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Review

Recent Advances in the Detection of Neurotransmitters

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Abstract: Neurotransmitters are chemicals that act as messengers in the synaptic transmission process. They are essential for human health and any imbalance in their activities can cause serious mental disorders such as Parkinson's disease, schizophrenia, and Alzheimer's disease. Hence, monitoring the concentrations of various neurotransmitters is of great importance in studying and diagnosing such mental illnesses. Recently, many researchers have explored the use of unique materials for developing biosensors for both in vivo and ex vivo neurotransmitter detection. A combination of nanomaterials, polymers, and biomolecules were incorporated to implement such sensor devices. For in vivo detection, electrochemical sensing has been commonly applied, with fast-scan cyclic voltammetry being the most promising technique to date, due to the advantages such as easy miniaturization, simple device architecture, and high sensitivity. However, the main challenges for in vivo electrochemical neurotransmitter sensors are limited target selectivity, large background signal and noise, and device fouling and degradation over time. Therefore, achieving simultaneous detection of multiple neurotransmitters in real time with long-term stability remains the focus of research. The purpose of this review paper is to summarize the recently developed sensing techniques with the focus on neurotransmitters as the target analyte, and to discuss the outlook of simultaneous detection of multiple neurotransmitter species. This paper is organized as follows: firstly, the common materials used for developing neurotransmitter sensors are discussed. Secondly, several sensor surface modification approaches to enhance sensing performance are reviewed. Finally, we discuss recent developments in the simultaneous detection capability of multiple neurotransmitters.

Keywords: neurotransmitter; nanomaterials; biosensor; electrochemical; review

1. Introduction

Understanding the complex functions of a brain remains one of the grand challenges of biomedical research. One possible way is to develop in vivo biosensors for monitoring the activities and the signal pathways of neurotransmitters in brain. Neurotransmitters are essential chemicals that can transfer information between the neuron cells. Otto Loewi was one of the first people to discover one type of neurotransmitter called acetylcholine in 1921 [1]. His work significantly impacted the human perception of how information is transmitted in animals. Subsequently, other types of neurotransmitters were later discovered, with over 100 different types known to date. Almost all neurotransmitters are essential to human mental and physical health and any abnormalities or changes in their activity may cause severe disease and mental disorders. Hence, monitoring of such neurotransmitters is critical for medical treatment and clinical analysis.

A biochemical sensor that can continuously monitor in real time the dynamic behaviors of the various neurotransmitters can be a powerful tool for monitoring and treating patients with neurological

brain disorders such as Alzheimer's disease, epilepsy, Parkinson's disease, and addiction. For instance, in Parkinson's disease (PD), the primary symptoms appear as a gradual deterioration of substantia nigra that controls motor functioning such as balance and movements [2]. This region of brain is located deep in the brain stem [3,4] where the dopamine produced in this area is responsible for neural communication between the striatum and the substantia nigra [5]. Parkinsonian symptoms appear when dopaminergic neuronal death exceeds a critical threshold of 70–80% [6]. The decreased level of dopamine is directly associated with the uncontrolled motor function, which leads to the inability to neutralize the imbalance in neurotransmitters [7]. In particular, the motor function in the striatum is dependent on the balanced equilibrium between dopamine and acetylcholine. The disruption in the balance of these two neurotransmitters can bring about the progression of PD [8–10]. It is also known that norepinephrine dysfunction is a contributing factor in PD, and serotonin and gamma(γ)-aminobutyric acid (GABA) may also affect the condition as secondary symptoms of PD [11,12]. Furthermore, histamine, the initial neurotransmitter and immune mediator, has been reported to be significantly elevated in the brain with PD [13,14]. The above findings illustrate that there is a complex interplay between various neurotransmitters that are closely related to the progression of neural diseases. Therefore, simultaneous detection of multiple neurotransmitters in vivo is urgently needed for the better understanding of mental disorders and for the development of treatment and therapy for such diseases.

The mesocorticolimbic dopamine system plays a crucial role in reward, motivation and learning [15–17]. It is also severely affected by drug or substance addiction. The ventral tegmental area (VTA) is the midbrain region that has been implicated in the rewarding effect of various addictive drugs such as cocaine [18], nicotine [19] and opiates [20]. Important neurotransmitter signaling pathways include limbic afferents to the nucleus accumbens (NAc), efferents from the NAc to VTA, dopaminergic projections from VTA to NAc, to prefrontal cortex (PFC) and to tegmental pedunculopontine nucleus (TPP) [16] as shown in Figures 1 and 2. In the event of drug administration, a wide range of neurotransmitters will change their dynamics as a result of either overproduction or inhibition. The above scenario showcases the potential application where a multi-analyte neurotransmitter-sensing probe could be used to advance our understanding of the brain from a neurological signaling perspective. Hence, the development of an implantable multi-analyte sensor that can simultaneously monitor the dynamics of multiple neurotransmitters as they occur in real time can be an extremely power tool.

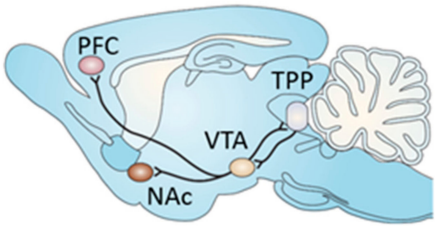

Figure 1. A diagram of a rat brain showing the mesocorticolimbic dopamine pathways. (Adopted from [15]).

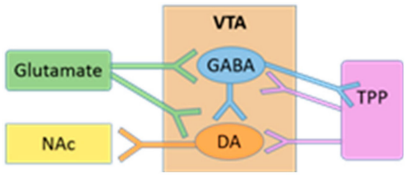

Figure 2. Schematic illustration of DA and GABA neurons in VTA and their projections to other parts of the brain. (Adopted from [15]).

In vivo monitoring is challenging because the response time of the neurotransmitters is fast, rapidly releasing and clearing from the extracellular space [21], and the concentrations involved are typically low [22]. Two of the most widely used techniques for in vivo monitoring of neurotransmitters are microdialysis and fast-scan cyclic voltammetry (FSCV). In microdialysis, a semi-permeable probe is injected into the brain and the analyte that is present in the brain is perfused through the probe and collected for chemical analysis using techniques such as high-performance liquid chromatography (HPLC) with mass spectrometry (MS) or fluorescence as a detector [23]. The main disadvantage of microdialysis is the low temporal resolution in the order of minutes since sample fluid must be drawn from the brain and collected for off-line analysis. FSCV has recently emerged as one of the leading techniques for in vivo neurotransmitter detection due to its fast sampling rate leading to high temporal resolution [21]. The in vivo electrochemical monitoring of neurotransmitters in the brain have been effective for electroactive species (e.g., dopamine, norepinephrine, serotonin, adenosine, etc.). However, several challenges remain to be solved: (1) many chemical species in the brain have similar oxidation/reduction potentials and the presence of many interfering species makes it difficult to conduct multi-analyte detection in vivo. (2) non-electroactive species (such as glutamate, histamine, acetylcholine, etc.) require enzymes (e.g., glutamate oxidase, acetylcholinesterase, etc.) to be detected electrochemically. The limitations associated with enzyme-based sensors are their instability, degradation in enzymatic activities and complex immobilization protocols. Hence, a novel sensing technique that is reliable and allows simultaneous real-time multi-analyte detection with high specificity, temporal and spatial resolution is greatly needed.

Currently, the need is great for establishing a new route to monitor the complex intercommunication of neurotransmitters in the brain. In particular, a measurement technology that is capable of parallel, rapid, and specific quantification of numerous analytes for the requisite extended time period in a living brain, without negatively impacting the implanted region is in demand. Existing in vivo measurement techniques are incapable of (1) multi-analyte detection with high temporal resolution in real time and (2) long-term monitoring without device failure.

Many works related to neurotransmitter detection have been published in recent years, with emphasis on both in vivo and ex vivo sensing. Various sensing mechanisms have been explored with a variety of nanomaterials used. For example, micromachined electrode array (MEA) is widely used for neurotransmitter detection in vivo because it provides facilitated communication between the sensor and the neuron [24]. The assembly of the microelectrode could greatly enhance the surface area for capturing the released neurotransmitters from cells, thereby minimizing the diffusional delay [25]. Several parameters are crucial in evaluating the performance of the sensor: the sensitivity and the limit of detection (LOD) of the sensor must be sufficient for the level of concentration for the target neurotransmitter in serum. Also, the selectivity of the sensor must be high enough because much interference may be present in the real sample. Reproducibility is also crucial for robust analysis. The electrodes may foul due to the adhering or adsorbing of the proteins in real samples [26]. Fouling can greatly impact the sensor response, hence it is necessary to develop electrode surfaces that are resistant to bio-fouling [27]. Detecting multiple neurotransmitters simultaneously is a very challenging task because many neurotransmitters possess similar molecular structures and physicochemical properties which make them difficult to differentiate one from the other. In this review, we summarize the primary materials used for sensor electrode development as well as the strategies for the in vivo and ex vivo detection of neurotransmitters. We also discuss the current state of the art in simultaneous detection of multiple species of neurotransmitters.

2. Materials for Biosensor Development

2.1. Carbon-Based Sensor

Carbon-based materials including carbon nanotubes (CNT) and graphene are widely used recently because of their excellent electrical conductivity, large surface area and low cost. There are

multiple allotropes for carbon-based materials, carbon nanotubes being one-dimensional structures and graphene being a two-dimensional material. The varying atomic structures in carbon-based materials could affect the electrical properties and the surface modification processes for the electrochemical neurotransmitter sensors.

Venton's group has published many works on carbon-based electrochemical biosensors. Rees et al. have developed a carbon nanopipette electrode (CNPE), shown in Figure 3, to detect dopamine using fast-scan cyclic voltammetry (FSCV), and the sensor is also successfully used in Drosophila: CNPE was inserted in the Drosophila larval ventral nerve, and the dopamine was stimulated with red light [28]. The CNPE was deposited in a quartz capillary model using CVD, then the quartz was etched to form a tapered carbon cylinder (Figure 3). Although the diameter of the tip may vary from device to device, they were still able to control the diameter of the electrode tip in the range of 50 to 400 nm. Compared to the traditional carbon-fiber microelectrodes (CFME), the CNPE sensor exhibited higher sensitivity towards serotonin. The CNPE sensor is also capable of detecting octopamine and serotonin, where a unique FSCV shape was obtained for each species. The stability of the CNPE is also shown to be promising when the potential was scanned from −0.4 V to 1.3 V. After evoking the dopamine release in Drosophila, the CNPE has successfully detected the oxidation signal. The CNPE is capable of detecting dopamine in the range of 0.1 to 10 μM with a detection limit of 25 nM. Although the sensitivity of their CNPE-based sensor still requires further improvement, their work has demonstrated that a carbon-based nanoelectrode can be used for the in vivo detection of neurotransmitters.

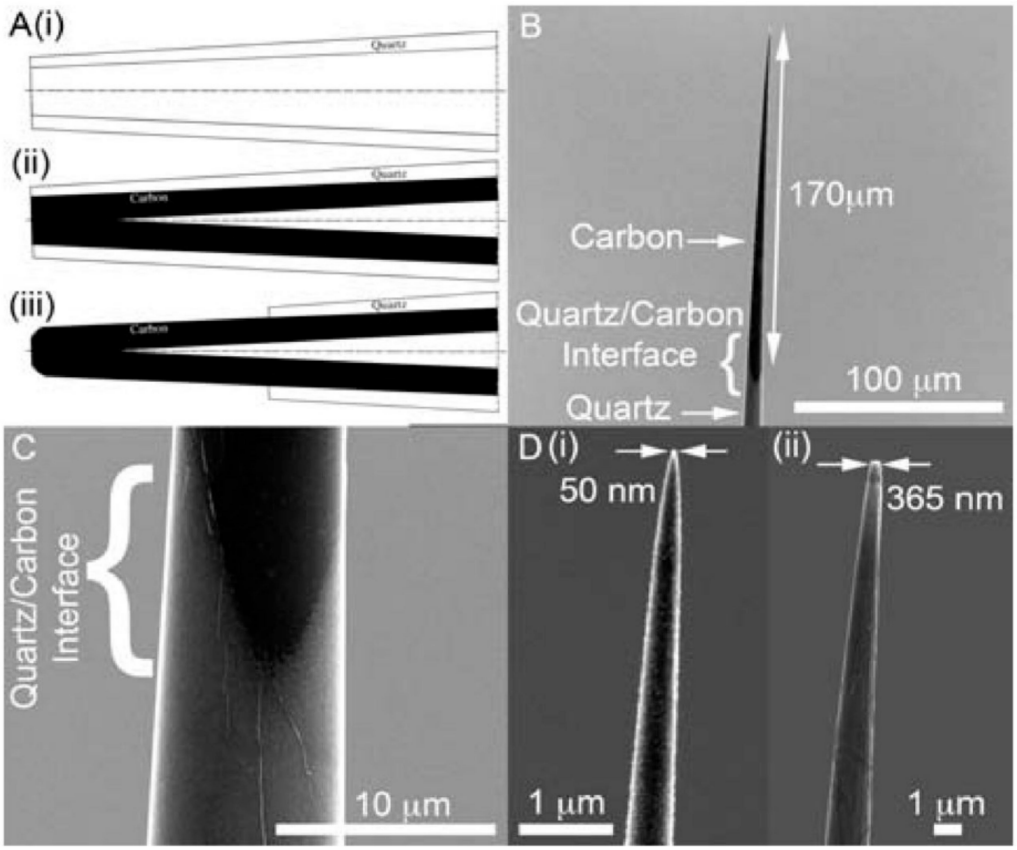

Figure 3. The carbon nanopipette electrode (CNPE) developed by Rees et al. Reprinted with permission from [28].

Alexander et al. have grown carbon nanospikes (CNS) on several types of metal wires to develop an electrochemical sensor for dopamine detection [29]. The carbon nanospikes were deposited on the metal using chemical vapor deposition, and the presence of carbon was proved to enhance the

sensitivity and the detection limit of pure metal wire. Four types of metal wires were tested in their work: tantalum (Ta), palladium (Pd), niobium (Nb), and nickel (Ni). While none of the metal wires were sensitive enough to detect 1 μM dopamine using FSCV, all the CNS-coated metal wires exhibit a clear oxidation and reduction peak when exposed to 1 μM dopamine solution. The CNS-Ta sensor shows different FSCV profiles for dopamine, uric acid and ascorbic acid, indicating good selectivity toward dopamine. Furthermore, the chemical selectivity of the CNS-coated metal wires was enhanced when compared to the pure carbon fiber electrode.

Carbon nanotube (CNT) yarn electrodes have also been developed for the in vivo detection of neurotransmitters where a CNT yarn is a macrostructure of CNTs containing several parallel CNT filaments. Schmidt et al. have developed CNT yarn disk-shaped (CNTy-D) electrodes to detect electro-active neurotransmitters using FSCV as illustrated in Figure 4 [30]. The sensitivity of the CNTy-D electrodes was significantly improved when compared to the conventional carbon fiber microelectrodes due to the greater surface roughness leading to a larger mass transport to the sensor surface. Moreover, the electrodes were able to detect dopamine in rat brain: at least 100 μm of the CNTy-D electrode was inserted into a rat brain slice containing the striatum. The dopamine concentration of approximately 300 nM was detected after the dopamine stimulation. Yang et al. explored several approaches to enhance the sensitivity of the CNT yarn microelectrodes (CNTYM) [31,32]. The laser-treated CNTYM increased the sensitivity over three times when monitoring dopamine, because of the increased surface area and adsorption sites. After treatment with KrF 248 nm pulsed excimer laser for 20 ns, the CNT bundles were standing up straighter according to the SEM images. The sensitivity of the CNTYM can also be increased by treating the electrode with O_2 plasma etching or an antistatic gun. With O_2 plasma etching on the CNTYM surface, the number of oxygen-containing functional groups increases and this leads to higher sensitivity towards dopamine detection. This is because a more hydrophilic surface is obtained due to increased functional groups, resulting in a larger current. Antistatic gun treated CNTYM, on the other hand, enhanced the sensitivity by the increased surface roughness and therefore larger surface area. By introducing different modification approaches, the carbon nanotube yarn electrodes can be a promising device platform for neurotransmitter detection.

Graphene, another widely studied carbon material, is also used extensively in neurotransmitter sensors because of its excellent conductivity, stability, and low cost. The structure of graphene is two-dimensional with the carbon atoms forming hexagonal lattices, providing a large surface area for chemical detection [33]. Tang et al. introduced a graphene-modified acupuncture needle for dopamine detection [34]. They modified the acupuncture needle with gold nanoparticles on the tip surface, then deposit graphene through electrochemistry. Graphene oxide dispersion was prepared by mixing graphene oxide with phosphate buffer solution. Then, a cyclic voltammetry-based reduction was performed in the dispersion in the presence of the acupuncture needle for graphene deposition. The modified acupuncture needle greatly increased the sensitivity compared to the bare needle when detecting dopamine because of the facilitation of graphene and gold nanoparticles. The presence of graphene enhanced the conductivity of the sensor, and gold nanoparticles further increased the surface area. Differential pulse voltammetry (DPV) was applied for dopamine recognition in their work, and the detection limit was found to be 0.24 μM.

Atta et al. reported a cyclodextrin/ionic liquid crystal/graphene composite electrode for multiple neurotransmitter detection including dopamine, epinephrine, norepinephrine and serotonin [35]. The sensor was fabricated by a mechanical casting method, and the presence of graphene increased the sensitivity of the sensor due to the large surface area and high electrical conductivity. Their sensor is capable of monitoring multiple neurotransmitters. In particular, the detection limit for epinephrine was as low as 10 pM, confirming the ultrasensitive nature of their sensing device. Moreover, the sensor was successfully applied in urine assays for epinephrine detection.

A 3D porous graphene oxide with gold nanoparticle composites was developed by Choo et al. for dopamine detection [36]. Figure 5 shows the fabrication approach of the sensor. Porous graphene

oxide was prepared using an ultrasonic probe, and then gold nanoparticles were incorporated. The 3D complex exhibited excellent sensitivity for dopamine detection using CV measurement and the detection limit of the sensor was 1.28 μM with linear response in the range from 0.1 μM to 30 μM. Also, the selectivity of the sensor is further verified using amperometry. The current change of 8 nA was obtained after adding 10 μM of dopamine, while no significant signal change was observed after adding the same concentrations of glucose and ascorbic acid. No significant signal was obtained when the sensor was tested with glucose and ascorbic acid.

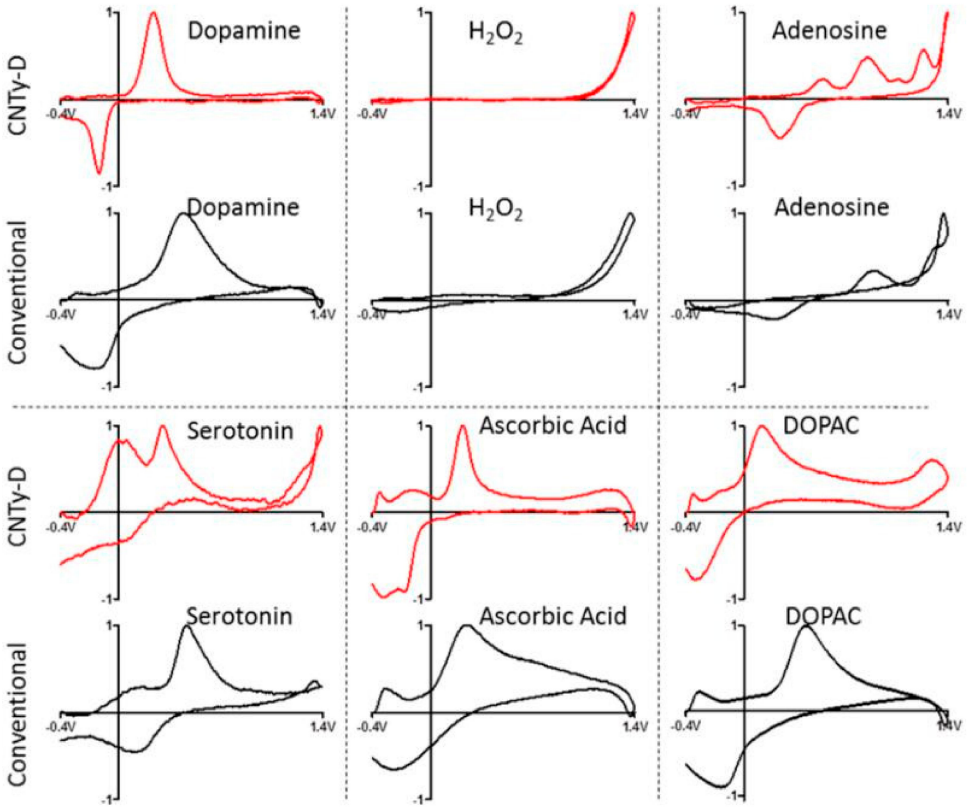

Figure 4. Fast-scan cyclic voltammetry diagram of CNT yarn disk shaped (CNTy-D) microelectrodes and conventional microelectrodes detecting different species. Reprinted with permission from [30].

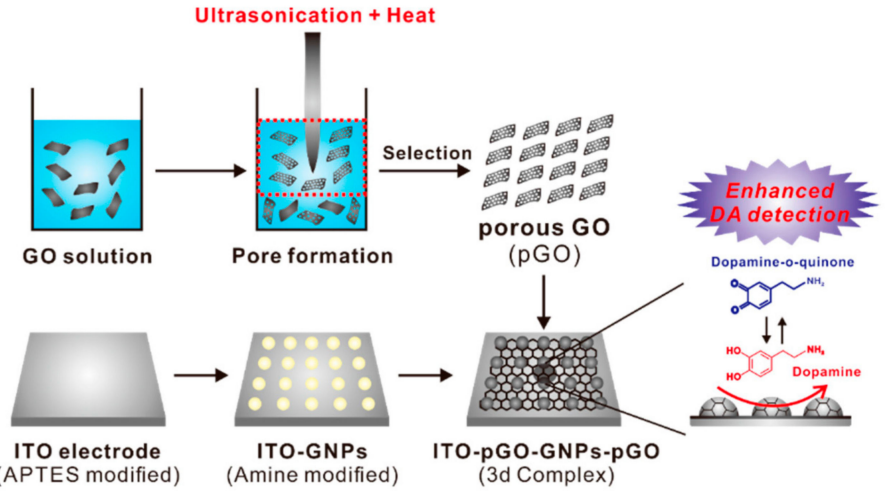

Figure 5. The modification process of 3D porous graphene oxide/gold nanoparticle composites. Reprinted with permission from [36].

Table 1 summarizes the recent works that used carbon-based material as a sensing platform for the detection of various neurotransmitters. Electrochemical sensing was the most commonly used technique because carbon-based materials, being good electrical conductors, are ideal to be used as working electrodes. Dopamine is the most focused analyte because of the excellent electrical property and also its presence being ubiquitous in many signaling mechanisms in the brain. Most sensors developed were able to reach a detection limit in the order of the micromolar level; however, in clinical diagnostics, a nanomolar level of detection is required. Moreover, the selectivity of the neurotransmitters is usually studied in the presence of uric acid (UA) and ascorbic acid (AA), since they are the two main interfering species in the real sample. The response times for most of the sensors were within 5 seconds to meet the requirements of the clinical applications.

Table 1. Carbon based sensor for neurotransmitter detection.

Material	Analyte	Measurement	LOD	Detection Range	References
Graphene, Carbon fiber	DA	DPV	1.36 µM	1.36–125.69 µM	[37]
Reduced Graphene oxide	DA	DPV	1.4 µM	6.8–41 µM	[38]
Carbon dots	DA	DPV	10 nM	0.01–100 µM	[39]
Graphene oxide, MWCNT	DA	DPV	1.5 µM	5–500 µM	[40]
Reduced Graphene oxide, MWCNT	DA	ECL	0.067 µM	0.2–70 µM	[41]
Graphene oxide	DA	Amperometry	0.277 µM	1–30 µM	[42]
Nafion-coated MWNT yarn	DA	DPV	0.01 µM	0.01–5 µM	[43]
Reduced Graphene oxide	EP	DPV	0.0012 µM	0.001–1000 µM	[44]
MWCNT	EP, NE	DPV	4.6 µM, 1.7 µM	7.5–48 µM	[45]
Graphene	EP	CV	0.24 µM	1–1000 µM	[46]
MWCNT	NE, 5-HT	SWV	0.2 µM, 0.01 µM	0.5–30 µM, 0.05–1 µM	[47]
MWCNT	NE	DPV	0.03 µM	0.2–100 µM	[48]
Graphene	NE	SWV	30 nM	0.08–600 µM	[49]
Graphene	Glu	Amperometry	2 µM	4–600 µM	[50]
Graphene	5-HT	Amperometry	1.6 nM	0.0027–4.82 µM	[51]
Reduced Graphene oxide	5-HT	DPV	0.1 nM	0.001–500 µM	[52]
MWCNT	5-HT	SWV	118 nM	0.006–62.8 µM	[53]
SWCNT	His	DPV	1.26 µM	4.5–720 µM	[54]
Carbon dots	ACh	Amperometry	1.7 µM	5–6885 µM	[55]
Reduced Graphene oxide	ACh	Colorimetric	39 nM	0.1–10000 µM	[56]

2.2. Polymer-Based Sensor

The use of polymer as an active sensing material is another common practice in the field of biosensors due to the polymer's unique electro-chemical property and the ease of synthesis. In particular, conducting polymers have received considerable attention in the chemical sensor development because of the excellent electrical conductivity and biological compatibility. The combination of carbon material and the polymer can also further improve the conductivity and the mechanical strength of the resulting composites [57]. Non-conductive polymers are also used for neurotransmitter sensor development. The insulating properties of non-conductive polymers could minimize the electrochemical signal produced from interferences, therefore, the selectivity of the sensor was improved [58]. Table 2 lists the recently published works on polymer-based neurotransmitter sensors.

Chauhan et al. introduced a fluorine-doped tin oxide electrode modified with Fe_2O_3 nanoparticles, poly 3,4-ethylenedioxythiophene (PEDOT), and reduced graphene oxide (rGO) for acetylcholine detection as depicted in Figure 6 [59]. The presence of rGO and PEDOT enhanced the electrical conductivity as well as increased the electroactive area and hence, the sensitivity of the sensor was improved. CV was performed for acetylcholine detection with a detection limit of 4.0 nM. A good sensor stability for the longer periods of time also benefited from the polymer and graphene.

Another polymer-based dopamine sensor was developed by Sangamithirai et al. Poly(o-anisidine) (POA) was chosen due to its promising biocompatibility and stability [60]. By introducing CNT, POA can be partially synthesized on the CNT surface, retaining its nanowire morphology. The high surface

area and promising ion-exchange characteristics of the nanowire-based POA have greatly enhanced the electrical signal transduction for dopamine.

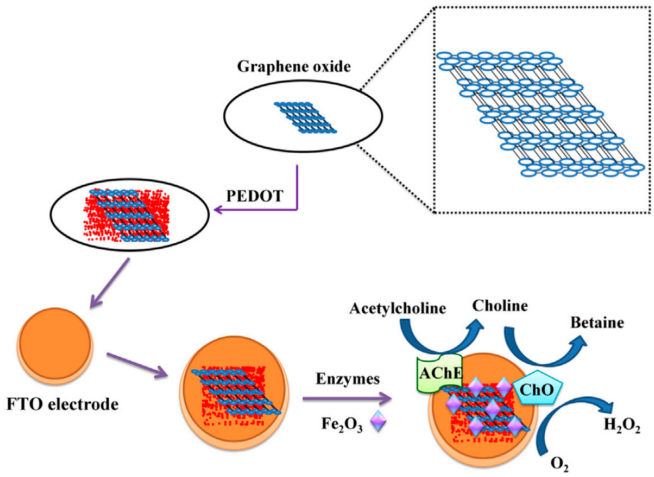

Figure 6. The modification process of PEDOT-based acetylcholine sensor. Reprinted with permission from [59].

Wu et al. introduced a selective poly-o-phenylenediamine (P-o-PD) sensor for dopamine detection [58]. Their work demonstrated the feasibility of o-PD as dopamine-imprinted MIP. A uniformly coated P-o-PD layer was polymerized on a gold electrode using repeated potential sweep, and the electrochemical properties of the product was affected by various factors including the template to monomer ratio, pH, and the number of CV scans. Thirty cycles with 100 mV/s scan rate for CV were performed during P-o-PD polymerization, and 0.5 M H_2SO_4 was introduced for template removal. Their modified sensor was found to be selective towards dopamine, and the detection limit of the sensor was reported to be 0.11 mg/L.

Tseng et al. developed an implantable microsensor array modified with overoxidized polypyrrole (OPPy) and enzyme for glutamate and dopamine detection [61]. By controlling the thickness of the coated OPPy film, their sensor is able to detect glutamate and dopamine selectively using constant potential amperometry. The detection limit of the sensor is 2.1 µM and 62 nM for glutamate and dopamine, respectively.

Table 2. Polymer-based sensor for neurotransmitter detection.

Material	Analyte	Measurement	LOD	References
Overoxidized polypyrrole	Glu/DA	Amperometry	2.1 µM/62 nM	[61]
Graphene/polypyrrole	DA	Amperometry	2.3 µM	[62]
Poly(hydroquinone)	DA	DPV	41.9 nM	[63]
Poly(2,4,6-triaminopyrmidine)	DA	DPV	0.017 µM	[64]
Polypyrrole	EP	DPV	298.9 nM	[65]
Poly(brilliant cresyl blue)	EP	CV	0.24 µM	[46]
Poly(phenyl trimethoxysilane)	NE	CV	0.1 µM	[66]
Poly(glutamic acid)	NE	DPV	0.43 µM	[67]
Polypyrrole/polyaniline	Glu	Amperometry	0.1 nM	[68]
Polypyrrole	Glu	Photochlorometric	0.18 nM	[69]
Poly(bromocresol green)	5-HT	DPV	80 nM	[70]
Polypyrrole	5-HT	SWV	33.22 nM	[71]
Methacrylic acid	His	CV	0.074 nM	[72]
Poly(3-thiophenemalonic acid)	tryptamine	Amperometry	41.7 nM	[73]

2.3. Aptamer-Based Sensor

An aptamer is a short DNA or RNA oligomer whose base sequences are carefully designed so that it binds to a specific target molecule of interest with high affinity. Aptamers are being touted as one of the most promising synthetic biomolecular receptors that can mimic the functions of antibodies [74]. Through iterative selection processes such as SELEX [75,76], the aptamer sequences are carefully chosen to optimize the binding efficiency [77]. Moreover, due to their stability, aptamers can be reused repeatedly by removing the bound target analyte with a washing solution [78]. Therefore, aptamers are of great interest to the biosensors community. Aptamers for neurotransmitter species have also been developed for their detection. Chavez et al. reported a serotonin sensor using aptamer-gold nanoparticle composite [79]. The composite responded colorimetrically to serotonin with a detection limit of 300 nM.

An aptamer-based dopamine sensor has been successfully demonstrated by several groups [79–85]. In Xu's work, they first modified the carbon nanoparticles on gold electrode, then immobilized thionine on the surface of gold nanoparticles [80]. Afterwards, they immobilized DNAs on the nanoparticles forming an electrochemical probe. Dopamine-binding aptamers were then added into the probe solution, which hybridized with the previously immobilized DNAs (see Figure 7). When DA is exposed to the AuNPs, the electrochemical probes (AuNP-thionine-DNA1 complex) will be released providing an electrical current as a transduction signal. DPV was used for DA detection, showing clear response with a detection limit of 1.0×10^{-8} M.

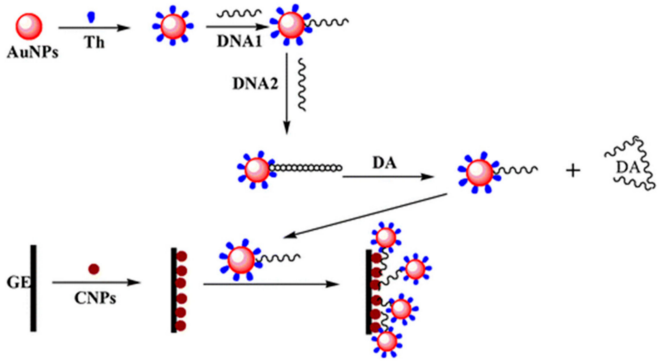

Figure 7. The schematic illustration of the aptamer-based dopamine sensor. Reprinted with permission from [80].

Despite the excellent LOD of the aptamer-based sensors (Table 3), the application of this sensing technology is still currently limited due to the complex chemistry and modification process. Although most aptamer-based sensors have been applied to ex vivo detection, they have great potential to be used in in vivo applications. For example, Li et al. have successfully developed an aptamer-based electrochemical biosensor for doxorubicin detection [86]. A phosphatidyl-choline (PC)-terminated monolayer was introduced to improve the sensor performance for the in vivo detection. While doxorubicin is a drug for cancer treatment and not a neurotransmitter, their work is a good demonstration that aptamer-based sensor is capable of in vivo real-time monitoring.

Table 3. Aptamer-based neurotransmitter sensors.

Analyte	Measurement	LOD	References
DA	DPV	10 nM	[80]
DA	DPV	0.22 nM	[81]
DA	Amperometry	1.8 nM	[82]
DA	DPV	700 ± 19.23 pM	[83]
DA	DPV	78 fM	[84]
EP	UV-Vis	0.9 nM	[85]
5-HT	Colorimetric	300 nM	[79]

2.4. Enzyme-Based Sensor

Enzymes are biological catalysts for chemical reaction. Some neurotransmitters such as glutamate and acetylcholine are hard to detect via the electrochemical method because of their non-electroactive properties. However, the present of enzymes could convert the neurotransmitters to produce H_2O_2, which is easy to detect [87,88]. Enzymes are also selective towards target analyte, which improves the performance of the neurotransmitter sensor. Table 4 summarizes the recent work on enzyme-based neurotransmitter sensors.

Wassum et al. designed a selective electrochemical sensor for glutamate detection using L-glutamate oxidase (GluOx) as a catalyst [89]. The silicon microprobe-based platinum microelectrode was coated with three layers (polypyrrole, nafion, and GluOx) to measure H_2O_2 concentration without interfering with other analyte in the fluid. GluOx on the outermost layer is able to convert the glutamate to hydrogen peroxide for in vitro detection of glutamate. Nafion and a polypyrrole layer on the inner layer can repel anions and cations to further improve the selectivity of the sensor. Their sensor was able to successfully detect glutamate in rats' basolateral amygdala via constant potential amperometry, and the results show that the glutamate transients in the basolateral amygdala increases when receiving a reward, and decreases when the earned reward was satiated.

Burmeister et al. developed a ceramic-based microelectrode array for simultaneous detection of choline (Ch) and acetylcholine (ACh) [90]. ACh is first converted to Ch using acetylcholinesterase, then converted to H_2O_2 using choline oxidase (ChOx). The selectivity of the sensor over DA and AA is improved when using meta-phenylenediamine-dihydrochloride (mPD) as a barrier. The sensor is able to detect ACh and Ch simultaneously via constant potential amperometry with the response time of 1 second and the detection limit of 0.2 µM.

Table 4. Enzyme-based neurotransmitter sensors.

Analyte	Measurement	LOD	References
Glu	CV	0.1 nM	[68]
Glu	Amperometry	0.32 µM	[91]
Glu	Amperometry	2.5 µM	[92]
Glu	CV	0.56 µM	[93]
Glu, ACh	CV	0.25 µM, 0.15 µM	[94]
ACh	Amperometry	0.2 µM	[90]

3. Sensor Modification

The sensitivity and selectivity of a sensor can be further improved on the basis of substrate material and geometry. A large number of surface modification approaches have been explored recently using advanced nanoscale fabrication and machining techniques. By introducing nanostructures, a higher surface-area-to-volume ratio can be obtained and the signal transduction can be amplified with higher sensitivity compared to the conventional sensing surfaces. Incorporating catalysts into the sensor can also enhance the performance of the chemical sensors by increasing the rate of a particular chemical reaction, leading to a sensitive and selective signal response. Molecular imprinting technique is another approach in improving the sensor selectivity towards the target analyte. This section summarizes the various sensor modification techniques for neurotransmitter sensors.

3.1. Nanostructure

The morphology of the sensing materials is essential for developing high-performance electrochemical sensors [95]. The preparation of the nanostructured sensing materials have been achieved by introducing carbon nanotubes, graphene nanosheets and metal nanoparticles [96]. Yang et al. evaluated three types of CNT-based nanofibers for dopamine and serotonin detection.

Different CNT preparation protocols affect the surface structure of the fiber, resulting in distinguished CV responses towards each neurotransmitter species [97].

A three-dimensional imprinted polymer array was reported by Li et al. for electrochemical detection of epinephrine [98]. As shown in Figure 8, ZnO nanorods were electrodeposited on ITO/PET films forming a 3D array. Afterwards, pyrrole mixed with epinephrine was electropolymerized on the ZnO nanorods surface. The nanorods structure greatly increased the surface area of the sensor, amplifying the electrochemical signal of epinephrine. The presence of epinephrine-imprinted pyrrole also improved the selectivity of the sensor, which will be further discussed in Section 3.3.

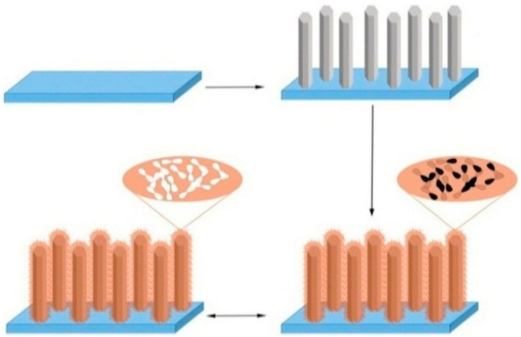

Figure 8. An array of zinc oxide nanorods coated with molecularly imprinted polymers for selective detection of epinephrine. Reprinted with permission from [98].

3.2. Catalytic Nanoparticles

Inclusion of the catalytic nanoparticles to the surface of the working electrode has been previously reported to improve the performance of the chemical sensors [99]. For the surface modification of the neurotransmitter sensors, various types of catalysts have been introduced during the modification processes.

Li et al. have doped gold nanoparticles with poly(o-phenylenediamine) (P-o-PD) forming a hollow microsphere structure for DA detection [100] as shown in Figure 9. The P-o-PD was prepared via chemical polymerization method. The hydrophobic property of o-PD/glycine salt has led to a hollow microsphere structure after polymerization. Upon doping with gold nanoparticles, the electroactive area increased markedly, providing more binding sites for dopamine. Their work has demonstrated the facilitation of gold nanoparticles as an effective catalyst.

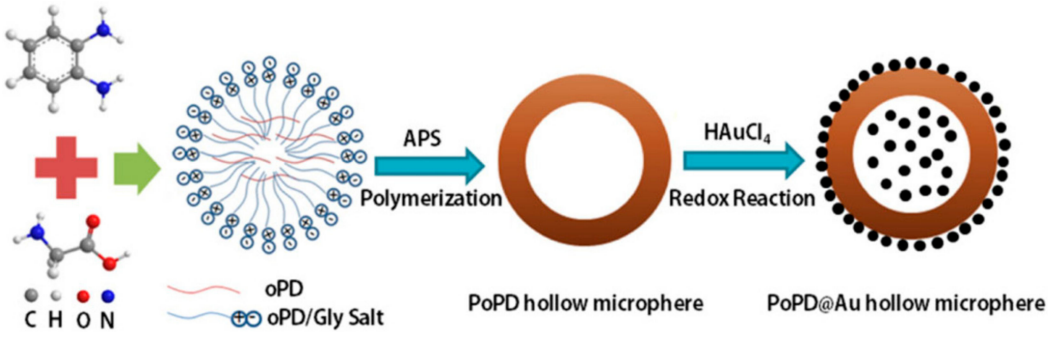

Figure 9. poly(o-phenylenediamine)/gold nanoparticle for dopamine sensing. Reprinted with permission from [100].

Metal and metal oxide nanoparticles are the most widely used catalysts because of their unique optical, chemical, electrical, and catalytic properties (Table 5). The presence of the catalyst can greatly increase the sensing area and also amplify the recognition signal. However, the surface modification may result in an increase in background noise due to the presence of other active

materials. Furthermore, the rate at which sensor electrode fouling occurs could also become faster [101]. Therefore, further attention may be required to protect the surface-modified electrodes from fouling during extended periods of use.

Table 5. Catalysts used in neurotransmitter detection.

Catalyst	Analyte	Measurement	LOD	References
Co_3O_4	DA	Amperometry	0.277 µM	[42]
Gold nanoparticles	DA	DPV	41.9 nM	[63]
Gold nanoparticles	DA	DPV	0.017 µM	[64]
Ag–Pt Bimetallic Nanoparticles	DA	DPV	0.11 µM	[102]
CuO/Mn_2O_3/Silver nanoparticles	DA	Chemiresistive	-	[103]
Pt_3Ni nanoalloys	DA	Amperometry	10 nM	[104]
Cu(II)	DA	DPV	0.08 µM	[105]
Fe_3O_4 nanorods	DA	Amperometry	7 nM	[106]
Silver nanoparticles	DA	UV–Vis	0.2 µM	[107]
SnO_2	DA	CV	6.3 nM	[108]
Au-Pd nanocrystals	EP	DPV	0.0012 µM	[44]
Gold nanoparticles	EP	DPV	80 nM	[109]
Gold nanoparticles	EP	DPV	298.9 nM	[65]
SiO_2	EP, NE	DPV	10 nM, 6 nM	[110]
Fe_3O_4, ZnO	EP, NE	DPV	4.6 µM, 1.7 µM	[45]
ZnO	NE,5-HT	SWV	0.2 µM, 0.01 µM	[47]
Palladium nanoparticles	NE	CV	0.1 µM	[66]
Gold nanoparticles	NE	DPV	0.03 µM	[48]
WO_3 nanoparticles	5-HT	DPV	1.42 nM	[111]
Fe_3O_4 nanoparticles	5-HT	DPV	80 nM	[70]
CuO	His	Amperometry	0.33 µM	[112]
Nickel oxide	ACh	Amperometry	26.7 µM	[113]

3.3. Molecular Imprinting Technique

Molecular imprinting technique is a strategy to improve the selectivity of a sensor by creating artificial recognition motifs in the polymer. Prior to polymerization, the functional monomer and template molecules are mixed together for self-assembly. After polymerization, the template molecules are embedded inside the polymer matrix. Target-specific molecular cavities complementary to the shape and the size of the analyte will be formed after the removal of the template molecules from the polymer. Therefore, the target analyte exhibits preferential binding to the recognition sites once the molecular-imprinted polymer (MIP) is exposed to the sample containing the chemical species. Moreover, the presence of a large number of these molecular cavities results in a large surface area, giving an amplified sensing signal. Several works have been reported in the area of neurotransmitter detection using the molecular imprinting technique in recent years.

Li et al. introduced an o-aminophenol based molecularly imprinted sensor for dopamine detection [114]. The selectivity of the modified sensor was improved by both molecular imprinting and the inclusion of copper oxide nanoparticles. Their results show a detection limit of 8 nM. Ascorbic acid and uric acid are also introduced as interferents, however the electrochemical signal of them were negligible, due to the high selectivity of the dopamine recognition sites formed in the polymerized o-aminophenol layer.

Tadi et al. have successfully developed an epinephrine sensor using a molecularly imprinted polymer using 2,4,6-trisacrylamido-1,3,5-triazine as a functional monomer from which they obtained the detection limit of 1.2 nM [115]. Sacramento et al. also reported an electrochemical sensor for acetylcholine (ACh) recognition. Polyaniline was synthesized in the presence of ACh and multiwalled carbon nanotubes to form a molecularly imprinted material. The detection limit for this sensor was 34.5 µM [116].

Vandenryt et al. have implemented an MIP-based serotonin sensor where a thermal readout technique was demonstrated [117]. The molecular recognition by the MIP resulted in the change in the heat transfer resistance that was dependent on the analyte concentration. This heat-based sensing method is beneficial in MIP-based sensors since the polymer does not need to be electrically conductive for signal transduction. Table 6 lists the recently developed MIP-based sensors with neurotransmitters being the template molecules. The artificial molecular recognition sites were shown to be effective in terms of the sensitivity and selectivity of the sensors.

Table 6. MIP-based neurotransmitter sensors.

Polymer	Analyte	Measurement	LOD	References
Poly(o-aminophenol)	DA	DPV	1.98 nM	[114]
Polyaniline	ACh	Potentiometry	34.5 µM	[116]
Polypyrrole	DA	DPV	10 nM	[118]
Polypyrrole	DA	DPV	33 nM	[119]
Poly(nicotinamide)	DA	CV	8 nM	[120]
Poly(2,4,6-trisacrylamido-1,3,5-triazine)	EP	DPV	12 nM	[115]
Poly(phenyl trimethoxysilane)	NE	CV	0.1 µM	[66]
EGDMA/MAA	His	CV	0.074 nM	[72]
EGDMA/AIBN/MAA/AM	5-HT	Thermal Resistance	100 nM	[117]

4. Simultaneous Detection of Multiple Species

Most work published so far has focused on individual detection of a single neurotransmitter species. However, in practical applications and for in vivo measurements, simultaneous determination of multiple species of analytes is the subject of great interest but also a grand challenge. Traditionally, multi-analyte sensing has been performed by developing an array of sensors commonly known as an electronic nose (e-nose) for gas phase samples and electronic tongue (e-tongue) for liquid phase detection [121]. Microdialysis is another commonly used sampling technique for analyzing multiple species [122]. In microdialysis, a small volume (typically a few microliters) of extracellular fluid is sampled through a semipermeable membrane located at the tip of the implanted probe at a fixed time interval. The sampled fluids are each collected in a separate container, stored in sequential order, for analysis offline using advanced techniques such as high-performance liquid chromatography (HPLC) and liquid chromatography–mass spectrometry (LC/MS). The advantages of microdialysis include accurate analysis of multiple species due to high-precision analytical tools (i.e., HPLC, LC/MS, etc.), long-term detection capability without the issue of electrode fouling, and minimally invasive sampling tools. However, the disadvantages are low temporal resolution (on the order of minutes), inability to measure in vivo, and expensive analysis methods. Hence, a novel multi-analyte sensor with high sampling rate, low cost, and in vivo measurement capability is needed. When developing simultaneous and multi-analyte sensors, the following concerns must be addressed: first, a single sensing technique must be applied to all the sensors in the array; second, each modified sensor must be sufficiently selective and sensitive toward the analyte; third, for in vivo detection, the developed sensor must be resistant to fouling in order to achieve long-term measurement. In previous work, dopamine (DA), uric acid (UA), and ascorbic acid (AA) were commonly chosen as the analytes, since they often coexist in the real biological samples. Zhang et al. developed a Poly(l-lysine)/graphene oxide-modified sensor for the simultaneous detection of DA and UA [123]. The polymerization of l-lysine is performed electrochemically through potential cycling on the graphene oxide-modified glassy carbon electrode. Their sensor shows two distinct oxidation peaks when DPV was applied to detect DA and UA simultaneously from the same sample solution. Also, the addition of one analyte had minimally interfered with the detection of the other. The detection limits of DA and UA are 21 nM and 74 nM, respectively.

Sun et al. have developed an electrochemical sensor for simultaneous detection of DA, UA, and AA [124]. Gold nanoparticles and MoS_2 nanosheets were chosen as the sensing material to

amplify the DPV response of the three analytes. They have reported that bare GCE, AuNPs/GCE or MoS_2/GCE alone were not able to distinguish among the three analytes. However, the combination of AuNPs and MoS_2 nanosheets was able to individually identify and also quantify the three species from the mixture of analytes. Figure 10 shows the DPV response and calibration curves when detecting DA, UA, and AA, simultaneously. The detection limits for DA, UA, and AA were 0.05 μM, 10 μM, and 100 μM, respectively.

A colorimetric sensor was developed by Jafarinejad et al. for the detection of dopamine (DA), norepinephrine (NE), and epinephrine (EP) [125]. They have designed a Au/Ag core-shell nanostructure, and it was able to individually quantify the analytes by obtaining the various absorbance spectra. A solution of gold nanorods and silver nitrate were mixed to develop a sensing solution. The addition of neurotransmitters works to reduce mediators, causing silver growth on the surface of the gold nanorods and leads to color changes in the solution. Unique color patterns were collected using UV-vis spectra after the sensing solutions reacted with different analytes. They also successfully detected DA, NE, and EP simultaneously using the colorimetric sensor array.

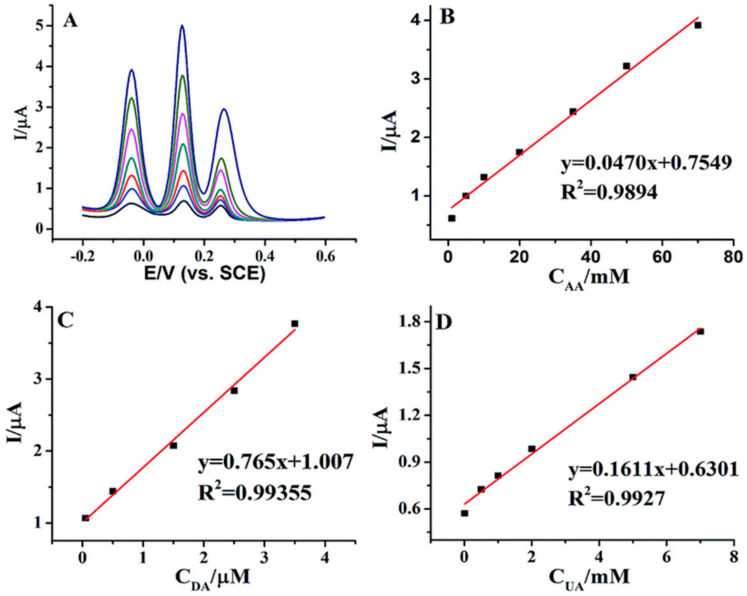

Figure 10. Simultaneous detection of DA, UA, and AA by Sun et al. (**A**) The DPV responses when exposed to AA, DA, and UA, simultaneously, and the calibration curves for (**B**) AA, (**C**) DA, and (**D**) UA. Reprinted with permission from [124].

Wojnicz et al. reported a multi-analyte sensor using liquid chromatography–tandem mass spectrometry (LC–MS/MS) analysis approach [126]. They were able to detect eight different neurotransmitters simultaneously including DA, NE, EP, Glutamate, 5-HT, γ-aminobutyric acid (GABA), 5-hydroxyindole acetic acid (5-HIAA), and 3-methoxy-4-hydroxyphenylglycol (MHPG) However, the limitations of this approach are the complexity and the high cost of the LC–MS/MS system.

Zhang et al. have successfully improved the sensitivity of the liquid chromatography/mass spectrometry (LC/MS) analysis using N-α-Boc-l-tryptophan hydroxysuccinimide ester (Boc-TRP) derivatives when detecting multiple neurotransmitters simultaneously. Their approach is capable of detecting GABA, glutamate, glycine, and citrulline with a detection limit of several nanomolar concentrations. Multiple amino acid neurotransmitters are also detected in rat brain microdialysates [127].

Barman et al. designed a AgNPs–penicillamine modified gold electrode electrochemical sensor for the simultaneous determination of DA and EP [128]. They first prepared the penicillamine

(PCA)-modified gold electrode by immersing the gold electrode in 1.0 mM PCA solution. After the self-assembly process, the electrode was dipped into AgNPs solution forming a AgNPs–penicillamine modified electrode. The sensor also showed high selectivity towards DA and EP in the presence of AA and UA. Another work reported by Tezerjani et al. introduced a graphene oxide nanosheets-based electrochemical sensor for the detection of DA, EP, and acetaminophen [129]. The detection limit of EP was calculated as 0.65 μM.

5. Optical Sensing of Neurotransmitters

Most papers reviewed in this article are based on electrochemical sensing techniques. However, many of them exhibit the level of detection limits that are still too high for in vivo measurements, and the electroactive species are prone to the interference problem in the signal acquisition. In terms of in vivo sensing of neurotransmitters, another popular and promising sensing technique besides electrochemical methods is the optical detection approaches. In most cases, optical sensors exhibit highly reproducible and sensitive readings with the limit of detection often reaching a nanomolar range or less [130]. Also, the interference from other chemical species could be minimized by utilizing a broad range of optical spectrum. Most importantly, the main benefit of optical sensors is that they provide high spatial resolution. Furthermore, it does not require electrical wiring or electrodes at the implanted probe for signal acquisition since the optical signals are generally transmitted through fiber optic cables. Spatial and temporal resolutions are equally important for in vivo detection of neurotransmitters since the release and uptake of such chemicals occur in a short time period, typically on a millisecond range [21], and in a highly localized fashion [131]. Therefore, a sensor should possess a sampling rate that is high enough to capture the concentration changes that occur in a millisecond timescale and also be small enough to identify which neurons are involved in such release and uptake of the chemical signals. Carbon nanotubes can be used as active materials in optical sensing due to their unique electrical and optical properties [132]. Kruss et al. have utilized a polymer functionalized single-walled carbon nanotubes (SWCNTs) to measure the changes in the near-IR fluorescence signal modulated by various neurotransmitters, which they have termed corona phase molecular recognition. They showed that the unique polymer composition (DNA, RNA, phospholipids, amphiphilic polymers, etc.) in combination with its close proximity to the SWCNT to which the polymers are wrapped around, have resulted in a selective detection of neurotransmitters with high spatial resolution [133]. Using this optical technique, a fluorescent nanosensor array for dopamine sensing with high spatial and temporal resolution was also demonstrated [134]. The sensor array was based on fluorescent carbon nanotubes, and able to monitor dopamine concentration from PC12 neuroprogenitor cells. The spatial and temporal resolutions have reached 20,000 sensors per cell and 100 ms, respectively.

López-Valenzuela et al. have introduced fluorescence detection system to detect Glutamate in the hippocampus, and the fluorescence measurement was able to reach one second resolution [135]. In their approach, glutamate oxidase was used to generate H_2O_2, which was quantified with Amplex Red, a fluorogenic probe. This probe reacts with H_2O_2 to produce resorufin which fluoresces at 590 nm when excited at 560 nm.

Kim et al. developed a wireless optical sensor for dopamine recognition in vivo [136]. The optical sensor contained a fluorescence sensing probe, micro-spectrometer, and a system electronics module. CdSe/ZnS quantum dots were attached on the optical probe for dopamine detection. The fluorescent sensing probe is able to detect dopamine with a detection limit of 100 nM. Their sensor also shows excellent selectivity over uric acid and ascorbic acid.

Baluta et al. reported a fluorescence-based sensor to detect dopamine [137]. Graphene quantum dots and low-temperature co-fired ceramics (LTCC) technology was introduced for dopamine recognition and sensor fabrication. The detection limit of their sensor was calculated to be 22 nM. Their sensor was able to achieve in vivo measurement, and the fabrication process was simpler compared to other optical sensors.

An ultra-sensitive optical sensor for GABA determination was reported by Huang et al. [138]. The sensor was based on raspberry-like meso-SiO_2 nanosphere functionalized silica microfibers. Silver or gold nanoparticles were further introduced to enhance the local electric field in near infrared. The concentration of GABA was monitored based on the transmission wavelength shift, and the detection limit of the sensor was reported to be 1×10^{-15} M.

Gupta et al. have used a Sulphur-doped carbon dots, with an average particle size of 6 nm, for the detection of DA from PC12 cells [139]. A significant quenching of the carbon dot fluorescence occurred at 425 nm when excited at 310 nm upon exposure to DA molecules. Table 7 below summarizes the recent progress in optical neurotransmitter sensors.

Table 7. Summary of recently published neurotransmitter sensors based on optical sensing approaches.

Analyte	Measurement	LOD	References
ACh	Colorimetric	39 nM	[56]
Glu	Photochlorometric	0.18 nM	[69]
5-HT	Colorimetric	300 nM	[79]
EP	UV-Vis	0.9 nM	[85]
DA	UV–Vis	0.2 µM	[107]
DA, NE, EP	Colorimetric	5 µg/mL, 1 µg/mL, 1 µg/mL	[125]
DA	Near-IR fluorescence	11 nM	[133,134]
Glu	Fluorescence	1 µM	[135]
DA	Fluorescence	100 nM	[136]
DA	Fluorescence	22 nM	[137]
GABA	Silica microfiber interferometry	1×10^{-15} M	[138]
DA	Fluorescence	47 pM	[139]
5-HT	Tapered microfiber interferometer	84 fM	[140]

6. Conclusions

The ability to identify and measure various neurotransmitters with high sensitivity and low-cost will provide a powerful tool for use in clinical diagnostics and neuroscience research. Many recently published works have reported on the nanostructured materials for highly sensitive detection. The use of carbon-based sensors in conjunction with electrochemical sensing strategies have dominated this field due to the promising electrical property, stability and low cost. Polymers are also widely used for enhancing the biocompatibility and the redox properties of the sensor. Although aptamer-based sensors exhibit ultra-selectivity and high sensitivity towards the analyte, the complicated modification procedure and chemistry have limited the commercialization of the sensor. However, aptamer-based biosensors show great potential to become a practical sensing device in the near future. For improving the performance of the sensor, catalysts such as metal and metal oxide nanoparticles can be utilized to enhance the sensitivity and selectivity. The miniaturization of the sensing device is also critical for enhancing the spatiotemporal resolution especially in in vivo environment. Furthermore, nanomolar detection limit with high sensitivity and reproducibility are essential for the sensor to be used in clinical setting.

Electrochemical sensors and optical sensor are the two most commonly applied methods for in vivo monitoring of neurotransmitters due to the many advantages they offer. However, the simultaneous detection of multiple neurotransmitters still remains a major challenge for both techniques. It is expected that (1) real-time continuous monitoring, (2) in vivo detection, (3) high spatiotemporal resolution, (4) simultaneous multi-analyte sensing, and (5) long-term stability of the implanted sensors will continue to be the main objectives of research in the field of neurotransmitter sensors in the foreseeable future.

Conflicts of Interest: The authors declare no conflict of interest.

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