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Voltammetric sensing of biomolecules at carbon based electrode interfaces: A review

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ABSTRACT

Biomolecules are integral constituents of living beings which regulate numerous biochemical functions of the body. Analysis of various small molecules (metabolites, neurotransmitters, amino acids, vitamins) and macromolecules (nucleic acids, proteins) is of prime importance in modern time due to increasing disbalance in natural metabolism of human body. Irregularities and alteration in concentration of biomolecules lead to different kinds of genetic, metabolic and cancerous diseases which have created a great requirement of highly sensitive, accurate and stable detection systems for their quick and specific screening. In this review, redox interactions of biomolecules at carbon based electrode interfaces have been discussed using voltammetry. It is divided into subsections, starting with an introduction into the field and a description of its current state. This is followed by a large section describing carbon nanomaterials (CNs) based voltammetric sensors for different small biomolecules and macromolecules. The next section of the review gives conclusion, challenges and future perspectives in sensing biomolecules at CNs based electrodes. Advanced approaches for fabrication of portable integrated electrochemical devices for various point of care diagnostic applications have also been included at the end.

1. Introduction

Various macromolecules and small molecules constitute basic building blocks of living organisms. Macromolecules generally involve protein, carbohydrates, nucleic acids and enzymes whereas numerous metabolites, fatty acids, neurotransmitters, amino acids, vitamins, hormones etc. are common small molecules. Studying biomolecules helps to understand their fundamental physiological functions in regulating proper growth and development of human body. Biomolecules can be endogenous or exogenous and are generously involved in many biological processes including storing and transmitting genetic information, regulating biological/neurological activities, transportation of small molecules/hormones along with catalyzing various biochemical reactions. In short, proteins are dietary compounds made up of amino acid monomers which contain a carboxylic acid group and amino group at the two ends. When food is consumed, the proteins are broken down into their constituent amino acids and rebuilt into the proteins of the body. Nucleic acids are the genetic components made up of nucleotide subunits. Polysaccharides (starch, glycogen), commonly known as carbohydrates, are made up of monosaccharides such as glucose. Majority of living cells are rich in carbohydrates which are the final products of many metabolic processes. Considering the small molecules, lipids (fat) are mainly fatty acid esters and considered as basic building blocks of biological membranes which perform major function in energy storage. Usually lipid is made up of glycerol, which is attached to three fatty acid chains making triglycerides (TG). Estimation of TG (butter, olive oil) concentration is extremely significant since it is an important diagnostic marker for coronary heart diseases and lipoprotein disorder. Vitamins are essential bionutrients required for

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proper growth and development of human body while neurotransmitters are chemical messengers. Furthermore, hormones are signaling molecules and metabolites are the products of various physiological processes. Biomolecules have been used as disease markers for many point of care diagnostic applications [1].

To quantify these biologically relevant molecules, electrochemical detection systems are best suited which have the potential to analyze the targets over wide potential range with high sensitivity and selectivity [1]. However, in the present review, we will specifically focus on voltammetric techniques. Voltammetric sensors apply potential to working electrode and measure the current by means of electrochemical oxidation or reduction of analyte. The current response is usually obtained in the form of peak which is proportional to the concentration of analyte [1–4]. In addition, voltammetric techniques have shown their great contribution in flourishing the concept of chemically modified electrodes (CMEs). Literature reveals multiple kinds of voltammetric sensors/biosensors which have been successfully designed over wide surfaces of transducers and modifying elements [5–12]. Carbon nanomaterials (CNs) based sensors are of potential interest as they exhibit numerous exotic catalytic, surface and electronic characteristics [13–16]. A large number of reports are available discussing key features of different carbonaceous materials and their significant role in various scientific applications [17–23]. CNs functionalized with chemical/biological receptors exhibit large electrode surface area and improved heterogenous electron transfer (HET) kinetics which leads to amplified redox signals [24–32]. After the extensive use of CNTs, GR, GO and C_{60} as electrode materials, the new counterparts such as CNDs, CNHs, and CNOs have been reported to exert excellent catalytic properties accelerating HET. Electroscreening processes of common small molecules such as neurotransmitters and nucleobases viz., guanidine and adenine have been successfully performed at newer carbon allotropes with high sensitivity and selectivity [17,18]. These innovative CNs have driven further motivation for extending the new realms of nanosensors towards detection of unconventional nucleic acid and protein biomarkers. Further, advancement has been observed with the application of CNs for *in vivo* applications. Various biomolecules from living cells have been detected at CNs electrodes for understanding their *in vivo* electrochemistry at molecular level [33]. Furthermore, onchip and offchip electrodes of CNs have also been designed for biomolecules detection [34].

Combining the extraordinary sensing features of functionalized CNs and excellent detection sensitivity of voltammetric techniques, the present review reports different CNs based electrode interfaces for the detection of biomolecules in last three years. Discussing advanced state-of-the-art methodologies, the review focuses on the basic redox phenomenon of small biomolecules and macromolecules using voltammetric techniques. Common difficulties related to the detection of biomolecules along with their possible solutions have been emphasized. The article has been updated with most recent articles since 2014. Discussing various novel aspects of sensing and biosensing based on CNs, the article imparts valuable information regarding clinical relevance of biomolecules, recent developments of newer carbon allotropes and great technological advancements in the field of sensing technology.

2. Fabrication of carbon nanomaterials modified electrode interfaces

To improve the solubility, dispersibility and compatibility of CNs based electrodes, functionalization of carbon framework has become quite important which enhances the efficiency towards biomolecular recognition [22,23]. Functionalized CNs modified electrodes exhibit increased catalysis of biomolecules with reduced overpotential and high current response. Till now, various kinds of physically and chemically functionalized CNs modified electrodes have been developed for sensing and biosensing applications. Physical mode of functionalization involves mechanical means such as ultrasonic, milling, crushing and friction to activate CNs surface while chemical functionalization include covalent and noncovalent modifications of CNs [22,23]. Nanocomposites of CNs with different organic functionalities like free radicals, dienophiles etc. are prepared by covalent functionalization of π framework of carbon whereas noncovalent functionalization involve van der Waals forces, hydrogen bonding, polymer wrapping and $\pi-\pi$ interactions of CNs with various bioreceptors, conducting polymers, CNs counterparts and other functional nanomaterials without altering its π framework [22,23]. These chemically or physically functionalized CNs results in the formation of various nanocomposites which are usually modified at the surface of solid electrodes to fabricate CNs based sensors and biosensors. The common ways to modify the surface of a pre-cleaned solid electrode such as glassy carbon electrode (GCE), screen printed electrodes (SPE), indium tin oxide (ITO), gold (Au) and platinum (Pt) electrodes follow different procedures. The most common ways include CNs nanocomposite film modification at solid electrode surface by casting few drops or by rubbing the electrode surface with the sensing material. Electrodeposition can also be used instead in order to create a uniform nano film on the surface and usually involves decorating the coating layer with conductive metal nanoparticles. Fabrication of biosensors using this type of electrode is usually produced through immobilizing of the biological compounds on the prepared film through physical adsorption, crosslinking, covalent bonding and embedding methods [23]. Furthermore, for preparing nanocomposite paste modified electrodes, CNs is mixed with liquid paraffin and some additive materials like binders to obtain conductive gel like paste. In this method of sensor fabrication, microsyringe or glass rod represents the electrode body which is filled with the paste and copper wire is usually used to make electrical connection. The modification is done by immersing the electrode body into the CNs nanocomposite paste suspension to prepare modified paste electrodes [35]. Reports suggest that modification of solid electrodes has successfully improved their sensing performances in terms of reproducibility, stability, resistance to surface fouling and low signal to noise ratio [35–39]. However, frequent uses and aging of modified electrodes are the factors which enable them to be regenerated during electrochemical measurements by simple polishing and cleaning of electrode surfaces. Along with the composition of the sensing material, reproducibility of electrode further depends on the storage condition which helps to control the overall activity of the modified electrode.

3. Voltammetric sensing of biomolecules at carbon nanomaterials based electrodes

In the present review, biomolecules have been divided into small molecules and macromolecules sections. Each of the subsection discusses voltammetric sensing and biosensing strategies developed for the selective biomolecule at carbon based electrodes in different real sample compositions. Sensing performances of CNs in terms of detection limit, reproducibility, stability, recovery in real matrices and anti-interference ability have been explained. A detailed critical discussion has been provided in following sections.

3.1. Small biomolecules

Small biomolecules are low molecular weight organic compounds which help in regulating biological processes of body and