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Electrochemical sensors and biosensors for determination of catecholamine neurotransmitters: A review

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ABSTRACT

This work describes the state of the art of electrochemical devices for the detection of an important class of neurotransmitters: the catecholamines. This class of biogenic amines includes dopamine, noradrenaline (also called norepinephrine) and adrenaline (also called epinephrine).

Researchers have focused on the role of catecholamine molecules within the human body because they are involved in many important biological functions and are commonly associated with several diseases, such as Alzheimer's and Parkinson. Furthermore, the release of catecholamines as a consequence of induced stimulus is an important indicator of reward-related behaviors, such as food, drink, sex and drug addiction. Thus, the development of simple, fast and sensitive electroanalytical methodologies for the determination of catecholamines is currently needed in clinical and biomedical fields, as they have the potential to serve as clinically relevant biomarkers for specific disease states or to monitor treatment efficacy.

Currently, three main strategies have used by researchers to detect catecholamine molecules, namely: the use electrochemical materials in combination with, for example, HPLC or FIA, the incorporation of new materials/layers on the sensor surfaces (Tables 1–7) and *in vivo* detection, manly by using FSCV at CFMEs (Section 10). The developed methodologies were able not only to accurately detect catecholamines at relevant concentration levels, but to do so in the presence of co-existing interferences in samples detected (ascorbate, for example).

This review examines the progress made in electrochemical sensors for the selective detection of catecholamines in the last 15 years, with special focus on highly innovative features introduced by nanotechnology. As the literature in rather extensive, we try to simplify this work by summarizing and grouping electrochemical sensors according to the manner their substrates were chemically modified. We also discuss the current and future of electrochemical sensors for catecholamines in terms of the analytical performance of the devices and emerging applications.

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Abbreviations: 5-HT, Serotonin (or 5-hydroxytryptamine); AA, Ascorbic acid; AC, Acetaminophen; Adr, Adrenaline (or epinephrine); BDD, Boron-doped diamond; BPPG, Basal plane pyrolytic graphite; CD, Cyclodextrin; CFE, Carbon fiber electrode; CFME, Carbon fiber microelectrode; CNTs, Carbon nanotubes; COMT, Catechol-*O*-methyltransferase; CPE, Carbon paste electrode; CV, Cyclic voltammetry; Cys, Cysteine; DA, Dopamine; DOPA, Dihydroxyphenylalanine; DOPAC, 3,4-Dihydroxyphenylacetic acid; EPPG, Edge plane pyrolytic graphite; Fc, Ferrocene; GC, Glassy carbon; Glu, Glucose; Gly, Glycine; GO, Graphene oxide; GR, Graphene; HOPG, Highly oriented pyrolytic graphite; HVA, Homovanillic acid; ITO, Indium thin oxide; LOD, Limit of detection; MAO, Monoamine oxidase; ME, Microelectrode; MIP, Molecular imprinted polymer; MWCNTs, Multi-walled carbon nanotubes; NA, Noradrenaline (or norepinephrine); NPs, Nanoparticles; NT, Neurotransmitter; PANI, Poly(aniline); PE, Paste electrode; PEDOT, Poly(3,4-ethylenedioxythiophene); PG, Pyrolytic graphite; Ppy, Poly(pyrrole); PVA, Poly(vinyl alcohol); PVC, Polyvinyl chloride; rGO, Reduced graphene oxide; RTIL, Room temperature ionic liquid; SAM, Self-assembled monolayer; SPE, Screen-printed electrode; SWCNTs, Single wall carbon nanotubes; Tyr, Tyrosine;TRP, Tryptophan; UA, Uric acid; VMA, Vanillylmandelic acid

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1. Catecholamines

In the mammalian brain, neuronal networks process vast amounts of information received from the subject's environment from various senses such as sight, hearing, and touch, which are then combined with signals from throughout the body.

The brain uses neurons to carry information throughout the brain using trains of electrical impulses. At the interconnection between neurons, called synapses, these electrical signals are converted in a sophisticated non-linear manner into chemical signals. Synaptic vesicles fuse with the cell membrane releasing their contents, the NTs, by exocytosis. The released NT diffuses both, within and outside of the synapse, where it acts on specialist receptors which can be on the releasing neuron (as part of a feedback control), in the next neuron in the chain (to pass the message on) or perhaps most importantly in surrounding neurons (to give a neuromodulatory action and allow integration of responses between neurons). For DA, this last action is the most important in terms of its function [1,2].

Catecholamines are neurotransmitters (NTs) and/or hormones in the peripheral and in the central nervous system [3,4]. They excite, inhibit or otherwise influence the activity of cells. This class of specialized chemical messengers is composed by dopamine (DA, represented in Fig. 1A), noradrenaline (NA, also called norepinephrine, Fig. 1B) and adrenaline (Adr, also called epinephrine, Fig. 1C).

In terms of biosynthesis, all the catecholamines (so named because they share the catechol moiety) are derived from a common precursor, the amino acid tyrosine (Tyr) [3,4]. The first step in catecholamine synthesis is catalysed by tyrosine hydroxylase to form dihydroxyphenylalanine (DOPA), which gives origin to DA after the action of DOPA decarboxylase (see Fig. 2).

DA serves as a NT in several important pathways in the central nervous system and has also an important biological activity in the peripheral nervous system. DA has also been associated with the reward system, the circuitry in the brain responsible for the motivation to seek out stimuli as well as the emotions of feeling satisfied and satiated in one's environment. It is thought that this system is activated by natural rewards such as food, drink and sex, as well as by addictive drugs [1]. For example, cocaine and other addictive drugs act by stimulating the release of DA from specific brain areas [3,4].

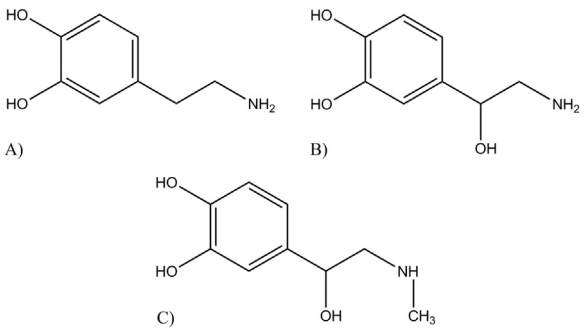

Fig. 1. Molecular structure of dopamine (A), noradrenaline (B) and adrenaline (C).

NA synthesis requires dopamine β-hydroxylase which catalyses the production of NA from DA. NA is a NT in the brain as well as in postganglionic sympathetic neurons where it influences sleep and wakefulness, attention and feeding behavior.

Adr is formed by the action of phenylethanolamine-*N*-methyltransferase over NA. Adr is a hormone released from the adrenal gland and it stimulates catecholamine receptors in a variety of organs [3,4]. It plays an important role during the times of physical or mental stress [5] and has been used as a common emergency healthcare medicine. Endogenous catecholamine levels have been measured in resting individuals and have been shown to be approximately 150–800 ng/L for NA and 10–50 ng/L for Adr and DA [6].

The effects of DA are mediated through interaction with five different receptors, usually referred to as D1-like (D1, D5) and D2-like (D2, D3, D4) [3,4]. DA receptors are found primarily in brain (in the substantia nigra/ventral tegmental area of the brain), although they also exist in kidney. The effects of NA and Adr are mediated through nine distinct receptors, named adrenergic receptors, grouped into three families (α1, α2, β), each containing three subtypes encoded by separate genes. As NA and Adr are important messengers in both, the peripheral sympathetic nervous system and the brain, adrenergic receptors are widely distributed in peripheral tissues as well as existing in high concentrations in the brain [3,4].

All three catecholamines are removed by reuptake into nerve terminals or surrounding glial cells by a Na^+-dependent transporter [3,4]. The two major enzymes involved in the catabolism of catecholamines are monoamine oxidase (MAO) and catechol *O*-methyltransferase (COMT). MAO and COMT are widely distributed throughout the body. As can be seen in Fig. 2, homovanillic acid (HVA) is the major metabolite of DA. There are also several pathways for the NA (see Fig. 3) and Adr degradation and the vanillylmandelic acid (VMA) is the major metabolite [3,4].

The relationship between these amine compounds and human pathologies has been known for more than 150 years [7]. Currently, in fact, it is known that they are involved in several physiological mechanisms and are related to some of the most prevalent human pathologies, such neurological disorders as Parkinson's disease, Alzheimer, schizophrenia and hyperactivity [7].