J Biosci (2020)45:44
DOI: 10.1007/s12038-020-0017-x

Review

Quantitative detection of neurotransmitter using aptamer: From diagnosis to therapeutics

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MS received 15 September 2019; accepted 28 January 2020

Neurotransmitters, the small molecule chemical messenger responsible for nervous system regulation and can control joy, fear, depression, insomnia, craving for carbohydrates, drugs, and alcohols. Variation in neurotransmitter levels is a characteristic manifestation of several neurological diseases. Accurate diagnosis of these diseases caused due to an imbalance in neurotransmitter level followed by impaired transmission of signals between neurons and other body parts remains a great challenge for the clinicians. Recent evidences reveal, artificial single-stranded nucleotides called 'aptamer' are widely used as biosensors, antibody substitutes, diagnostic agents, and for targeted therapy. These aptamers are superior candidate both for early detection and diagnosis of many neurological disorders caused due to suboptimal level of neurotransmitters. Presently, non-invasive neurotransmitter detection by aptamer has been found to be an easy, fast, and cost-effective choice. In addition, increased specificity, stability, affinity, and reproducibility of aptamers, high throughput screening of aptamer-based sensing platforms have been observed. Moreover, clinical applicability of aptamer has also proved to be efficacious, though still at a preliminary stage. Herein, we review salient features of aptamer-based sensing technology used for neurotransmitter detection particularly their chemical modifications, selection, assay development, immobilization, therapeutic efficiency, and stability for early diagnosis of diseases caused due to neurotransmitter imbalance.

Keywords. Aptamer; neurological diseases; neurotransmitter; sensing

1. Introduction

Neurotransmitters are essential small molecules transmitting neurological signals throughout the body. Upon active electrical stimulation, these molecules are generally released in the synaptic cleft *via* exocytosis from one neuron to another neuron or gland or muscle cells and activate the next phase of signaling processes (Kandel *et al*. 2012). The neurotransmitters are mostly related to physiological functions like sleep, behavior, movement, cognition, dream, and many others. Stress, unhealthy lifestyle, neurotoxins, abuse of caffeine, drugs, and alcohol can cause alteration or disruption in the signaling pathway due to an imbalance in neurotransmitter levels that may lead to the manifestation of many neurological diseases. Till date, more than 100 neurotransmitters have been discovered and subsequently grouped according to their chemical structures such as amino acids, monoamines, and gasotransmitters. Among them, monoamine neurotransmitters dopamine (DA), serotonin (5-HT), epinephrine (ER), and norepinephrine (NER) deserves special mention due to their crucial role in development of several mental illnesses like Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), prion disease, multiple sclerosis (MS), schizophrenia, migraine, depression, and so on. These debilitating neurological diseases are affecting people on a large scale globally. The recent worldwide AD report states that some 35 million people are affected by this fatal disease and this number is increasing drastically. It is expected that by 2050, the digit will turn up to 115.4

Published online: 18 February 2020

million; whereas the PD report highlights some 7–10 million people are affected by this disease throughout the world (Prince *et al*. 2015; Parkinson's News Today *https://parkinsonsnewstoday.com/parkinsons-disease-statistics/*). The inability to definitely diagnose neurological disorders means that it is also difficult to effectively treat them: for example, various natural resources, natural amino acids as well as peptide-based compounds act as remediable sources but most of them are largely ineffective due to various drawbacks (Mukhopadhyay *et al*. 2017; Chaudhury and Mukhopadhyay 2018; Chaudhury *et al*. 2019). There is thus, enormous need for neurotransmitter detection as an essential criterion to identify the neurotransmitter imbalance of brain disorders so that mental illnesses can be better diagnosed and treated.

Multiple traditional methods have been adopted for accurate and authentic quantification of neurotransmitters, both *in vivo* and *in vitro* condition. Most of these quantification methods are based on electrochemical, fluorescence, colorimetric, spectroscopic, chromatographic, rapid high-performance liquid chromatography-mass spectrometry, chemiluminescence, enzyme-linked immunosorbent assay, surface plasmonic resonance (SPR), etc. (Fabregat *et al*. 2014; Seckin and Volkan 2005; Kong *et al*. 2011; Moghadam *et al*. 2011; Paivi *et al*. 2009; Carrera *et al*. 2007; Nalewajko *et al*. 2007; Nichkova *et al*. 2013; Choi *et al*. 2013). These methods have provided scope for precise neurotransmitter quantification, but few disadvantages prevented their application in the rapid diagnostic scheme: they show reduced spatial resolution and long operation time. Hence, tools for real-time monitoring of neurotransmitter levels in body fluids, which are simple, easy, fast, require low sample volume, and minimal treatment could be of high value in the medical field, especially in the market of preventive medicine.

Currently, various sensor platforms for neurotransmitter detection have been designed, including carbon electrodes and molecular imprinted polymers (Wang *et al*. 2014; Peeters *et al*. 2012). Aptamer-based platforms are an ideal choice for neurotransmitter detection. They offer many advantages over other sensing elements, including chemical modification, platform immobilization, enhanced temperature stability, and regeneration capability, which are fruitful outcomes for selective binding of molecules in a sensor platform altering by a single functional group. The combination of various other materials and aptamers led to the development of a number of successful sensors for neurotransmitter detection, which have revolutionized the branch of clinical diagnostics (Balamurugan *et al*. 2008; Zhou *et al*. 2014). In this concise review, were ported the recent status, application, and overall advanced sensing mechanism adapted by aptamer-based sensor towards *in vivo* neurotransmitter detection. Some cutting edge and high tech strategies for the establishment of an aptamer-based sensor as an efficient diagnostic tool have also been proposed.

2. Physiological relevance of neurotransmitter

Neurotransmitter plays a vital role in the regulation of neuronal transmembrane potential. They are released at the synaptic junction and allows passing of impulse from one nerve fibre to another and also to different structures throughout the nervous system (Patestas and Gartner 2009). Neurotransmitters can be grouped according to their chemical structures, mode of action, and physiological functions. DA, 5-HT, and Acetylcholine (Ach) are essential neurotransmitters and the main choice of interest due to their vital functions in the brain. DA is the major excitatory neurotransmitter which is associated with many normal physiological functions of brain. Abnormal concentration of DA is linked with several diseases' pathology and is the main reason for PD pathogenesis. 5-HT has major role in mood, calmness, maturity, decision making, learning, memory, cognition, anxiety, and depression. It was also evidenced to play an important role in the maintenance of chemical balance and proper functioning of the central nervous system along with its association to various physiological processes such as appetite maintenance, bowel movement, and digestion (Martinowich and Lu 2008; Barnes and Sharp 1999; Tierney 2001). Moreover, the imbalance in 5-HT concentration has a direct connection with suicidal tendency along with various neurological as well as psychological conditions (Jacobs and Azmitia 1992; Bernhardt 1997). Ach is another important neurotransmitter which controls the autonomous nervous system (Brown 2006). The imbalance and dysregulation of Ach are responsible for several memory-related complications like AD. Therefore, the major role of following neurotransmitters' and real-time monitoring of the concentration is a vital phenomenon for diagnosis of the problem caused by their variations (figure 1).

3. Challenges before conventional detection method of neurotransmitter

Neurotransmitter measurement can be done by numerous techniques like fluorimetric, chromatographic, spectroscopic, spectrophotometric, and so on.

Though these methods are capable of target analysis due to a few shortcomings, they are replaced by innovative and advanced technological schemes. Recently, the aptamer-based approach has grabbed the attention because of its practical applications, including high affinity, avidity, low cost, fast response, reduced variability, and time making it an appropriate choice for measuring the dynamicity of neurotransmitters.

The main challenges due to *in vivo* monitoring of neurotransmitters are related to quick response time against rapid release and clearance of neurotransmitter from extracellular space, minimum concentration, and large signal to noise ratio, device fouling, and gradual degradation with time (Si and Song 2018). To address this situation *in vitro* assessment of neurotransmitters in a patient's body fluids should be explored along with its eventual clinical application. Despite the success in carbon and metal-based nanoparticles for enhanced detection of neurotransmitters and increased use of electrochemical and optical-based sensors, their biomedical applications is still a challenge because their association with immune system remains undiscovered till date (Wang *et al*. 2016; Holzinger *et al*. 2014; Mehrotra 2016). This immunogenic incompatibility of electrochemical and optical-based sensor systems led to the exploration of other advanced sensing strategies such as aptamer-based sensing mechanism due to its compatible attitude towards the immune system.

4. Aptamer: the artificial oligonucleotide with immense possibilities

Aptamers are artificial, short, single-stranded, and target recognition nucleic acid molecules that can specifically bind to a large number of targets such as peptides, metal ions, organic dyes, amino acids, antibodies, proteins, whole cells, viruses, and bacteria with great affinity (Colas *et al*. 1996; Lupold *et al*. 2002; Mannironi *et al*. 2000; Geiger *et al*. 1996; Williams *et al*. 1997; Mallikaratchy *et al*. 2006; Chen *et al*. 2008; Tang *et al*. 2007; Lorger *et al*. 2003; Kanwar *et al*. 2010; Bruno and Kiel 1999). Their binding efficiency can be compared to that of antibody in the range of nano- to picomole and has the ability to recognize target in an epitope-specific manner (Meyer *et al*. 2011; Michaud *et al*. 2003). The chemical synthesis approach produces aptamer on a large scale and enables proper access to introduce modification in a requisite manner.

The combinatorial process for *in vitro* selection and evolution of aptamer is known as Systematic Evolution of Ligands by Exponential Enrichment (SELEX) (figure 2). It mainly consists of three steps: selection, partition, and amplification. Briefly, in SELEX, a random oligonucleotide library is intended to bind to a definite target molecule, and the molecule with higher affinity binds tightly whereas the unbound molecules get washed away. Then the bound molecules are amplified by polymerase chain reaction (PCR) for the enrichment of the population. Major modifications of the conventional SELEX process aims for better selection platform, stringency, reduce the selection time, and to increase the hit rates (McKeague and DeRosa 2012; Stoltenburg et al. 2007; Davis and Szostak 2002). The oligonucleotide library was modified by the inclusion of fixed regions or by enhancing the structural diversity through initial pool design (McKeague and DeRosa 2012). By multiplex SELEX technology, simultaneous aptamer selection for up to 30 targets can be done very quickly and cost-effectively whereas, multiplex SELEX coupled with next-generation sequencing known as VENN multiplex SELEX selects closely related but molecularly distinct targeted aptamers with distinct binding properties (*https://www.basepairbio.com/multiplex-selex-venn-multiplex-selex/*). Some more advanced technologies like cell-SELEX, *in vivo* SELEX, microfluidics SELEX, and tissue SELEX are also in practice (Kim *et al*. 2009; Coulter *et al*. 1997; Huang *et al*. 2010; Reid *et al*. 2009; Morris *et al*. 1998). Separation of aptamers can be executed by various affinity-based methods including the exploitation of protein tags (e.g. His, or Strep-tag) which is utilized for initial purification of the target, and modification of target proteins by biotin coupled with modified streptavidin magnetic beads or sepharose (Darmostuk *et al*. 2015; Mayer and Hover 2009; Turcheniuk *et al*. 2013; Griffin *et al*. 1993).

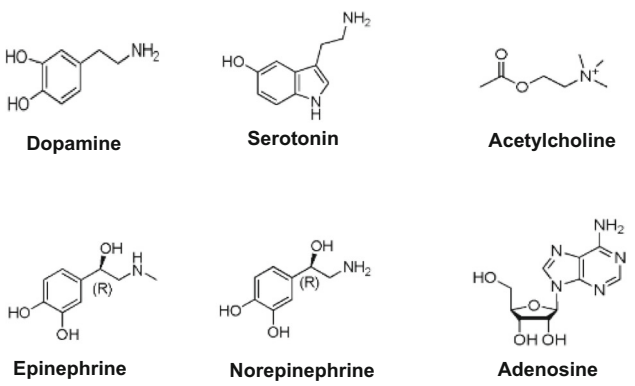

Figure 1. Chemical structure of neurotransmitters.

5. Chemical modifications of aptamer for improved binding of neurotransmitter

Aptamers are susceptible toan extremely short half-lives, inadequate binding affinity, nuclease degradation, and rapid excretion through renal filtration (Pagratis *et al*. 1997; Ortigao *et al*. 1991; Dass *et al*. 2002; Morrissey *et al*. 2005). Therefore, to overcome these drawbacks, the attempts of using post-SELEX chemical modifications of nucleic acid became an interesting strategy. Various chemical modifications include modification of bases, phosphodiester linkage, sugar rings, nucleic acid terminals, 3′ or 5′ end capping with inverted thymine, biotin-streptavidin, cholesterol, and PEGylation (Dass *et al*. 2002; Ng *et al*. 2006; Eid *et al*. 2015). Enhanced binding affinity can be produced by base modification or by substitution of two non-bridged phosphate bound oxygen atoms in nucleic acids by replacement of sulphur (Abeydeera *et al*. 2016; Cho and Juliano 1996). These are the examples of some chemical modification phenomenon adopted by aptamer for sensitive binding towards the target molecule. Small molecules like neurotransmitters are the key biological entity due to their ability to easily diffuse through the cell membranes (Ashour and Wink 2011). These aptamers have a wide range of applications and undergo various chemical modifications for tight binding of neurotransmitters to its respective platforms. An example of chemical modification of aptamer has been evidenced in the RNA DA aptamer (Walsh and DeRosa 2009). The attempt to determine the DA pockets for the proposed RNA aptamer in which recognition was done by the five nucleotides and a complementary region within two loop structures was observed in the DNA homolog. Thereby, mutants of the nucleic acid were prepared by incorporation of base substitution at various key sites. This modification evidenced that these same bases play a key role in improved binding of DA. Another electrochemical RNA aptamer-based sensor was fabricated for DA detection (Farjami *et al*. 2013). In RNA aptamer, the introduction of alkanethiol or protein at one of the distal ends is an inefficient phenomenon. Therefore, due to the abundance need for steric freedom for the aptamer-target interaction, one of the advantageous outcomes may be the introduction of an additional cysteamine positive charge layer on the electrode surface led to the formation of an outstanding DA aptasensor. Recently, another study demonstrated a boronic acid modified aptamer with affinity for ER (Gordon *et al*. 2019). The boronic acid-modified aptamer was efficiently used against small molecule like neurotransmitter ER. To this end, boronic acid was used as modification due to various advantages such as formation of reversible covalent bond with the diol group present in the neurotransmitter ER. This chemical modification of the platform surface leads to the fine-tuned binding of the neurotransmitter to its target

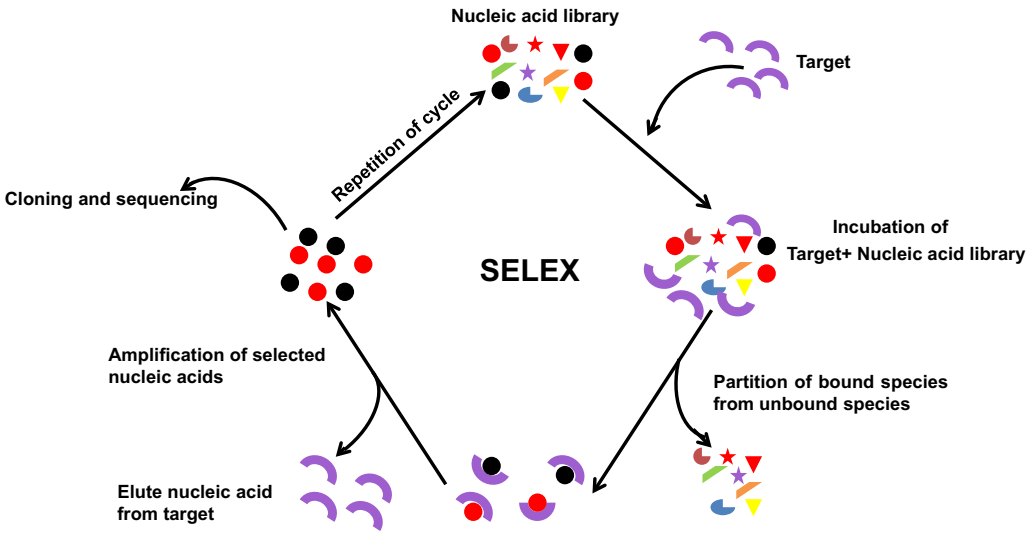

Figure 2. Schematic representation of conventional SELEX technique. The SELEX cycle begins with a nucleic acid library which is to start the cycle. The library is then incubated with the target and then the target is washed for removal and discard of unbound species, before the bound species are cluted out and amplified by polymerase chain reaction (PCR) for subsequent rounds of enrichment. The amplified sequences go for next round of SELEX. Multiple cycles are to performed before sequencing and final aptamer characterization.

molecule. Therefore, all the above findings support that chemical modification is a versatile strategy and can be adapted as per requirement.

6. Selection and immobilization of aptamer for neurotransmitter

In the last few years, a large number of selection protocols have been established but most of them are not appropriate for small molecules due to their small size. Few selection techniques circumvent the need for target immobilization which has been explored in small molecules and will be discussed here.

Capillary electrophoresis-SELEX (CE-SELEX) has a profound affinity for the target and thus decreases the number of selection cycles required for successful enrichment of the molecule (Nutiu and Li 2005). Capture- SELEX utilizes beads that are modified with oligodeoxynucleotide complementary for a small docking sequence and finally deposited in the random nucleic acid library. Following this, annealing of the entire nucleic acid library to the complementary sequence of the beads, then the beads are incubated with the target. Finally, the sequences binding to the target undergoes structural modifications leading to the detachment from the bead and is selected (Song *et al*. 2011). For target immobilization, most notable matrices used with variable chemistries for the coupling reactions are- magnetic beads and agarose. Magnetic beads generally simplify the selection protocols by using magnet during separation of bound and unbound sequences. Additionally, they can be analyzed by flow cytometry representing the possibility of binding along with determination for coupling of the target to that of the beads (Tolle *et al*. 2015). Not only magnetic beads, agarose are also the widely used matrix for small-molecule aptamer selection and require a membrane-bound column for separation of bound and unbound sequences. It can also be used for many techniques and are able to undergo higher density target immobilization than magnetic beads (Huizenga and Szostak 1995).

Other general strategies of target immobilization for small molecule, e.g. neurotransmitter, demonstrated that a multiplexed matrix for dopamine detection was immobilized by using the standard method. At first, the amino group of DA had been immobilized via primary amine group for formation of an amide bond with the surface-tethered carboxyl group. Following, the bond formation density of this surface-tethered DA was made feasible for aptamer recognition by altering the ratios of hydroxyl-terminated and carboxyl-terminated thiols (Nakatsuka *et al*. 2018). Moreover, other examples of aptamer immobilization showed that an RNA aptamer specific for DA was tethered on the cysteamine-modified gold electrode by an alkanethiol C6 linker (Alvarez-Martos and Ferapontova 2016). This immobilization strategy was successful in distinguishing the current signals of other neurotransmitters from that of DA. Following the above positive outcomes, it can be addressed that selection and immobilization are of great necessity for sensor- based application of aptamer towards neurotransmitter detection.

7. Strategies for neurotransmitter sensing by aptamer-based sensor

Nowadays, many materials have shown the successful result in the detection of various small molecules especially neurotransmitters. The use of reported aptamers for different neurotransmitters (table 1) as a promising sensing material is another widely used practice in the field of biosensor because of its unique selectivity, improved sensitivity, greater biocompatibility, and ease of synthesis along with reduced immunization and contamination. Particularly, a modified electrode with aptamer has grabbed much attention in the field of electrochemical sensor development due to its biocompatibility as well as efficient electrical conductivity. Recently, Chavez *et al*. introduced an aptamer-gold nanoparticle (Apt-AuNPs) conjugated assay for 5-HT detection by adsorbing the aptamer to citrate stabilized AuNPs (Chavez *et al*. 2017). The presence of aptamer and AuNPs increased the stability of the assay against salt aggregation as a consequence of 5-HT binding. Upon binding of an analyte to the aptamer resulted in a target-DNA complex on the surface of AuNPs. This whole mechanism improved the stability of AuNPs and is still under investigation. Hence, the sensitivity of the assay was improved and resulted in a smart colorimetric outcome with a very low sample volume of 10 μL and a short response time of less than 15 min. Another study on the aptamer-gold electrode with spindle-shaped gold nanostructure sensor was performed for DA detection (Taheri *et al*. 2018). Spindle-shaped gold nanostructure was selected due to a specified morphology which increased the surface area of the gold electrode for aptamer immobilization. By introducing the gold nanostructure in the sensor configuration increased the electrocatalytic activity, contact surface, enhanced ability to trap target molecule, successful transfer of electrons, high level of biocompatibility, and non-immunogenic to *in vivo*

studies (Liu *et al*. 2006; Alkire *et al*. 2008; Lorenz and Plieth 2008; Daniel and Astruc 2004). Additionally, based on previous reports it was also observed that gold surface generally creates self-assembled aptamer monolayer and helps in fast, specific detection of DA in the presence of interferences (Sperling *et al*. 2008; Bain et al. 1989; Chidsey 1991; Malem and Mandler 1993; Giz *et al*. 1999; Raj *et al*. 2001). Interestingly, aptamer modified with mesoporous silica on graphite oxide polymer led to the development of a chemiluminescence sensor for significant detection of DA (Sun *et al*. 2018a). This work demonstrated the feasibility and advantages of graphite oxide polymer towards DA detection. The graphite oxide polymer possesses sufficient biocompatibility, rich functional groups, specific surface area, and easy separation characteristics. Based on the above features of graphite oxide the DA aptamer was immobilized on the polymer surface with further modifications led to the accurate detection of DA in urine. These recent findings conclude and summarize that aptamer can act as a potential sensing element for effective detection of small molecules especially, neurotransmitter in the future (figure 3).

8. *In vivo* applicability of aptamer-based sensor in neurotransmitter detection

Numerous strategies have been adapted to interpret the role of the aptamer-based sensor in *in vivo* neurotransmitter detection. According to a recent study, an electrochemical aptamer-based sensor showed simultaneous detection of DA in presence of ER, NER, catechol, uric acid (UA), and ascorbic acid (AA) (Taheri *et al*. 2018). The sensor was less prone towards interferences and this proved its efficacy towards real sample analysis. In addition, 10 human serum samples of two groups (5 treated and 5 controls) were evaluated in the sensing platform. The sensor was able to distinguish between the serum samples of treated and control. More interestingly, one major variation was detected in the result by high-performance liquid chromatography (HPLC) method which showed the No. 5 human serum sample to be normal, but the aptamer-based method could detect that more accurately as a patient sample with the DA level as 32 pg/mL which is higher than normal (30 pg/mL). Moreover, as an example, another colorimetric aptamer-based sensor was fabricated for adenosine detection (Kong *et al*. 2018). The sensor was based on Exonuclease-III (Exo-III) assisted with the cycling of DNA amplification and G-quadruplex-induced with aggregation of AuNPs in the salt solution. The sensor-based assay was successful in distinguishing adenosine from other interfering agents. Moreover, the sensor was evaluated in human urine samples but its activity was hampered due to the long reaction time of 2 h. Therefore, a further analytical study should be conducted for improving the feasibility of the sensor. Another study for a fluorometric aptamer-based sensor with molybdenum disulfide (MoS_2) quantum dots (QDs) and MoS_2 nanosheets was fabricated for accurate detection of DA (Chen *et al*. 2019). The sensor showed a fruitful result in terms of sensitivity and selectivity and also efficiently investigated the possible quenching mechanism present in the study. Additionally, the applicability of the adopted strategy was examined in human serum and hydrochloride injection samples showing the recovery rate in the range of 96%–104.8%. This phenomenon proved the accuracy and its practical applicability. The sensor was also applied for fluorescence imaging of live cells indicating its potential application in the physiological system. So, recent literature gave positive feedback on the detection of neurotransmitter by the aptamer-based sensor. But a few discrepancies in some aspects of sensing technology require some additional study with a large number real sample analysis for a valid and justified conclusion on this issue.

Table 1. List of aptamers for different neurotransmitters

Sl. nos.	Aptamer source	Neurotransmitter	References
1.	DNA homologue RNA aptamer	Dopamine (DA)	Walsh and DeRosa (2009)
2.	RNA aptamer	Dopamine (DA)	Mannironi *et al.* (1997)
3.	DNA aptamer	Dopamine (DA)	Zheng et al. (2011)
4.	DNA aptamer	Serotonin (5-HT)	Dinarvand *et al.* (2019)
5.	DNA aptamer	Acetylcholine (ACh)	Bruno *et al.* (2008)
6.	DNA aptamer	Nor-epinephrine (NER)	Kammer *et al.* (2014)

9. Assay development for detection of neurotransmitter

Besides, sensing nowadays several other techniques such as aptamer-based assays are used for the detection of neurotransmitters. Recently, a study reported that a

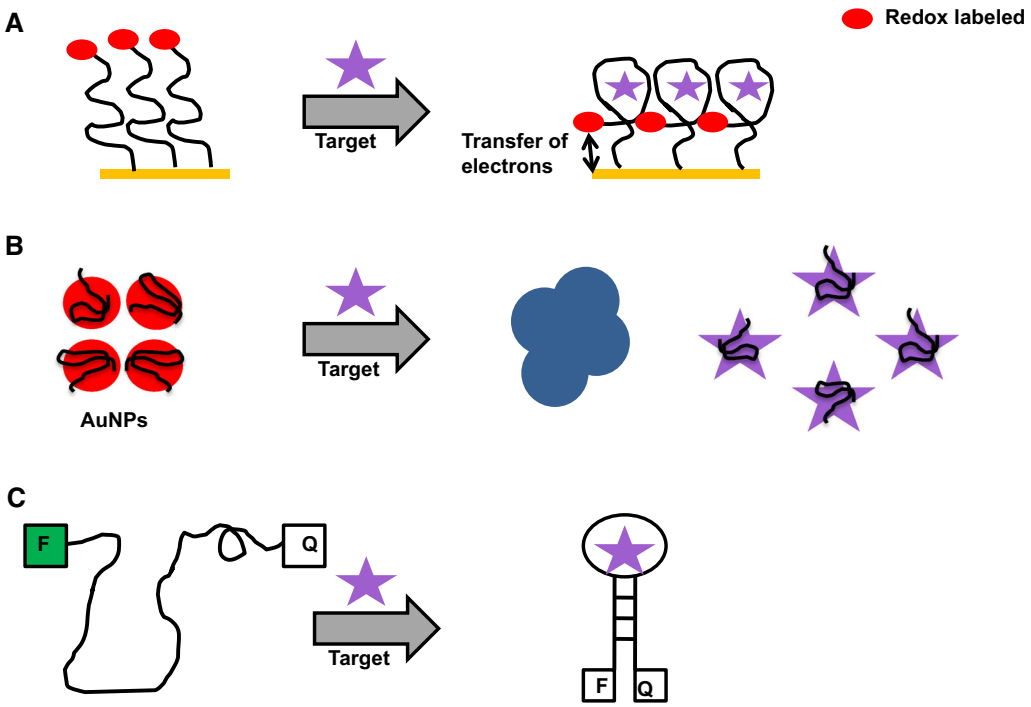

Figure 3. Examples of three different types of aptasensor most widely used for small molecule targets such as neurotransmitters. AuNPs-gold nanoparticles. **F**-fluorophore. **Q**-quencher. **(A)** Electrochemical detection of small molecules by aptasensor. The aptamer is immobilized on the sensing platform and redox labeled. Therefore, the conformational change of aptamer upon target binding brings the redox labeled probe close to the sensing platform to allow the transfer of electrons. **(B)** The aptamer is non-specifically absorbed on the AuNPs surface and thereby prevents their aggregation. However, upon binding to the target molecule AuNPs aggregate leading to a colour change from red to blue. **(C)** The aptamer is labeled with a suitable quencher and fluorophore. Upon binding with the target molecule the aptamer undergoes conformational changes bringing the fluorophore and quencher close together, thereby quenching the fluorescence.

plasmonic assay for 5-HT was designed with Apt-AuNPs conjugate and responded to 5-HT in relevant biological levels (Chavez *et al*. 2017). More excitingly, the assay illustrated a simple mixing of the samples with Apt-AuNPs conjugate with an incubation time of 5mins. Finally, with the addition of NaCl, the total assay was completed within 15 minutes. Therefore, the added stability of the analyte-bound conjugates allowed the use of the 5-HT assay in biofluids. Moreover, other related studies demonstrated that a competitive enzyme-linked aptamer assay (ELAA) was performedwith 57-mer RNA DA aptamer along with its 57-mer homolog DNA aptamer (Kim and Paeng 2014). The assay was performed in serum samples and was diluted with 3kDa dialysis membrane for removal of serum proteins. Additionally, the assay showed a massive improvement of 10^4 times with the DNA homolog of aptamer than that of original RNA aptamer obtained by conventional selection process SELEX. The assay was highly sensitive with good recoveries from the serum media. Therefore, this method is an excellent tool to monitor DA in serum. Similarly, another screening method by ELAA was validated for DA detection (Park and Paeng 2011). The assay was done by using a 67-mer RNA aptamer, which was immobilized by site-directed immobilization with biotin at the 3′ end of aptamer and at neutravidin plate. Moreover, the assay was performed by 0.01 g mL^{-1} of aptamer and 1.205×10^{-7} M DA-HRP (horseradish peroxidase) conjugate using the optimized protocol. Therefore, the optimized ELAA method showed 1% recovery from the serum media and proved the utility of aptamer assay in DA detection. But few literatures about assay based neurotransmitter detection by aptamer have been evidenced. Furthermore, detailed studies with other assay-based methods such as western blot, dot blot, pull-down assay, etc. should be conducted for a concrete conclusion.

10. Aptamer for neurotransmitter in diagnostics and targeted therapy

As mentioned earlier neurotransmitters are the principle molecule for regulation of the nervous system. Upon disease onset or progression, the change in the

level of their concentration can be considered as a diagnostic tool. Until now very few aptamers have been selected for neurotransmitters like DA, 5-HT, ER, Ach, etc., and is taken into consideration (Zheng *et al*. 2011; Chavez *et al*. 2017; Kammer *et al*. 2014; Bruno *et al*. 2008). Among them, abnormalities in the concentration of DA, 5-HT, and ER are detectable in biological samples and deserves special mention because of their implementation in sensor (Zheng *et al*. 2011; Chavez *et al*. 2017; Kammer *et al*. 2014). Indeed, RNA aptamer specific for DA was selected with K_d = 1.6 μM and was successful in the development of a potent DA biosensor (Mannironi *et al*. 1997). This nucleic acid aptamer altered the three- dimensional folding favored the aggregation of AuNPs along with a colorimetric change (Zheng et al. 2011). Not only the sensing mechanism various assays have also been developed as a diagnostic tool. The assay developed by Chavez *et al*. can be used as a potent tool for detection of 5-HT (Chavez *et al*. 2017). Therefore, this easily identifiable colorimetric output could be coupled to various portable devices like tablets, smartphones, etc. for on-the-spot analysis. Similarly, an RNA aptamer selective and sensitive for electrochemical detection of DA was designed and the sequence of this anti-DA RNA aptamer was converted into its DNA counterpart. This DNA counterpart was examined in an *in vivo* study assessing its capability at reversing cognitive deficits caused by the non-competitive *N*-methyl-D-aspartate (NMDA) receptor antagonist, MK-801 in a rat model but the specificity and the binding capacity of the DNA homolog are at stake as it didn't act as a genuine aptamer (Röthlisberger *et al*. 2017). Furthermore, another work demonstrated the delivery of dopamine binding aptamer (DBA)payload into the brain by using transferrin receptor (TfR) (Esposito *et al*. 2018). This TfR is highly expressed on the surface of the endothelial cell and has been reported to mediate transcytosis of therapeutic protein ligands through the blood-brain barrier (BBB). The work was done by using a short DNA aptamer ligand for inducing RMT which was conjugated as a carrier to the PEGylated liposomes to drive DBA-payload across the BBB. In this approach, the aptamers were used both as the payload as well as a transport mediator and were efficient in promoting the delivery of the functional DBA ligands from the peripheral injection site to the brain. Other related studies addressed the use of aptamers for directly targeting the *in vivo* brain functions (Holahan *et al*. 2011). In order to bypass the blood-brain barrier (BBB), dopamine binding DNA aptamers (DBA) has been injected in the nucleus accumbens of the rat's brain thereby, showing its ability to regulate the NMDA-receptor induced cognitive deficits proving the effective binding of the aptamer to dopamine in *in vivo* conditions. Moreover, various new neurotransmitter-binding aptamers along with effective strategies for delivery of aptamers across the blood-brain barrier (BBB) are required to evidence the maximum potential of the aptamers in targeted therapy. Recently, another similar study evidenced that the systemic administration of the modified liposomes led to the proper delivery of the dopamine aptamers into the brain (McConnell *et al*. 2018). In this study, cocaine induced behavioural experiment elevated the neural concentration of dopamine, thereby systemic pre-treatment with that of dopamine aptamer loaded liposomes reduced the cocaine-induced hyperlocomotion. On the other hand, multiple controls such as transferrin-negative liposome control and transferrin positive liposomes which have been loaded with either a non-binding, base-substituted dopamine aptamer or a random oligonucleotide were used in the experiment. But none of these used controls could alter cocaine-induced hyperlocomotion. Therefore, this work is a crucial example of the application for the versatile multi-aptamer payload or targeting system.

11. Conclusion and future perspectives

Here in this review, we address the substantial progress in aptamer-based neurotransmitter sensing, considering different modifications and sensing strategies of the aptamer, biocompatibility with body fluids, and its application in the medical field. However, it is already discussed that aptamer-based sensing has many advantages than other analytical methods. But further progress in the design and sensing strategies of aptamer is of great necessity because until now not a single study has successfully illustrated its applicability in intact biological fluid such as cerebrospinal fluid (CSF). As reported in the literature, a fluorometric aptamer-based sensor was applied for live cell imaging which proved its applicability in a physiological system (Chen *et al*. 2019). But, aptamer-based sensing mechanism towards live cell imaging can be further improved by the development of potent aptamer radiopharmaceuticals keeping in mind about the hazardous effect of radioactive compounds. Additionally, it can also be improved by chemical labeling and PEGylation. To combat these apparent challenges towards application of aptamer-based neurotransmitter sensing in intact biological fluid, the sensors need further enhancement such as advancement in

SELEX technique with new approach like next-generation sequencing and high throughput selection protocol like CE-SELEX, VENN-multiplex SELEX, optimized immobilization, updated chemical modifications as well as sensitive and selective approach for a particular neurotransmitter. Furthermore, the studies in various biological fluids like CSF, plasma, serum, blood, and urine of patients with variation in different neurotransmitters are necessary for medical diagnostics. Along with the sensor techniques, various assays coupled with aptamers such as pull-down assay, western blot, dot blot, lateral flow assay, etc. could also be impoverished as a diagnostic tool for neurotransmitter detection. Such an easy and cheap diagnostic method is very much required for routine analysis of neurotransmitter. Moreover, a current finding stated that small molecule-based neurotransmitter can be selectively and reversibly recognized by DA and L-tryptophan aptamers (Nakatsuka *et al*. 2018). This nucleic acid-based aptamer can efficiently recognize small molecule targets on substrates and are used for side-by-side target comparison along with the identification and characterization of neurotransmitter. Therefore, this advanced technological procedure is still under investigation but showed a future direction for the establishment of multiplexed-substrate based neurotransmitter diagnostic tool. Another current finding by Chavez *et al*. showed the attachment of colorimetric sensing assays to electronic gadget for point-of-care and on spot diagnosis and this same procedure could be adapted for other types of aptamer-based sensor for neurotransmitter detection so that it could be a small, easy, and cheap portable device (Chavez *et al*. 2017). Regardless of all the above findings, the establishment of aptamer-based neurotransmitter sensor as a clinical diagnostic tool will be at stake if the focus is not paid on proper commercialization. High throughput screening of neurotransmitter-based aptamer sensor will be beneficial for early detection of diseases caused due to a suboptimal level of neurotransmitters and their metabolites.

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Corresponding editor: BJ Rao