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Review

Recent advances in graphene-based biosensors

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ABSTRACT

A detailed overview towards the advancement of graphene based biosensors has been reviewed. The large surface area and excellent electrical conductivity of graphene allow it to act as an "electron wire" between the redox centers of an enzyme or protein and an electrode's surface. Rapid electron transfer facilitates accurate and selective detection of biomolecules. This review discusses the application of graphene for the detection of glucose, Cyt-c, NADH, Hb, cholesterol, AA, UA, DA, and H_2O_2. GO and RGO have been used for the fabrication of heavy metal ion sensors, gas sensors, and DNA sensors. Graphene based FETs have also been discussed in details. In all these cases, the biosensors performed well with low working potentials, high sensitivities, low detection limits, and long-term stabilities.

Contents

Abbreviations: A, adenine; AA, ascorbic acid; Ab, antibody; AuNP, gold nanoparticle; BDD, boron doped diamond; CdS, cadmium sulfide; CEA, carcinoembryonic antigen; CEEs, chloroethylethyl sulfide; β-CD, β-cyclodextrin; C, cytosine; CMG, chemically modified graphene; CNT, carbon nanotube; CNF, carbon nanofiber; CRG, chemically reduced graphene; CR-GO, chemically reduced graphene oxide; CS, chitosan; CVD, chemical vapor deposition; CV, cyclic voltammetry; Cyt-c, cytochrome c; DA, dopamine; DET, direct electron transfer; DMMP, dimethylmethylphosphonate; DNA, deoxyribonucleic acid; DNT, dinitrotoluene; D_2O, heavy water; DPV, differential pulse voltammetry; EDTA, ethylenediamine triacetic acid; EG, epitaxial graphene; EIS, electrochemical impedance spectroscopy; ET, electron transfer; Fe_3O_4, iron (II, III) oxide; FET, field effect transistor; G, guanine; GC, glass carbon; GO, graphene oxide; GOx, glucose oxidase; GR, graphene; Hb, hemoglobin; HCN, hydrogen cyanide; HOPG, highly oriented pyrrolytic graphite; HRP, horseradish peroxide; IL, ionic liquid; H_2O_2, hydrogen peroxide; IgE, immunoglobulin; ITO, indium tin oxide; $LiTaO_3$, lithium tantalite; MB, molecular beacons; Mb, methylene blue; MG, methylene green; MGNF, multilayer graphene nanoflake; MnO_2, manganese dioxide; NADH, nicotinamide adenine dinucleotide; NP, nanoparticle; PANIw, polyaniline nanowire; PB, Prussian blue; PBS, phosphate buffer solution; PE-CVD, plasma-enhanced chemical vapor deposition; PMMA, poly(methyl methacrylate); ppb, parts per billion; ppm, parts per million; PSS, polystyrene sulfonate; PSSA-g-PPY, poly(styrenesulfonic acid-g-pyrrole); PtNP, platinum nanoparticles; PPy, polypyrrole; RGO, reduced GO; rGSFs, reduced graphene sheet film (rGSF); RNA, ribo nucleic acid; RSD, relative standard deviation; SDBS, sodium dodecyl benzene sulfonate; Sic, silicon carbide; SRB, sulfate-reducing bacteria; ssDNA, single strand deoxyribonucleic acid; S/N, signal to noise background ratio; T, thymine; UA, uric acid.

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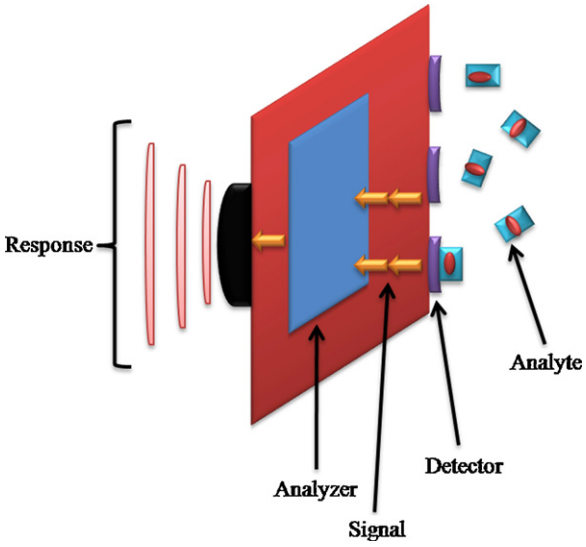

Fig. 1. Schematic presentation of a biosensor.

1. Introduction

The historic development of enzyme electrodes by Leland C. Clark in 1962 opened a new area of research in medical science and technology (Clark and Lyons, 1962). Research on enzyme electrodes in various fields such as physics, chemistry, material science and biotechnology has resulted in more sophisticated and trustworthy biosensors. They are suitable for application in medicine, agriculture, biotechnology, as well as by the military and in bioterrorism detection and prevention (Wang, 2008; Chaubey and Malhotra, 2002; Yogeswaran and Chen, 2008). Recent work has examined 'reagentless systems', in which reagents are already immobilized and do not need to be added by the user (Schuhmann et al., 1993; Schmidt and Schuhmann, 1995; Senillou et al., 1999). Biosensors comprise a selective interface in close proximity to or integrated with a transducer, which relays information about interactions between the surface of the electrode and the analyte either directly or through a mediator (Fig. 1) (Yogeswaran and Chen, 2008). Biosensors can be categorized depending on the transducing mechanism: (i) resonant biosensors, (ii) optical-detection biosensors, (iii) thermal-detection biosensors, (iv) ion-sensitive FET biosensors, and (v) electrochemical biosensors (Chaubey and Malhotra, 2002). Electrochemical biosensors possess advantages over the others because their electrodes can sense materials present within the host without damaging the system (Chaubey and Malhotra, 2002). However, the sluggish ET of the biomolecules limits electrochemical efficiencies of the sensors (Kim et al., 2007; Huang et al., 2010a,b; Shao et al., 2010; Wang, 2005). This is because of the structural features of the proteins and their unfavorable orientations at the surface of the electrodes. Generally electroactive prosthetic groups are embedded deep within the protein structure. To minimize the ET distance, nanomaterial "electron wires", should be incorporated between the redox centers of the enzyme or protein and the electrode's surface (Shao et al., 2010).

Nanotechnology has allowed new applications of nanomaterials in electrochemical sensors and biosensors (Yogeswaran and Chen, 2008). Various nanomaterials, including metal NP, metal alloy NP, magnetic NP, nanowires, CNT, and CNF have been used as electrical connectors between the electrodes and the redox centers of the biomolecules (Shao et al., 2010; Kim et al., 2007; Huang et al., 2010a,b; Sun et al., 2001; Shi and Ma, 2010; Haun et al., 2010; Yun et al., 2007). The use of metallic NP as biosensors is problematic because of their inconsistent signal amplification. The existence of CNT with metallic impurity is the main drawback while using in the modification of electrode (Pumera, 2009, 2010). Such metallic impurities are electrochemically active and can dominate the electrochemistry of CNT. Impurities present at 50 ppm can be toxicological hazards as they can participate in redox reactions with the biomolecules (Pumera, 2009).

The discovery of graphene in 2004, added a new dimension to electrochemical biosensor research (Novoselov et al., 2004). The use of graphene can avoid the problems associated with metal alloy NP and CNT. The unique properties of graphene (fast electron transportation, high thermal conductivity, excellent mechanical flexibility and good biocompatibility) give it potential applicability in electrochemical biosensors (Pumera, 2009; Pumera et al., 2010; Allen et al., 2010; Brownson and Banks, 2010). Table 1 shows the comparative study of biosensing efficiency between CNT-based and graphene-based biosensors. Proper conjugation between biological molecules such as enzymes, ssDNA, RNA, Ab, receptors, and aptamers needs to be developed for graphene based electrochemical sensing electrodes. Appropriate functionalization of graphene and the immobilization of biomaterials on it are important, as functional groups can create defects on graphene surfaces (Shao et al., 2010).

1.1. Synthesis of graphene

There are several reported methods for the syntheses of graphene (Choi et al., 2010; Dreyer et al., 2010; Kuila et al., 2010; Park and Ruoff, 2009), including exfoliation and cleavage of natural graphite, CVD, PE-CVD, electric arc discharge, micromechanical exfoliation of graphite, epitaxial growth on electrically insulating surfaces, such as SiC, opening CNT and the solution-based reduction of GO (Choi et al., 2010; Kim et al., 2009; Kuila et al., 2010). Novoselov et al. (2004) discovered graphene sheets after the mechanical exfoliation of HOPG, a method now known as the scotch-tape method. Since their discovery, researchers have