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Conducting polymer-based electrochemical biosensors for neurotransmitters: A review

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ABSTRACT

Neurotransmitters are important biochemical molecules that control behavioral and physiological functions in central and peripheral nervous system. Therefore, the analysis of neurotransmitters in biological samples has a great clinical and pharmaceutical importance. To date, various methods have been developed for their assay. Of the various methods, the electrochemical sensors demonstrated the potential of being robust, selective, sensitive, and real time measurements. Recently, conducting polymers (CPs) and their composites have been widely employed in the fabrication of various electrochemical sensors for the determination of neurotransmitters. Hence, this review presents a brief introduction to the electrochemical biosensors, with the detailed discussion on recent trends in the development and applications of electrochemical neurotransmitter sensors based on CPs and their composites. The review covers the sensing principle of prime neurotransmitters, including glutamate, aspartate, tyrosine, epinephrine, norepinephrine, dopamine, serotonin, histamine, choline, acetylcholine, nitrogen monoxide, and hydrogen sulfide. In addition, the combination with other analytical techniques was also highlighted. Detection challenges and future prospective of the neurotransmitter sensors were discussed for the development of biomedical and healthcare applications.

1. Introduction to electrochemical biosensors

Biosensors are analytical devices composed of biological sensing elements that are capable of producing sensitive and selective analytical signals. The physiochemical changes due to the interactions between a target and the corresponding biorecognition elements, such as enzymes, proteins, and antibodies, are converted into quantifiable electronic signals by a transducer, where the amount of signal generated is directly related to the analyte concentration. Biosensors are used in various applications, such as medical diagnosis, drug discovery, food safety, and environmental monitoring. Various types of biosensors have been reported, including optical, mechanical, colorimetric, piezo-electric, and electrochemical biosensors (Turner et al., 1987). According to the International Union of Pure and Applied Chemistry (IUPAC), biosensors can be classified in two ways based on their composition: 1) transducers including mass-based, electrochemical, and optical biosensors, or 2) type of bioelements including biocatalytic and affinity sensors. Biocatalytic sensors are fabricated by immobilization of enzymes, cells or tissue slices that identify the target analyte and generate electroactive molecules. By contrast, affinity sensors depend on a specific binding interaction between the analyte and an immobilized biological elements such as an antibody or aptamer (Wang, 2006). The performance evaluation of biosensor is mainly based on its sensitivity, limit of detection (LOD), linear dynamic range, reproducibility, selectivity, response to interferences, and other features.

Electrochemical biosensors are part of the electrochemical cell that consists of either three or two electrodes. A typical three electrode system consists of a working, a reference, and a counter electrode. The working electrode consists of a chemically stable solid conductive material, such as platinum, gold, or carbon; the reference electrode usually consists of silver metal coated with a layer of silver chloride (Ag/AgCl); and a platinum wire is typically used as the auxiliary electrode. In contrast, a two-electrode system consists of working and reference electrodes only. Electrochemical techniques can be classified into three main categories based on the types of measurements (Bard et al., 1980, Wang et al., 2001): (1) current (voltammetric and

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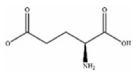
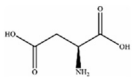
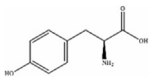
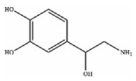
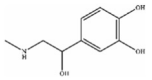
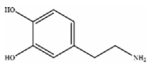
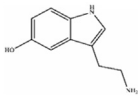
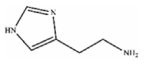
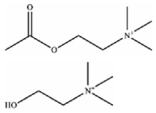
amperometric), (2) potential difference (potentiometry), and (3) impedance (electrochemical impedance spectroscopy). Of them, biosensors based on current measurements are mostly common in use. Current measurement based sensors are characterized by applying a potential to a working electrode *versus* a reference electrode and measuring the current. The current is a result of electrolysis due to the electrochemical reduction or oxidation at the surface of the working electrode. However, this process depends not only on the mass transport rate of molecules to the electrode but also on the electron transfer rate at the electrode surface. There are various types of voltammetric methods such as linear sweep, cyclic, hydrodynamic, differential pulse, square-wave, and stripping voltammetry. In voltammetry, a potential is scanned over a set potential range, and the current response is generally a peak or a plateau that is proportional to the concentration of analyte in the measured sample. However, in amperometry, a constant potential is applied at the working electrode with respect to the reference electrode, and the changes in current caused by the electrochemical reduction or oxidation are directly monitored with respect to time. Overall, amperometric biosensors are more selective and sensitive because the technique relies on a constant specific potential for a given analyte, therefore, it can minimize the interference effect of other electroactive substances. Potentiometric sensors are based on measuring the potential of an electrochemical cell while drawing a negligible current. They function under equilibrium conditions and monitor the accumulation of charge, at zero current, that is caused by selective binding at the electrode surface. Such chemical sensors can be turned into biosensors by coating them with a biological element, like an enzyme, that catalyzes a reaction to form ions which sensed at the modified electrode when the ions bind to suitable ion exchange membrane. The potentiometric sensors are non-invasive, real time, low cost, and ease of miniaturization. Electrochemical impedance spectroscopy (EIS) measures the resistances and capacitances of the materials by a small amplitude sinusoidal AC excitation signal. The frequency is varied over a wide range to produces the impedance spectrum. The in-phase and out-phase AC current responses are then determined to obtain the resistive and capacitive components of the impedance, respectively. Impedance methods enable the monitoring of charge transfer at high frequency and mass transfer at low frequency; therefore, impedimetric detection techniques are primarily used with affinity-type biosensors (Turner et al., 1987; Skoog et al., 1998).

2. Neurotransmitter sensors

Neurotransmitters (NTs) are endogenous chemicals that are involved in the transmission of signals from one neuron to another or between non-neuronal body cells across chemical synapses exchanging information throughout the brain and body (Patestas and Gartner, 2006). Produced by glands such as the pituitary, pineal and adrenal glands, NTs are stored in vesicles clustered at neuronal terminals. An action potential at a synapse stimulates the release of NTs, which cross the synaptic gap to reach the receptor site of the other neuron or cell, where they are reabsorbed. A new action potential is then created at the axon terminal of the next neuron followed by a similar release of NTs subsequently, communicating information to another adjacent neuron. Thus, a complex cascade is initiated *via* neurons that eventually elicits a biological response. Since the discovery of the first neurotransmitter in 1921, more than one hundred chemical messengers have been identified, which are involved in synaptic transmission (Yamada et al., 1998). NTs can be classified according to their 1) molecular structure; 2) mode of action either direct or as neuromodulator; and 3) physiological function either excitatory or inhibitory. However, in this review, the classification is based on their chemical structure, therefore they are divided into four groups: amino acids primarily (glutamic acid, aspartic acid, and tyrosine), biogenic amines (epinephrine, nor-epinephrine, dopamine, serotonin and histamine), acetyl choline (acetyl-choline and choline), and soluble gases (such as nitric oxide and hydrogen sulfide).

Table 1
Classification of neurotransmitters, associated diseases and chemical structures.

Category	Analysts	Associated diseases	Chemical structure
Amino acid	Glutamic acid	Seizures, neural degeneration, lethargy and cognitive dysfunction	
	Aspartic acid	Stroke, chronic fatigue syndrome, depression, Huntington's disease	
	Tyrosine	Parkinson's disease, behavioral deficit	
Biogenic amines	Nor-epinephrine	Schizophrenia, depression, ADD (Attention deficit disorder)	
	Epinephrine	Depression, Addison's disease, palpitation, high blood pressure	
	Dopamine	Tourette's disease, schizophrenia, psychosis, depression, Parkinson's disease, ADD	
	Serotonin	Depression, anxiety disorders, especially obsessive-compulsive disorder	
	Histamine	Immune system disorder, schizophrenia, convulsion, seizure, and Parkinson's disease	
Acetyl choline	Acetyl choline, choline	Depression, Alzheimer's disease, dementia	
Soluble gases	Nitric oxide	Huntington's, Alzheimer's Parkinson's disease, vascular stroke.	
	Hydrogen sulfide	Down syndrome, Chronic obstructive pulmonary disease	

Various aspects of these NTs are summarized in Table 1. Moreover, NTs play a key role in the functioning of the brain and control various behavioral and physiological conditions that affect daily life, for example, learning, memory, sleeping, consciousness, mood and the regulation of muscle tone, heart rate and blood pressure (Tomkins and Sellers, 2001; Dunn and Dishman, 1991; Freed and Yamamoto, 1985). Variations in the production, secretion, uptake and/or metabolism of these chemicals may lead to various mental and physical disorders, such as Huntington's, Alzheimer's, Parkinson's diseases, schizophrenia, epilepsy, thyroid hormone deficiency, glaucoma, congestive heart failure, and different types of cancers. Hence, timely and accurate determination of NTs level in various physiological media (such as urine, plasma, and cerebral fluids) is imperative for effective diagnosis, monitoring of the disease, therapeutic interventions as well as to understand the role of these chemicals in brain functions. Various analytical tools has been reported for the quantification of NTs in biological matrices. These include mass spectroscopy, fluorimetry, chemiluminescence, chromatography, and capillary electrophoresis (Zhang et al., 2007; Santos-Fandila et al., 2013; De Benedetto et al., 2014; Wang et al., 2012; Li et al., 2011; Zhao and Suo, 2008; Lapainis et al., 2009). Most of them are complex, expensive, require tedious procedures, and suffer from poor sensitivity and selectivity. By contrast, electrochemical methods are known to provide low-cost, simple, sensitive, fast response time and selective determination of various biological species. The advent of chemically modified electrodes brought rapid improvements in the field of electroanalysis, meeting the higher demands for sensitivity and