Aptamer based biosensor platforms for neurotransmitters analysis

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ABSTRACT

Neurotransmitters control the signal transmission in chemical synapses via their release from the presynaptic neuron and subsequent binding and activation of receptors in the postsynaptic neuron. The resulting paracrine signaling can be understood as the chemical language of information processing in the nervous systems, which is fundamental for brain function and dysfunction during neurological diseases. The ability to measure neurotransmitter concentrations with high spatiotemporal resolution is therefore substantial to understand the full complexity of neuronal communication. Aptamer based biosensors are an increasingly important tool to achieve this goal since these synthetic receptors can be easily tailored for specific tasks, different from other bioreceptors. In this review, we give an overview of the most relevant neurotransmitters, their function, and the respective aptamer sequences for their selective binding but also discuss current developments in selection technology for other small molecules. Within our considerations, we reflect analytical characteristics such as selectivity, limit of detection, sensitivity, multiplexing capabilities, and put particular attention to the spatial and temporal resolution of recently reported aptamer sensors. Finally, we discuss challenges for the development of neurotransmitter sensitive neural probes, missing features for ideal aptamer sensors, and future directions for the development of neurotransmitter sensors.

1. Introduction

Understanding how nervous systems exert their complex functions holds an essential role in fundamental brain research and still remains a grand challenge [1]. Of particular importance is the study of the intricate interplay between electrical signals through local ion currents and the corresponding release of biochemical neurotransmitters (NTs) at chemical synapses between neurons in the central nervous system (CNS) [2,3]. NTs are endogenous neurochemicals that play a crucial role in signal transmission and information transfer across the large majority of all neurons and underlie various biological and physiological processes including cognition and behavior [4]. NTs are usually directly synthesized at presynaptic terminals and loaded into synaptic vesicles. Incoming action potentials then cause a local influx of calcium, triggering a fusion of vesicles with the cell membrane and release of NTs into the synaptic cleft. NTs then rapidly diffuse to the postsynapse and bind specific receptors which can trigger various signalling processes, such as the opening of ion channels or activation of second messenger cascades. Due to the multitude of NT types and corresponding pre- and postsynaptic receptors, different NTs induce a very large and complex cascade of biological responses which dominate virtually all brain functions [5,6].

NTs are highly diverse and a neuroactive molecule must therefore fulfil several requirements in order to be qualified as a NT. First,

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the process of molecule synthesis, storage, and release must arise in the same neuron. Second, its release can induce specific activity in the postsynaptic neuron. Last and most importantly, the same effect can be generated by exogenous administration and a specific molecular perturbation can block the induced action on the target cell [7]. Based on the above criteria, over 200 NTs have been identified to date and the list of NTs keeps expanding as more neuroactive biomolecules are being discovered. Based on their chemical structure, the canonical NTs can be classified into at least six different types: amino acids (glutamate (Glu), glycine, and gamma-aminobutyric acid (GABA)), monoamines (epinephrine (EP), norepinephrine (NE), dopamine (DA), serotonin (ST), and histamine (HIS)), acetylcholine (ACh), purines (adenosine and adenosine triphosphate (ATP)), soluble gases/gasotransmitters (carbon monoxide, nitric oxide, and hydrogen sulfide) and neuropeptides (somatostatin β-endorphins, vasopressin, neurotensin, substance P, and neuropeptide Y) [8]. Almost all NTs are crucial for both physical and mental health in human, and changes in their regular function often result in severe disease and mental disorders [9]. For instance, studies have shown the defective functioning of brain NTs, such as DA, HIS, Glu, and ACh, is implicated for the pathogenesis of Alzheimer's disease. The expression levels of ST and NE are associated with the symptoms of depression [10,11]. More information about various major NTs and their linkages to neurological diseases are summarized in Table 1.

As NTs are essential agents in the nervous systems, understanding the fundamentals of brain functions, and identifying the basis of neurological diseases requires a timely and accurate analysis of NTs levels [12]. Moreover, real-time monitoring of NT release in the brain or neural cell cultures strongly contributed to advance our understanding on how the CNS processes and stores information to create accurate behavior [13]. For instance, the study of DA release in freely moving rats has revealed that a behavioral stimulus can evoke a transient increase in dopamine, providing the first direct evidence of how specific NT release can control behavior on a subsecond timescales [14]. However, the fast release and clearance of NTs in the extracellular space, as well as the low analyte concentrations in the presence of various interfering biomolecules make the detection of NTs challenging. At present, many analytical techniques have been proposed for the quantitative determination of NTs [15]. In clinical diagnosis, microdialysis with the integration of high-pressure liquid chromatography (HPLC), mass spectroscopy (MS), and capillary electrophoresis (CE) is conventionally used for NTs analysis [16,17]. Although these analytical techniques exhibit high sensitivity and selectivity, they all require complicated sample pretreatment, are time-consuming and lead to low spatiotemporal resolution. Positron emission tomography (PET) as a powerful neuroimaging tool can indirectly measure NTs levels in a non-invasive manner. By imaging the local concentration of a range of NT receptors, it accurately quantifies NT dynamics in the living brain, which is effective for diagnosing early stages of various neurological disease. Nonetheless, PET requires the use of radioactive components, has relatively low spatiotemporal resolution, and the high operating cost also limits its wide application [18,19]. Another widely used method is fast-scan cyclic voltammetry (FSCV), which offers the advantages of high

Table 1
Summary of NTs that have been involved in the development of aptasensors.

Neurotransmitters	Localization of cell bodies	Concentrations range	Associated diseases
Dopamine	Hypothalamus, midbrain, brainstem	CSF: 0.5–25 nM Blood:10–480 pM Urine: 0.33–4 mM	Parkinson's disease, Alzheimer's disease, Depression Epilepsy Schizophrenia
Serotonin	Raphe nuclei, gastrointestinal tract	CSF: 0.53–5.23 nM Serum: 270–1490 nM Urine: 300–1650 nM	Parkinson's disease Depression Epilepsy Anxiety Schizophrenia
Epinephrine	Sympathetic nervous system	0.02–0.46 nM	Depression, Addison's disease, High blood pressure
Norepinephrine	Locus coeruleus in the brainstem	0.4–10 nM	Insomnia, Parkinson's disease Depression
Histamine	Hypothalamus	CSF:51–388 pM Blood: 0.6–7.4 nM Urine: 34.6–392.4 nM	Schizophrenia, Convulsion, Seizure, Alzheimer's disease
Acetylcholine	Basal ganglia, basal forebrain nuclei, cortex, brainstem, spinal cord	CSF: 0.1–6 nM Blood:7.6–9.7 nM	Depression, Alzheimer's disease, Dementia
Adenosine triphosphate	Widespread in brain and spinal cord	2–4 mM	Alzheimer's disease, Huntington's disease, Stroke
Glutamate	Widespread in brain and spinal cord	0–61 μM	Parkinson's disease Alzheimer's disease Epilepsy Anxiety Schizophrenia
GABA	Widespread in brain and spinal cord	0.58–1.36 μM	Parkinson's disease Insomnia Alzheimer's disease Epilepsy Schizophrenia
Substance P	Hypothalamus, limbic system, pituitary gland, spinal cord	0–23.5 pM	Natural opiate
Hydrogen sulfide	Hippocampus, hypothalamus	50–160 μM	Down syndrome, Chronic obstructive pulmonary disease

sensitivity, wide linear response, good stability, and reproducibility. Owing to its fast sampling rate and high temporal resolution, FSCV represents an effective method for in vivo monitoring of electroactive species, such as catecholamines [20,21]. However, the detection of non-electroactive species (eg, Glu, HIS and ACh) requires their conversion by enzymes, which remains a challenge due to spatial resolution and invasiveness [22]. Moreover, many NTs possess similar molecular structures and physicochemical properties, which makes it difficult to distinguish one from the other. For instance, Glu and GABA are both highly prevalent in the CNS. Glu represents the metabolic precursor of GABA in the biochemical pathway and differs in structure by only a single carboxyl group, yet its impact on neural activity is drastically different [23]. Similarly, DA, NE, and EP are sequentially synthesized from the same amino acid precursor L-DOPA, making them difficult to distinguish due to their overlapping electrochemical signatures [24]. Lastly, despite advances in surface modification strategies, the strong adsorption of the reactive product and electrofouling impairs the live time of corresponding sensors [25]. Regarding the selectivity for NTs detection, a limited number of functional groups for molecular recognition impedes the development of potent receptors for low-weight NTs. The development of highly specific bioreceptors for the detection of most NTs in the living brain is therefore still an active field of research.

One strategy that has become popular during the past years is the selection of aptamers, mostly short single-stranded DNA or RNA molecules isolated from nucleic acid libraries via the systematic evolution of ligands by exponential enrichment (SELEX) process [26]. Due to their inherently high binding affinity, aptamers have emerged as competitive bioreceptors to recognize small molecules with high specificity. Compared to antibodies, aptamers can be chemically synthesized at low cost with minimal batch-to-batch variation, and have lower immunogenicity and higher thermostability under harsh conditions. Importantly, the binding profile of an aptamer can be precisely controlled by employing different selection strategies and manipulating the selection conditions during the SELEX process, promising a tuneable binding specificity [27]. Furthermore, the engineered sequences of aptamers are endowed with programmable structures, enabling conformational flexibility and diverse structure-switching functionalities, such as aptamer splitting and target-induced strand-displacement [28]. Moreover, the easy modifications of aptamers, including various anchor and signal tags, can facilitate diverse applications, thus meeting wide detection purposes [29,30]. To date, aptamers that recognize various NTs have been reported. The earliest NT-binding aptamer was reported by the group of Szostak in 1993 where they isolated two ATP aptamers with different binding affinities [31,32]. Since then, with the advancement of SELEX methods, aptamers against other NTs have been isolated, including DA, ST, HIS and Glu (Table 2) [33–37]. Consequently, various aptamer-based biosensor platforms have been deployed for NTs detection in the past decades. Recently, Sinha et al. reviewed the application of aptamer-based sensor towards in vivo NTs detection for disease diagnosis and therapy [38]. Nakatsuka et al. summarized aptamer-modified biosensors in optical platforms, especially the translation to in vivo imaging of NT release [39].

In this review, we summarize recent works on aptamer-based biosensor platforms for highly sensitive and specific detection of NT release dynamics with unprecedented spatial and temporal resolution. First, we introduce the general concept of SELEX and recent developments on aptamer isolation for small molecules and already reported NT aptamers. Then, we survey various aptamer modifications and structure designs implemented to advance the sensing mechanism. Based on their transducer principles, the diverse applications of biosensors incorporating aptamers for NTs detection are reviewed, including electrochemical and optical platforms. Finally, aptamer-based sensor devices deployed for in vitro, ex vivo and in vivo NTs analysis are discussed, representing the state-of-the-art techniques for real-time monitoring of NT levels and NT release in the brain, Scheme 1.

2. SELEX

In 1990, Ellington and Szostak coined the term “aptamer” and Tuerk and Gold termed the process of isolating aptamers SELEX. Aptamers are oligonucleotides typically ranging from 20 to 80 nucleotides in length and selected in vitro or in vivo from large randomized libraries to bind target molecules with high affinity and specificity [56]. The nature of the aptamer-target interaction depends on the characteristics of the target molecule. Small molecules tend to be integrated into aptamer structures through stacking interactions, electrostatic complementarity and/or the formation of hydrogen bonds [57].

The starting single-stranded DNA (ssDNA) library generally consists of up to 10^{14-16} different sequences each containing a random region flanked by two constant sequence regions. Although the reported random regions' length ranges from 22 to 200 nucleotides, a small random region (30−50 nucleotides) provides sufficient diversity for successful aptamer selection while keeping the synthesis cost low [58]. Generally, the DNA-based SELEX protocol consists of four steps: selection, partition, amplification, and regeneration of ssDNA. During selection, 0.5−2 nmol of the initial ssDNA library are incubated with the target under specific conditions that may resemble the environment where the target naturally occurs. After this incubation step, a partitioning strategy is used to separate the aptamers in complex with the target from the non-binding molecules. Once the aptamers are recovered, they are amplified using PCR to regenerate the ssDNA library with lower variability and then use this for a new selection round [59].

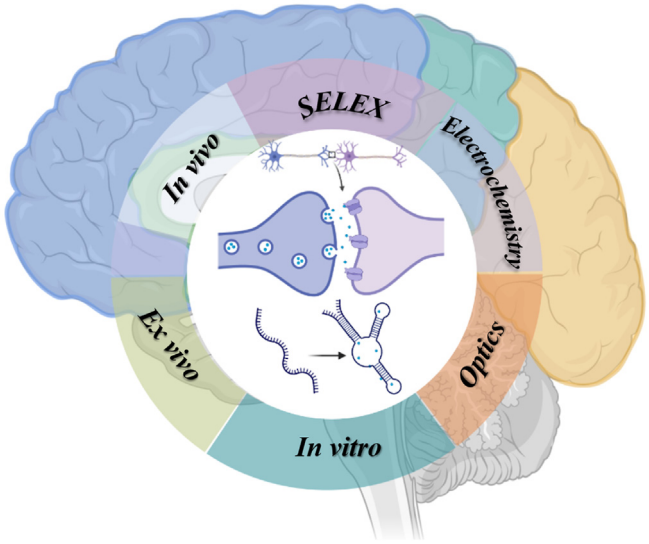
There are multiple methods for each main step in SELEX protocols. The partition method used in SELEX will depend on the nature of the target molecule. In general, partition methods can be classified as homogenous or heterogeneous, the former does not require immobilization of the target nor the library and the later requires immobilization of either the target or library, Fig. 1. For large targets like proteins, there are homogenous methods with high efficiencies [29]. One example of such a method is capillary electrophoresis, however, despite its high partition efficiency this method is not suitable for small molecules because it needs a large molecular weight difference between the library and the target to separate the complex from the non-binder molecules [60–63]. Thus, SELEX for small molecules often relies on heterogenous partition methods that involve the immobilization of the target on a functionalized surface or immobilization of the library (capture SELEX). Using these partition strategies, several aptamers for NTs have been selected. Nonetheless, there were some affinity and specificity issues for these aptamers that might be explained by the limitation of those methods [64].

The target immobilization-based approach is not a simple process because the exposed area of the target to the solution is drastically reduced, which diminishes the number of possible binding sites for aptamers to interact. This is particularly important for small molecules since they already have a very small surface area. Additionally, because of the fewer active sites for conjugation, immobilization of small molecules requires linkers or moieties that can change their physiochemical properties increasing the risk of nonrecognition to the target in free solution [65]. In Capture SELEX, the ssDNA initial library is immobilized on the immobilization matrix (magnetic beads) through hybridization of a docking sequence incorporated into the random region with a

Table 2
Aptamers selected for NTs and their modifications.

Analyte	Sequence (5′- 3′)	Affinity (K_d)	Anchoring molecule	Reporter molecule	Split aptamer	Complementary strands
DA	GTC TCT GTG TGC GCC AGA GAC ACT GGG GCA GAT ATG GGC CAG CAC AGA ATG AGG CCC[a]	0.7 μM	Thiol [40]	Fc [40] MB [42] AQ [43]	[41,42]	[43]
	CGA CGC CAG TTT GAA GGT TCG TTC GCA GGT GTG GAG TGA CGT CG	150 nM	Thiol [33] NH_2 [44]	FAM [33]	–	–
ATP	ACC TGG GGG AGT ATT GCG GAG GAA GGT	6 μM	Thiol [45,46] Biotin [50]	Fc [45] Cy5 [50] FAM [51]	[47]	[48,49]
	TGG CGT CTG CAT GCA GGT CGA CGC ATG CGC CG	70.61 ± 20.91 nM	SAO[b] [36]	FAM [36]	–	–
ST	CGA CTG GTA GGC AGA TAG GGG AAG CTG ATT CGA TGC GTG GGT CG	30 nM	Thiol [52,53] NH_2 [54]	MB [53] FAM [33]	–	–
Glu	GCA TCA GTC CAC TCG TGA GGT CGA CTG ATG AGG CTC GAT	32 ± 8 μM	Thiol [35]	Fc [35]		
HIS	ATT TCT ATG CTG CAG CCA ACT TTT CCA TAC TTC CAG CTT ACC ATT TAT C	72.8 ± 13.9 nM	Biotin [55]	–	–	–
	AGC TCC AGA AGA TAA ATT ACA GGG AAC GTG TTG GTT GCG GTT CTT CCG ATC TGC TGT GTT CTC TAT CTG TGC CAT GCA ACT AGG ATA CTA TGA CCC CGG	3.08 ± 1.03 nM	Biotin [34]	–		
Neuropeptide Y	AGC AGC ACA GAG GTC AGA TGC AAA CCA CAG CCT GAG TGG TTA GCG TAT GTC ATT TAC GGA CCT ATG CGT GCT ACC GTG AA	295 ± 28 nM	NH_2 [37]	–	–	–

[a] This aptamer meets nonspecific interaction with other NTs.
[b] SAO (short anchoring oligomer).



Scheme 1. The overall framework of this review showing a human brain in the background, overlaid by the topics of the chapters and two neurons with a magnified synapse and aptamers in the center. Created with BioRender.com.

complementary oligonucleotide that is also immobilized on the magnetic beads through streptavidin-biotin interaction. Then, the target is added to the DNA-loaded beads and since aptamers can fold into secondary structures to bind its targets this event can release binding DNA sequences from the beads during the selection step. Since the aptamers are now in solution, they can be used to perform the following steps of SELEX. The competition between hybridization of the docking sequence to the immobilization oligonucleotide and the aptamer binding to its target might be the reason why these methods require more than 10 rounds of aptamer selection in most cases because it can influence aptamer folding and secondary structure [29,56,64].

To improve the success of SELEX and the quality of novel NT aptamers, developing optimized selection protocols for small molecules is valuable. Recently, there have been a number of interesting approaches to small molecule aptamer selection. Yoshikawa et al. reported a new system for multiplexed selection of aptamers with high specificity without the need of counter-selection by combining multitarget capture SELEX and a next generation sequencing instrument to perform real-time specificity assays along with sequence identification [66]. Using this system, aptamers for kynurenine metabolites that differ by a single hydroxyl group were obtained. From the same group, Qu et al. described a novel strategy called structure-switching particle display for the rapid and label-free selection of aptamers for metal ions [67]. Using this strategy, they obtained excellent affinity and specificity ssDNA aptamers for Hg^{2+} and Cu^{2+} within four rounds. Another interesting protocol is the Graphene-Oxide SELEX, graphene oxide is a derivative of graphene with oxygen groups-decorated structure that allows the adsorption of ssDNA due to noncovalent interaction via van der Waals forces, hydrogen bonds, π-π stacking, or dipole-dipole interactions. Using this material, the GlyP-1 aptamer was selected after eight Graphene-Oxide SELEX cycles and exhibited a dissociation constant of 30.73 nM [68]. Finally, Chatterjee et al. described the GOLD-SELEX protocol, which takes advantage of the natural adsorption of ssDNA on the surface of gold nanoparticles (GNPs) to immobilize the stating library. When the target is included in the colloidal mixture only binding aptamers are detached from the surface of GNPs because they have a higher affinity for the target than for gold. This facilitates the separation of aptamers from nonbinding molecules that remained bounded to the gold surface. Using this method an aptamer against dichlorvos, a pesticide was selected in eight rounds [64]. All the recent developments improved small molecule aptamer selection, which can be combined with the inclusion of base-modified libraries to further improve SELEX success and provide better aptamers, particularly for difficult NT targets [29].

3. Electrochemical aptasensors for NT detection

Electrochemical techniques represent valuable analytical methods in the field of biomarker detection with features of low cost and easy operation. Taking advantages of high sensitivity, selectivity,

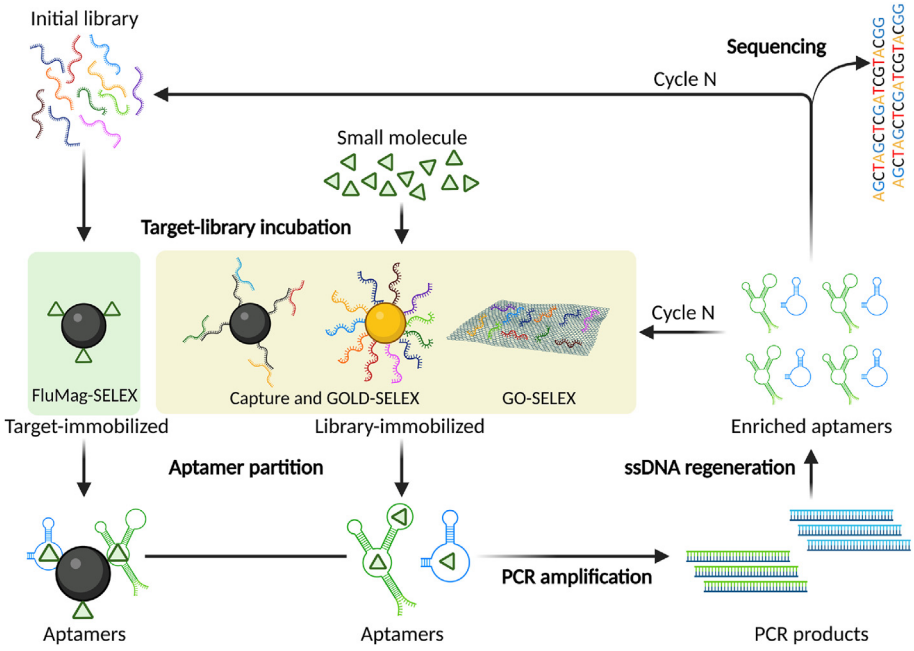


Fig. 1. Small molecule SELEX protocols. The general steps of SELEX protocols for small molecules are shown in bold. The SELEX always starts with the initial library. In Capture-SELEX, GOLD-SELEX and GO-SELEX, the partition step is performed on the basis of the library immobilization (yellow area). For other methods (for example FluMag-SELEX), magnetic beads or other surfaces are used to immobilize the targets through chemical conjugation or using linkers (green area). Created with BioRender.com.

and fast response time, electrochemical aptasensors have attracted considerable attention for small molecules detection. Moreover, their easy miniaturization and compatibility with portable devices enables on-site detection, which holds great potential for point-of-care, in vivo, and clinical applications [69,70]. Based on the measurement principle, the electrochemical techniques can be categorized into different subtypes. Herein, we focus primarily on commonly used techniques and their recent developments in NTs detection, including amperometry/voltammetry, electrochemical impedance spectroscopy (EIS), electrochemilumines-cence (ECL) and field-effect transistor (FET).

3.1. Amperometric/voltammetric

Amperometric/voltammetric methods are versatile electroanalytical techniques that measure the current arising from electrochemical oxidation or reduction at the working electrode as a function of the applied electrode potential. A main advantage of these technique is that the concentration of the electroactive species can be derived straightforwardly from the current intensity [71]. Since catecholamines are electroactive compounds, their electrochemical characteristics have been intensively studied by these methods. However, the overlapping NTs redox potentials may cause signal confusion especially in complex matrices which would influence the analytical accuracy. By implementing aptamers as biorecognition element, highly selective and sensitive electrochemical aptamer-based (E-AB) sensor for NT detection have been demonstrateds [72,40]. In an E-AB sensor for DA detection, a RNA aptamer was covalently immobilized on the gold electrode via an alkanethiol linker, which forms a stable and selective receptor layer for DA binding (Fig. 2A) [73]. A current signal emerged due to DA oxidation facilitated by the specific binding of DA to the aptamer, while interfering signals were impeded by the RNA-modified electrode surface. This method avoids the overlapping response between DA and competitive NTs, and allows selective monitoring of DA levels in biological fluids. To improve the electrochemical oxidation signal of DA, signal amplification strategies inherent to E-AB sensors were developed. Through adding a reducing reagent tris (2-carboxyethyl) phosphine (TCEP), the oxidized, aptamer associated DA can be reduced and by this electrochemically recycled, enabling an increase in the anodic current. This electrochemical redox cycling strategy can achieve nM level detection in DA analysis [74]. Furthermore, nanomaterials with high electrocatalytic activity and large surface area were also used as transducer to enhance DA oxidation signal and improve sensing performance [52,53].

Many other NTs are non-electroactive and require aptamer-associated redox reporters to indicate the aptamer-target binding process. In such an E-AB sensor design, aptamers are modified with methylene blue (MB), ferrocene (Fc), or other redox tags and an anchor group for coupling to the electrode surface at their other terminal end [40,79,45]. Upon target-binding, the modified aptamers undergo conformational rearrangement that repositions the redox tag relative to the electrode surface. Thus, a variation in the efficiency of electron transfer can be detected and the obtained electrochemical signal is proportional to the concentration of target. A newly selected aptamer against Glu was implemented in an electrochemical biosensor after attaching of Fc redox probes to facilitate amperometric Glu detection. The proposed aptasensor exhibited sensitive Glu detection with detection limits at fM level (Fig. 2B) [35]. Such E-AB sensors exhibit high selectivity, rapidity, and simplicity, and are suitable for NTs analysis. However, in some cases the target dependent conformational change cannot effectively alternate the redox characteristics of the electroactive labels. For example, the ST aptamer owns a large stem-loop structure for target binding causing only a small signal decrease due to high stability of the stem part of the aptamer [33]. To solve this problem, the redox tag was attached at the middle (29th base) of the aptamer sequence, causing a considerable current decrease upon ST adding and increased sensitivity in comparison to terminal-redox labeling [80].

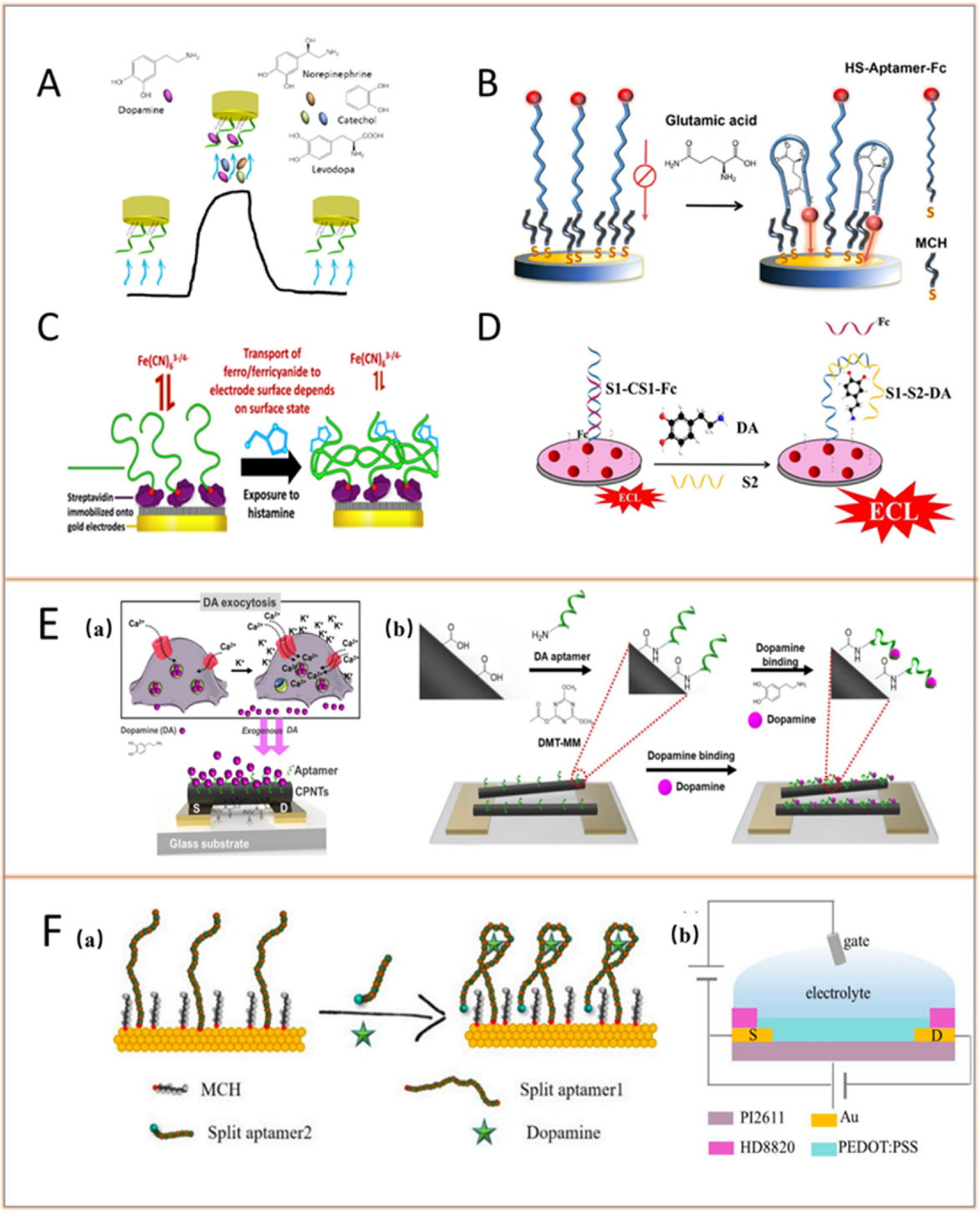


Fig. 2. (A) Schematic representation of the chronoamperometric response of an aptasensor to dopamine, selectively trapped from the flow of NTs over the sensor surface. Adapted with permission from Ref. [69]. Copyright 2016 American Chemical Society. (B) Scheme of the EAB aptasensor working principle for the detection of glutamic acid via ferrocene- and thiol-tagged aptamer receptors. Adapted with permission from Ref. [74]. Copyright 2021 Springer-Verlag GmbH Germany, part of Springer Nature. (C) Impedimetric aptasensor for HIS detection. Adapted with permission from Ref. [75]. Copyright 2020 Elsevier. (D) Schematic diagram of the fabrication of ECL aptasensing platform and the ECL method for the determination of DA. Adapted with permission from Ref. [76]. Copyright 2022 Elsevier. (E) a)Schematic illustration of liquid ion gated FET aptasensor and the release process of DA in PC12 cells through ion acceleration; b) Chemical conjugation mechanism between source and drain electrodes for DA detection. Adapted with permission from Ref. [77]. Copyright 2020 Springer Nature. (F) a) Schematic representation of amperometric aptasensor for DA; b) Schematic configuration of flexible OECT using the same aptasensor in a) as gate for DA detection. Adapted with permission from Ref. [78]. Copyright 2020 MDPI.

Likewise, the ATP aptamer shows only small conformational changes during target binding. To overcome this issue, a strand modification method has been proposed using complementary DNA (c-DNA) strand to hybridize with a portion of aptamer sequence to form a duplex probe [48,49]. During hybridization, the structure of the single strand, surface tethered aptamer changes from a folded conformation to a rigid duplex, causing a slow electron transfer (ET) and reduced background currents. The c-DNA is displaced from the duplex complex upon target binding to aptamer and shifted back to a flexible single strand, which enables improved ET efficiency between redox reporter and the underlying electrode. By employing this displacement-based signaling mechanism, significantly enhanced signal gain with 84% have been obtained for ATP detection, comparing to only the 20% signal increase with single strand aptamer. Moreover, through regulation of the number of aptamer-involved base pairs within the duplex, a tunable signal gain and the response rate of these synergically stabilized duplex probes can be achieved [81]. Another alternative design strategy is the splitting of the aptamer into several fragments. In the absence of target molecules, these fragments are separated due to lacking secondary structures. In the presence of the target, the aptamer fragments reassemble together with the target into a target-aptamer complex. This aptamer splitting design holds significant potential in the development of sandwich aptasensors avoiding false-positive or nonspecific signals, particularly for small molecules analysis [82]. To minimize interfering aptamer affinity, the foreknowledge of target-binding domain and scaffold regions is required since non-binding loop regions are preferred for splitting. Among the few reported split aptamers, the ATP aptamer was extensively studied and even a multi-level logic gate was designed [47]. For the latter, the electrode was modified by a capture split aptamer fragment through covalent thiol-gold bonds. When the analyte solution was applied containing the second split strand with Fc tag, a stable sandwiched structure formed between ATP, capture and Fc tagged aptamer fragment. This system showed reduced amperometric background signals and consequently a lower LOD by more than one order of magnitude. Moreover, the electrochemical signal output can be applied to realize a novel bioelectronic logic circuits and a final net XOR analysis. Similarly, the specific anti-DA aptamer was split and a c-DNA strand with anthraquinone (AQ) tag was employed. In the presence of DA and a second MB-labeled fragment, an aptamer-DA complex was formed and the release of c-DNA was induced. The two competitive redox-label AQ and MB reported independently on the binding process and enabled a novel dual-signal ratiometric electrochemical biosensor [43]. Recently, a new conception of bivalent split aptamer signal probe to improve sensing sensitivity for ATP was reported [83]. The two split aptamers will form a triple complex upon ATP binding, thus producing an increased current signal of MB tags. By adding a DNA template strand to hybridize the MB labeled aptamers, a bivalent signal probe can be formed. Target binding at one site largely improved the affinity of its adjacent site, which resulted in a 3.5 folds signal increase.

The attachment of redox reporters to aptamers can be complex, expensive, time-consuming and may affect the aptamer's affinity. Alternatively, the redox-probe MB can intercalate into the aptamer through specific interaction with its guanine bases. The target-binding event will induce the release of MB from the electrode surface, producing a decrease in the amperometric current associated with NTs concentration [84,85]. Furthermore, electrocative nanocomposites can serve as redox probe to amplify the performance of aptasensors. A silver nanoparticle-decorated graphene oxide (AgNPs-GO) complex was utilized as redox probe for ATP detection [86]. The GO substrate provided a large number of loading sites for AgNPs and the nanocomposite interacted with aptamer via π-π stacking. By ATP adding, the formation of a target-aptamer complex caused a detachment of AgNPs-GO from the electrode surface, resulting in a decrease of the current signal. Furthermore, the NTs binding with aptamers can directly affect the interfacial ET reaction of the nanocomposite with the electrode. In another example, the integration of the signal probe Prussian blue (PB) with AuNPs/CNTs modified electrode was reported for DA detection [87]. Noteworthily, although nanocomposites can enhance the sensors performance, their utilization increases the sensor complexity and the biocompatibility needs to be assessed before implementation in vivo settings.

3.2. Electrochemical impedance spectroscopy (EIS)

EIS is a widely used technique to characterize the resistive and capacitive elements of the electrode impedance. Typically, a small sinusoidal AC voltage (approximately 2−10 mV) with a wide frequency range is applied and the electric impedance is determined in response [75]. EIS has been recognized as an effective method for the development of aptasensors towards small molecules because minute changes in the charge-transfer resistance or variations in capacitance of surface are directly correlated to the concentration and not limited by the small mass of NTs [88]. Moreover, EIS can facilitate label-free NTs detection since solution-phase instead of aptamer-tagged redox probes are used [89]. In an impedimetric aptasensor for HIS, a newly selected aptamer strand was immobilized onto gold electrode surface via streptavidin and biotin. Here, the variation of the charge transfer resistance for the reversible oxidation and reduction of $[Fe(CN)_6]^{3-/4-}$ is monitor as function of HIS-aptamer binding events which induce aptamer conformational change and therefore charge transfer resistance chances (Fig. 2C) [55]. Since the surface properties have a big impact on the electrode impedance, electrodes modified by nanocomposites with enhanced conductivity and electroactive surface area have been frequently utilized for NTs detection. For example, tungsten oxide (WO_3) films with intercalated Li^+ ions was used for the detection of ATP [90]. The conductivity of the sensing surface was largely enhanced by this material and thus the background signal decreased during EIS measurements. The aptasensor in a fully lithiated state exhibited a larger detection range, lower detection limit and superior selectivity compared to non-lithiated conditions. Mahmoud et al. developed a highly specific molecular imprinted based aptasensor for label free electrochemical detection of HIS [91]. A glassy carbon electrode was modified with carboxylated carbon nanotubes and gold nanoparticles, followed by electro-polymerization of ophenylenediamine. The modified surface provided dual recognition for HIS based on increased impendence after target exposure and enables a high selectivity in human plasma and canned tuna. Overall, EIS has been widely used for aptasensor development however, non-specific aptamer-independent binding of matrix components to the electrode in complex samples such as serum, stool, or full blood interferes EIS sensor's selectivity and sensitivity. Therefore, the implementation of excellent antifouling blocking for backfill molecules is essential for this class of transducer [76].

3.3. Electrogenerated chemiluminescence (ECL)

Another transducer principle utilized for NT aptasensors is electrogenerated chemiluminescence (ECL) in which energetically excited states are formed during the electron-transfer reactions at an electrode surface and light is emitted latterly when the excited fragments decay to the ground state [92]. ECL takes advantages of control over emission position and reaction time, which is beneficial for its sensitivity and for simple sensor operation [93]. A typical ECL co-reactant system is $Ru(bpy)_3^{2+}$ and tri-n-propylamine (TPA)

due to its high ECL efficiency and wide linear range. An examplary 'off-on' ECL aptasensor used an electrode modified with the mixture of Nafion, AuNPs, and Ru $(bpy)_3^{2+}$. Afterwards, a split fragment DA aptamer and its complementary strand with Fc tag were hybridized and loaded onto the ECL platform. Here, Fc quenched the ECL signal of the emitter via energy or electron transfer, which suppressed the electroluminescence when DA was absent. In the presence of DA, target binding induced a conformational displacement, resulting in a release of Fc labeled strands from the electrode surface, which can be detected by the increase of ECL intensity via "off-on" signal mode (Fig. 2D). Moreover, the use of a tetrahedron structured DNA (ts-DNA) was reported to construct an ECL aptasensor for ATP detection [94]. The ts-DNA was employed to conjugate an ATP aptamer with the signal probe $Ru(phen)_3^{2+}$ which was intercalated to the aptamer hybrid, thus introducing the co-reactant for ECL emission. Upon ATP association with its aptamer, the signal strand dissociated and the $Ru(phen)_3^{2+}$ was released. The change in emission intensity was used to quantify the ATP concentration. Quantum dots (QDs) represent a new class of nanomaterials that can be used as light emitting probes in ECL aptasensors [95]. Cadmium-based QDs is one example with high brightness, tunable emission maxima, and high stability against chemical degradation [96]. In an "off-on" ECL aptasensing platform, CdTe QDs were used to modify the electrode and the dissolved oxygen was considered as the coreactant, which facilitated a strong ECL emission. The receptor was formed by partial hybridization reactions between an anchor strand, aptamer, and signal probe. The signal probe, containing G-quadruplex/hemin, catalyzed the reduction of dissolved oxygen, leading to a decrease of the ECL intensity. The presence of the target ATP induced a disassembly of the aptamer, and thus decreased the signal-probe loading, resulting in increased ECL signals ("on" state) which enabled a nM ATP detection in human serum [97].

3.4. Electrical aptasensors

3.4.1. Transistors based on silicon

Field effect transistor (FET) biosensors are considered as promising electronic transducers, due to their compatibility with Si technology and their high sensitivity based on intrinsic signal amplification [98]. Generally, FET biosensors are three-terminal devices, where the flow of charge carriers (electrons or holes) between the source and drain is regulated via a third gate electrode [99]. The FET biosensors are further classified into n-type and p-type transistors according to their charge carriers and doping methods [100]. Typically, the solid gate electrode of FET biosensors is substituted by a liquid gate. These devices make use of the potential drops on the solid-liquid interface of the gate electrode and the channel materials, which are both placed in the same fluid. Since the entire bias applied between gate and channel drops within the electrochemical double layers, an alteration of the douple-layer composition, for instance due to a receptor-analyte binding process, efficiently alternates the charge carrier density and the resulting source-drain current, which typically is more efficient than standard solid gating for SiO_2/Si substrates [101].

The implementation of silicon nanowires (SiNW) as 1D nanomaterial further advanced the performance of FET biosensors due to their high surface to volume ratios facilitating fM LODs [102,103]. An ultrasensitive multiple-parallel-connected (MPC) SiNW-FET biosensor was developed for real-time detection of dopamine release from living PC12 cells, which can be employed to monitor the DA at ultralow level in the urine/blood of patients with pheochromocytomas or paragangliomas and in the extracellular fluid of Parkinson's disease patients [104]. Later, the same group developed a SiNW-FET biosensor for simultaneous dual target determination of DA and neuropeptide Y, including the monitoring of the kinetics of the release of the NTs during exocytotic events [105]. Sessi et al. performed hybrid integration of bottom-up silicon-nanowire Schottky-junction FETs (SiNW SJ-FETs) with complementary-metal-oxide-semiconductor (CMOS) readout and amplification electronics [106]. An array of 32 × 32 aptasensors with a 100 μm pitch was established for DA detection with fM LOD. The CMOS process was introduced to facilitate highly integrated devices with superior sensitivity of ~1 V/fM due to the amplification capabilities of the transistor and larges numbers readout at the same time. This sensing platform was able for control or reference measurements and self-validation on a small spatial footprint.

3.4.2. Organic electrochemical transistors and organic FETs

Besides solid-state transistors, devices comprising synthetic semiconducting molecules or polymers as channel material have been utilized for biosensor applications since they can be operated without gate dielectric and feature rapid detection, low cost, facile fabrication, and multiparameter sensing [77,107]. Some organic field effect transistors (OFET) have been processed on flexible polymer substrates since compliant material properties enhance the device wearability, solution-processability, and reduces the immune response of implantable sensors [108]. A high-performance conducting polymer FET biosensor was developed based on polymer nanotube and liquid-ion gated transistor for DA detection released from PC12 cells via Ca^{2+} / K^+ ion triggers [109]. As shown in Fig. 2E, the aptamers with stem-loop structure were directly attached to the surface of the CPNT channels. The two major stem-loop domains of the aptamer recognized the NT with high specificity by forming a DA binding pocket, which triggered changes of the interfacial charge distribution, resulting in an indirect doping effect.

Another class of polymer transistors, which exposes their conjugated polymer channel directly to the sample fluid, are organic electrochemical transistors (OECT). However, in OECTs, the source-drain current is alternated by an ion induced redox depoping within the channel instead of a field effect modulation of the charge carrier density as for FETs [78,110]. The OECT platform can be employed for the high-sensitivity and label-free analyte detection in a wide concentration range and with the advantages of easy fabrication, ion-to-electron conversion, biocompatibility, and fast switching speed. OECTs have been used for the detection of various small molecules such as ATP and DA [46,42]. For the later, a split aptamer was immobilized on a gold electrode, which was utilized as amperometric sensor directly or as gate in an OECT sensor configuration. In the presence of the target DA, a sandwich structure was formed between the capture strand, the DA target, and the probe strand. The latter was labeled with the redox reporter MB. The amperometric sensor detected dopamine with a LOD of 1 μM, while the flexible OECT biosensor exhibits an ultralow LOD of 0.5 fM (Fig. 2F). The low detection limit was attributed to the intrinsic amplification properties of OECTs. The superior sensor performance, as well as the flexible properties of the OECT-based aptasensor, are considered as promising features for their integration in neuronal in vitro or in vivo probes.

3.4.3. 2D and G-FETs

Two-dimensional (2D) materials such as metal oxides, transition metal oxides, metal dichalcogenides, transition metal chalcogenides, hexagonal boron nitride, black phosphorus, and graphene exhibit remarkable electrical properties due to their atomic sized thicknesses and are therefore implemented in FET devices. The large surface area, high electron mobility, biocompatibility, and easy surface functionalization of the 2D materials make them a promising candidates for FET based biosensing [111]. Andrews et al.

developed a high-performance In_2O_3-FET biosensor by depositing this 2D-material on the SiO_2/Si substrate. Then thiol modified aptamers were bound to the surface of In_2O_3 [112]. This sensor was capable to detect DA and ST in the physiological relevant range with fM detection limits and could be implanted in brain tissue for NTs release monitoring. Moreover, the same group reported a flexible In_2O_3 nanoribbon-FET biosensor on soft polyethylene terephthalate (PET) substrates for multiplexed NTs detection and to reduce the immune response during brain implantation [113].

Another versatile 2D material is graphene, which possesses a hexagonal carbon structure with a fully conjugated and delocalized π-electron system and exhibits an extraordinary sensitivity to surrounding charges and electric fields [114]. Graphene-based FETs (G-FET) allowed ultrasensitive dopamine detection with the low LOD down to 10^{-18} M in both PBS buffer and brain homogenate samples. Xu et al. developed a 3D graphene foam based FET biosensor for ATP and achieved a wide detection range from 0.5 pM to 50 mM even in human serum and cell culture conditions [54]. Compared with the 2D graphene, the 3D graphene foam exhibited higher compressive strength and larger specific surface due to the porous/hollow structures, which led to a higher sensitivity. Moreover, flexible G-FET biosensors have been reported that can be implanted in animals for chronic monitoring of NT release [115,116]. Through electrografting, a site-selective functionalization of the G-FET channel surface was performed with aptamers for the simultaneous monitoring of DA and ST [44]. This biosensor exhibited outstanding flexibility and ultralight mass of 28 mg with a cellular-scale dimension of 50 × 50 μm. This G-FET biosensor was capable of sensing DA and ST in PBS, artificial cerebrospinal fluid, and harvested mouse brain tissues. Furthermore, this group has implanted the G-FET for in vivo real-time monitoring of DA release [117].

4. Optical aptasensors for NTs detection

Optical aptasensors are widely used for NT detection and unfurl their strengths especially in vitro settings since, unlike electrochemical aptasensors, they do not require electrical wiring or electrodes to acquire their signals [118]. Optical aptasensors can combine high sensitivity and reproducibility with competitive temporal but also 3D spatial resolutions [6]. For optical measurements, colorimetric or fluorescent tags are commonly used as reporter molecules, which contain valuable characteristics such as different absorption or emission wavelength and intensity of relevance for multiplexing approaches.

4.1. Colorimetric aptasensors

Colorimetric tests such as lateral flow assays are well established since they do not require expensive instrument and results can be observed through the color changes with the naked eyes [119,120]. However, some approaches suffer from low sensitivity, only qualitative signal readout, and complex procedures. To improve the colorimetric sensor performance, researchers implemented gold nanoparticles (AuNPs) as a reporting probes and aptamers as receptors. As such, AuNPs can be easily synthesized, possess high extinction coefficients, and have a strong distance dependence on involved optical processes [121]. In this regard, the mainly employed transducer principle is the color change from red to blue during the transformation from dispersed to aggregated AuNP, respectively. Correspondingly, various NT aptamers were utilized for colorimetric aptasensors. One example is the 58-mer DA-binding aptamer, which undergoes a conformation change in the present of DA from a random coil shape to a rigid tertiary structure, which leads to salt-induced AuNP aggregation [122]. In recent years, colorimetric aptasensors were also developed for ATP, ST, and HIS detection [123–125]. However, to explore possible cor ı between AuNPs, aptamers, and target molecules, the DA - amine adsorption onto citrate-capped AuNPs in the presence of ssDNA was investigated [126]. The results showed that DA strongly adsorbed on AuNPs and random DNA same as specific aptamer receptors displayed a similar color change. Therefore, the DA induced colorimetric sensor response cannot be generally attributed to the specific interaction with aptamer receptors and control experiments are indispensable. Noteworthy, colorimetric tests are not limited to solution phase sensing, but can also be implemented on hydrophobic paper. These paper-based sensors possess the advantage of being easy to fabricate, portable, readily available, and able of handling small samples with microliter volumes [127]. Accordingly, lateral flow assays were also established for NTs identification. Dalirirad et al reported such test for on-site detection of DA in urine, where they utilized a quantification based an Image J analysis (Fig. 3A) [128]. To improve the versatility of colorimetric aptasensors and to transform them to portable diagnostic tools for NTs detection, a bionic electronic-eye (E-eye) device for in-time detection of adenosine was developed [129]. This device was based on the binding of two adenosines on one aptamer to prevent that the aptamer absorbed onto the surface of AuNPs and to maintain the AuNPs aggregation under high salt conditions. The linear detection range of this device for artificial urine samples was 5.0–50.0 mM with a LOD of 0.48 mM. Meanwhile, a smart phone was used for data collection and multiple samples were loaded to a microwell plate for simultaneous examination. Moreover, gold nanorods (AuNRs) were also used for colorimetric aptasensor fabrication based on a side by side self-assembly of aptamers onto the surface of AuNRs for adenosine detection [130]. Adenosine specific aptamers were correspondingly immobilized at the side position of AuNRs. The adenosine addition triggered the self-assembly of the modified AuNRs to form a side-by-side connected sandwich structure. Increasing adenosine concentration led to a blue shift of the solution color.

Although the colorimetric biosensors are easy and inexpensive, the most reported colorimetric aptasensors have only been operated in deionized water or buffer solution, which is rather compatible with in-vitro studies then with in-vivo applications. In addition, some targets molecules showed nonspecific interaction characteristics to AuNPs, which may cause a misinterpretation of test result and demands cautious study evaluation.

4.2. Fluorescent aptasensors

Aptamer-based fluorometry mainly utilizes molecular beacons, which alter their specific fluorescence emission upon binding of an analyte. Therefore, the fluorophore is commonly attached to the aptamer. Common fluorophores for neurotransmitter detection are fluorescein [33], cyanine-5 (Cy5) [134,50], carboxyfluorescein (FAM) [51,135], and chlorin e6 (Ce6) [136]. The second important ingredient is a quencher, which reduces the fluorescence intensity of the fluorophore. The actual quenching mechanism depends on the chemical nature of the quencher, see below. The aptamer related transduction mechanism typically involves a change of the distance between quencher and fluorophore upon target binding and an associated aptamer conformation change [131,137,138]. Typically, fluorescent aptasensors can be separated in two categories according to the mechanism of the change of the fluorescent signal. The first one is based on the direct measurement the fluorescent intensity of the detection system. A fluorometric sensor based on FAM-labeled ATP aptamers and magnetic nanoparticles was reported [139]. The FAM-aptamer was bound to the magnetic nanoparticles to form the multifunctional probe for magnetic separation, recognition of ATP, and fluorescence emission. When the ATP was added, ATP adsorbed

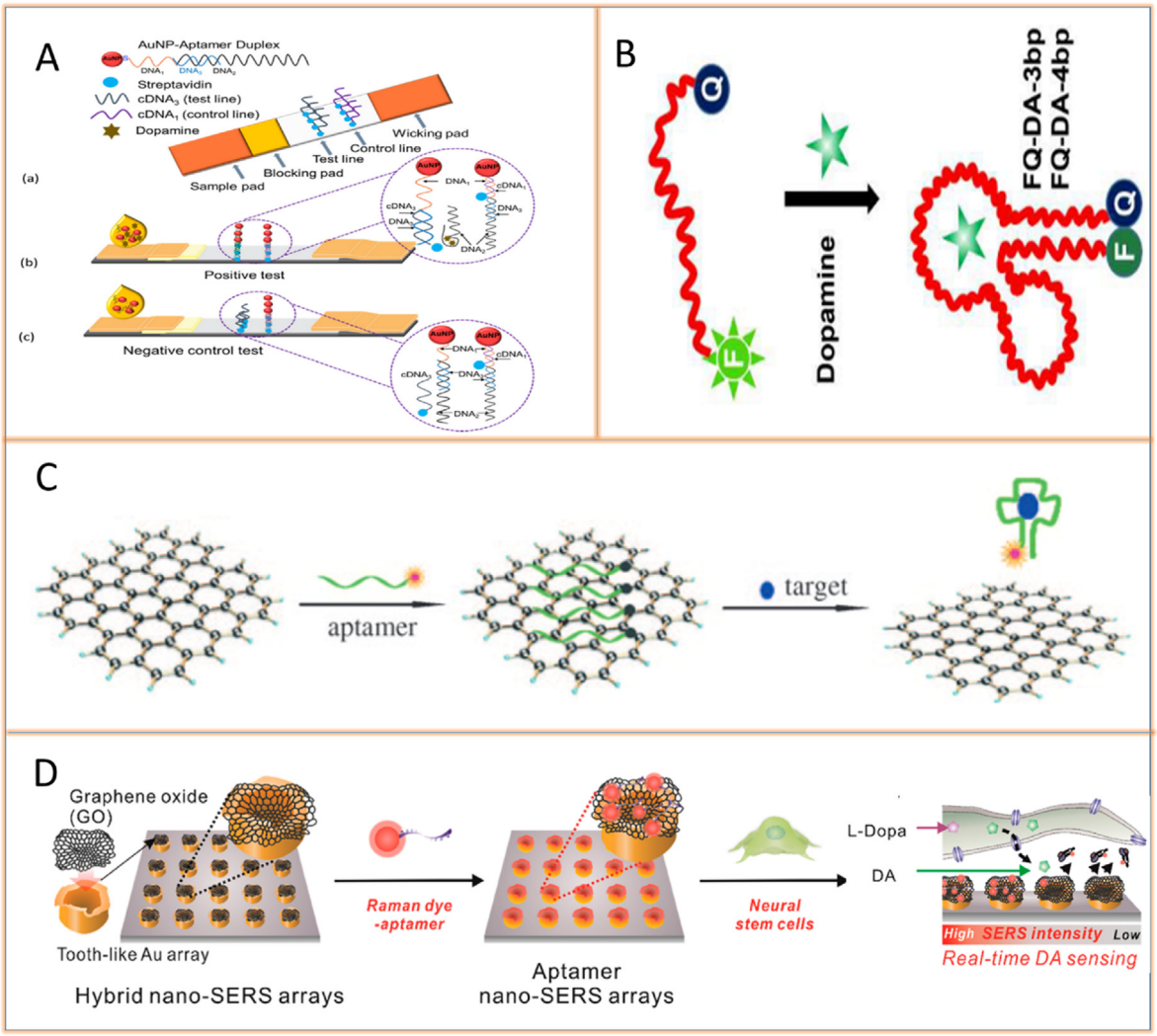


Fig. 3. (A) Duplex dissociation design with aptamer-based lateral flow test strip for DA detection. Adapted with permission from Ref. [125]. Copyright 2020 Elsevier. (B) A quenching based fluorescence aptasensor containing a fluorophore and quencher for DA detection. Adapted with permission from Ref. [131]. Copyright 2021 Elsevier. (C) Schematic of fluorescent aptasnesor based on FAM as donor and GO as quencher in FRET for DA detection. Adapted with permission from Ref. [132]. Copyright 2010 WILEY-VCH Verlag GmbH & Co. KGaA. (D) Schematic illustrating of the graphene oxide (GO)-hybrid for nano-SERS monitoring of DA in live cells. Adapted with permission from Ref. [133]. Copyright 2020 American Chemical Society.

to the FAM-tagged aptamer. After the magnetic separation, the fluorescence of the supernatant was enhanced by increasing fluorophore concentration. This fluorescent aptasensor can be applied for the quantitative detection of ATP in spiked human urine and serum samples. Another example from this category used SYBR Green I for the fluorescence detection in combination with the exonuclease III for signal amplification for DA analysis in mouse brain tissues [140]. The second category is based on fluorescent resonance energy transfer (FRET), which commonly involves two dyes as fluorophore and quencher, where energy is transferred non-radiatively between this donor-acceptor dye pair (Fig. 3B) [141]. This process is highly efficient, when the donor-acceptor pair exhibits a large overlap between the emission spectrum of the donor and the absorption spectrum of the acceptor at a distance of less than 10 nm [142,143]. Several signal generation strategies are distinguished for this principle including fluorescent signal "on-off-on", fluorescent quenching with signal "on-off", and fluorescent recovery with signal "off-on" [95,144]. Furthermore, various nanomaterials were employed to be the fluorescent donors including fluorophores, semiconductor QDs, and upconversion nanoparticles [132,145,146]. For instance, GO was employed with FAM as donor-acceptor pair to fabricate a FRET fluorescence aptasensor for DA detection relying on an "off-on" mechanism (Fig. 3C) [147]. The FAM-tagged DA aptamer was adsorbed onto the surface of GO by π-π stacking interactions, causing a fluorescence quenching (signal "off"). In the presence of DA, the aptamer bound the analyte associated with a conformational switching from random coil to a rigid stem-loop structure, which decreased the affinity between aptamer and GO. Consequently, the aptamer was released from GO, which terminated the quenching and caused an increase in the fluorescence intensity (signal "on"). Similarly, poly (9, 9-bis (6′-N,N,N-trimethylammonium) hexyl) fluorine phenylene (PFP) was used as energy donor in FRET process for DA detection [51]. Another reported work used single-wall carbon nanohorns (SWCNHs) as quencher for FAM labeled aptamers mediated by π-π stacking between SWCNHs and an aptamer for DA detection [148]. The influence of surface charge on the quenching rate was investigated. It was found that the negatively charged SWCNHs exhibited a quenching rate of 60% when SWCNHs (zeta potential −21 ± 5.4 mV) were directly used for quenching. After $MgCl_2$ was employed to increase the positive charge in the detection

system, the quenching rate grew to 94.7%, demonstrating the importance of electric charges during π-π stacking mediated quenching processes.

Besides molecular fluorophores, semiconductor QDs represent another popular class of fluorescent materials for aptasensor developments due to their versatile properties such as broad excitation bands, symmetric and narrow emission, tunable emission wavelength, long fluorescence lifetime, and photobleaching resistance [149,150]. In a fluorometric DA assay, aptamers functionalized with MoS_2 QDs were used as fluorescence donor and MoS_2 nanosheets as receptor. In the presence of DA, the aptamers were separated from the MoS_2 nanosheets facilitating a fluorescence recovery [151]. You et al. proposed a split aptamer ratiometric fluorescent aptasensor based on blue-emitting carbon dots (CDs) and red-emitting silica-coated CdTe QDs (QDs@SiO_2) for specific detection of adenosine [152]. The CDs and QDs@SiO_2 were modified separately with one part each of the two strands of the split aptamers of adenosine, respectively. The GO was used to absorb two aptamers and quench the fluorescence of CDs. The presence of adenosine induced the formation of a sandwich complex of ABA1-CDs/adenosine/ABA2-QDs@SiO_2, which caused a fluorescent recovery of ABA1-CDs since the CDs separated from GO. This aptasensor represents a ratiometric turn-on strategy for fluorometric, colorimetric and visual determination of adenosine in spiked human urine. To simplify the process, a label-free fluorescent aptasensor based on carbon QDs (CQDs) and AuNPs was developed for DA detection [153]. The AuNPs were firstly conjugated with thiol-tagged aptamers and then modified with CQDs, which adsorbed to the aptamers through electrostatic interactions, causing a quenching of the fluorescence. DA addition leads to a release of the CQDs from the surface of AuNPs and a recovery of the fluorescence. Furthermore, it was reported that two-dimensional fluorescent nanomaterials such as silver nanoclusters can be employed as fluorescent donors for the development of fluorescent aptasensor [154].

Other attractive nanomaterials for optical transducers are upconversion nanoparticles (UCNPs) due to their capability of transforming two or more incident photons of low energy into one emitted photon with higher energy. UCNPs feature a low autofluorescent background, high prevention of photodamages, and deep tissue penetration of excitation light [155]. Rabie et al. developed a single-crystal core-shell-shell "sandwich" structured UCNPs for a fluorescent DA aptasensor [156]. This aptasensor employed β-NaYF4:Yb, Er codoped UCNPs and β-NaYF4:Yb, Er@NaYF4 as the alike "active shell" to measure the DA release from stem cell-derived dopaminergic-neurons via simple luminescence resonant energy transfer. Although, fluorescent aptasensors have been widely used for the investigation of samples extracted from organisms or tissue, there is still a challenge to establish in-vivo tests due to the complex background from the biological environment, the low signal-to-noise ratio of the aptasensors, and the toxicity of the fluorescent dyes.

4.3. Other optical sensors

Surface plasmon resonance (SPR) makes use of light-stimulated resonant oscillations of conduction electrons located at metallic surfaces, thus offering high sensitivity to processes that occur on metal-liquid interfaces facilitating low LODs for targets detection [157]. Using this method to detect small NT molecules exhibited remarkable performances since it overcome the limitations of small size and low molecular weight inherent to this type of targets [133]. Furthermore, strategies to enhance the SPR signal and lower the detection limits are reported for aptasensors [158].

Moreover, a light addressable potentiometric sensor (LAPS) for the detection of local ATP secretion from single type II taste receptor cells (TRC) was proposed [159]. In this biosensor, a major part of ssDNA molecule was pre-immobilized on the surface of the LAPS chip, while the rest part was complementary to ATP aptamer. When ATPs were presented, the aptamer separated from the supporting ssDNA and bound to ATP. During this process, the LAPS chip was scanned by a laser, and its locally light-activated charge carriers in the chip were affected by the chemical processes on the solid-liquid interface. The aptamer desorption led to alterations of cell surface charges, which could be monitored by the working potential shifts of the LAPS chip. This sensor can be used to detect the local ATP secretion from different types of ATP-secreting cells.

Choi et al. designed a GO-hybrid nanosurface-enhanced Raman scattering (SERS) array for in situ detection of DA [160]. The tooth-like GO-hybrid nano-SERS structures were fabricated via laser interference lithography, followed by electrochemical deposition, and a final modification with GO nanosheets (Fig. 3D). The Raman-dye modified aptamer was immobilized on the surface of a GO-hybrid nano-SERS array, resulting in a strong Raman intensity, while in the presence of DA, the Raman intensity decreased. This SERS aptasensor exhibited not only a high sensitivity, selectivity, and reproducibility but also represents a noninvasive detection method with minimal cell damage.

All in all, while colorimetric sensors are easy the implement and provide a visual readout, they have their strengths when only qualitative test results are required. Fluormetric sensors are more involved but facilitate low LODs also due to the utilization of versatile nanomaterials, while their toxicity remains a critical issue especially for in vitro and in vivo settings. SPR, LAPS and SERS-based methods require specialized equipment but provide ultra-low LODs and high lateral resolution.

5. In vitro/in vivo detections and other applications

The ultimate goal for the development of NT aptasensors is to achieve real-time, sensitive and selective detection of dynamic NTs concentration in nervous systems. In neuroscience, several models have been established to assess the practical feasibility of developed techniques for biological applications, including in vitro, ex vivo and in vivo models. These methodologies have become indispensable tools for studying NT release dynamics under physiological condition and evaluating the potential behavior of aptasensors under biomimetic microenvironments.

5.1. In vitro applications

In vitro literally means in glass and is used as a general term for cells in culture. In vitro models are commonly used for characterizing the sensing performance of NT aptasensors, because of their cost-effectiveness, relatively straight-forward establishment, and fast and standardized investigation procedure. Generally, in vitro techniques for studying NT release dynamics are conducted on cell-based models which mimic the CNS microenvironment and often incorporate more than one cell line. Moreover, in vitro techniques are also beneficial from an ethical point of view, as they prevent the unnecessary harm of animals [161].

The SH-SY5Y cell line was used as a model for DA release since it possesses similar biochemical characteristics as human dopaminergic neurons. Zeng et al. introduced a DNA-nanoprism fluorescent probe to nongenetically engineer the cell surface for ultrasensitive imaging of DA release at a single cell level [162]. Fluorophore-labeled aptamers and quencher-labeled c-DNA strands were used for DA sensing. DNA-nanoprism were formed by self-assembly and easily anchored onto the cell membrane via cholesterol tags functionalized at bottom vertices. Once capturing

released DA, the c-DNA strand dissociated from the probe, causing a recovery of the fluorescent signal. This neuronal probe was used to explore the cellular localization and dynamic changes of DA over spatial and temporal scales. By elevating the extracellular K^+, the SH-SY5Y cells depolarized and bright green fluorescent puncta occurred on the cell surface, representing the dynamic release of DA in proximity to the cell surface (Fig. 4A). However, high K^+ failed to promote DA signals on the cell surface in the absence of extracellular Ca^{2+} or when the extracellular Ca^{2+} was chelated by EGTA. This result validated that the K^+-stimulated DA release is Ca^{2+} influx-dependent and demonstrates the potential of DNA probes for in situ monitoring of DA release dynamics on the level of individual cells.

In another work on DA release detection, an electrochemical aptasensor was constructed with MB intercalated aptamers to amplify the sensor signals in SH-SY5Y cell lines [164]. To evoke DA vesicles release, a K^+ solution was added to depolarize the cell membrane. The aptamer sensor showed a time-dependent DA release for SH-SY5Y cells reaching its maximum value between 6 and 8 min. Furthermore, the sensor enabled the investigation of deleterious effects of toxins or drugs on cells by detecting the alterations of DA release. Additionally, the rat phaeochromocytoma (PC12) cell line has been used as in vitro model for DA release, which was originally isolated from a tumor in the adrenal medulla of a rat. This model is highly versatile regarding pharmacological manipulation, ease to culture, individual cells possess small vesicles similar to neurons, and there is a deep background knowledge on their proliferation and differentiation. Park et al. fabricated liquid-ion gated FETs from modified conducting polymer nanotubes for the detection of the exogenous DA release from the PC12 cells [109]. The aptamer modified conducting polymer was operated as a gate modulator, thus promising high sensitivity for DA monitoring. They also used different concentrations of K^+ solution to promote Ca^{2+} influx in the cell membrane and induce a rapid DA release. Here, a clear correlation between K^+ concentrations and the amount of detected DA was obtained.

For in vitro detection of ATP, Ruan et al. developed a novel nanopipette tool for electrochemical intracellular ATP sampling on the single-cell level, using ATP split aptamers [163]. Assisted by a three-dimensional (3D) micromanipulator and a microscope, the nanopipette was steered to penetrate the target HeLa cells and human embryonic kidney 293 (HEK 293) cells. During the intracellular sampling process, an increase of ion current rectification (ICR) was detected due to the formation of highly negatively charged aptamer complexes (Fig. 4B). Current changes due to ATP binding were larger in HeLa cells compared to HEK 293 cells, reflecting the higher metabolic ATP requirements of cancerous HeLa cells. Similarly, Yu et al. demonstrated a photocontrolled nanopipette sensing of cellular ATP gradients at the single-cell level [165]. By using azobenzene incorporated ATP aptamer strands, a significant conformational change can be induced under ATP/vis conditions, causing large ICR signal changes that are correlated to intracellular ATP concentrations. Moreover, the nanopipette could be used for local cellular ATP gradients of individual H9C2 cardiac myoblasts. At different altitude relative to the cell membrane, the ICR intensity increased with a smaller distance and the intracellular position exhibited the maximum signal, indicating high ATP concentrations in the cytoplasm.

Several studies for in vitro analysis of ST release based on aptamer-coated nanopipettes have been reported, facilitating the fast quantification of ST release from patient-derived serotonergic neurons [166]. Treatment with ST releasing drugs caused a clear increase in extracellular ST concentration. In contrast to electrochemical measurements, direct imaging of release events provided higher spatial resolution of ST release around the cell membrane. Moreover, a near-infrared fluorescent nanosensor for imaging ST release on platelets was proposed [167]. The ST aptamer was wrapped around single wall carbon nanotubes (SWCNTs) to promote the dispersion of the hydrophobic SWCNTs in aqueous solution. The conformational change of the DNA upon ST binding affected the exciton decay routes, leading to increase in the fluorescence intensity. By studying the release patterns from single cells, a 15 s time delay between application of ionomycin (an ionophore that increases cell activity) and extracellular ST detection was observed. ST levels remained elevated for 50 s before decreasing again (Fig. 4C). The imaging patterns varied correspondingly with the ST release events, suggesting that serotonin stored in the dense granules requires a certain time to be released. These experiments demonstrated the high spatial resolution of fluorescent aptasensors, highlighting their potential for studying electrophysiological processes in space and time (on the scale of seconds but still not milliseconds).

Despite advances in NTs sensing, the currently established in vitro models can not entirely simulate the integrated environment of the CNS. Other major drawbacks of the in vitro models are the significant inter- and intra-laboratory variability due to differing culture conditions and cell passages and the lack of interindividual differences [161]. Thus, the in vitro prediction profile offers only limited information and is suitable merely for the initial test of implantable aptasensor research. More detailed information regarding their potential behavior in CNS must be obtained from ex vivo and in vivo models.

5.2. Ex/in vivo applications

Ex vivo models are generally based on tissue extracted from organisms and transferred into a controlled external environment that resembles the natural conditions. Ex vivo models are relatively inexpensive and mimic the real physiological conditions more closely than in vitro systems due to the preservation of the tissue integrity, thus providing more relevant information but potentially suffer from decaying cell activity over time [161,168].

In order to study NT release in intact tissues, Zan et al. developed a neural probe for multiplexed neurochemical monitoring via site-selective electrografting of aptamers on G-FETs [44]. The probes feature excellent flexibility and ultralight mass, allowing their implantation into deep brain areas with very litter tissue damage. Two different aptamers, for detecting DA and ST, were immobilized by electrografting onto the two side-by-side G-FET channels. NT-binding then caused conformational changes within the aptamer which altered the doping level of graphene, leading to a measurable source-drain current modulation. For the ex vivo experiments, the neural probes were then implanted into brain tissue from wild-type mice (Fig. 5A). By using electrical and/or pharmacological stimulation, the DA (10 μM, 2 μL) or ST solution (100 nM, 2 μL) was infused into the brain tissue through an injection site. The electrical responses of the sensor changed within a few seconds and slowly returned its original state, reflecting the diffusion of the NT away from the sensor surface. These multiplex ex vivo studies represent an important foundation for monitoring the release of DA and ST in intact tissues, thereby demonstrating the potential to employ aptasensors in vivo.

In vivo means the use of cells in their natural multicellular environment or experiments performed on intact organisms rather than on isolated cells in culture. Animal experiments in intact organisms are necessary to evaluate the complex interplay of different processes within the body and serve as an important testbed for potential clinical applications of biosensors. However, they are also expensive, time consuming, ethically controversial, and a gap between pre-clinical animal models and humans persists

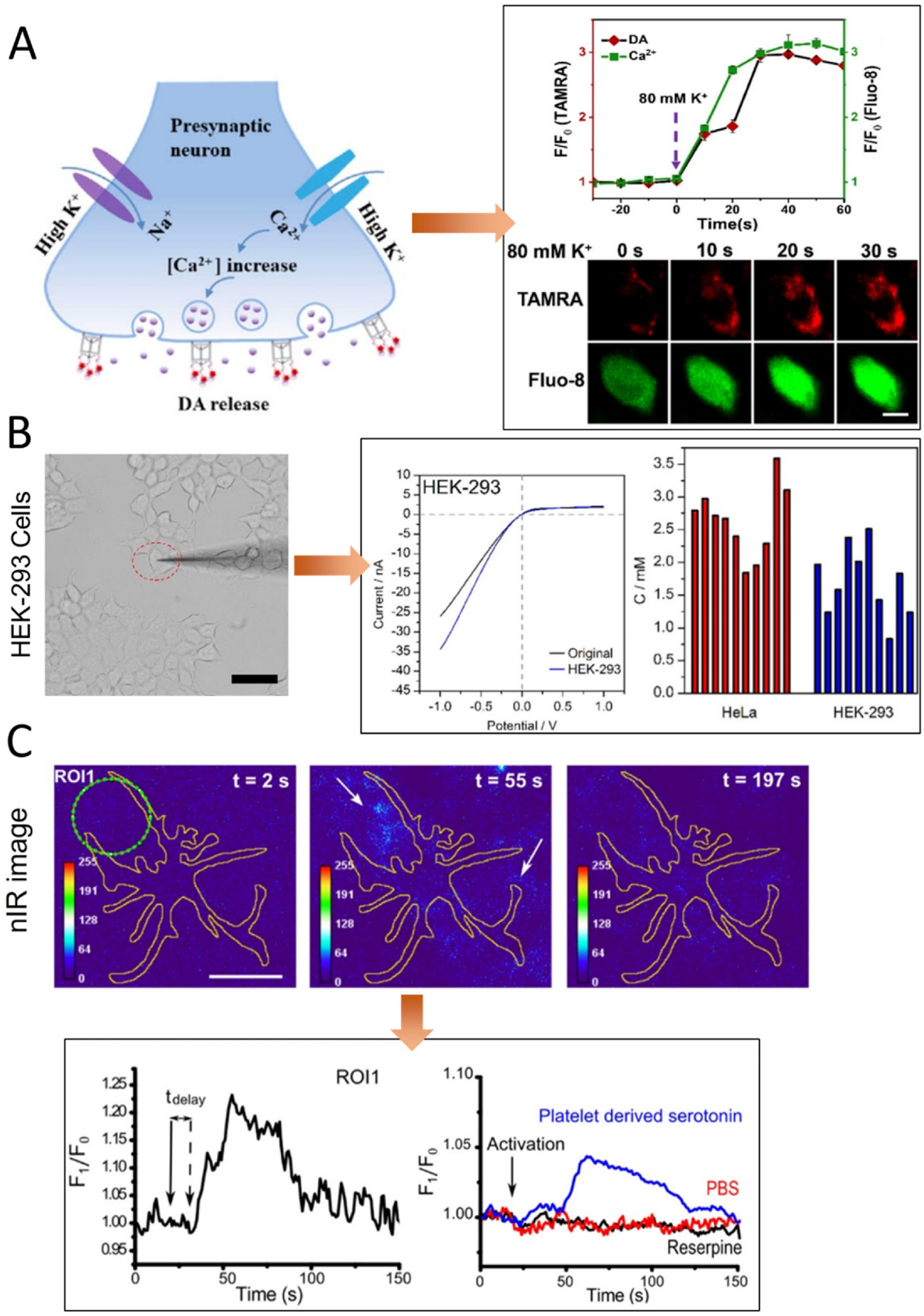


Fig. 4. Monitoring NTs release in vitro by aptasensors. (A) Cell-surface-anchored DNA-nanoprisms utilized as fluorescent aptasensors for imaging of dopamine release from SH-SY5Y cells. Adapted with permission from Ref. [159]. Copyright 2020 American Chemical Society. (B) Nanopipette aptasensors detecting intracellular ATP release in HEK-293 cells. Adapted with permission from Ref. [161]. Copyright 2021 American Chemical Society. (C) Fluorescent nano aptasensors imaging serotonin release from platelets. Adapted with permission from Ref. [163]. Copyright 2019 American Chemical Society.

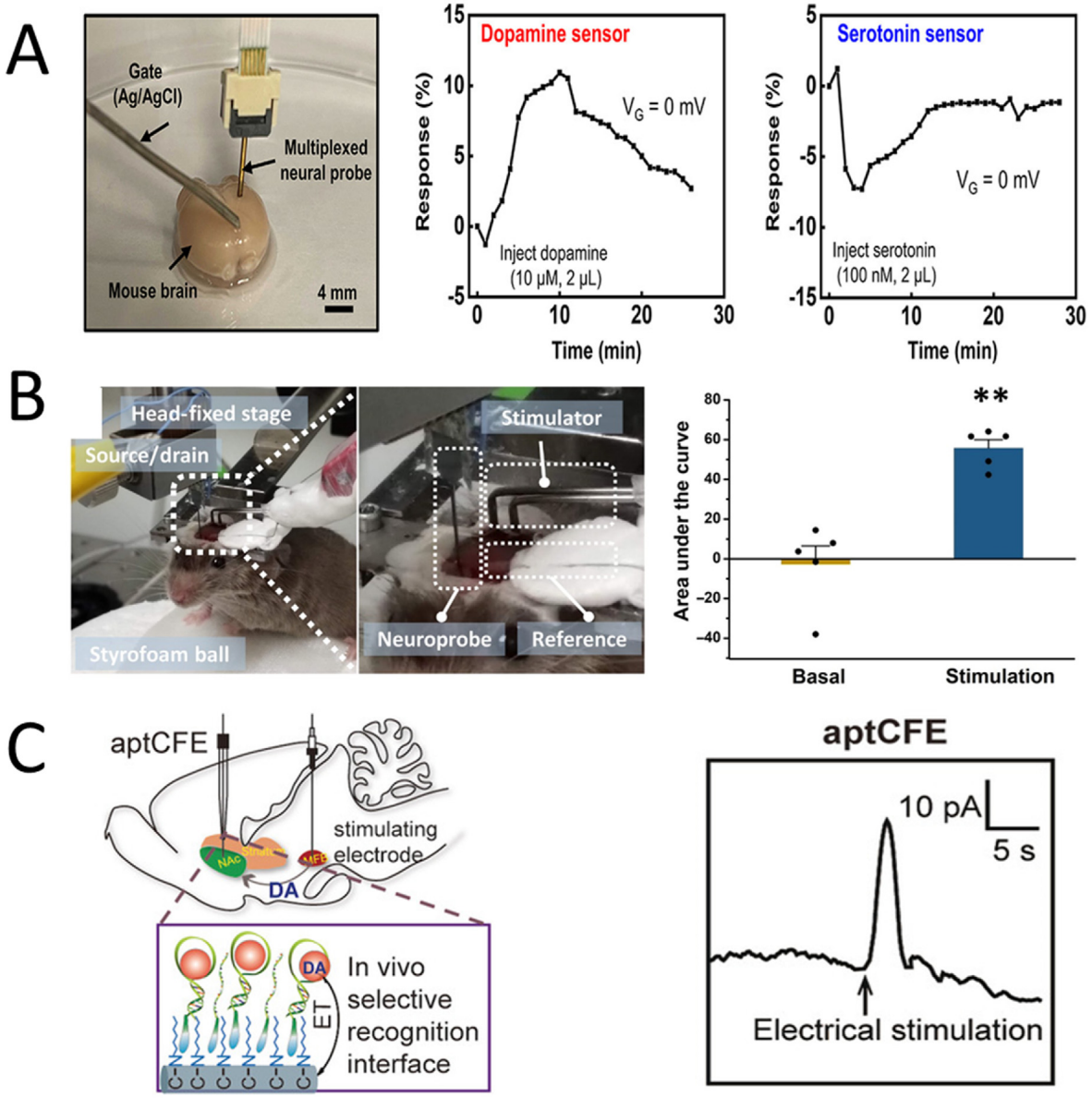


Fig. 5. (A) Ex vivo study in harvested mouse brain tissue. Source-drain current response at $V_G = 0$ mV for DA (middle) and ST (right) detection. Adapted with permission from Ref. [54]. Copyright 2022 American Chemical Society. (B) Photographs of an in vivo experiment, where the neuroprobe, reference electrode, and stimulator were implanted into the brain of a head-fixed mouse, left and middle. Right figure shows calibrated responses for in vivo determination of basal and post-electrical stimulation levels from the same mouse, respectively ($V_{GS} = 300$ mV). Adapted with permission from Ref. [166]. Copyright 2021 AAAS. (C) Left: scheme of aptCFE for in vivo DA sensing. Right: current responses of aptCFE in the rat NAc upon electrical stimulation of rat MFB (3 s at 60 Hz, 300 mA, 2 ms per phase). Potential: +0.30 V vs. Ag/AgCl. Adapted with permission from Ref. [167]. Copyright 2020 Wiley-VCH GmbH.

[161]. In vivo studies are therefore only performed after careful characterization of biosensor behavior in situ and in vitro.

To realize the monitoring of NTs in vivo, Zhao et al. established a mouse model that lacked the expression of a specific serotonin reuptake transporter, resulting in higher basal and stimulated serotonin levels [169]. They then developed aptamer-FET neuroprobes based on ultrathin In_2O_3 film with high on/off ratios for ST sensing and fM detection limits in ex vivo experiments. For in vivo measurements, the neuroprobes were implanted into the striatum of awake mice and a stimulating electrode was located just above the cell bodies of serotonergic neurons in the brain stem (Fig. 5B). Electrical stimulation of serotonergic neurons triggered ST release from synapses in the striatum which was captured by ST-specific aptamers, causing a measurable charge redistribution within the FET channel. Similarly, aptamer-graphene FETs have been used for real-time DA-monitoring in vivo [117]. While implanted into in the striatum of anesthetized mice, the sensor showed minimal interferences and responded rapidly to the release of DA after pharmacological stimulation, suggesting the suitability of the sensor for neuroscience studies.

In another work, carbon fiber microelectrodes (CFEs) were modified with aptamers using cholesterol anchoring groups and the assistance of a hexylamine monolayer through noncovalent lipid-alkyl chains reactions [170]. To characterize the capability of aptamer-assembled CFEs, the sensor was then used to record the DA release in the nucleus accumbens of the rat brain (Fig. 5C). Upon

Table 3
Comparison of different strategies of aptasensors for NTs detection.

Target	Strategy	Detection method	LOD	Range	Reaction time	Application	Ref.
DA	Apt/cysteamine/gold	CA	62 nM	0.1−1 μM	1 s	Serum	[73]
DA	Apt/HCS/MB	DPV	67 nM	0.2−700 μM	–	In vitro	[164]
DA	GCSC-GO/apt	DPV	0.75 nM	1−1000 nM	60 min	Serum	[53]
DA	AuNPs/Nafion/apt	ECL	0.32 nM	1−50 nM	10 min	Serum	[41]
DA	SiNW	FET	0.01 nM	0.01−10 nM	–	In vitro	[104]
DA	iOECT,	FET	0.5 fM	5 fM-1 nM	10 min	In vitro	[42]
Glu	Apt/gold/Fc	ACV	1.3 fM	0.01 pM-1 nM	10 min	aCSF	[35]
ST	Nanopipette/apt	Voltammetry	–	0−25 nM	10 min	In vitro	[166]
ST	Apt/AuE	ACV	0.017 fM	1 pM-10 nM	30 min	Serum	[53]
ST	Ultra In_2O_3	FET	–	10 fM-100 μM	1 min	In vivo	[169]
HIS	MIP/AuNPs/cCNTs	EIS	0.11 nM	0.35−35 nM	15 min	Plasma	[91]
HIS	Streptavidin/apt/gold	EIS	4.83 mM	1 μM −5 mM	30 min	–	[55]
ATP	AgNPs-GO/apt	DPV	5 nM	10−850 nM	120 min	Serum	[86]
ATP	MNP/Apt/AuNPs	DPV	5.2 pM	0.01 nM-10 μM	12 min	Serum	[79]
ATP	DNA scaffold/split apt	SWV	41 nM	0.1−200 μM	20 min	Urine	[83]
ATP	rGO-AuNCs/apt/MB	DPV	0.1 nM	0.1 nM-1 mM	2 min	In vivo	[85]
ATP	COF/apt	EIS	9.9 fM	20 fM-10 nM	120 min	Serum/urine	[89]
ATP	Graphene foam	FET	0.5 pM	0.5 pM-50 μM	5 min	Serum	[54]
DA	AuNPs	Colorimetric	0.36 μM	0.54−5.4 μM	20 min	–	[122]
DA	Exonuclease III	FL	80 pM	0.1−10 nM	60 min	Ex vivo	[140]
DA	MoS_2 QDs/nanosheets	FL	45 pM	0.1−1000 nM	30 min	serum	[151]
DA	PFP/FAM-GO	FL	1 nM	0−0.1 μM	3 min	Serum	[51]
HIS	AuNPs	Colorimetric	8 nM	19−70 nM	–	–	[125]
EP	AuNPs	Colorimetric	0.9 nM	0.02−2 μM	10 min		[127]
Adenosine	FAM–Fe_3O_4/PDA	FL	89 nM	0−800 μM	45 min	Serum/urine	[139]
Adenosine	CDs/CdTe QDs/GO	FL	2.4 nM	0−320 nM	120 min	Urine	[152]

electrical stimulation of the medial forebrain bundle region, a current burst occurred which was ascribed to the DA release, reaching its maximal value within few seconds. These examples demonstrate that NT release can be monitored by aptasensors even in vivo with cell scale lateral resolution and a temporal resolution of a few seconds. However, it still lags behind the recording capabilities of neuronal probes for electrophysiological signals.

6. Conclusion and future perspectives

The analysis of spatio-temporal variations of NT concentrations provides insight into communication within neuronal networks and improves our understanding of physiological and pathological processes of neuron-related diseases. Despite intensive research, there is yet no complete sensor that can detect NT levels with cellular resolution in the millisecond range with high specificity and long-term durability in chronic implantations. In this review, we have summarized the recent studies on aptamer sensors that have been performed to advance NT recording technology. Aptamer receptors possess inherent strengths for implementation in NT probes, such as high affinity and stability, and have been widely utilized in various electrical and electrochemical sensors which feature fM detection limits (Table 3). Furthermore, electrical/electrochemical NT probes can be deeply implanted into the brain tissue to provide simultaneous multiplexed signals. Among optical sensors, colorimetric tests are easy to perform at low expenses, but come at the cost of providing only qualitative test results or relatively high detection limits. In contrast, fluorescence-based optical sensors provide high sensitivity, as well as high temporal and local resolution. However, recording from deep tissue layers remains challenging. The promising detection characteristics of electrical aptasensors have been demonstrated in several in vitro, ex vivo and in vivo studies, however additional studies are required for chronic in vivo monitoring of NTs release dynamics.

To further advance the applications of aptamers in the analysis of NTs, there are several challenges that need to be addressed in future studies. Firstly, new aptamers toward various NTs still need to be selected. To date, only a small number of NTs aptamers have been identified and used for target recognition, while other NTs that hold essential roles in various brain functions, such as ACh and GABA, still remain unaddressed. Furthermore, some existing aptamers face cross-selectivity issues to structurally related NTs with a comparable binding affinity, yielding non-conclusive outcomes during in vivo investigations [171]. Secondly, biofouling due to nonspecific adsorption of extra cellular matrix components as well as the immunogenicity of the probes due to the mechanical mismatch between soft tissue and rigid electrodes cause sensor degradation, which must be carefully evaluated during in vivo tests.

NT release is a rapid and highly-localized process that is followed by immediate cellular reuptake. Consequently, free NTs only remain in the extracellular space on the order of milliseconds. So far, sub-second monitoring of NT dynamics in vivo have not been demonstrated for aptasensors, posing the question of how to achieve such fast target-aptamer binding kinetics. Current SELEX technology usually attempts to yield low K_d values, however for recording of transient NT signals, a balance of fast association and dissociation processes is required. The fundamentals for this balance need to be already established in the selection process. Another issue is the oligonucleotide stability under in vivo conditions, since the degradation of aptamers by nucleases can cause the loss of the detection capability of the sensor. To improve the stability of aptamers, modifications on nucleobases including the sugar and phosphate groups can extend the aptamer's lifetime in tissue. Finally, complex brain activities such as sensory perception or behavior are the results of the interplay of various types of neurons and NTs, while most sensor concepts detect only a single target in a single location. The accurate and simultaneous detection of multiple NTs and neural electrophysiological signals, for instance by high-density, flexible-microsensor arrays, could therefore provide detailed and high-dimensional information on spatio-temporal activity patterns. Such devices would be a major step forward for neuroscientific studies to gain a deeper understanding of the relation of neurochemical signals and neural information processing. Moreover, they could enable new diagnostic applications, such as chronic Glu sensors for the early and reliable detection of tissue hyperexcitability that precedes epileptic seizures, and

therefore improve the reliability and efficacy of the diagnosis and treatment of neurodegenerative diseases.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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Corrigendum to "Aptamer based biosensor platforms for neurotransmitters analysis" [Trac. Trends Anal. Chem. 162 (2023) 117021]

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The authors regret that in section 3.4.3, the reference is missing for the sentence: 'Graphene-based FETs (G-FET) allowed ultrasensitive dopamine detection with the low LOD down to 10^{-18} M in both PBS buffer and brain homogenate sample.' The missing reference is 'M. Abrantes, D. Rodrigues, T. Domingues, S.S. Nemala, P. Monteiro, J. Borme, P. Alpuim, L. Jacinto, Ultrasensitive dopamine detection with graphene aptasensor multitransistor arrays J. Nanobiotechnol. 20 (2022) 495.'

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