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# Advanced materials for optical sensing and biosensing of neurotransmitters

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ABSTRACT

Many physiological disorders, including Parkinson's, Alzheimer's and schizophrenia, are associated with variations in the biological levels of neurotransmitters and affect, e.g., learning, sleeping, memory, consciousness, and mood. Real-time, ultrasensitive and accurate detection of neurotransmitter levels in biological fluids not only improves the quality of a patient's life but also can reduce the cost of treatment. Advanced materials can offer remarkable opportunities in the design of bioimaging methods. With advanced materials, hopes of introducing "molecule-sensitive" methods with *in-situ* scientific instrumentation capability increase. This review aims to highlight recent advancements in materials used for detection of important neurotransmitters and focuses on the analytical features of the optical-based methods available.


**Contents**



*Abbreviations:* 5-HT, serotonin; AA, ascorbic acid; ACh, acetylcholine; AChE, acetyl cholinesterase; Asp, aspartic acid; ATP, adenosine triphosphate; ATTO-590, $C_{37}H_{39}ClN_2O_9$; BSA, bovine serum albumin; CDs, carbon nanodots; Chox, choline oxidase; CNPs, carbon nanoparticles; CNS, central nervous system; CNTs, carbon nanotubes; CPO-I, 2-(3,5-dinitrophenyl)-4–5-oxazolone; CPO-II, 2-(4-nitrophenyl)-4-[4-(1,4,7,10-tetraoxa-13-azacyclopentadecyl)benzylidene]-5-oxazolone; CPO-III, 2-(4-tolyl)-4-[4-(1,4,7,10-tetraoxa-13-azacyclopentadecyl)benzylidene]-5-oxazolone; CPs, conjugated polymers; DA, dopamine; DBA, DA-binding aptamer; DTSSP, dithiobis(sulfosuccinimidylpropionate); ECL, electrochemiluminescence; EP, epinephrine; GABA, γ-amino butyric acid; GCE, glassy carbon electrode; Glu, glutamic acid; GO, graphene oxide; GSH, glutathione; HB-1, hyper branched viologen polymer; HRP, horseradish peroxidase; ITO, indium tin oxide; Lac, laccase; LCG, lucigenin; LOD, limit of detection; MBA, 4-mercaptophenylboronic acid; MPN, mesoporous silica nanoparticle; MWCNTs, multiwalled carbon nanotubes; NCs, nanoclusters; NEP, norepinephrine; NIR, near infrared; NTA, nitrilotriacetic acid; PAMAM, polyamidoamine; PBS, phosphate buffer solution; PEG, polyethylene glycol; PEI, polyethyleneimine; PMA, polymethacrylic acid; $PPESO_3$, poly(2,5-bis(3-sulfonatopropoxy)-1,4-phenylethynylenealt-1,4-poly(phenylene ethylene)); QDs, quantum dots; RRS, resonance Rayleigh scattering; RSD, relative standard deviation; SAMs, self-assembled monolayers; SERS, surface-enhanced Raman spectroscopy; TGA, thioglycolic acid; UA, uric acid.

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## 1. Introduction

Neurotransmitters are released from nerves to transmit signals from neurons to a target neuron synapses. Neurotransmitters can be categorized according to their functions into excitatory and inhibitory. The most common excitatory neurotransmitter is glutamate, although glycine and dopamine (DA) have excitatory actions. They convince a nerve cell to produce an action potential, an electrochemical impulse that nerve cells use to transmit signals. In contrast, inhibitory neurotransmitters [e.g., γ-amino butyric acid (GABA) and serotonin (5-HT)] block the signal-transmission process. However, some neurotransmitters possess both properties (e.g., DA). Moreover, some catecholamines, namely DA, norepinephrine (NEP) and epinephrine (EP), play another important role in the central nervous system (CNS) as hormones, and they also affect the regulation of blood pressure, heart rate and lipolysis [1].

Neurotransmitters play important role in many brain functions, including behavior and cognition. They affect and adjust muscle tone and heart rate, and regulate learning, sleeping, memory, consciousness, mood and appetite [2–7].

Changes in the concentration of neurotransmitters in the CNS have been associated with many mental and physical disorders {e.g., Parkinson's, Alzheimer's, schizophrenia, glaucoma, Huntington's, epilepsy, arrhythmias, thyroid hormone deficiency, congestive heart failure, sudden infant death syndrome (SIDS), depression and anxiety [3,4,6,8–17]}. Thus, the quantitative detection of the neurotransmitter in different human fluids appears to be important for diagnosis, monitoring disease state and therapeutic interventions. Table 1 shows the normal concentrations of neurotransmitters in various media.

Real-time and accurate detection of the concentration of neurotransmitters in urine, plasma and cerebral fluids could improve the treatment process and prevent unnecessary drug treatment. So far, more than 100 neurotransmitters have been identified, but this review covers only more common neurotransmitters, including DA, ACh, glutamate, aspartate, GABA, 5-HT, EP and NEP in various physiological mediums (e.g., serum, plasma, urine and cerebral fluids) utilizing optical methods [e.g., fluorescence, luminescence, chemiluminescence, electrochemiluminescence (ECL) and spectrophotometry]. Moreover, it emphasizes figures of merits and most recent materials used in analysis of neurotransmitters.

Numerous methods based on separation-detection methods (e.g., GC, HPLC and CE, electrochemical and flow-injection-based methods) were applied to determine neurotransmitters in various biological environments (Table 2). Although separation-based methods can offer good selectivity and low limits of detection (LODs), they often are costly, require sophisticated equipment, are time consuming and need complex pre-treatment steps. Also, various electrochemical-based methods are very sensitive but their repeatability is poor, while spectroscopic methods are very cheap and rapid and their repeatability is better than electrochemical methods. Also, the sensitivity of most spectroscopic methods is better or comparable with separation and electrochemical-based methods. In the following, there are examples of advanced materials for optical sensing and biosensing of neurotransmitters.

**Table 1**
Normal concentration of neurotransmitters in biofluids

| Neurotransmitter | Medium | Concentration range | Ref. |
|---|---|---|---|
| ACh | Blood | 8.66 ± 1.02 nM | [6] |
| DA | Plasma | 0.04–4.50 nM | [17] |
| GABA | Cerebrospinal fluid | 9 ± 5 to 55 ± 27 ng/mL | [18] |
| NEP | Plasma | 0.45–2.49 nM | [19] |
| EP | Plasma | 0.02–0.46 nM | [19] |
| 5-HT | Plasma | 101–283 ng/mL | [20] |
| Glutamate | Plasma | 61 μM | [21] |

**Table 2**
Figures of merits of the conventional methods for detection of neurotransmitters

| Analysis Method | Type of Analyte | Dynamic range | LOD | Ref. |
|---|---|---|---|---|
| Spectrophotometric | NEP | 1.0–20.0 mg/mL | – | [22] |
| | EP | 0.2–5.0 mg/mL | | |
| | DA | 0.4–4.0 mg/mL | | |
| Spectrophotometric | 5-HT | 0.025–0.5 mM | 2.3 μM | [23] |
| Spectrophotometric | EP | 4.8–800 μM | 0.26 μM | [24] |
| | NEP | 4.8–600 μM | 2.46 μM | |
| HPLC–MS | NEP | 0–4000 ng/mL | 9.6 ng/mL | [25] |
| | EP | 0–63 ng/mL | 1.9 ng/mL | |
| | DA | 0–1000 ng/mL | 6.5 ng/mL | |
| | 5-HT | 0–250 ng/mL | 0.78 ng/mL | |
| LSV[a] | 5-HT | 0.05–10 μM | 48 μM | [26] |
| UFLC–MS/MS[b] | GABA | 8.0–4000 ng/mL | – | [27] |
| | Glu | 16–8000 ng/mL | | |
| | NE | 4.0–2000 ng/mL | | |
| | DA | 4.0–2000 ng/mL | | |
| | 5-HT | 4.0–2000 ng/mL | | |
| UHPLC-MS/MS[c] | DA | 5–1000 ng/mL | 2 ng/mL | [28] |
| | 5-HT | 5–1000 ng/mL | 2 ng/mL | |
| | NEP | 50–1000 ng/mL | 20 ng/mL | |
| | EP | 20–1000 ng/mL | 5 ng/mL | |
| | Glu | 50–1000 ng/mL | 20 ng/mL | |
| | GABA | 50–1000 ng/mL | 20 ng/mL | |
| Amperometry | DA | 0.5–50 μM | 0.07 μM | [29] |
| Amperometry | EP | 0.5–100 μM | 0.07 μM | |
| SWV[d] | DA | 0.5–20 μM | 0.1 μM | |
| SWV | EP | 5–100 μM | 1 μM | |
| Chemiluminescence | EP | 0.05–1.0 μg/mL | 0.03 μg/mL | [30] |
| | NEP | 0.1–1.00 μg/mL | 0.05 μg/mL | |
| | DA | 0.1–1.00 μg/mL | 0.04 μg/mL | |
| DPV[e] | DA | 0.7–5 μM | 0.3 μM | [31] |
| | 5-HT | 1–30 μM | 50 μM | |
| LC–MS/MS[f] | ACh | 1–250 ng/mL | 15 pg/mL | [32] |
| HPLC | ACh | 10–1000 pmol | 3 pmol | [33] |
| MALDI-TOF MS[g] | ACh | 1–1000 fmol/μL | 0.3 fmol/μL | [34] |

[a] Linear sweep voltammetry.
[b] Ultra-fast liquid chromatography/tandem mass spectrometry.
[c] Ultrahigh performance liquid chromatography–tandem mass spectrometry.
[d] Square wave voltammetry.
[e] Differential pulse voltammetry.
[f] Liquid chromatography–mass spectrometry.
[g] Matrix-assisted laser desorption ionization time-of-flight mass spectrometry.

## 2. Optical sensors and biosensors

### 2.1. Quantum dots

Quantum dots (QDs), with sizes in the range 2–10 nm, are promising materials for sensitive, precise determinations in biologic media. QDs possess some unique properties (e.g., broad absorption peaks, high-emission quantum yields, narrow and symmetric emission peaks and good chemical and optical stabilities, and their surfaces can be changed to enhance quantum yields).

Mu and co-workers developed a florescence-based method for detection of DA by applying CdSe/ZnS QDs that stabilized with adenosine (Fig. 1). The QDs and DA were connected by nucleotides containing various amino and hydroxyl groups, offering the possibility to interact with DA via non-covalent bonds (e.g., hydrogen bonding and electrostatic interactions). Importantly, adenosine had a negligible effect on the emission profiles and the morphology of the oil-soluble QDs and provided a very stable signal for 24 h in phosphate-buffer solution (PBS) at pH 7.4. DA could be oxidized by ambient $O_2$ to give dopamine–quinone. The oxidized form of DA acted as an electron acceptor for QDs whose non-radiative emission led to the fluorescence quenching. The DA-QD-based