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Electrochemical Biosensors and Their Applications in Detection of Infectious Disease

Yilin Chen*

Pennon Education, Qingdao, China

* Corresponding Author: chenyilinnnn@gmail.com

Abstract. The emergence of the new viruses, bacteria and parasites leads to the widespread infection of the disease. This requires an efficient testing instrument with high sensitivity, high selectivity and rapid speed of detection. The electrochemical method is introduced to the clinical test of a wide range of disease nowadays. Compared with the traditional method of disease detection, the electrochemical biosensor has a relatively better performance in diagnosing disease. Therefore, this work focuses on the application of electrochemical biosensors in disease diagnosis. The basic structure and the mechanism of the electrochemical biosensor is similar to the primary battery. The current can be circulated through a series of electrochemical redox reactions, and it can be generated mainly in three ways in enzymatic electrochemical biosensor. The electrode materials are mainly made by inert metals and carbon-based material. When using electrochemical biosensor to detect various infectious disease, different bioreceptors are needed to be used. They are mainly antibodies and nucleic acid probes. The nucleic acid probes can be used in all virus-caused, bacteria-caused and parasites caused disease, while the antibodies can only be used in viral disease detection. The disease-detecting electrochemical biosensor has a good prospect in the future.

Keywords: Electrochemical Biosensor; Infectious Disease; Electrode; Detection.

1. Introduction

Nowadays, it is a hot research issue to detect infectious disease accurately, conveniently, and speedily. The infectious disease can be defined as a disorder that directly caused by pathogens such as viruses, bacteria, fungi, or parasites which can be transferred between the organisms. In past few years, the outbreak of COVID-19 pandemic has killed millions of people, resulting in a huge blow to the worldwide economy and the quality of human life. Previously, the mainstream detecting method is the lateral flow. Though low-threshold operation of the lateral flow assay really provide a convenient and fast way to detect the disease. However, there is a poor performance in detection accuracy of lateral flow assay because of the limitation of antibodies concentration. Moreover, the Corona virus mutates at a rapid rate due to the irreparability of the mistake made during replication process. This unfavorably leads to a huge challenge of the biosensor to detect the disease and an emergency to find a reliable diagnostic tools to assist the accurate treatment used to reduce the virus transmission. The method of using an electrochemical biosensor to detect the infectious disease is a good choice. Electrochemical biosensors are proven to be pivotal in the early detection of infectious diseases, providing rapid and accurate results that are essential for timely intervention [1].

The electrochemical biosensor is a sophisticated analytical device that combines the biological elements and electrochemical transducer together, in order to detect the specific pathogen such as antigen, viruses, bacteria. There are several advantages such as high sensitivity, high selectivity and high detecting speed which could perfectly satisfy our requirements for disease detector. Compared with the traditional diagnostic methods such as polymerase chain reaction and enzyme-linked immunosorbent assay, the electrochemical biosensor has superiority of less time-consuming and cost-effective. Moreover, it is also a considerable sensitivity and selectivity for electrochemical biosensor.

This paper gives a detailed overview of the electrochemical biosensor. Additionally, the immobilization process of the bioreceptor is outlined. Moreover, the mechanisms of the biosensors when using this biosensor to detect viral, bacterial and parasites disease are also explained.

2. Electrochemical Biosensor

2.1. Working Principles

In this part, the components of the electrochemical biosensor are introduced. The more detailed information about electrode material, roles and structure are explained.

Three electrode system is very important in electrochemical biosensor. It includes working electrode, reference electrode and counter electrode. Working electrode is a sensor or transducer responding to reaction [2]. In this primary-battery-like structure, the working electrode acts as a negative electrode. The negative electrode is the site of oxidation reaction that loses electrons to produce current, which could be detected and disposed. Reference electrode exhibits a steady and well-known electrode potential. It is often based on a saturated calomel electrode (SCE) or silver-silver chloride Ag/AgCl electrode [2]. The reference electrode does not participate in the reaction of the working electrode. Instead, due to the stable electrode reaction, the reference electrode can establish a constant potential which is of great importance to a valid and accurate measurements of working electrode potential. The counter electrode completes the current circuit by providing a current connection in between the electrocatalytic solutions and the working electrode in electrochemical cell [2]. The counter electrode can be simply interpreted as the positive electrode in the primary battery. The counter electrode can receive the electrons released from working electrode. It can generate a reduction reaction, which is complementary to the oxidation reaction occurs on the working electrode, to transfer the current to the power supply.

Other than the electrodes, the bioreceptor is also a key bio-recognition elements of the electrochemical biosensor, such as enzymes, antibodies and nucleic acids. In the reaction process, the target molecules can specifically binding to the bioreceptors that immobilized on the working electrode and triggers a response that can be detected by the transducers. Subsequently, the chemical signal will be converted to a measurable signal that can be analyzed to produce an analyte concentration reading. In the electrochemical biosensor, the bioreceptor firstly determine the application of the sensor, because different bioreceptor can binding to different analyte specifically. Secondly, the specific binding sites of the bioreceptor determines the sensitivity and the selectivity. It can help the electrochemical biosensor to produce a reliable results.

Besides, the method of signal processing is also important in the electrochemical biosensor. After generating the current, the electronics of sensors could detect it and produce a primary signal. Then, this signal is needed to be amplified and filtered which can enhance the accuracy and precision of the signal reading. Finally, the calibration curve is needed for working backwards to produce a analyte reading.

2.2. Generation of the Primary Signal

The primary signal is the key to achieve accurate detection. To generate the current on the working electrode is important for the enzymatic electrochemical biosensor. There are three generations of enzymatic electrochemical biosensor.

As to the first generation of enzymatic electrochemical biosensor, the electrons are transferred through a series of redox reaction. When the analyte arrives at the working electrode, it firstly reacting with the enzyme immobilized on the electrode to form intermediate products. This is the common step of all types of the generation. The differences of those four generations are mainly on the using of electron carriers. In the first generation, the hydrogen peroxide, a strong reducing agent is used as the electron carriers. Finally, an electrochemical oxidation of the H_2O_2 occurs and the electrons are released to form the current. The first generation is really simple to be designed. It has been well-developed so that a rich experience of operation can lead to a high accuracy. However, the disadvantage is also significant. The H_2O_2 build up can leads to a damage of the equipment. This generation relies on high level of oxygen. In the low oxygen level environment, the first generation of biosensor can lead to a inaccurate measurement.

The second generation of sensor uses the artificial mediator as the electron carriers. Compared with the first generation, the second generation certainly address some limitation of the first generation. The second generation of sensor eliminate the needs of oxygen in the first generation, which can help the electrochemical biosensor to perform better in the low oxygen level environment. Furthermore, the mediator has a higher sensitivity and selectivity that could make the results more accurate. However, this generation is more complex to design and have a higher cost. Though getting rid of the limitation of the oxygen, the second generation of sensor is still affected by the temperature and pH.

The third generation of sensor is more special than the other two generations. The main difference of the third-generation of sensor is that the enzyme is immobilized on the electrode surface as well as the mediator. As for the previous sensors, the enzyme is manually added into the aqueous solution [3]. This feature of the third generation of sensor can allow the electrons directly transfer to the modified working electrode, which can reduce the signal loss. Meanwhile, it can also increase the sensitivity and the response time of the biosensor.

2.3. Electrode Material

Semiconductors, ceramics, metals, and organic materials are widely used to fabricate the electrode of the electrochemical biosensor [3]. There are some examples of electrode made from metals and organic materials.

For the working electrode and the counter electrode, the inert metals such as platinum and gold is a suitable choice to be used in its manufacture. The inert metals have a considerable chemical stability and electrical conductivity, which are important factors to produce a reliable reading of the sensor. Respectively, platinum has an excellent catalytic properties for the electrochemical reaction. This could increase the sensitivity of the electrochemical biosensor and minimize the signal loss. However, high cost is the stubborn problem of the platinum electrode material. In addition, the platinum has a low biocompatibility. The biocompatibility is a measurement of the biosensor that refers to the ability of the electrode material to perform its function without damaging the tissues. This means that the platinum can not be used in the wearable technique of the biosensor, which would harm the human body. Instead, gold can perfectly solve this problem. Gold has a higher biocompatibility than the platinum. Gold is easy to be surface functionalized. It means that the immobilization process of the biomolecules such as antibodies, DNA molecules and enzymes is easier to be carried out on the gold electrode. However, a high cost is still a problem of the gold electrode, and the the electrochemical biosensor with the gold electrode is complex to be designed and manufactured.

The most widely used organic electrode material is carbon-based such as glassy carbon, graphite and some advanced technique such as carbon nanotubes (CNTs). These CNTs are often functionalized to enhance their ability to immobilize biomolecules and improve electron transfer capacity [4]. Graphene is also a good choice for electrode material. This material has garnered significant attention for its exceptional electron transfer capabilities, large surface area, and mechanical stability [5]. The glassy carbon is more common to be used as the electrode material. Glassy carbon combines the pros and cons of those two inert materials. Glassy carbon simultaneously has high electrical conductivity, chemical stability, and biocompatibility. It is easy to be functionalized. However, there is also an obvious disadvantage. The brittleness of the glassy carbon limit the fabrication and it makes the electrochemical biosensor unstable in dynamic reacting environments.

3. Application in Infectious Disease Detection

The infectious disease includes the viral disease, bacterial disease and parasites disease. Actually, the difference between those electrochemical detection biosensor is the various bioreceptors which are used in biosensors.

The antibodies are a common bioreceptor used in electrochemical biosensor. This method for virus-caused disease detection has a high sensitivity and selectivity. Because the shape of antibodies are highly specific to its corresponding antigens and the strong affinity between the antigen and the antibodies can allow a detection though a low analyte concentration presented. Moreover, this method has a high potential of miniaturization, which means that the advanced development such as combining with point-of-care techniques is possible. Inversely, there are also some disadvantages. The low detection limit makes it possible to detect even small amounts of the virus in the sample, which is a significant property in clinical test [6]. Firstly, the non-specific binding of the substrate with the antibodies can cause a result of false positive. Secondly, the immobilization process of the antibodies may face some challenges. The weak attachment between the antibodies and the electrode needs to be solved. Besides, the density of the active antibodies on the working electrodes have to maintain in a high level. Thirdly, this electrochemical biosensor is not portable because the temperature, pH, even humidity can affect the activity of the antibodies.

Recently, using electrochemical biosensor to detect the nucleic acid to diagnose the disease is more widely used and developed. An electrochemical nucleic acid biosensor was developed with covalent immobilization of DNA or RNA probe for single-strand DNA (ssDNA) on the modified glassy carbon electrode (GCE) [7]. This ssDNA can specifically binding to the complementary target DNA to form a double stranded DNA complex, and it can generate the signal. Compared with the antibodies biosensor, the sequence of the nucleic acid gives the biosensor a higher specificity. Furthermore, there is a fact that the antibodies electrochemical biosensor can only detect the virus-caused disease. So one of the disadvantage of the antibodies electrochemical biosensor is a relative small amount of disease that can be detected. However, the DNA or RNA probe can perfectly tackle this problem. This method can detect all infectious disease such as viral, bacterial and parasites, because all these pathogens contain their genetic material which is complementary to the specific nucleic acid probe. Besides, the technical advancement of combining DNA probe electrochemical biosensor with the on-substrate PCR makes it reality in trace amount DNA detection [8]. Due to the high programmability, stability, and biocompatibility of the nucleic acids, they are popular in the development of dynamic circuits and nanostructures, which has facilitated the creation of highly sensitive DNA-based biosensors [9]. The continuous advancements in DNA-based electrochemical biosensors hold great promise for early detection and diagnosis of various diseases, especially in the context of infectious diseases where rapid and accurate detection is crucial [9].

In the future, the electrochemical method will be integrated with digital and microfluidic technologies. In addition, this could revolutionize point-of-care diagnostics, offering real-time monitoring and personalized healthcare solutions [5]. The electrochemical biosensor can detect the disease accurately, which has a significant impact on public health strategies, particularly in the early detection and management of infectious diseases [10]. With the development of the advanced technique that could combine with electrochemical biosensor, there will be a big progress in sensitivity, specificity, and practical applications of this critical diagnostic tools [10].

4. Conclusion

In conclusion, this essay introduced the information of the electrochemical biosensor for infectious disease detection. In this primary-battery-like structure, the signal could be generated by using multiple mediators such as hydrogen peroxide. This artificial mediators have high sensitivity, which can make the detection of the electrochemical biosensor sensitive and rapid. Moreover, the electrode can be modified by the nano-materials. This could significantly increase the detection efficiency. The electrode materials are mainly made from inert metal and organic substance. Those materials are all have high electrical conductivity and stability. Nowadays, the electrochemistry method has been introduced to detect a wide range of disease by using the antibodies or nucleic acid probe as the bioreceptor which have a high sensitivity and selectivity. The antibodies electrochemical biosensor can detect the virus-caused disease, while nucleic-acid electrochemical biosensor can detect viral, bacteria and parasites disease. The electrochemical biosensor is a useful tool to detect the infectious disease, and it has a fantastic development potential to become a mainstream testing instrument. It could contribute to the personalized treatment and disease monitoring.

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