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STUDY ON DETECTION METHODS FOR NOREPINEPHRINE IN BIOLOGICAL SAMPLES

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ABSTRACT: Norepinephrine (NE) is an important catecholamine neurotransmitter that acts as a biochemical messenger in central nervous systems and neuronal cells of mammals, which is secreted and released by the adrenal medulla and the noradrenergic neurons during the synaptic transmission. It is often used for treating bronchial asthma, myocardial infarction hypertension and organic heart disease. Abnormal release of NE will contribute to the occurrence of many nerve related diseases, such as paraganglioma, ganglia neuroblastoma, ganglion neuronal, and Parkinson's disease. In addition, increased NE concentration in plasma is associated with coronary heart disease and with muscle sympathetic nerve traffic in human obesity. Furthermore, NE is involved in the occurrence and development of cardiac hypertrophy through the activation of myocardial adrenergic receptors on cell membranes in myocardial tissue. Therefore, the rapid, sensitive, and selective detection of NE level is significant for monitoring physiological function and diagnosing diseases. In this article the studies of detection methods for NE in recent years are reviewed.

INTRODUCTION: Norepinephrine (NE) is a catecholamine (CA), which acts as hormone and neurotransmitter. The human adrenal medulla releases about 20% NE, while the adrenergic neurons are responsible for the major NE production [1, 2]. As a stress hormone, NE affects parts of the brain, in which attention and responding actions are controlled. Together with epinephrine (E), NE also underlies the fight-or-flight response, directly increasing heart rate, triggering the release of glucose from energy stores, and increasing blood flow to skeletal muscle. NE can also suppress neuroinflammation when it is released diffusely in the brain from the locus ceruleus.

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When NE acts as a drug it increases blood pressure by the increasing of vascular tone through α-adrenergic receptor activation [3, 4]. The quantification of NE concentration in biological system provides important information about its physiological adverse effects such as anxiety, diabetes, pain, heart disease and other neurological disorders like Parkinson and Alzheimer diseases [5, 6]. Therefore, the highly selective detection of NE is of great importance in pharmaceutical analysis and clinical diagnosis. In this paper, the attributes of different analytical technique for the determination of NE in recent years are reviewed.

2. Analytical Methods:

2.1. Fluorescence method: In recent years, fluorescence measurements have received more attention owing to their operational simplicity, high sensitivity, good reproducibility and real-time detection. A series of fluorescence probes have been designed for the detection of biomolecules and metal ions. For example, gold nanoclusters (AuNCs), which exhibit molecule-like properties

including discrete electronic states and size-dependent luminescence have received great attention. Fluorescent silicon nanoparticles (SiNPs), which have a zero-dimensional silicon-based nanostructure, have been widely used in biology, owing to their good biocompatibility, low cytotoxicity, and antiphotobleaching capability. Colloidal quantum dots (QDs) which exhibit broad absorption profiles and narrow emission with high quantum yields and allow the chemical modification of functional groups on their surfaces make QDs naturally suitable for serving as fluorescent platforms for sensing and imaging in biology [7-9].

Alam *et al.,* [10] developed a method for the determination of the three CAs of E, NE, and dopamine (DA) at sub-nanomolar levels. They found that the luminescence of the complexes formed between the CAs and Tb^{3+} ion was strongly enhanced in the presence of colloidal silver nanoparticles, which caused a transfer of the resonance energy to the fluorophores through the interaction between the excited-state fluorophores and surface plasmon electrons. With the optimized condition, the intensity of luminescence with the system was linearly related to the concentration of the CAs. The linear range of concentration was 2.8–240 nM for NE and the limit of detection was as low as 0.64 nM. They successfully determined CAs in pharmaceutical preparations, and demonstrated successful recovery experiments for urine and serum samples.

Wei *et al.,* [11] developed a simultaneous detection method for NE and E by anchoring molecularly imprinted polymers (MIPs) on the surfaces of two different color QDs. NE-QDs@MIP using NE as template and E-QDs@MIP using E as template were synthesized on the surfaces of CdTe@SiO_2 and CdTe/CdS/ZnS/SiO_2 QDs, respectively. The QDs@MIPs nanosensors had distinguished selectivity and high binding affinity to the corresponding template molecule. The mixture of NE-QDs@MIP and E-QDs@MIP could be excited at the same excitation wavelength and the simultaneous detection of NE and E was realized by monitoring the two different color fluorescence signals without spectral overlap. Under the best conditions, the fluorescence intensity of each kind of QDs@MIP decreased linearly with the increase of the concentration of the corresponding template molecule in the range of 0.08–20μM. The limit of detection for NE and E were 9 and 12 nM, respectively.

2.2. HPLC method: High-performance liquid chromatography (HPLC) is a powerful tool that enables the separation of complex mixtures into individual components, and is a highly sensitive and reproducible analytical technique. In recent years, HPLC has been combined with many sensitive detection techniques and has experienced continuous improvement of stationary phases, which have improved its sensitivity and specificity. HPLC is currently widely used for the analysis of drugs and dosage forms with respect to quality control, quantitative determination of active ingredients and impurities, monitoring drug blood concentration in patients, and bioequivalence assessment [12-14].

Mu *et al.,* [15] developed a new HPLC strategy, which was coupled with on-line gold nanoparticle-catalyzed luminol chemiluminescence (CL) detection for the simultaneous detection of CAs in rat brain. NE, E and DA could strongly strengthen the CL signal of the on-line luminol system catalyzed by gold nanoparticles. CAs promoted the formation of more gold nanoparticles to further catalyze the luminol–H_2O_2 CL reaction. They successfully separated the NE, E and DA with isocratic elution using a mixture of methanol and 0.2% aqueous phosphoric acid within 8.5min. Under the best conditions, the limit of detection was in the range of 1.32–1.90 ng/mL. The recoveries of CAs added to rat brain sample were >94.6%. The validated HPLC-CL strategy had been successfully used to determine NE and DA in rat brain without prior sample purification.

Liu *et al.,* [16] developed a simple and specific HPLC method coupled with fluorescence detection for the simultaneous determination of NE, DA, and E in human urine. They derivatized the samples with 1,2-diphenylethylenediamine and used the isoprenaline as internal standard. Then they separated the CA derivatives on a Kromasil C18 column with methanol and sodium acetate buffer as mobile phase. The limits of detection for all CAs ranged from 0.2 to 1.1ng/mL.

They successfully used the method to determine the CAs in human urine for 14 patients with Alzheimer's disease and 14 healthy volunteers. It was concluded that the mean levels of CAs in urine of the patients with Alzheimer's disease were all lower than those for healthy volunteers. And they used the cluster analysis and independent samples T-test to distinguish the Alzheimer's disease patients and healthy volunteers.

2.3. Electrochemical method: Since the early 70s electrochemistry technique has been used as a powerful analytical method for monitoring electroactive species in living organisms. NE is an electroactive compound that can be oxidized electrochemically. Therefore, the development of electrochemical sensors for the determination of NE has been the focus of research over the past decade. However, it is known that the accumulation of the final reaction products which can polymerize and thus the fouling effect of the electrode surface make a serious hindrance when NE are oxidized directly at the bare electrode surfaces. Moreover, NE exists in natural environment together with some small biomolecules like ascorbic acid and uric acid, which oxidizes at bare electrodes in almost the same potential region as NE. Among various attempts to overcome the above-mentioned problems, much attention has been paid to the use of electrodes modified for the development of suitable sensors. Numerous materials, such as metal nanoparticles, polymers, carbon nanotubes, fullerenes, graphenes, and enzymes, have been used as modifiers to construct highly sensitive and selective NE biosensors [17-19].

Wang *et al.,* [20] fabricated a new electrochemical sensor for simultaneous determination of NE and serotonin (5-HT). The electrochemical behavior of NE and 5-HT were investigated using CV and SWV at the MWNTs-ZnO/chitosan composites modified screen-printed electrode. The results showed that the current responses of NE and 5-HT greatly enhanced due to the high catalytic activity of composites. The peak potentials of NE and 5-HT were separated at about 90mV and 280mV, respectively. The peak currents of NE and 5-HT were linearly dependent on their concentrations in the range of 0.5–30μM and 0.05–1μM, with the limit of detection of 0.2 μM and 0.01 μM, respectively. Furthermore, the modified electrode was successfully applied to detect the level of NE and 5-HT in rat cerebrospinal fluid with excellent selectivity and sensitivity.

Mazloum-Ardakani *et al.,* [21] reported the development and utilization of a new nanocomposite consisting of benzofuran derivative-functionalized multiwalled carbon nanotubes and ionic liquid for the modification of glassy carbon electrode. The novel sensor showed excellent electrocatalytic activities for the oxidation of NE and 5-HT. Furthermore, they didn't find the obvious interference for the detection of NE and 5-HT in the presence of common interferents such as uric acid and ascorbic acid that coexisted compounds with NE and 5-HT in biological systems. Differential pulse voltammetry showed two linear dynamic ranges of 0.1–30.0 μM and 30.0–1000.0 μM for NE and one linear dynamic ranges of 5.0–900.0 μM for 5-HT. The limits of detection for NE and 5-HT were 49 nM and 2μM, respectively. The proposed method was successfully applied for the quantitation of NE and 5-HT in human serum.

2.4. Capillary electrophoresis method: In recent decades, capillary electrophoresis (CE) has been developed for trace analysis because of its small sample size of only nanoliters to femtoliters, short analysis time, and biocompatible environments. In addition, rapid separations are feasible with CE because high voltages can be applied to short capillaries and separation efficiency is not dependent on column length. To identify biological and pharmaceutical analysis, CE is coupled to a variety of detectors, including fluorescence, mass spectrometry, and electrochemical detection [22-24].

Xu *et al.,* [25] presented a simple and sensitive method for the quantitation of the three major CAs in human urine by CE with on-line CL detection. This method was based on the enhancing effect of E, NE, and DA on the CL reaction between luminol and the Ag (III) complex in alkaline solution. They performed the separations and determination with an electrophoretic buffer consisting of 20.0 mM sodium borate and 1.0 mM luminol. Under the best conditions, the three CAs were separated and detected in less than 8 min and the limit of detection for NE was 1.0×10^{-7} M.

The proposed method was applied to the detection of the CAs in urine samples from 12 healthy individuals and 26 pheochromocytoma patients. The results suggested that this method might be useful for monitoring the CA levels in routine screening and to diagnose pheochromocytoma. Liu *et al.,* [26] developed a new and sensitive strategy for the quantitation of NE, synephrine, and isoproterenol by CE separation and indirect electrochemiluminescence detection based on their quenching effects on the tris(2,2'-bipyridyl)-ruthenium(II)/tripropylamine system. Under the best conditions, the three analytes were well separated within 9 min. The limits of detection were 2.6×10^{-8} mol/L and in real human urine samples were 2.6×10^{-7} mol/L for NE. The applicability of the proposed strategy was showed in the determination of 20 human urine samples from diabetic patients and healthy persons. The results obtained showed that the level of NE in patients was higher than that in healthy persons.

2.5. Other methods: In addition to these main approaches mentioned above for NE detection, still a few special techniques with high sensitivity have been applied. Zhu *et al.,* [27] proposed a simple and fast colorimetric method for the determination of CAs in pharmaceutical samples using Ag^{+}–3,3',5,5'-tetramethylbenzidine as a colorimetric probe. Chen *et al.,* [28] reported the determination of ultra-trace CAs based on hot electron-induced cathodic electrochemiluminescence at a naturally oxide-covered tantalum electrode.

Kamruzzaman *et al.,* [29] designed a terbium-sensitized spectrofluorimetric method for determination of CAs in a serum sample with micelle medium. Grunhut *et al.,* [30] developed a flow-batch analyzer for the CE determination of CAs in pharmaceutical preparations.

CONCLUSIONS: NE is one of the most important biochemical messengers in mammalian central nervous systems, existing in the nervous tissue and biological body fluids. Many diseases and the caducity process are related to changes of its concentration, thus the quantitative determination of trace NE in biological fluids provides important information on its physiological functions and the diagnosis of some diseases in clinical medicine [31, 32].

This review has highlighted the significant developments in rapid and alternative techniques for the detection of NE in recent years. We believe the development of NE sensors with better sensitivity and specificity, lower cost, simplicity, along with in vivo analytical technique is still the future effort.

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CONFLICT OF INTEREST: The author declares that there is no conflict of interest.

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