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Mini review

Research Progress and Application Prospects of Electrochemical Glucose Sensors

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The detection of glucose plays an important role in the diagnosis, treatment and control of human diseases. The enzyme-based electrochemical sensors for glucose detection have the advantages of high sensitivity, good selectivity and mild conditions. However, the enzyme activity is easily interfered by external conditions, which limits the application of enzyme-based sensors. By contrary, enzyme-free sensors can overcome these shortcomings and achieve continuous glucose monitoring. Recently, various materials have been developed and applied for electrochemical detection of glucose. This review summarized the recent progress and application prospects of enzyme-based and enzyme-free electrochemical glucose sensors.

Keywords: Electrochemical glucose sensor; glucose oxidase; enzyme-free; nanomaterials; wearable sensor

1. INTRODUCTION

Glucose is the most widely distributed and important monosaccharide in nature. It plays an important role in the field of biology. Since glucose was isolated from beet roots by Margraves and co-workers in 1717, its physical and chemical characters have been widely investigated [1, 2]. The fasting level of glucose in the normal human blood is in the range of 4 ~ 6 mM. Hypoglycemia and hyperglycemia have adverse effects on human health. For example, hypoglycemia can make people feel hungry or comatose, while hyperglycemia can increase the risk of diabetes under certain circumstances. The benefit of strict control on the blood glucose concentration in diabetic patient has been universally acknowledged. Monitoring of blood glucose has markedly reduced the risk of diseases caused by diabetes, making the diabetic patient keep a healthier life, and avoiding expensive and fatal complications of advanced diabetes. In addition, the determination of glucose content is also one of the indicators to measure the quality of fruits and vegetables, which can be used as a reference for fruit and vegetable cultivation. For these considerations, accurate, fast, simple and real-time determination of glucose is of great importance for clinical diagnosis and food industry. At present, there are many kinds of detection methods for quantitative analysis of glucose, including fluorescence, UV-Vis spectroscopy, mass spectrometry, electrochemistry, electrochemiluminescence and so on [3-5]. Among them, electrochemical methods have gained more and more interest because of their merits including low cost, fast response and simple operation [6]. Electrochemical glucose sensors have been commercialized and widely used especially in clinical analysis. In this review, we summarized the progress and application prospects of electrochemical glucose sensors, which can be divided into enzyme-based and enzyme-free sensors. Furthermore, wearable devices for monitoring blood glucose were also addressed.

2. ENZYME-BASED SENSORS

Enzyme-based amperometric glucose sensors have experienced three generations of changes (Fig. 1) [7]. Glucose oxidase (GOx) is the most common enzyme and the basis of many glucose sensors. It not only has high selectivity for the catalytic oxidation of glucose, but also can withstand various pH and temperature [8]. In addition, glucose dehydrogenase (GDH) is another kind of enzyme used to construct glucose sensors. The enzymes can be classified according to the cofactors including flavin adenine dinucleotide (FAD), nicotinamide adenine dinucleotide (NAD) or pyrroloquinoline quinone (PQQ) [2]. Among them, FAD and PQQ are closely bound to GDH, while NAD is not bound to GDH. Although GDH is oxygen-independent, the specificity of FAD-GDH and PQQ-GDH is lower than that of GOx [7]. In addition, oxidoreductases usually cannot directly exchange the electron with electrode because of the steric distance between electrode and redox centre of enzyme. Thus, the immobilized enzymes require a small-molecule redox mediator or structured electrode to transport the electron to the sensor surface.

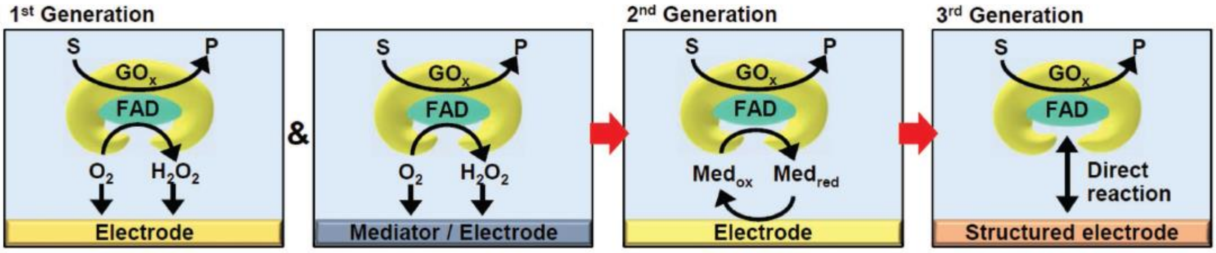

Figure 1. Generations and sensing principles of the enzymatic glucose sensor. Reprinted with permission from reference [7]. Copyright 2018 John Wiley and Sons.

2.1 First generation of enzyme-based glucose sensors

In 1962, the GOx-modified Pt electrode was prepared by Leland C. Clark and used for the quantitative detection of blood glucose [9]. This marks the birth of the first generation of sensors. The first generation of glucose sensor usually relies on the GOx-catalyzed glucose oxidation and the measurement of the consumed H_2O_2 or O_2 [10]. The advantages of the first-generation glucose sensors are simplicity and low cost, and provide miniaturized applications for in clinic. However, the high potential for detection of the produced H_2O_2 limits the application due to the coexistence of other electroactive substances such as paracetamol (AP), ascorbic acid (AA) or uric acid (UA) with glucose [7, 11]. In the past, a lot of attempts have been made to eliminate the interference from these electroactive substances [2]. Usually, two main strategies have been used: one is to reduce the overpotential of the oxidation-reduction reaction of H_2O_2 by electrocatalyst, and the other is to modify a selective permeation membrane with anti-interference ability on the electrode surface.

Biomimetic nanomaterials (nanoenzymes) with enzyme-like activity have attracted extensive attention for the last few years. Among them, nanozymes, which mimic oxidase and peroxidase, are expected to realize the detection of glucose. This interest relies on the uniqueness of nanoenzymes. In constrat to natural enzymes, nanoenzymes show high catalytic activity, tolerance to pH or temperature change, low cost and ease of large-scale preparation [12]. For instance, nanoparticles with peroxidase-like activity have been merged into the designing of the first-generation glucose sensor [13]. The catalytic rate constant for H_2O_2 reduction by Pb nanoparticles (NPs) is significantly improved. Compared with natural enzymes, the catalytic rate constant of these nanoenzymes for 570 nm PbNPs was increased by 4 orders of magnitude, indicating that the combination of these nanoenzymes with GOx has broad application prospects in glucose detection. Willner's group found that the hemin/G-quadruplex can act as a HRP-mimicking ribozyme for electrocatalytic reduction of H_2O_2 [14]. In this work, H_2O_2 produced by GOx is electrocatalytically reduced. Metal organic frameworks (MOFs) are organic-inorganic hybrid materials with intramolecular pores formed by self-assembly of organic ligands and metal ions or clusters through coordination bonds. In recent years, MOFs have been widely used in various fields. Xie's group developed a sensor for measuring glucose, in which MOF composites were coated with GOx on the gold electrode [15]. However, the clinical application of the electrode was limited due to the high potential (0.7 V).

2.2 Second generation of enzyme-based glucose sensors

Although the first generation of enzyme-based glucose sensors have the above advantages, the oxygen-dependence and the interference of electroactive substances still make researchers to develop alternative co-reaction substrates. Using the synthesized electron acceptor instead of O_2, the electron is transported from the enzyme's active center to electrode surface. The electron transfer has fast kinetics and good reversibility at low overpotential. Based on the medium of PQQ-GDH and ferrocene (Fc), the electrochemical blood glucose meter was offered for the first time by Medisense company [8]. This promoted the commercialization of glucose sensor and completely changed the self-monitoring of diabetic patients. After that, various organic/inorganic chemicals have been used as the electronic mediators, such as Fc derivatives, $[Fe(CN)_6]^{3-/4-}$, and Os^{2+}/Os^{3+} complexes [2]. These media have the advantages of low potential, high chemical stability, fast reaction with reduced enzyme and low water solubility.

Carbon nanostructures such as graphene and carbon nanotubes are widely used to support these redox media. It can not only minimize the possibility of medium leaching, but also make the electron transfer rate more efficient. For example, Fc was covalently linked with graphene oxide (GO) to form the graphene dielectric complex, which was further used for binding with GDH enzyme [16]. Other two-dimensional nanomaterials have also attracted people's attention. For example, Pumera's group designed the second-generation glucose sensors with various two-dimensional nanostructures, including MoS_2, WS_2, WSe_2, and $MoSe_2$ [17]. It was found that the conductivity and electrochemical response of WS_2 and WSe_2 were better than that of their counterparts. The detection limits of WSe_2- and WS_2-modified electrodes are 52 mM and 82.6 mM, respectively. Parlak and co-workers integrated these two-dimensional layered nanomaterials with other nanostructures and deposited AuNPs on the MoS_2-modified electrode, enhancing the signal and preventing the aggregation of nanomaterials [18]. Lee's group indicated that Au_{25} nanoclusters can be used as the counter anions of imidazole (Fig. 2) [19]. The Au_{25}-ionic liquids were prepared for the construction of GOx-based glucose sensor. The high sensitivity is owing to the significant affinities of the liquids for enzyme substrates, as well as the high redox mediated properties and high conductivity of Au_{25} nanoclusters.

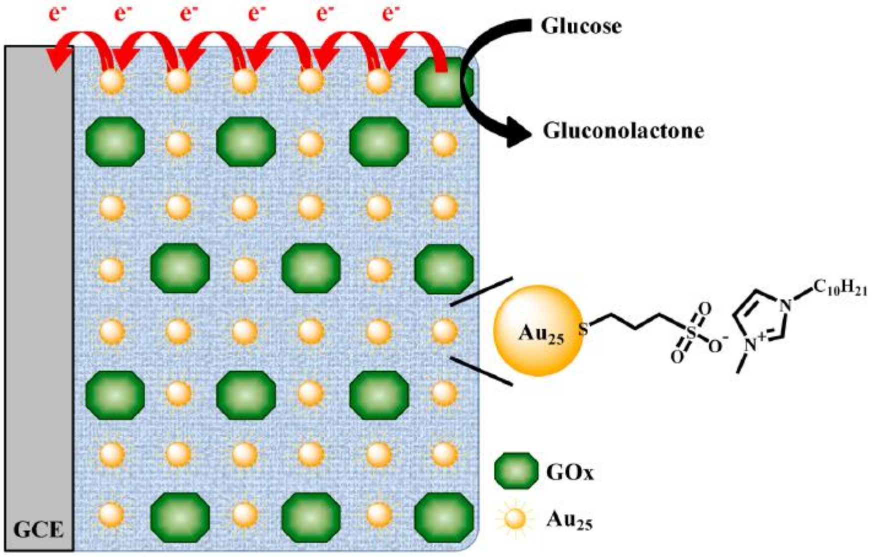

Figure 2. Schematic illustration of processes occurring in a GOx-DMIm-Au25 composite electrode. Au25-mediated electrooxidation of glucose-reduced GOx and ensuing electron hopping transport through Au25 sites in a GOx-DMIm-Au25 composite electrode. The anodic current is proportional to the concentration of glucose, which forms the basis for amperometric detection of glucose. Reprinted with permission from reference [19]. Copyright 2014 American Chemical Society.

2.3 Third generation of enzyme-based glucose sensors

The third generation of enzyme-based glucose sensor is based on the direct electron transfer (DET) between the redox center of enzyme and electrode in the absence of mediator. Compared with the first and second generation of enzyme-based glucose sensors, third-generation sensor can work under the conditions near the redox potential of enzyme, and requires neither O_2 nor other electroactive molecule as the electron mediator. However, the active center of the catalytic enzyme is hidden in the interior of the molecule, and the enzyme fixed on the surface of the electrode is easy to be allosteric, resulting in the decrease of catalytic activity. For this view, a large number of studies have shown that nanomaterials can shorten the electron tunneling distance between the enzyme and the electrode surface through the partial expansion of enzyme in the adsorption process, thus increasing the accessibility of redox center and promoting the DET [2]. However, this topic has been controversial since many evidences are opposed to the DET property of nanostructured electrode. For example, Bartlett and co-workers suggested that the redox peak at near ±0.4 V may not be attributed to the DET between GOx and electrode since the impurities from commercial enzyme sources such as flavin and catalase can be adsorbed on the surface [20]. The adsorption of FAD during enzymatic denaturation has shown the redox behavior. Wilson suggested that nanomaterial with the similar size to enzyme may produce a strain in protein when the enzyme was immobilized onto the electrode, thus leading to FAD extrusion [21]. However, few literatures provide the evidences for DET by directly catalyzing the oxidation of glucose at a negative potential near the redox potential of enzyme. It has been shown that GOx immobilized on the boron doped diamond (BDD) electrode functionalized with aminopropyltriethoxysilane (APTES) by glutaraldehyde crosslinking of APTES and amino group promoted the DET reaction (Fig. 3) [22]. APTES/glutaraldehyde-conjugated compounds provide the electron tunneling channel to connect the active centre of enzyme with BDD. The signal was collected in the O_2-free solution, indicating that the current response is produced by DET and glucose is directly oxidized by GOx. In this process, $FADH_2$ is reduced to $FADH_2$. Glucose was detected in ± 0.4V and AA and UA showed no interference.

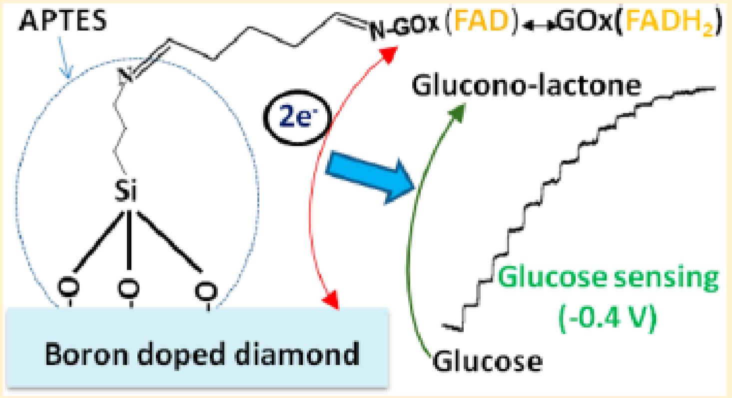

Figure 3. Schematic Illustration for the Chemical Functionalization of the BDD Surface with APTES and GOx by Glutaraldehyde Cross-Linking. Reprinted with permission from reference [22]. Copyright 2014 American Chemical Society.

In the past decade, several groups have explored reasonable investigations to verify the DET. A typical example is the modification of GOx with free mercaptan groups, and maleimide-modified AuNP was connected to the enzyme close to its active site (Fig. 4) [23]. This made the bound enzyme be wired to the electrode. According to the crystal structure of natural GOx, five mutations were found with different distances near the active centre of FAD. Compared with other mutants, H447C mutant has the shortest distance from the introduced cysteine and FAD cofactor. The H447C-AuNP conjugates exhibited a higher current for glucose oxidation. Despite this, the DET behavior is still questionable because AuNP can serve as the electron shuttle between the redox center of enzyme and electrode. Therefore, the method should belong to the second-generation sensor. In addition, enzymatic degumming can help to shorten the tunnel distance between enzyme and electrode, thus providing an alternate way for designing of glucose sensors. Hall's group studied the electron transfer efficiency of a non-glycosylated mutant of GOx [24]. The mutant GOx was immobilized on the electrode by the polyhistidine group. The mutant made the enzymes closer to the electrode and achieved the fast DET in anaerobic solution (~350 s^{-1}). Furthermore, the purified and deglucosed GOx was attached onto the electrode surface for investigation by Courjean and co-workers [25]. The strong catalytic reaction to glucose was observed with a half wave potential near -0.4 V. In general, despite many efforts to explore the DET-based glucose sensors, this topic is still controversial and challenging. To date, none of reports can prove a reliable DET sensing mechanism.

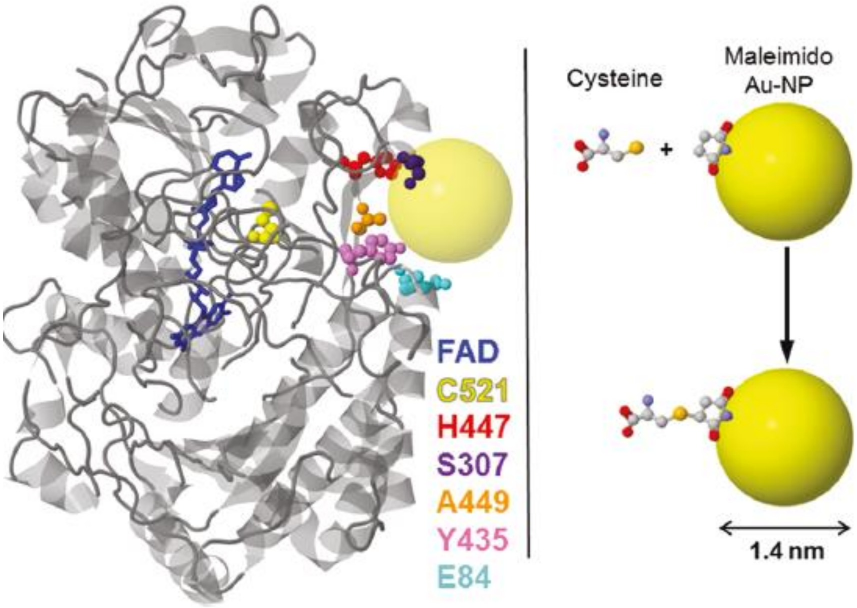

Figure 4. Ribbon diagram of a GOx monomer (from A. niger) with the FAD molecule shown in blue (left). Schematic drawing of the covalent-binding chemistry of cysteine to a maleimide-modified AuNP (right). Reprinted with permission from reference [23]. Copyright 2011 American Chemical Society.

3. ENZYME-FREE SENSORS

Some disadvantages of natural enzymes limit the applications of enzyme-based sensors although they show high selectivity and sensitivity. For example, the immobilization steps of enzyme are complex and the accurate usage of enzyme is difficult to guarantee. Moreover, the activity of natural enzymes is easily affected by the external environment such as temperature and pH. Thus, more and more attention has been paid to enzyme-free glucose sensors. The sensor based on the direct electrooxidation of glucose on nanostructered electrode is expected to be the fourth generation glucose sensor [9, 26]. The key factor in designing of nonenzymatic sensor is to select a suitable catalyst for direct electrochemical oxidation of glucose. Based on the synergy strategy of multi-functional and multi-morphology nanomaterials, enzyme-free glucose sensors have widely development prospects. According to the types of nanomaterials, glucose sensors can be divided into many kinds, such as noble metal nanomaterials, metal oxides and sulfides, carbon nanomaterials, metal organic frameworks, conductive polymers and so on.

3.1 Noble metal nanomaterials

Noble metal nanoparticles might be the ideal candidate materials to replace enzymes. Firstly, noble metal nanomaterials have good electrical properties and biocompatibility, and have broad application prospects in the field of bioelectronics. Secondly, they have high catalytic property and can catalyze many organic reactions with low activation barriers. A large number of methods have been proposed by using platinum- or gold-based electrodes since the electrochemical oxidation of glucose by lead anode in sulfuric acid electrolyte was reported [26]. For example, Park and co-workers developed an enzyme-free electrochemical method for monitoring glucose in blood and serum using mesoporous platinum electrode [27]. Platinum nanomaterials with different structures, such as nanoflowers, nanoparticles and dendrites, have been used to study the direct electrochemical oxidation of glucose [28-31]. For instance, Zhai and co-workers proposed a very sensitive glucose sensor by using platinum nanoparticles (PtNPs)-polyaniline (PAni) hydrogel heterostructure (Fig. 5) [32]. The PtNPs were uniformly loaded on the three-dimensional nanostructured matrix of PAni hydrogel.

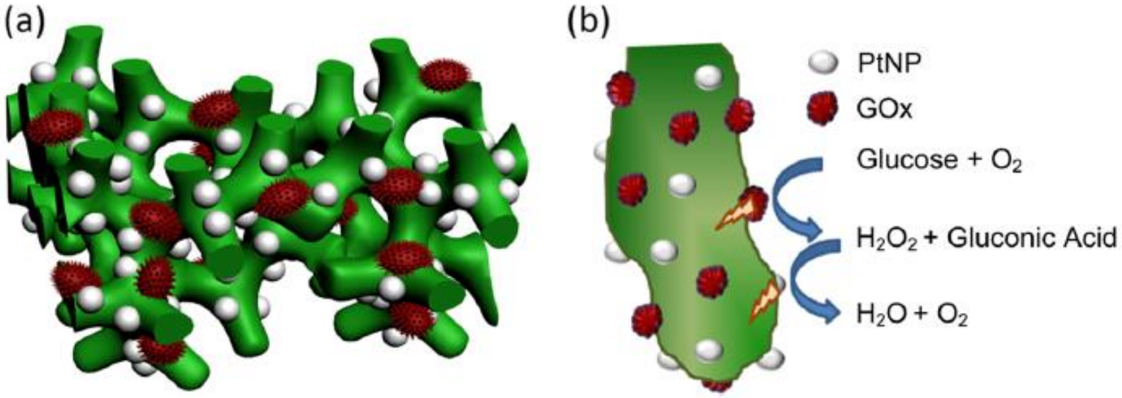

Figure 5. (a) Schematic representation of the 3D heterostructure of the PtNP/PAni hydrogel, in which the PAni hydrogel acts as a matrix for the immobilization of the GOx enzyme and homogeneous loading of PtNPs. (b) A 2D scheme showing the reaction mechanism of the glucose sensor based on the PtNP/PAni hydrogel heterostructure. Reprinted with permission from reference [32]. Copyright 2013 American Chemical Society.

The electrocatalytic activity of gold electrode is better than that of platinum electrode. This may be attributed to the filling of d-orbital of gold and the poor adsorption/electroadsorption of organic compounds involved in electrooxidation on gold surface. At the same time, gold nanomaterials have been used to improve the charge transfer through the conductive matrix, thus accelerating the bioelectrocatalytic process. Many glucose sensors based on gold nanomaterials have been developed, including gold nanocorals, porous gold, gold submicrostructure, nanoporous gold, gold nanowire arrays, gold nanotube arrays, gold nanoparticles, gold nanofractal films and 3D gold film electrodes [33-37]. Similar to platinum and gold, palladium nanomaterials with different micro nanostructures have also been widely studied [38]. However, in addition to the expensive price, the electrochemical glucose sensors based on noble metal nanomaterials are faced with the following problems. First, the activity of noble metals may be damaged by irreversible adsorption of oxidation intermediate and chloride ion. Second, the sensitivity of the sensor is low because of the slow kinetic reaction. Third, the selectivity of the noble metal electrode is poor because some endogenous substances and other sugars may be oxidized at the detection potential.

3. 2 Transition metals and their oxides and sulfides

Zinc, copper, nickel, manganese, cobalt, iron and their oxides and sulfides have also been used for the electrooxidation of glucose due to their enhanced catalytic performance and relatively low price [1, 39-42]. The mechanism and performances of nickel electrodes for electrochemical oxidation of glucose have been investigated. It was proposed that the mechanism of glucose oxidation on nickel electrode is based on Ni(III)/Ni(II) redox coupling reaction [43]. To improve the performances of glucose sensors, a lot of researches have been reported by using NiO nanostructure [44, 45]. For example, the sensitivity of NiO-modified carbon microspheres for glucose detection was found to be 30.19 μA mM^{-1} cm^{-2}, but the detection limit was only 1.279 mM. This value is higher than the physiological range of glucose. Moreover, the graphene-coated NiO nanofibers have good sensitivity and selectivity for glucose detection.

Copper, copper oxide (CuO), cuprous oxide (Cu_2O) and cuprous sulfide (Cu_2S) have also been successfully used in the oxidation of glucose [46-50]. CuO is a p-type semiconductor with narrow band gap (1.2 eV) and its electrocatalytic applications have been widely studied. CuO-based enzyme-free glucose sensors have attracted wide attention because of its good stability, easy synthesis, low cost, and different redox properties of CuO under different reaction conditions,. For instance, Babu and co-workers. developed a CuO-modified copper electrode with high sensitivity (791.9 μA mM^{-1} cm^{-2}) for glucose detection [51]. CuO with a sandwich structure prepared by microwave-mediated precipitation method has also been used for glucose detection [52]. When the applied potential was 0.6 V, the diffusion controlled oxidation of glucose was carried out on the surface of sandwich structure of CuO.

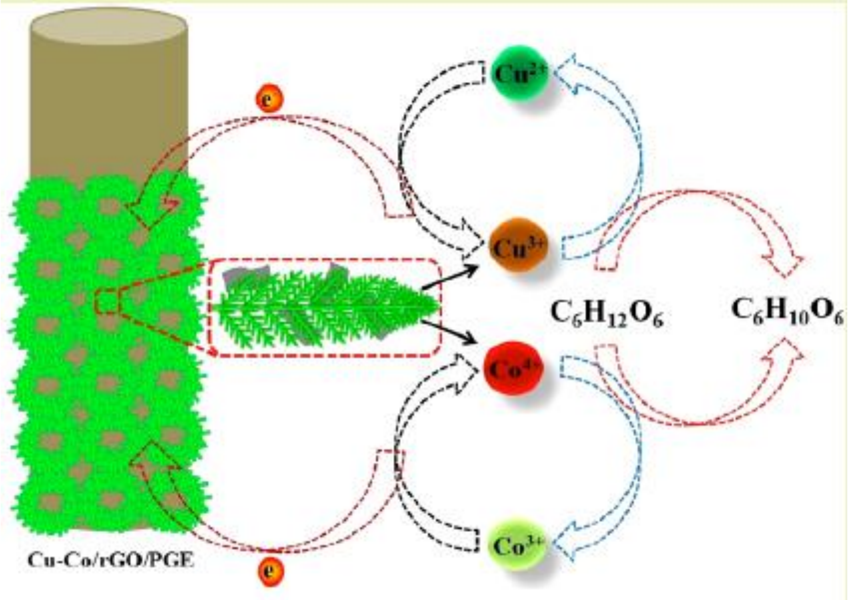

Figure 6. Glucose electrooxidation mechanism at Cu-Co/rGO/PGE. Reprinted with permission from reference [53]. Copyright 2018 American Chemical Society.

Cobalt is an excellent electrocatalyst since its oxidation state can be changed in alkaline medium. Cobalt oxide nanomaterials synthesized on different substrates have been used to detect glucose with high sensitivity and selectivity [54]. Glucose was detected on CoO-deposited graphene with a detection limit of 8 mM [55]. CoOOH was electrodeposited on Ti surface for glucose detection [56]. The macroporous structure surrounded by mesoporous structure made the electrode display layered mass transfer channels and sufficient active sites, allowing the detection of glucose with high sensitivity. Moreover, three-dimensional Cu-Co/rGO deposited in a pencil graphite electrode (PGE) was used for glucose detection (Fig. 6) [53].

3. 3 Carbon nanomaterials

Carbon-based materials (e.g. carbon dots, carbon nanotubes, carbon fibers, graphene and fullerene) have attracted wide attention due to their unique physical and chemical properties. At the same time, the composites of carbon materials and metal or metal oxide nanomaterials have also been explored as the new catalysts [57-59]. Carbon nanotubes and their composites with high aspect ratio, low cost, biocompatibility, good electron transfer kinetics and electrochemical inertia have also been used for the manufacture of glucose sensors. Li’s group developed a glucose sensor by using Pt-decorated carbon nanotubes [60]. The linear calibration range of the sensor is 0.16-11.5 mM, and the detection limit is 55 mM. The retention rate of catalytic activity reached 90% after one month. The result is attributed to the high density of oxygen-rich groups on Pt-decorated carbon nanotubes. The oxygen-rich groups were helpful to improve the biocompatibility of glucosidase and maintain its biological activity.

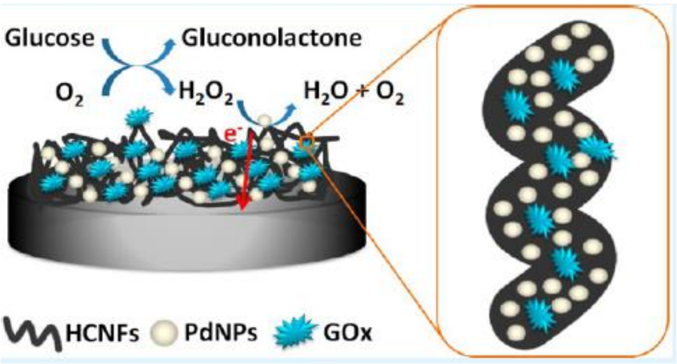

Figure 7. Schematic illustration of the sensing platform for H_2O_2 and glucose based on immobilization of palladiumhelical carbon nanofiber (Pd-HCNF) hybrid nanostructures and glucose oxidase (GOx) with Nafion on a glassy carbon electrode (GCE). Reprinted with permission from reference [61]. Copyright 2013 American Chemical Society.

Graphene is a kind of single carbon atom sheet with two-dimensional hexagonal crystal structure. Graphene−based electrode materials have the advantages of high surface area, good chemical stability and processability, and remarkable compatibility. Additionally, graphene can be fixed on the surface of various substrates or edges with oxygen atoms, enhancing the electronic conductivity of substrate materials. A sensitive glucose sensor was constructed by the synergistic combination of graphene with Pt/Pd NPs [62]. The response of the electrode toward potential interference is negligible. It has been shown that hybrid materials based on carbon nanofiber (CNF) can dramatically reduce the overpotential of hydrogen peroxide and improve the electron transfer rate. For example, a sensitive glucose sensor was developed with helical CNF (HCNF) as the carrier of PdNPs (Fig. 7) [61]. The sensor showed good sensing properties for the reduction and oxidation of H_2O_2 at 0.05 and 0.5 V, which is attributed to the high uniformity and small size of PdNPs as well as the good electronic conductivity and high surface area of HCNF. Moreover, the outer electrolyte layer is helpful to exclude the potential interactions.

3. 4 Conductive polymers

The integration of conductive polymer hydrogel and catalytic nanomaterial is a promising study in the development of novel glucose sensors. The three-dimensional continuous conductive matrix of the hybrid nanomaterials facilitates the immobilization of enzyme and the electrocatalytic oxidation of H_2O_2 by the catalysts. The typical examples include the 3D nanostructured polyaniline (PANI) hydrogel heterostructure matrix and PtNPs decorated in the PANI-coated boron nitride nanotube (BNNT) (Fig. 8) [29]. Moreover, some catalytic nanomaterials embedded in xerogels have also attracted much attention. For example, the xerogel matrix embedded with monolayer-protected AuNPs has been used to fix GOx (Fig. 9A) [63]. Compared with the films without NPs, this method has higher sensitivity, faster response speed and wider linear range. They also designed the first generation of glucose sensor by doping GOx in the xerogel by layer-by-layer assembly (Fig. 9B) [64]. The xerogel layer was then covered with polyphenol electropolymer as well as polyurethane semipermeable membrane.

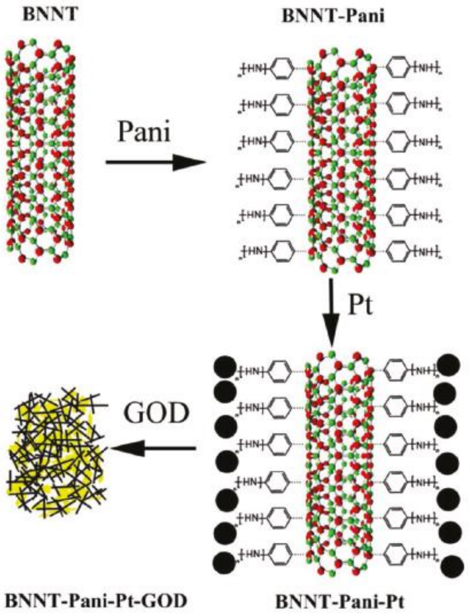

Figure 8. Schematics of the Fabrication of BNNTs-Pani-Pt-GOD Nanobiocomposites. Reprinted with permission from reference [29]. Copyright 2011 American Chemical Society.

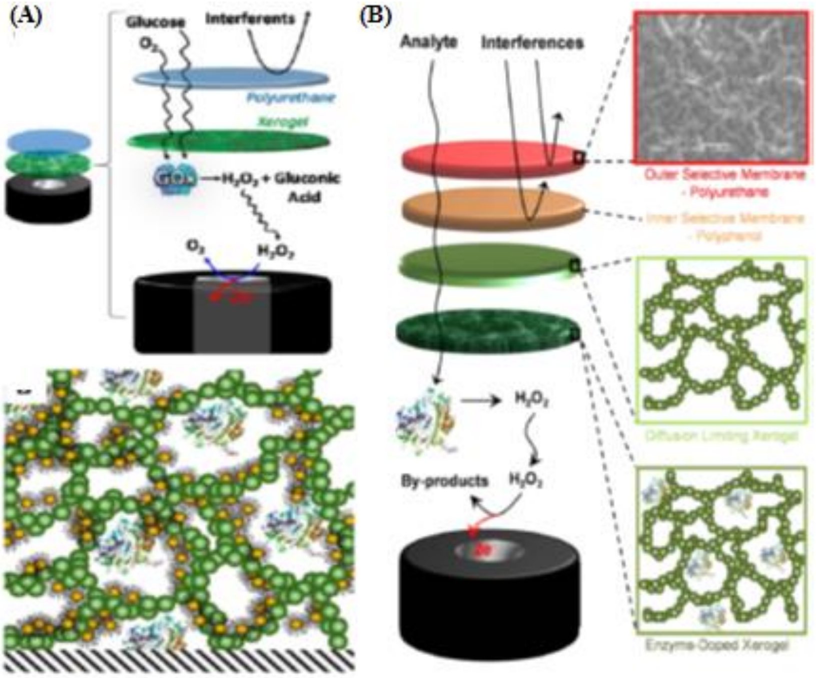

Figure 9. (A) Schematic illustration of 1st generation glucose biosensor scheme with GOx embedded in a MPTMS xerogel and capped with polyurethane (top). Xerogel structure embedded with GOx and doped with C6-MPCs with average diameters of 8 and 2.0 (±0.8) nm, respectively (bottom). Reprinted with permission from reference [63]. Copyright 2013 American Chemical Society. (B) Schematic of layered strategy of a xerogel-based, firstgeneration amperometric glucose biosensor featuring an enzymedoped and diffusion-limiting xerogel layers and capped with semipermeable electropolymerized polyphenol and polyurethane outer membranes. Reprinted with permission from reference [64]. Copyright 2015 American Chemical Society.

The nonconductivity of hydrogel polymer backbones reduces the electron transfer efficiency, resulting in a lower response for glucose detection. Integrating conductive nanomaterials (e.g. carbon or metal materials) into hydrogels is considered as one of effective strategies to improve the conductivity. In Schmidtke's group, single-walled carbon nanotubes were added to Fc-modified polyethyleneimine redox hydrogels to enhance the sensitivity for glucose detection [65]. Leech's group prepared multi-walled carbon nanotubes and Os-doped redox hydrogels to achieve a stable glucose oxidation current [66]. Compared with the traditional gels, the hydrogels obtained by the self-assembly of Fc-modified phenylalanine monomers exhibit great application prospects. In Minteer's group, DNA gels were functionalized by binding with four alkyl amino ions in the phosphate groups or intercalation of toluidine to the double helix of DNA [67]. The enzyme-mediated electron transfer can facilitate the practical sensing applications of redox hydrogels in the future.

4. WEARABLE ELECTROCHEMICAL SENSORS

For patients with diabetes, online blood glucose monitoring is very important since the existing devices often bring pain and are invasive and difficult to operate [68, 69]. Wearable devices are an early upgrade for noninvasive detection of human diseases [70], which can be easily integrated into the body by wearable clothes, watch lenses and rings, so as to continuously monitor glucose in tears, sweat and saliva (Fig. 10) [7]. Thus, the devices can perfectly replace the existing detection platforms [71].

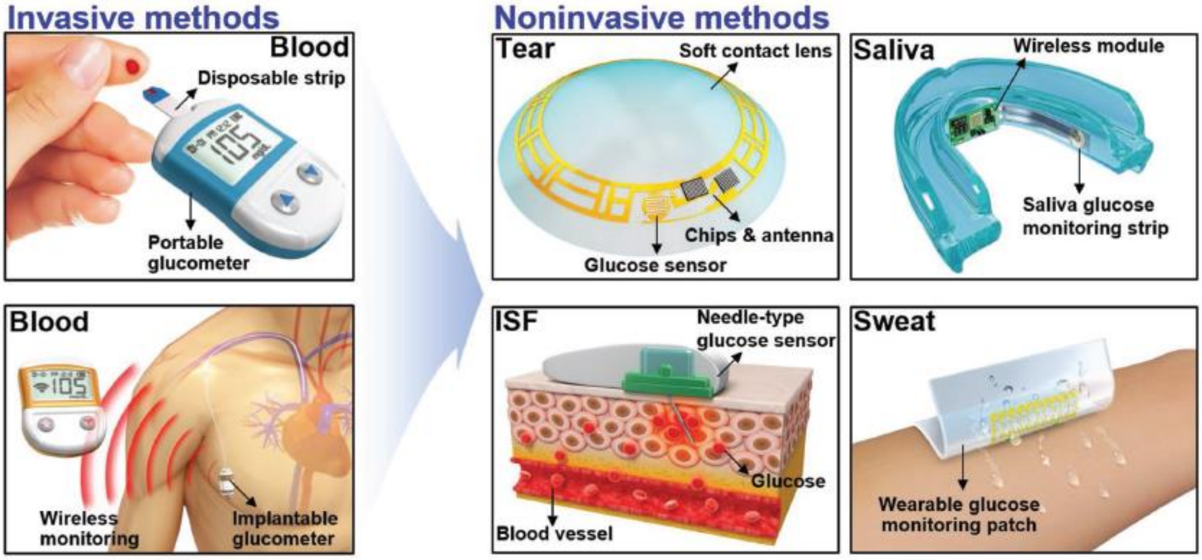

Figure 10. Evolution of glucose sensors from invasive to noninvasive electrochemical glucose monitoring system. Reprinted with permission from reference [7]. Copyright 2018 John Wiley and Sons.

Wearable electrochemical sensors have the advantages of miniaturization and can work at the low voltage produced by internal biochemical reaction or external stimulation. Wang's group developed an all-printedenzyme-based noninvasive glucose sensor [72]. The linear response of the sensor is related to the physiological glucose level, and the interference of common coexisting electroactive substances can be ignored. Lately, a wrinkled, stretch, nanohybrid fiber-based wearable sensor was proposed to continuously monitor glucose in human sweat (Fig. 11) [73]. In this work, the nanofiber was obtained by the nanogold partially covered with rGO/polyurethane composites. Under the synergistic action, a large number of active sites of $Au(OH)_{ads}$ and high percentage of oxygen-containing groups in rGO effectively promoted the dehydrogenation of glucose during the oxidation. The detection limit of the sensor is about 500 nM. This enzyme-free system with stretch and patch has a good future because it requires a simple manufacturing procedure. The sensor can be integrated into clothing or body accessory to continuously monitor glucose in human sweat. Furthermore, a nonenzymatic, painless device for continuous monitoring blood glucose was designed by the micro-needle array with a Pt black layer [74]. The Pt sensor electrode integrated with Ag/AgCl as the opposite and reference electrode was used to detect glucose with a sensitivity of 1.62 µA/mM and a detection limit of 50 µM. Moreover, a disposable sweat integrated with glucose sensor strip has been designed and used to measure the glucose concentration in sweat and monitor other important signs of body function, such as heart rate and O_2 saturation in blood (Fig. 12) [75]. The strip contains three carbon working electrodes and two Ag/AgCl reference electrodes. The sweat is accumulated by the chromium hydride layer of magnesium. The sensor can successfully monitor glucose concentration in sweat before and after exercise.

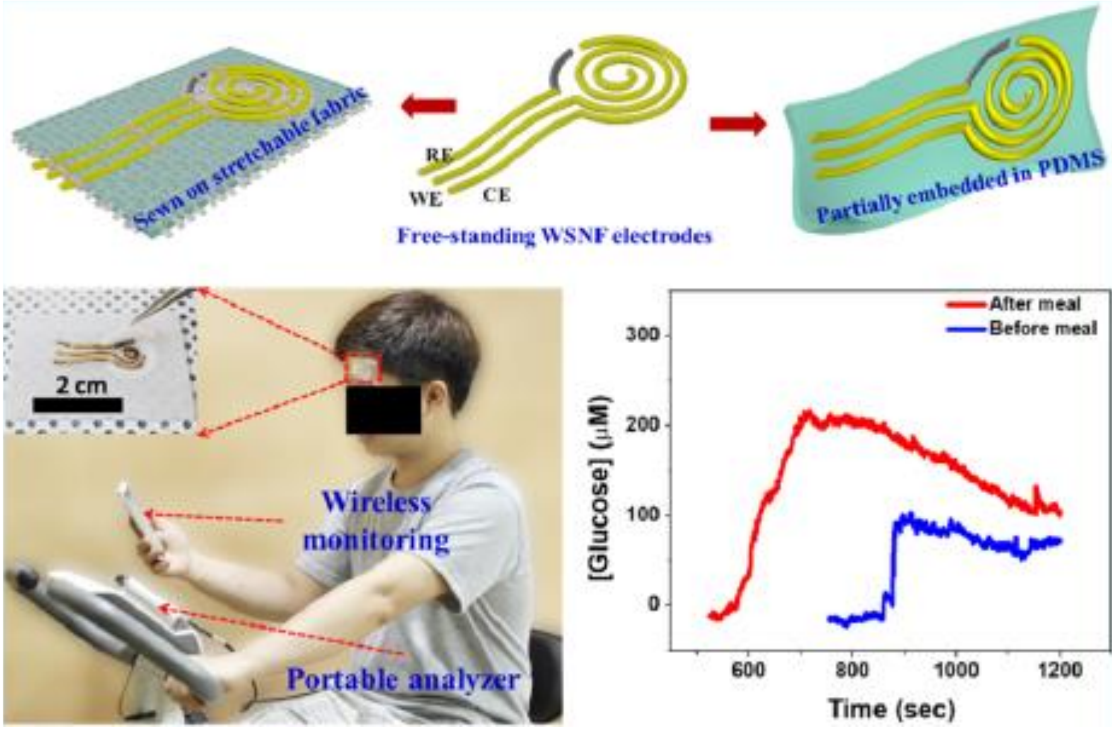

Figure 11. Schematic diagram of the fabrication process for free-standing WSNF electrodes (CE, WE, and RE) partially embedded on a PDMS substrate or sewn onto stretchable fabric to produce a stretchable WSNF glucose sensor. Reprinted with permission from reference [73]. Copyright 2019 American Chemical Society.

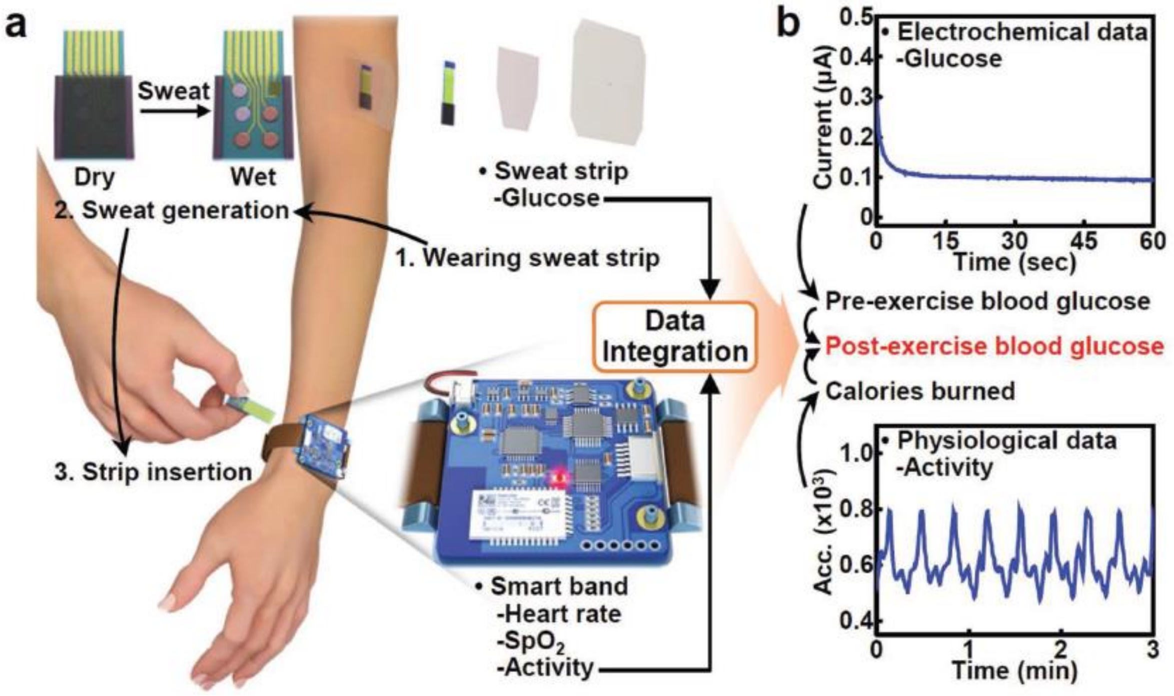

Figure 12. Overview of the wearable health management system. a) Schematic illustration of the wearable health monitoring system consisting of a disposable sweat-analysis strip for glucose measurement and a wearable smart band for monitoring heart rate, blood oxygen saturation level (SpO2), and physical activity. b) Schematic illustration showing combined use of electrochemical and physiological data. Reprinted with permission from reference [75]. Copyright 2018 John Wiley and Sons.

5. CONCLUSION

In summary, more and more researchers have paid attention to develop nanomaterials-based sensors in view of the distinctive advantages of nanomaterials, including high surface area, excellent conductivity, enzyme-like size and easy functionalization, The enzyme mimicking properties of nanoenzymes have opened up a new way to design enzyme-free electrochemical glucose sensors. However, these devices still face many key challenges for the commercial applications. The future work of nanomaterials-based sensors still focuses on solving the problems of compatibility, specificity and stability in bological samples. Moreover, integrated portable and implantable devices can be developed for continuous monitoring of important signs of body including glucose.

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