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The progress of luminescent assay in clinical diagnosis and treatment of diabetes mellitus

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ABSTRACT

Diabetes mellitus is a worldwide proliferated noninfectious disease in these years. Although it is not dangerous for life, but the complications such as kidney disease, blindness, foot disease or nerve damage will result in severe degradation of the vital quality of the diabetics. So, the monitoring of those diabetes related indexes is very important for controlling and treatment of the disease. More accurate and convenient methods for their assay are in expect. The electrochemiluminescent (ECL) and chemiluminescent (CL) analysis have received high attention because of their excellent sensitivity, low back-ground signal and other advantages. Especially combined with some biological measures, they have shown excellent specificity, and flexibility for a wide range of analytes, leading to their usefulness in clinical tests including diabetes. This paper will review the progress of this luminescent assay for diabetes mellitus in present years.

1. Introduction

The prevalence of diabetes is increasing rapidly throughout the world [1]. The International Diabetes Federation had estimated about 415 million population of diabetes in 2015 and given a prediction of rise to 642 million by 2040 [2]. Here type 2 diabetes mellitus (T2DM) is the main portion which was accounted for 85–95%, and the prevalence of T1DM has also continuously increased by 2–3% in certain parts of Europe and USA [2,3]. Undoubtedly, diabetes is already one of the commonest noninfectious diseases worldwide.

The blood glucose monitoring is required for diabetic patients to direct the medicining to secure a normal level of glucose in the body, thus reducing the risk of severe complications such as kidney disease, blindness, foot disease or nerve damage [4]. Also there are other indexes needed to be detected for more clinical or basic medical purposes such as glycosylated hemoglobin (HbA1c), islet autoantibodies, C-peptide, glucagon and so on [5].

Be emerged with the development of multitudinous analytical methods on those important indexes of diabetes, the luminescent methods including chemiluminescence (CL) and electrochemiluminescence (ECL) [6,7] have been employed and served as attractive approach for fast and simple quantitative assay, because of their high sensitivity and the requirement of relatively simple instrumentation. Furthermore, the CL or ECL approach is in great promising for clinical point-of-care testing (POCT) [8].

The CL assays for many clinical indexes have been reported for decades [9–11]. Here the luminescent signal is triggered during a chemical oxidation of luminophore by some oxidant, meanwhile the reaction was impressible from those target molecules, thus establishing the viable approach for their quantifying with high sensitivity. The ECL, as a later method coupled the CL with electrochemistry, has the particular advantage of low-background noise, higher sensitivity and higher temporal/spatial resolution of the signal, as we all know that the signal-to-noise ratio was the core to reach lower limits of detection. The most commonly used ECL reagents are $Ru(bpy)_3^{2+}$ and luminol, and more complete lists can be found in reviews of Richter [12] and Miao [13]. With hundreds of million dollars in sales per year [13,14], the ECL of $Ru(bpy)_3^{2+}$ has achieved overwhelming success for in vitro diagnosis (IVD) because of its extremely high sensitivity, wide dynamic range, rapidness, simplicity, and stable labels by coupling with immunoassays and DNA probe assays. The popularity of luminol is mainly resulting from its low cost, easy functionalization, and broad bioanalytical applications [15]. In recent years, nanomaterials such as quantum dots (QDs), carbon based nanomaterials, composite materials, and metal nanoparticles have also been studied as ECL reagents [16]. In this paper, we will briefly review the progress of CL, ECL assay of some diabetic indexes for diagnosis and treatment.

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2. The ECL Sensors for Blood Glucose Assay

Glucose is the primary energy source in the body. Its level in blood has been appointed for diagnosis of diabetes or hypoglycemia. Besides the need in glucose monitoring in the case of diabetes patients, it is also an essential element for non-diabetic acute-care patients in order to control the vital signs [17]. Therefore, the development of fast, sensitive, selective and reliable methods for glucose monitoring is important in clinical diagnosis and some other related fields [18]. The current market, for glucose assay, especially those for home glucose monitoring, is dominated by finger-prick type blood glucose sensors. These sensors detect H_2O_2 using amperometric detection, providing a fast response (~5 s) within a dynamic sensing range (10–600 mg/dl) for measuring blood glucose levels [19]. Meanwhile, some new techniques and materials have been investigated in these years.

2.1. The ECL/CL Biosensors for Glucose Assay

Since the first report of Haghighi and Bozorgzadeh about the ECL behavior of Si in 2002 [20], some glucose monitoring techniques based on ECL detection have been reported. Among various ECL systems, luminol is considered as one of the most popular ECL luminophor due to its low oxidation potential, inexpensive reagent consumption and the high emission yields [21,22]. So, special attention has focused on the ECL studies concerning luminol for glucose analysis [23]. The luminol-based ECL glucose biosensors are built up on the oxidation of glucose by the catalysis of glucose oxidase (GOD), which had the advantages of being a simplified but sensitive strategy. The glucose in the solution reacts with the dissolved oxygen (O_2) in the presence of GOD to generate gluconolactone and H_2O_2 (Eq. (1)). Under positive potential and with the help of assistant materials (such as nano-materials) the luminol will be oxidized into its radical anion and then react with H_2O_2, at the electrode surface to produce its excited state (3-amino phthalate anion), which finally emit the ECL at 425 nm (Eq. (2)). The intensity of the ECL signal is directly proportional to the concentration of H_2O_2 which is related to the concentration of glucose.

$$D-glucose + O_2 \overset{GOD}{\rightarrow} H_2O_2 + D-gluconolactone \quad (1)$$

$$2H_2O_2 + Luminol \rightarrow 3-aminophthalate + N_2 + 3H_2O + hv \quad (2)$$

Many efforts have been paid to develop more sensitive and durable ECL biosensors for glucose assay with GOD as bio-recognition element to ensure the sensing selectivity. In recent years, continuously emerged nanomaterials have been affirmed to be the powerful essence not only for GOD supporting, but also to enhance the ECL effect or GOD activity maintenance. Yuan [24] et al. have synthesized the well-distributed hollowed gold nanosphere to encapsulate GOD (Au shell@GOD) (about 20 ± 5 nm) in a simple way and develop an ECL glucose biosensor. Behzad Haghighi [25] et al. have introduced a PdNPs decorated multi-walled carbon nanotubes (nanoPd/MWCNTs) to modify glassy carbon electrode (GCE) to construct the ECL glucose biosensor. Xu [26] et al. have proposed a glucose biosensor based on gold nanoparticle-catalyzed luminol ECL on a three-dimensional sol-gel network. Chen [27] et al. have developed a chitosan doped poly(diallyldimethylammonium chloride) (PDDA) matrix to immobilize GOD onto glassy carbon electrode for ECL biosensing of glucose. They have also developed a carbon-nanotube/Nafion modified GCE as the sensing matrix of ECL glucose biosensor [28]. The same team has further fabricated a polyNiTSPc/MWNT modified GCE for glucose ECL biosensor constructing [29]. Wang [30] et al. have developed a novel luminol ECL strategy based on TiO_2/CNTs nanocomposite for glucose biosensing. Su [31] et al. have developed a novel facile signal-off ECL biosensor for glucose assay based on the integration of chitosan, CdTe quantum dots and AuNPs on the GCE. Chai and Yuan [32] et al. have developed a highly sensitive ECL glucose biosensor through immobilizing GOD on a GCE modified with C_{60} embedded in tetraoctylammonium bromide (TOAB+) film. Zheng et al. [33] have synthesized a poly(luminol/aniline) nanowire composite (PLANC) on the surface of graphite electrode for ECL sensing of glucose. M. J. Chaichi et al. [34] have introduced a stable and sensitive glucose biosensor fabricated by covalent immobilizing GOD via direct coupling of chitosan-induced Au/Ag nano-alloy dispersed in ion liquid with a H_2O_2 sensitized CL by the catalysis of Cu^{2+}. Rong Lei [35] et al. have proposed a novel ECL glucose biosensor based on mesoporous molecular sieve silica matrix for immobilization of enzyme and luminophore using sol-gel method.

2.2. The Non-Enzymatic ECL Glucose Sensor

However, these so-called biosensors have poor stability because of the probable deactivation of GOD if there was unsuitable acidity, temperature or moisture. In addition, the GOD is often suffered by some chemicals or time consuming fabrication procedure during its immobilization onto the electrode [36]. Thus, other researchers have focused on non-enzymatic glucose ECL sensors. Chen et al. [37] proposed a novel non-enzymatic design based on palladium nanoparticles (PdNPs) functionalized carbon nanotubes (FCNTs) catalyzed ECL of luminol for glucose sensing. Guo et al. [38] have synthesized a kind of perovskite nanomaterial ($LaTiO_3$-$Ag_{0.1}$) to develop the non-enzymatic ECL sensor based on it. The $LaTiO_3$-$Ag_{0.1}$ could effectively catalyze the glucose oxidation to enhance luminol's ECL. They [39] have also developed another non-enzymatic ECL glucose sensor using Au-HS/SO_3H-PMO (Et) nanocomposites. Linlin Liu et al. [31] have developed a non-enzymatic ECL sensor of glucose based on the integration of chitosan (CHIT), CdTe quantum dots (CdTe QDs) and Au nanoparticles (Au NPs) on the GCE. In those researches, the traditional ECL luminophores such as luminol [40,41], Ru $(bpy)_3^{2+}$ [42] and quantum dots (CdS, CdSe, CdTe or ZnS) [43] have been well studied. Aside from these ECL sensing materials, graphitic carbon nitride (g-C_3N_4), is also a worthy extension of carbon material in applications [44,45].

Fan et al. [46] have reported a non-enzymatic ECL glucose sensor based on the competitive reaction between glucose and phenoxy dextran (DexP) with concanavalin A (ConA). The hybrid of graphitic carbon nitride nanosheet and 3,4,9,10-perylenetetracarboxylic acid (g-C_3N_4-PTCA) as signal probe was modified onto the GCE for immobilizing DexP. Recently, Yin-Zhu Wang et al. [47] have developed a new non-enzymatic glucose ECL sensor based on attapulgite (Att) integrated with semiconductor material TiO_2. It is in prospect to discover more materials for development of effective enzyme-less ECL sensors for glucose detection.

3. The Fast Assay of HbA1c by CL

HbA1c, is defined as the ratio of HbA1c toward total hemoglobin. It is considered to be a very useful diagnostic marker for diabetic patients besides the glucose level [48]. Compared with blood glucose, the HbA1c level is a more longlasting diagnostic index and has been designated as an index of average glucose level during the past 6 to 8 weeks (the lifetime of Hb). The clinical reference range of the HbA1c level is 5 to 20%, with 4 to 6% considered as normal [49]. Consequently, the measurement of HbA1c level is important for long-term control of the glycemic state of diabetic patients [50].

A number of detection methods are currently available for quantifying the HbA1c level including electrophoresis/electroendosmosis [51], ion exchange chromatography [52], high-performance liquid chromatography (HPLC) [53], affinity chromatography [54], immunoassay [55], and liquid chromatography-tandem mass spectroscopy (LC-MS/MS) [51], in addition to fluorometry [56] or colorimetry [57], etc. Most of these methods usually employed chromatographic separations, bio-recognized by immune proteins or interacted with boronic acid derivatives before the detection, and then the purified HbA1c is quantified with various optical or electrochemical transduction. The International

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