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A Cu_2O-Based Photoelectrochemical Sensor for Sensitive and Selective Detection of Glutathione

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Abstract

Glutathione (GSH) plays a crucial role in cellular redox homeostasis, immune regulation, and metabolic processes, and its abnormal expression is closely associated with various diseases. Therefore, the development of sensitive and reliable analytical strategies for GSH detection is of significant importance for disease diagnosis and biomedical research. In this work, a photoelectrochemical (PEC) sensing platform based on a Cu_2O-modified electrode was developed for the sensitive detection of GSH. Owing to its p-type semiconductor characteristics, Cu_2O exhibits strong resistance to interference from reductive substances in complex biological environments. More importantly, Cu_2O can react with the thiol group of GSH through a redox process, leading to structural variation of the Cu_2O surface and consequently inducing a measurable change in the photocurrent signal. The Cu_2O photoelectrode was fabricated on an indium tin oxide (ITO) substrate via electrodeposition and systematically characterized by cyclic voltammetry, electrochemical impedance spectroscopy, and photoelectrochemical measurements. Experimental conditions, including electrodeposition time, applied bias, and reaction time, were optimized to achieve optimal sensing performance. Under the optimized conditions, the PEC sensor exhibited a linear response toward GSH in the concentration range of 1 - 40 μM with a detection limit of 0.38 μM (S/N = 3). In addition, the sensor demonstrated excellent selectivity against various interfering biomolecules and showed satisfactory reproducibility. This study provides a simple and effective PEC sensing strategy for GSH detection and highlights the potential of Cu_2O-based photoelectrodes for biochemical analysis and biomedical applications.

Keywords

GSH, Cu_2O, Photoelectrochemical

1. Introduction

Glutathione (GSH) plays a pivotal role in maintaining cellular redox homeostasis, as well as in immune regulation and metabolic processes [1]. Abnormal expression of GSH has been closely associated with a variety of diseases, including diabetes, Parkinson's disease, Alzheimer's disease, and various cancers. Therefore, the development of highly sensitive methods for GSH detection is of great significance for early disease diagnosis and therapeutic intervention [2]-[4]. In recent years, considerable efforts have been devoted to the development of analytical strategies for GSH detection. For instance, Liu *et al.* reported a fluorescent probe for the selective detection of GSH in living systems [5], while Zhou *et al.* developed an electrochemiluminescence-based approach, thereby expanding the available methodologies for GSH analysis [6]. These techniques enable the assessment of cellular physiological states and even provide insights into disease progression. However, most of these methods rely on a single signal output, which is inevitably susceptible to interference from complex biological backgrounds, thus limiting their analytical accuracy and reliability. Consequently, the development of novel sensing strategies with improved anti-interference capability remains highly desirable.

Photoelectrochemical (PEC) analysis has emerged as an advanced analytical technique that integrates the advantages of photochemistry and electrochemistry, enabling significantly reduced background signals and enhanced detection sensitivity [7] [8]. Owing to its superior analytical performance and compatibility in complex biological environments, PEC provides a promising platform for the sensitive detection of disease biomarkers [9]. In the design of high-performance PEC sensors, the choice of photoactive materials is of critical importance. Based on their semiconductor properties, these materials are generally classified as n-type and p-type. n-Type semiconductors, typically employed in anodic PEC systems, can generate pronounced photocurrent responses. However, the adsorption of reductive species at the electrode interface often induces nonspecific signal variations, thereby compromising detection selectivity, particularly in complex biological matrices [10]. In contrast, p-type semiconductors, where holes act as the majority charge carriers, are commonly utilized in cathodic PEC systems. The directional transfer of photogenerated electrons from the electrode to the solution effectively suppresses interference from reductive species, endowing these systems with superior anti-interference capability. Therefore, p-type photoactive materials are more suitable for GSH detection. Importantly, to achieve high specificity, the selected material should be capable of undergoing specific interactions with GSH, such as bond energy variation or functional group transformation, thereby translating molecular recognition events into measurable photocurrent signals.

Based on the above considerations, the selection of an appropriate p-type photoactive material is crucial for constructing high-performance PEC sensing platforms. Cuprous oxide (Cu_2O), a typical p-type semiconductor, has attracted considerable attention as a photocathode material due to its excellent resistance to

interference from reductive species in complex biological environments, enabling stable photoelectrochemical performance [11]. In addition, Cu_2O possesses a suitable bandgap that allows efficient light absorption in the visible region, endowing it with great potential for photoelectric conversion. Upon illumination, Cu_2O can effectively generate and separate photogenerated charge carriers, facilitating the conversion of light energy into measurable electrical signals, which is essential for sensitive PEC sensing [12] [13]. Moreover, Cu_2O exhibits low cytotoxicity and good biocompatibility, making it particularly advantageous for applications in biological systems. Compared with many other inorganic materials, it causes minimal cellular damage and does not induce significant cytotoxic responses. These characteristics collectively render Cu_2O a promising candidate for photoelectrochemical sensing and biomedical analysis.

Based on the above considerations, in this work, we developed a three-electrode PEC sensing platform based on photoactive materials for the sensitive and selective detection of GSH. This strategy enables accurate analysis of intracellular redox states and provides valuable insights into oxidative stress-related biological processes and disease progression.

2. Experimental Section

Reagents such as GSH, BSA, and Asp were purchased from Aladdin (Shanghai, China). ITO were purchased from Nanjing Geology Technology Co. (Nanjing, China). All solutions were prepared in ultrapure water using a Millipore Milli-Q system (Billerica, MA).

Experimental Setup

All current measurements were recorded with a CHI-660E electrochemical workstation (Chenhua, China). The electrolyte used for the tests was a 5 mM $K_3[Fe(CN)_6]/K_4[Fe(CN)_6]$ (1:1) and 0.1 M KCl solution. Data were analyzed with Origin 2024. Preparation of ITO electrode: The borosilicate capillaries were soaked in piranha solution (98% H_2SO_4:30% H_2O_2 = 3:1) for 1 h before the ITO electrodes were drawn, then cleaned with deionized water to ensure that the residual piranha solution in the tubes was washed, and vacuum-dried at 60˚C for use.

50 mM CH_3COONa and 1 M $Cu(CH_3COO)_2$ to 50 mL of deionized water, and stir vigorously for 30 minutes until thoroughly mixed to obtain the electroplating solution. A nanotube sputtered with a platinum film was used as the working electrode, a commercial platinum rod as the counter electrode, and a commercial Ag/AgCl electrode as the reference electrode. On an electrochemical workstation, in *I-t* mode, a constant potential of −0.2 V was applied and maintained for 100 s. The electrode was then removed, rinsed with deionized water, and dried, completing the preparation of the Cu_2O working electrode.

3. Results and Discussion

Cu_2O, as a p-type photocathode material, exhibits excellent resistance to interfer-

ence from reductive species in complex biological environments, enabling stable photoelectrochemical responses. More importantly, Cu_2O can specifically interact with the thiol (–SH) group of GSH through a redox process, leading to structural and electronic variations at the electrode surface, which are subsequently translated into measurable changes in the photocurrent signal. Specifically, during this process, the copper species in Cu_2O are reduced to lower-valence Cu^+ by GSH, while GSH is oxidized to glutathione disulfide (GSSG). This interfacial redox reaction modulates the photoelectrochemical properties of Cu_2O, thereby enabling sensitive signal transduction for GSH detection. The reaction can be described as follows (Figure 1):

$$Cu_2O + 2GSH \rightarrow 2Cu^+ + GSSG + H_2O$$

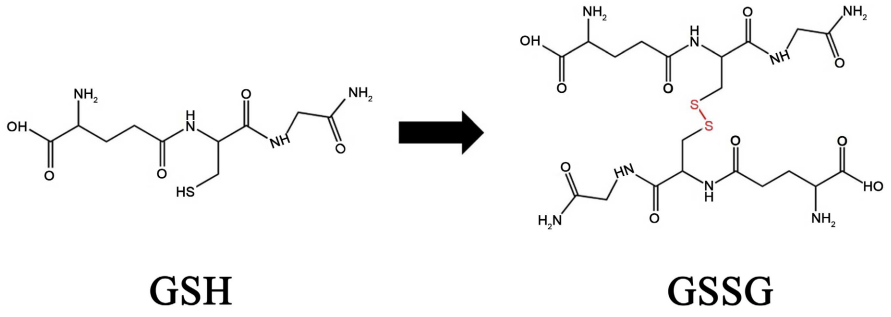

Figure 1. Schematic diagram of the GSH-to-GSSG transformation.

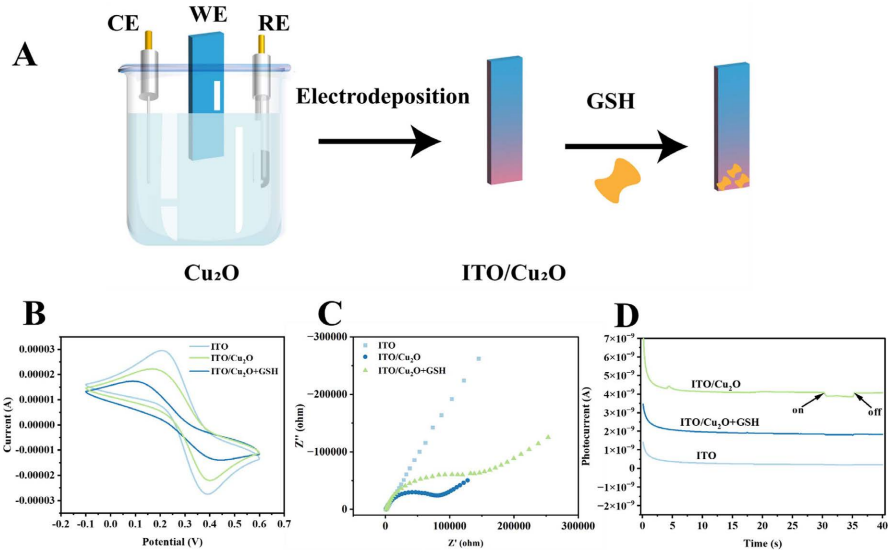

Figure 2. (A) Schematic diagram illustrating the GSH-based detection principle for Cu_2O; (B) CV curves for ITO, ITO/Cu_2O, and ITO/Cu_2O + GSH; (C) EIS curves for ITO, ITO/Cu_2O, and ITO/Cu_2O + GSH; (D) PEC curves for ITO, ITO/Cu_2O, and ITO/Cu_2O + GSH.

As shown in Figure 2(A), an ITO/Cu_2O electrode was successfully prepared by uniformly depositing Cu_2O onto the surface of an ITO electrode via electroplating. Subsequently, the electrode was placed in a GSH environment. Based on a redox

mechanism, copper ions on the Cu_2O surface interacted with the –SH groups of GSH, causing changes in the structure and electronic state of Cu_2O, while GSH was oxidized to GSSG. This interfacial reaction modulated the photoelectrochemical properties of Cu_2O, leading to significant changes in the photocurrent signal and thereby enabling the detection of GSH. Specifically, when Cu_2O reacts with GSH, a coordination reaction occurs, forming a coordination complex. This complex deposits on the surface of the Cu_2O electrode, hindering the transport of photo-generated electrons and thereby causing a weakening of the photoelectric signal. This reaction-driven sensing strategy not only provides a new approach for GSH detection but also offers new insights for the design of PEC-based biosensors.

To verify the electrode fabrication process and its feasibility, a series of electrochemical and photoelectrochemical characterizations were performed. As shown in **Figure 2(B)**, the bare ITO electrode exhibits a relatively high oxidation peak current in cyclic voltammetry (CV) due to its excellent conductivity and rapid electron transfer kinetics. Upon stepwise modification with Cu_2O and its reaction products with GSH, the CV peak current gradually decreases, indicating the progressive coverage of the electrode surface by the Cu_2O/GSH layer. Consistently, electrochemical impedance spectroscopy (EIS) results (**Figure 2(C)**) reveal a gradual increase in charge transfer resistance, further confirming the successful formation of the interfacial layer. In addition, the photoelectrochemical performance of the as-prepared Cu_2O electrode was evaluated. The results demonstrate that the Cu_2O electrode exhibits a distinct cathodic photocurrent under illumination. After reacting with GSH, a significant decrease in photocurrent is observed, indicating a sensitive response toward GSH and preliminarily confirming the feasibility of the proposed sensing platform.

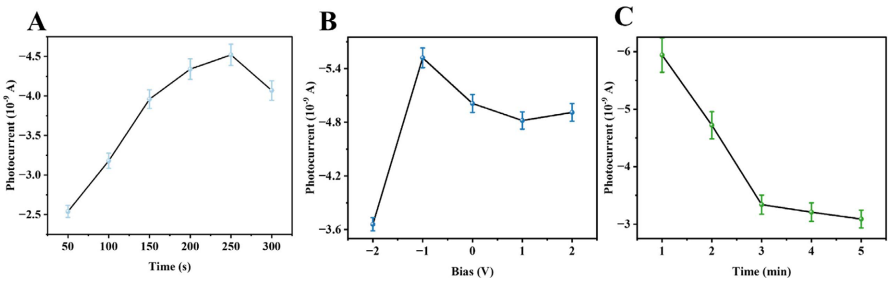

Figure 3. Optimization of Experimental Conditions (A) Optimization of electroplating time; (B) Optimization of bias voltage; (C) Optimization of reaction time.

To achieve optimal sensing performance, key experimental parameters were systematically optimized. First, the electrodeposition time of Cu_2O was investigated. As shown in **Figure 3(A)**, the photocurrent gradually increases with increasing deposition time and reaches a maximum at 250 s. Beyond this point, the photocurrent decreases, which can be attributed to the excessive thickness of the Cu_2O layer that hinders charge transfer. Therefore, 250 s was selected as the opti-

mal electrodeposition time. Subsequently, the applied bias was optimized. As illustrated in Figure 3(B), the photocurrent response of the Cu_2O electrode was evaluated under different bias potentials, and the maximum photocurrent was obtained at −1 V. Accordingly, −1 V was chosen as the optimal working potential.

In addition, the reaction time between Cu_2O and GSH was examined. Using 1 μM GSH as a model system, the effect of reaction time on the photocurrent response was evaluated. As shown in Figure 3(C), the signal gradually stabilizes with increasing reaction time and reaches a plateau after 3 min. Therefore, 3 min was selected as the optimal reaction time for subsequent experiments.

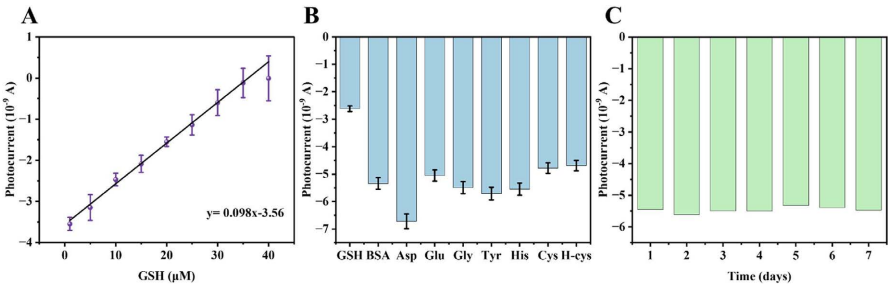

Figure 4. Sensor Performance (A) Linearity of copper (I) oxide in detecting GSH; (B) Selectivity testing; (C) Stability testing.

The sensing performance of the integrated micro photoelectrode was subsequently evaluated. As shown in Figure 4(A), the photocurrent signal gradually decreases with increasing GSH concentration, indicating a sensitive response of the system toward GSH. Further analysis reveals a good linear relationship between the photocurrent response and GSH concentration in the range of 1 - 40 μM. The corresponding linear regression equation is $y = 0.098 - 3.56x$ with a correlation coefficient (R^2) of 0.99. The limit of detection (LOD) was calculated to be 0.38 μM at a signal-to-noise ratio (S/N) of 3, demonstrating the high sensitivity of the proposed sensing platform. To evaluate the selectivity of the sensor, several potential interfering species, including Glu, His, Gly, Asp, Tyr, Cys, H-cys, and bovine serum albumin (BSA), were investigated under identical conditions. As shown in Figure 4(B), only GSH induces a significant photocurrent response, while negligible changes are observed for other analytes, indicating excellent selectivity of the sensor (n = 3). The reproducibility of the sensor was assessed using seven independently fabricated micro photoelectrodes from the same batch. As presented in Figure 4(C), the photocurrent responses are highly consistent, confirming the good reproducibility and reliability of the fabrication process (RSD = 0.082, n = 7).

4. Conclusion

In summary, a Cu_2O-based photoelectrochemical sensing platform was successfully developed for the sensitive detection of glutathione. The Cu_2O photoelectrode was fabricated through a simple electrodeposition method on an ITO sub-

strate, forming a stable photoactive interface. Benefiting from the p-type semiconductor characteristics of Cu_2O, the constructed sensor exhibits strong anti-interference capability in complex environments. The detection mechanism relies on the redox reaction between Cu_2O and the thiol group of GSH, which induces structural variation of the Cu_2O surface and leads to a measurable decrease in photocurrent. After systematic optimization of experimental parameters, including electrodeposition time, applied bias, and reaction time, the sensor demonstrated excellent analytical performance with a linear detection range from 1 to 40 μM and a detection limit of 0.38 μM. Moreover, the sensor exhibited high selectivity toward GSH over other amino acids and proteins, as well as good reproducibility among independently prepared electrodes. Overall, this work presents a simple and efficient PEC sensing strategy for GSH detection and provides new insights into the application of Cu_2O-based photoelectrodes in biochemical sensing. Although we have not yet conducted cell or serum experiments, this strategy still offers a potential research direction for detection in the field of biology.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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