were added in 100 mL water and stirred to a transparent solution. This artificial urine was referred to the research reported by Somchai et al. [31] and Brown et al. [32]. Then 1 U uricase was added to 10 mL artificial urine to decompose with uric acid in water bath at 37 °C for 10 min. The resulting solution was kept at 4 °C for future use.

2.4. Adenosine sensing assays

10 μL of 5 μM aptamer was added to the 96-well plate, then 10 μL different concentrations adenosine or artificial urine sample was added. Then the 96 well plate was put onto the shaker and incubated for 5 min. After that, 160 μL of AuNPs was added, and the 96 well plate was shaken for another 15 min. At last, 20 μL 3% NaCl was added into the mixed solution. In the end, the adenosine sensing assays was detected by the microplate reader or the E-eyes.

2.5. The schematic of the bionic electronic-eye

The structure of bionic E-eyes system (Fig. 1C) includes hardware devices and a smartphone [33]. The hardware devices include wide-angle lens, darkroom, multiwell plate stage and electro luminescent, which provides a stable environment of illumination for detection. The smartphone (iPhone 4S, Apple Inc.) is used for data collection and data analysis. And an app was developed to detect adenosine. The detection process is showed in Fig. 1D, including calibration, detection, and data upload section. Through collecting, processing and analyzing the image of color change after biochemical reaction in the multi-well plate, the concentration of biochemical compound can be detected in real-time and on-site with the help of bionic Eyes.

3. Result and discussion

3.1. Characterization of AuNPs

After the synthesis, the AuNPs were characterized by TEM and microplate reader. As showed in Fig. 2 A, the AuNPs disperse well in solution, and the diameter is about 17 nm.

The TEM images of AuNPs after adding 3% NaCl solution without/with the aptamers are showed in Fig. 2 B and 2C. The AuNPs would aggregate under the high salt solution without the aptamers(Fig. 2 B). In the existence of the aptamers, the aptamers would be adsorbed onto the surface of AuNPs and prevent the

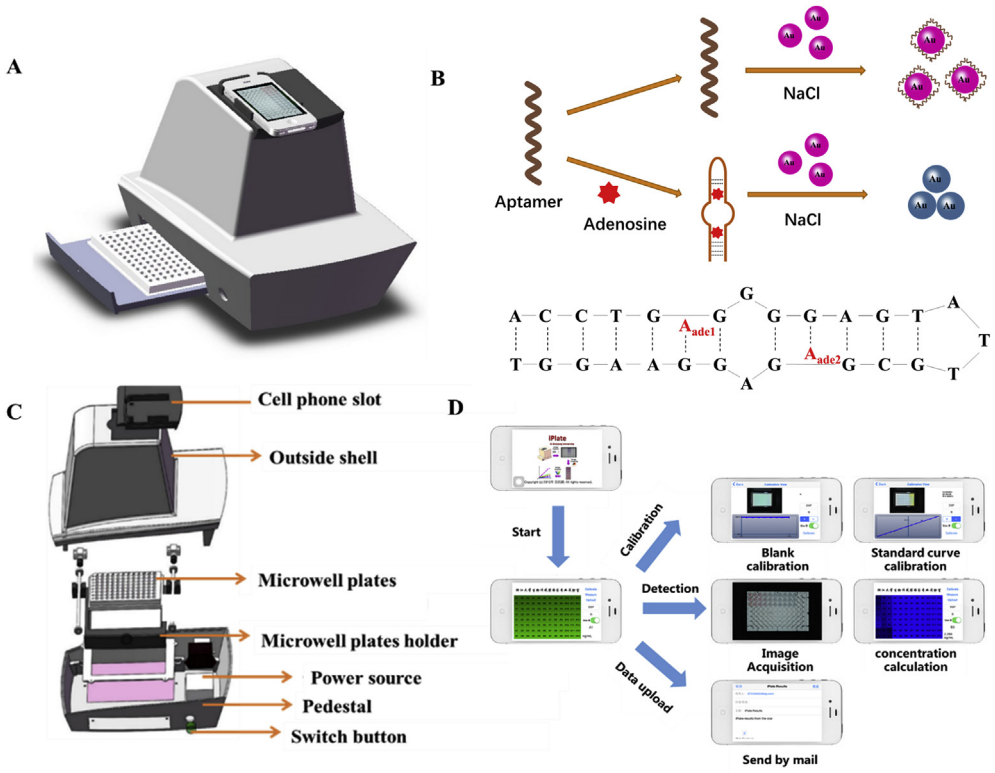

Fig. 1. (A) The schematic of the bionic electronic-eye (E-eye). (B) The sensing mechanism of the colorimetric aptasensor for adenosine detection. (C) The structure of the bionic electronic-eye (E-eye). (D) The detection process of the software.

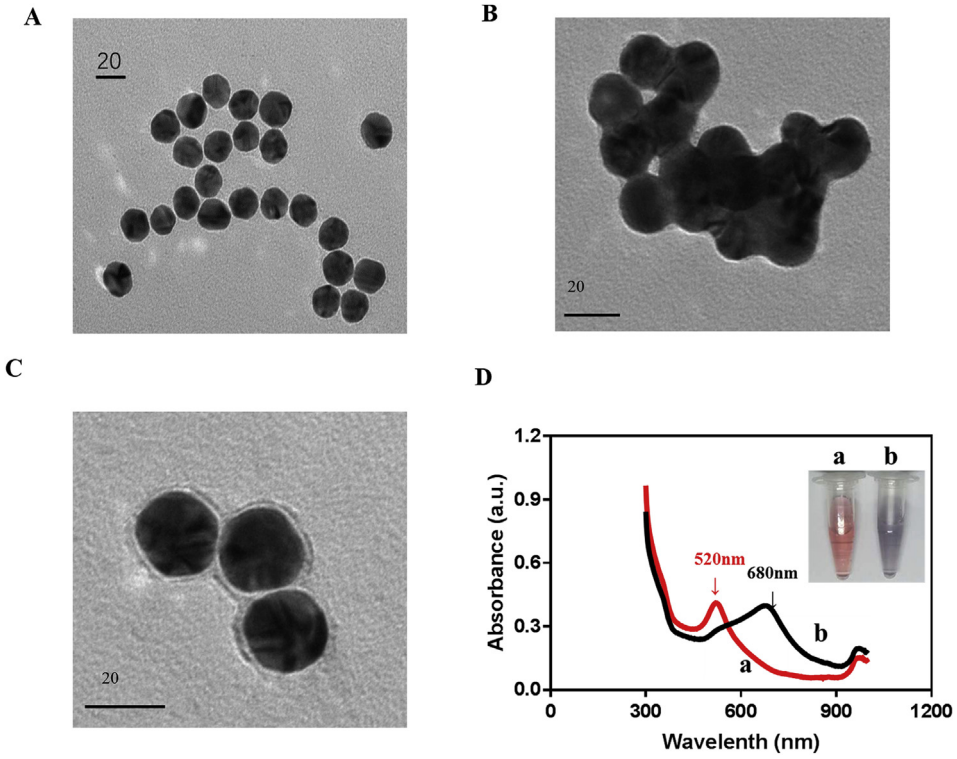

Fig. 2. (A) The TEM images of AuNPs. (B) The TEM images of AuNPs after adding 3% NaCl solution. (C) The TEM images of the aptamer adsorbed on AuNPs after adding 3% NaCl solution. (D) The UV–vis absorption spectra in the (a) absence and (b) presence of 3% NaCl solution.

aggregation of AuNPs (Fig. 2C). Fig. 2 D displays the UV–vis absorption responses of AuNPs with/without 3% NaCl. The dispersed AuNPs remained red and displayed an absorbance peak at 520 nm (curve a). On the contrary, when the 3% NaCl was added, the AuNPs aggregated and the solution color changed from red to purple, in which case the solution displayed an absorbance peak at 680 nm (curve b). The higher of the absorbance values rate at these two wavelengths(Ex(680/520)), the more AuNPs aggregated [34].

3.2. Optimization of the aptamer and incubation time

The performance of AuNPs in high salt solution with 4 kinds of aptamers, which were unmodified aptamer and aptamer modified with amino, thiol and biotin, have been compared to evaluate the effect of the aptamer modification. Fig. 3 A shows the Ex(680/520) of 4 kinds of aptamers at concentration of 1, 2.5, 5, 7.5, 10, 12.5, 15 μM in AuNPs and 3%NaCl solutions. At same concentration, the Ex(680/520) of unmodified aptamer was higher than the others, which means AuNPs with unmodified aptamer was the easiest to aggregate in high salt solution. Therefore the modification of aptamer with amino, thiol and biotin enhanced the stability of the aptamer absorbing onto the surface of AuNPs. And compared to aptamer-amino and aptamer-thiol, less aptamer-biotin was needed to prevent the AuNPs from aggregation in high salt solution.

To evaluate the most suitable aptamer for the adenosine detection, 50, 30, 10 μM adenosine were added into 10 or 15 μM different aptamer solutions. The Ex(680/520) of the solutions after adding AuNPs and 3% NaCl are showed in Fig. 3 B C D. As seen in Fig. 3 B, the Ex(680/520) of 10 or 15 μM aptamer-amino mixed solutions with 50 μM adenosine were 1.32 and 1.30, slightly higher than the value of solutions with 30 μM adenosine, which were 1.23 and 1.17 respectively. However, when the 10 μM adenosine was added, the value dropped to 0.50 and 0.34 respectively. The same result was gained when the aptamer-thiol was used (Fig. 3C). The Ex(680/520) of 10 μM aptamer-thiol mixed solution with 50 μM, 30 μM, 10 μM adenosine were 1.21, 0.94, 0.36 respectively, and the Ex(680/520) of 50 μM aptamer-thiol mixed solution with 50 μM, 30 μM, 10 μM adenosine were 1.20, 0.98, 0.33 respectively. The results showed a narrow detection range for adenosine and a less stability of the bond between the aptamers and AuNPs.

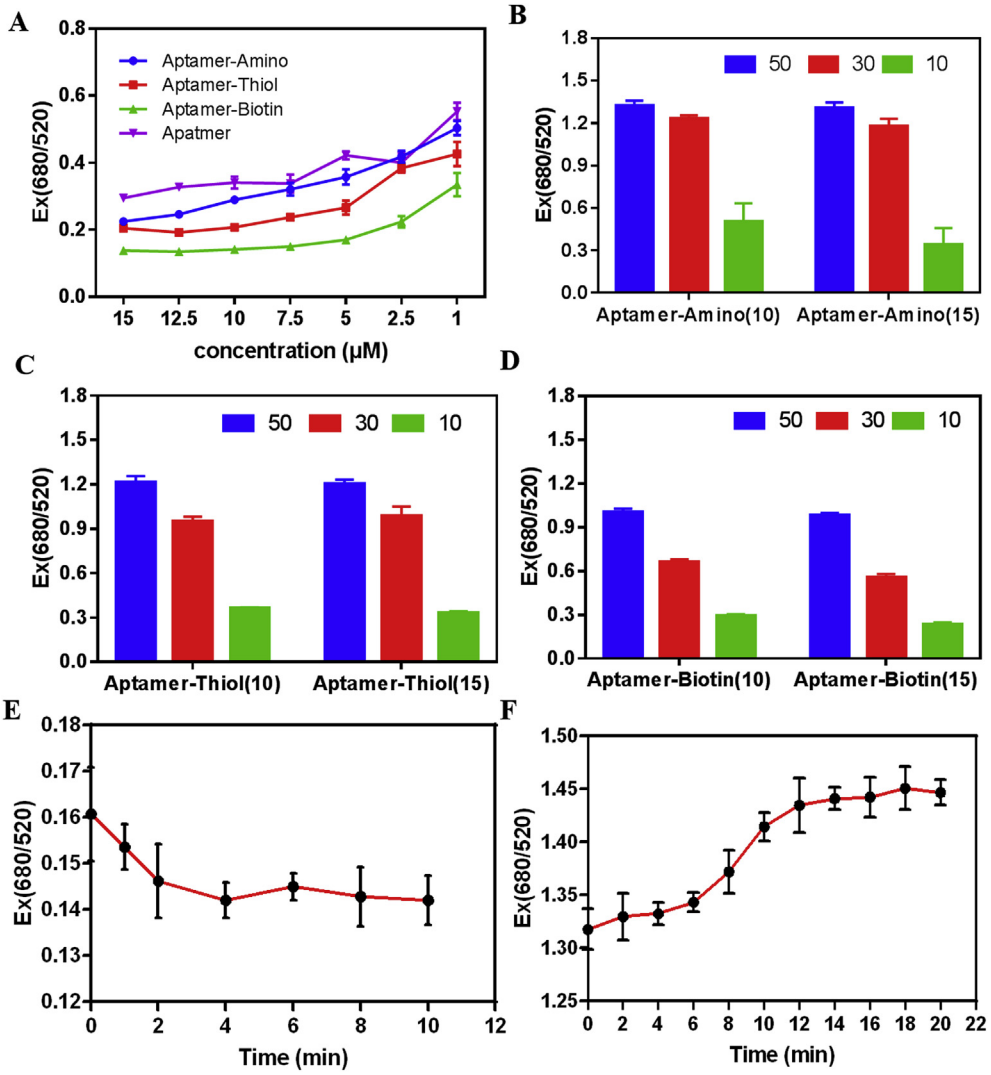

Fig. 3. (A) The values of Ex(680/520) of AuNPs solutions with 3% NaCl solution and different kinds of aptamers at concentrations of 0, 2.5, 5.0, 7.5, 10.0, 12.5, 15 μM. The values of Ex(680/520) of AuNPs solutions added with 3% NaCl solution and 10 or 15 μM Aptamer-Amino (B), Aptamer-Thiol (C) and Aptamer-Biotin (D) with 10, 30, 50 μM adenosine. (E) The value of Ex(680/520) of AuNPs with 10 μM Aptamer-biotin and 3% NaCl after incubating for 0, 2, 4, 6, 8, 10 min. (F) The value of Ex(680/520) of AuNPs with 60 μM adenosine and 10 μM of aptamer was mixed and incubated for 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20 min.

However, the detection of the biotin-modified aptamer showed an excellent result (Fig. 3D). Ex (680/520) of 10 μM aptamer-biotin with 50 μM, 30 μM, and 10 μM adenosine were 1.0, 0.65, 0.29 respectively, and Ex (680/520) of 15 μM aptamer-biotin were 0.97 and 0.55, 0.23 respectively. Compared to the detection with Aptamer-Amino and Aptamer-Thiol, a larger detection range was gained. This result can be attributed to the unique molecular structure of biotin. Biotin has two amino groups that can enhance the electrostatic attraction between aptamers and negatively charged AuNPs. Meanwhile, the sulfur atom in thiophene group of the biotin can also react with AuNPs. Therefore, the bond between the AuNPs with Aptamer-Biotin was the most stable. Similar results was observed by the detection added with 10 μM and 15 μM Aptamer-Biotin, however the detection with 10 μM Aptamer-Biotin showed a better liner relationship. Therefore, 10 μM biotin-modified aptamers were selected for adenosine detection.

To explore the most suitable incubation time, 10 μM of aptamer was added into AuNPs and incubated for different time (0, 2, 4, 6, 8, 10 min). After the incubation, 3% NaCl was added into the mixture to facilitate the aggregation. As showed in Fig. 3 E, the Ex(680/520) of 4 min group was stabled around 0.14 as same as the control group, which meant the surface of AuNPs was wrapped completely by the aptamers. As for the incubation time of the reaction between the aptamer with adenosine, 60 μM adenosine and 10 μM of aptamer were mixed with different incubation time (0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20 min), after that, 3% NaCl was added and then Ex(680/520) was tested. The result is showed in Fig. 3 F. The value of Ex(680/520) was stabled around 1.45 after 12 min, indicating the AuNPs had aggregated completely, which means that most of the aptamers bound to the adenosine in 12 min irreversibly.

3.3. Selectivity of adenosine detection system

Different kinds of homologues compounds, such as guanosine, cytidine, uridine and thymidine were selected to evaluate the selectivity of adenosine detection system. The control group had the same volume of the AuNPs solution and nucleosides. The solution aggregation rate, which indicated the level of AuNPs aggregation, was calculated as showed in formula (1). As Fig. 4 shows, the aggregation rates of mixed solution with 20 μM adenosine or 1 mM cytidine were 0.86 and 0.28 respectively. The aggregation rates of mixed solution added with 1 mM uridine, thymidine, 50 μM guanosine respectively were 0.05. The result showed that the aptamers had very week binding abilities to these nucleosides at those concentration, which means the adenosine detection system has a good selectivity.

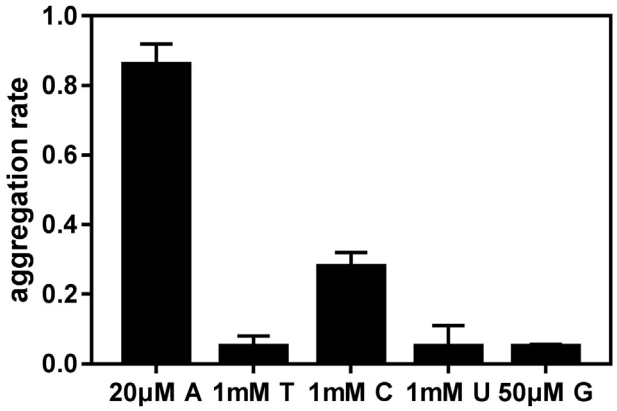

Fig. 4. The aggregation ratio of response to 20 μM adenosine, 1 mM thymidine, cytidine, uridine and 50 μM guanosine respectively.

$$\text{aggregation rate} = \frac{(\text{Ex}(680/520)_{\text{nucleotide}} - \text{Ex}(680/520)_{\text{control}})}{\text{Ex}(680/520)_{\text{control}}} \quad (1)$$

3.4. The performance of the biosensor

Based on the result of optimization, 10 μM biotin-modified aptamers was chosen for the detection of adenosine. The detection results with microplate reader are showed in Fig. 5A and B, the detection range was 5.0–60.0 μM with the LOD of 0.17 μM, and the equation was $y = 0.0180x + 0.105$ with a correlation coefficient of 0.985. For the detection with bionic E-eyes system, the RGB values of the solution was detected and the rate of blue/red was used as the indicator for the aggregation of AuNPs, which was positively correlated with the concentration of adenosine. 5–80 μM adenosine was detected by E-eyes (Fig. 5C), and the linear range (Fig. 5 D) was 5.0–60.0 μM with the LOD of 0.39 μM, the linear equation was $y = 0.013x+1.19$ with a correlation coefficient of 0.9608. By comparison, the detection ranges gained from these two systems were the same, and the detection limit from E-eyes was the double of that from the microplate reader. The result proved that the E-eye system can be a replacement for the microplate reader as a portable adenosine detection instrument. Besides, compared with other methods (Table 1), this adenosine detection system has many advantages, such as suitable detection range, lower cost, easy operation, and most importantly, less detection time.

3.5. The detection in artificial urine

We found that the uric acid could bind with aptamers and affect the detection of adenosine, for its similar structure with adenosine. The uric acid is the end metabolite of various nucleoside and excretes through urine. Therefore, the uricase was added into the solution to eliminate the effect of uric acid. As showed in Fig. 6 A, without uricase, the Ex(680/520) of 1 mM uric acid, 50 μM adenosine and artificial urine was 1.39, 1.34, 1.31 respectively. However, when the uricase was added to preprocess the same solution, the Ex(650/520) of the samples after adding 1 mM uric acid and artificial urine decreased to 0.25 and 0.21 respectively and that after adding the 50 μM adenosine remained 1.34. It showed that uricase could decompose the uric acid and meanwhile the adenosine was unaffected. Therefore, the artificial urine was preprocessed by uric acid and then the 5–80 μM adenosine was detected. The calibration curve of the detection is showed in Fig. 6 B. The linear range was found to be 5.0–50.0 μM with a linear equation $y = 0.025x+0.14$ ($R^2 = 0.9923$). The limit of detection was 0.48 μM.

4. Conclusion

In this work, a sensitive, rapid and in-situ colorimetric aptasensor for adenosine detection was developed by bionic E-eye. The stability of AuNPs with four different aptamers was compared and the 10 μM biotin-modified aptamer was selected for the best. And incubation time of aptamer bound with AuNPs and adenosine was optimizated, which was 4 and 12 min respectively. The selectivity of the aptasensor was tested and the system could distinguish adenosine from other homologues compounds. A homemade biomimetic electronic-eye (E-eye) was established and the performance of the adenosine detection was compared between microplate reader and E-eyes. The linear range was both from 5.0 μM to 60.0 μM and a LOD of 0.17 μM with microplate reader 0.39 μM with E-eyes. Therefore the E-eyes could be a portable

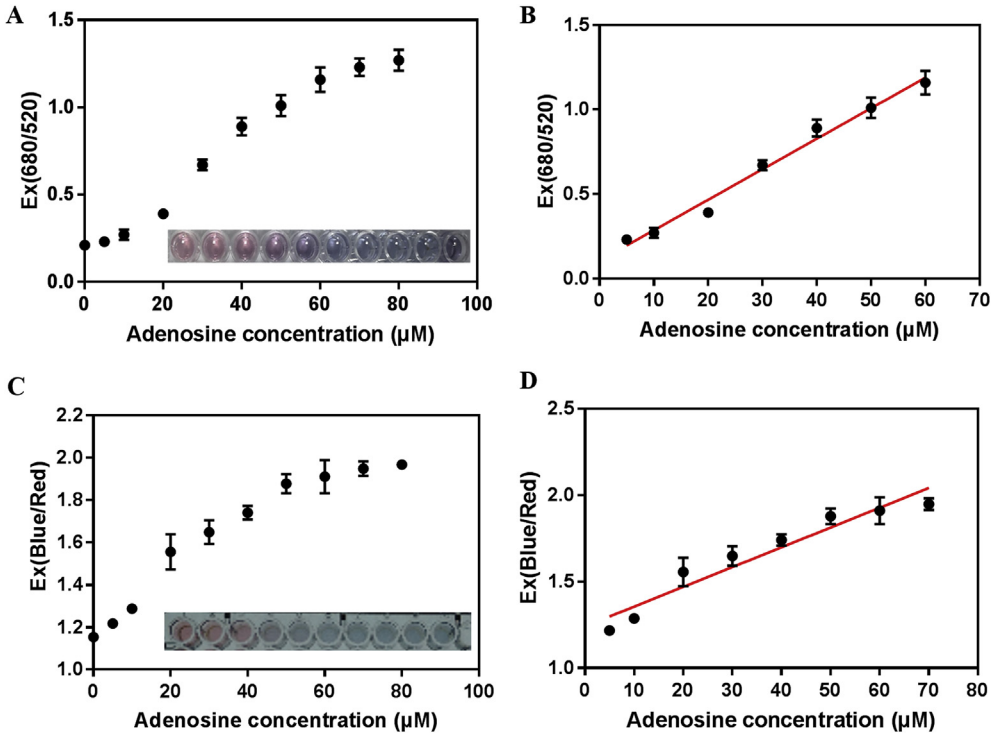

Fig. 5. (A) The S-curve of Ex(680/520) of the detection of adenosine with the microplate reader. (B) The Calibration curves of the detection of adenosine with the microplate reader. (C) The S-curve of Ex(680/520) of the detection of adenosine with the E-eyes. (D) The Calibration curves of the detection of adenosine with the E-eyes.

Table 1
Comparison of the adenosine detection based on aptamers.

Method	Detection Range	Detection Limit	Detection Time	Portability
Fluorescence [35]	30 μM–680 μM	6 μM	4 h	No
Fluorescence [36]	1 μM–100 μM	0.42 μM	7 h 20 min	No
Colorimetric [37]	0.25 mM–1 mM	0.25 mM	30 min	No
Colorimetric [19]	50 nM-6 μM	17 nM	2 h	No
Colorimetric [38]	10 μM - 80 μM	0.3 μM	12.5 h	No
This work	5.0 μM–60.0 μM	0.39 μM	20 min	Yes

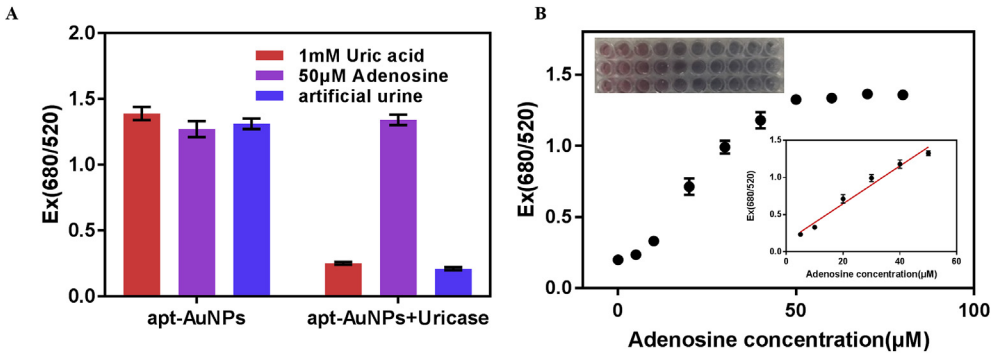

Fig. 6. (A) The Ex(680/520) of 1 mM uric acid, 50 μM adenosine and artificial urine with/without uricase. (B) The value of Ex(680/520) and calibration curves of the detection of adenosine in artificial urine and picture of the color change of the artificial urine with different adenosine concentration. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

replacement of microplate reader for detect the adenosine. In addition, the developed method also exhibits the promising prospect on real sample detection. When the adenosine detection system was in artificial urine, the detection range was from 5.0 to 50.0 μM, and the LOD was 0.48 μM, which means the adenosine detection system can be effectively used in practical applications. Furthermore, the adenosine detection system has many advantages including suitable detection range, low cost, easy operation and rapid in-situ detection. This adenosine detection system may become a promising method for point-of-care applications.

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.

CRediT authorship contribution statement

Shuqi Zhou: Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft. **Ying Gan:** Conceptualization, Methodology, Writing - review & editing. **Liubing Kong:** Methodology, Software. **Jiadi Sun:** Methodology, Writing - review & editing. **Tao Liang:** Visualization, Writing - review & editing. **Xinyi Wang:** Writing - review & editing. **Hao Wan:** Supervision, Writing - review & editing. **Ping Wang:** Supervision, Project administration.

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