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Chapter

Aptamers and Possible Effects on Neurodegeneration

Fatma Söylemez and Çağatay Han Türkseven

Abstract

Aptamers are a new class of recognizing agents which are defined as short biomolecules like oligonucleotides and peptides that are used in diagnostics and therapeutics. They can bind to specific targets with extremely high affinity based on their structural conformations. It is believed that in the near future, aptamers could replace monoclonal antibody. The biggest advantage of using aptamers is that the process is in vitro in nature and does not require the use of animals and they also have unique properties, such as thermal stability, low cost, and unlimited applications. Aptamers have been studied as a biomaterial in numerous investigations concerning their use as a diagnostic and therapeutic tool and biosensing probe. DNA aptamers were also used for the diagnosis and treatment of neurodegeneration and neurodegenerative diseases. For example, functional nucleic acid aptamers have been developed to detect Aβ fragments in Alzheimer's brain hippocampus tissue samples. Aptamers are promising materials for diverse areas, not just as alternatives to antibodies but as the core components of medical equipment. Although they are in the preliminary stages of development, results are quite encouraging, and it seems that aptamer research has a very bright future in neuroscience.

Keywords: aptamers, neurodegeneration, diagnosis, biosensors, SELEX

1. Introduction

Aptamers, first introduced by Tuerk and Gold and Ellington and Szostak, are short chains of DNA or RNA oligonucleotides that bind to small molecules, peptides, and macromolecules, such as proteins of various sizes and conformations [1]. Aptamers are oligonucleotides that are possible of targeting specific molecules. The name aptamer is derived from the Latin word *aptus* which means to fit. A very interesting property of aptamers for therapeutic use is the ability of aptamers to bind with high selectivity. They are small double- or single-stranded DNA or RNA molecules. Aptamers have been extensively used in basic research, to ensure food safety and to monitor the environment. Furthermore, aptamers have a promising role in clinical diagnostics and as therapeutic agents [2].

1.1 Properties of aptamers

Aptamers are short single-chained oligonucleotides that fold into a defined 3D structure with which they bind specifically and with high affinity to defined target molecules (**Figure 1**) [3]. Aptamers usually consist of 15–50 nucleotides and have

a molecular weight ranging from 5 to 15 kDa [4]. Multiple aptamers have been generated so far, successfully binding to a wide variety of different objects such as small molecules, proteins, and cells. Similar to the antibody-antigen interaction, the recognition between aptamers and their target is very specific.

Recently aptamers are capable of binding different targets such as large protein complexes, simple inorganic molecules, and total cells [5]. Thus, aptamers can be regarded as nucleotide analogues of antibodies [6]. However, the production of aptamers is easier and less expensive than antibodies.

Their binding properties are similar to those found for antibodies, being in the nanomolar to the picomolar range [7], and aptamers have been identified to distinguish between members of a protein family, as they recognize target structures in an epitope-specific manner [8]. Compared with antibodies, nucleic acid aptamers have many advantages in their suitability for clinical application and industrialization, including almost no immunogenicity, efficient penetration, less batch variation, easy modification, cost-effectiveness, and short production times [9] (**Table 1**).
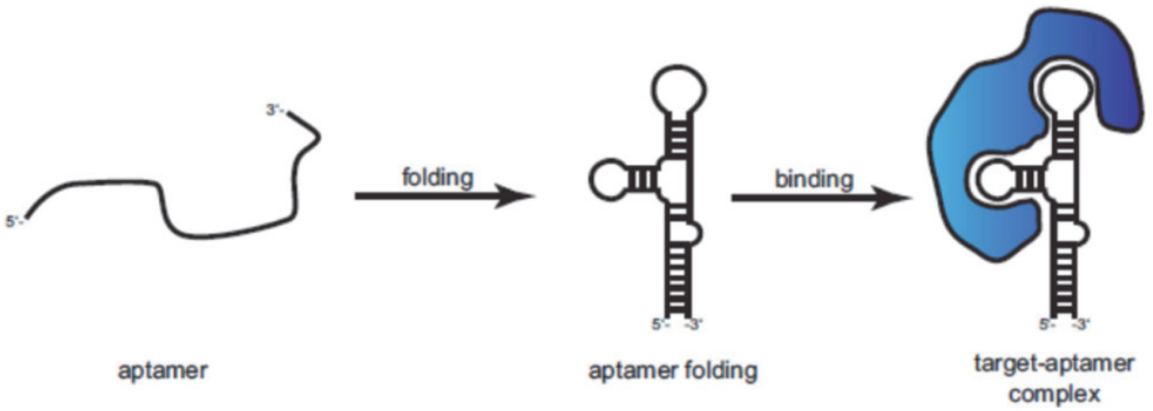

Figure 1.
Schematic representation of binding of an aptamer to a target protein. After binding, the aptamer interacts with a target molecule such as protein to fold into a 3D structure, which forms a stable target aptamer complex [3].

APTAMER	ANTIBODIES
Aptamers are oligonucleotide and protein.	Antibodies are protein in nature.
Uniform activity regardless of batch	Varies from batch to batch
Wide variety of chemical modifications to molecule for diverse functions.	Immune system determines target site of protein.
No evidence of immunogenicity	Significant immunogenicity
They are more stable at high temperature and they can be regenerated easily after denaturation	Temperature sensitive
Entire selection is a chemical process carried out in vitro and can therefore target any protein	Selection requires a biological system, therefore difficult to raise antibodies to toxins (not tolerated by animal) or non-immmunogenic target.
Aptamers are single stranted DNA or RNA oligonucleotide or peptides.	Antibodies are monoclonal or polyclonal.

Table 1.
Comparison between aptamer and antibody.

1.2 Types of aptamers

Nucleic acid aptamers are short single-stranded DNA or RNA molecules and can be selected from complex libraries by a technique called "systematic evolution of ligands by exponential enrichment" (SELEX). These aptamers are capable of binding to the target molecule with high affinity and specificity. Nucleic acid aptamers are functionally similar but have some differences in their stability and accessibility (**Table 2**). DNA aptamers are less reactive and relatively stable because of the C—H bonds at the 21st position of the deoxyribose sugar of DNA nucleotides. This chemical difference gives DNA aptamers an inherent advantage in stability over RNA aptamers [10].

RNA aptamers are defined as RNA oligonucleotides that bind to a specific target with high affinity and specificity, similar to how an antibody binds to an antigen [11]. RNA aptamers are less stable than DNA aptamers due to the presence of a reactive hydroxyl group (—OH) in the 21st position of the ribose sugar in the RNA nucleotides. This —OH group is especially deprotonated, particularly in alkali solutions. The resulting anionic 21-O can be nucleophilically attached to the phosphorus atom of the phosphodiester bond, leading to hydrolysis of RNA molecules. It was found that the nuclease resistance of RNA aptamers increased when the 21-hydroxyl group was removed from RNA sugars [10, 12]. Because of the C—H bonds of the DNA nucleotides at position 21 of the deoxyribose sugar, DNA aptamers are less reactive and relatively stable. Due to this chemical difference, DNA aptamers are more stable than RNA aptamers.

Another type of aptamer developed around 1996 was peptide aptamers. The concept, originally introduced by Roger Brent, proposed a short amino acid sequence embedded ("double constrained") within the context of a small and very stable protein backbone ("scaffold") [13, 14]. Peptide aptamers are conjugated protein molecules with specific binding affinity to target proteins formed under intracellular conditions. The typical structure of peptide aptamers is a short peptide region inserted within a scaffold protein. The short peptide region is responsible for binding with the target protein. The scaffold protein helps to increase binding affinity and specificity by a restriction on the conformation of the binding peptide [15]. Thus, peptide aptamer applications range from in vitro detection of various proteins in a complex mixture to in vivo modulation. In addition, peptide aptamers

RNA APTAMER	DNA APTAMER	PEPTİDE APTAMER
From complex secondary and tertiary structure	From complex secondary and tertiary structure	Structure constrains by scaffoled
From diverse 3D structure	Less diverse 3D structure than RNA aptamer	3D structure constraints by scaffold
Bind target with the entire sequence	Bind target with the entire sequence	Bind target variable region only
Biosenseor, diagnostic, therapeutics applications	Biosenseor, diagnostic, therapeutics applications	Biosenseor, diagnostic, therapeutics applications

Table 2.
Comparison of RNA, DNA, and peptide aptamers.

have been recognized as therapeutic molecules due to their anticancer and antivirus activities.

1.3 Aptamer production: selection and identification of aptamers

Aptamers are a new class of recognizing agents that came into light in 1990 [16]. Tuerk and Gold developed a method known as systematic evolution of ligands by exponential enrichment or popularly called as SELEX method for selection of aptamers against target [17]. The method is in vitro in nature and does not require the use of animals. Aptamers are chemically synthesized and selected for their high affinity and specificity for a certain target through the SELEX process (**Figure 2**).

The process starts with synthesizing a random DNA oligonucleotide library (**Figure 2**). This library consists of a diverse pool of ssDNA fragments (10^{15}). When selecting RNA aptamers, the library needs to be converted into an RNA library. Subsequently, the target is introduced in the pool, non-binding fragments are removed by several washing steps, and the remaining fragments are amplified by PCR or RT-PCR. A new pool of oligonucleotides is created using the selected fragments and another round is performed. Usually 8–15 rounds are performed in order to obtain a high-affinity aptamer.
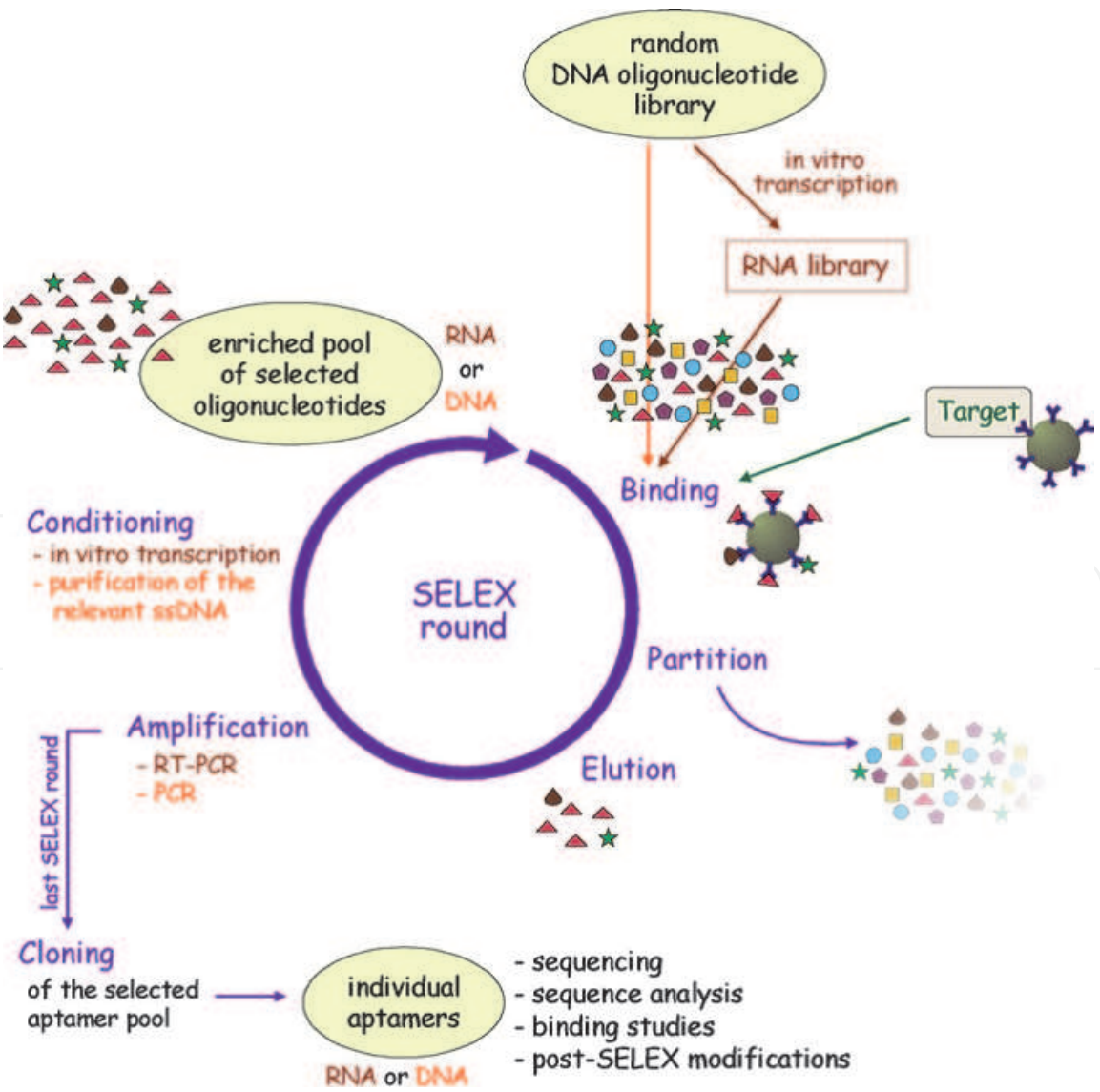

Figure 2.
Schematic illustration of an in vitro selection cycle.

Since the early 1990s, systematic evolution of ligands by exponential enrichment and similar methods have been reported to efficiently select RNA and DNA aptamers [10]. Thereafter, nucleic acid aptamers have been extensively researched and applied. The identification of aptamers is achieved by an in vitro selection process, also termed SELEX. In this method, a synthetic nucleic acid library that contains up to 1015 different sequences and structures is incubated with the desired target molecule, unbound sequences are removed, and target-linked sequences are recovered and amplified using PCR or RT-PCR [3, 18]. This cyclic process is repeated several times (5–16) until the nucleic acid population has been substantially enriched for target-specific sequences. Nucleic acid libraries offer the largest collection of compounds available so far for screening and selection purposes. The monoclonal aptamer sequences are accessible by cloning and sequencing these libraries. But the latest generation sequencing approaches allow in-depth evaluation of the selection process [19, 20]. A wide range of selection methods and strategies have been described since the first reports in 1990. The basis of these variations is based on the separation method used or chemical modifications added to the nucleic acid libraries.

2. The application of aptamers as molecular tools in neurosciences

Aptamers have a number of diagnostic and therapeutic applications, such as biosensors and target inhibitors. Due to simple preparation, easy modification, and stability, aptamers have been used in the diverse areas within molecular biology, biotechnology, and biomedicine [2]. In general, aptamers are used in diagnostics, pathogen recognition, cancer recognition, stem cell recognition, monitoring environmental contamination, biosensors, and therapeutics. Aptamers are being used in versatile applications. However, their use as a molecular research tool in neuroscience is limited. There are very few studies on the production of aptamers targeting neuroscience-related target proteins such as ion channels or application for neuronal cell behavior by inhibiting specific proteins.

Neurodegenerative diseases are defined as hereditary and sporadic conditions which are characterized by progressive nervous system dysfunction. These disorders are often associated with atrophy of the affected central or peripheral structures of the nervous system. Alzheimer's disease (AD) is the most common cause of dementia and is characterized by progressive loss of memory and other cognitive functions. It is considered a major epidemic worldwide, where currently more than 35 million people live with this disease. By 2050 it is estimated this figure will reach 115 million [21]. AD is characterized by two major abnormalities; abnormal extracellular amyloid β-protein (Aβ) disposition and intracellular neurofibrillary tangle (NFT) formation, both leading to neuronal degeneration. The generation of Aβ is triggered by B-site amyloid precursor protein cleaving enzyme 1 (BACE1). Thus, BACE1 is a prospective target for interfering with Aβ production and the treatment of AD [22]. A DNA aptamer selected by Liang et al. has been shown to bind to BACE1 with high affinity and good specificity, exhibiting a distinct inhibitory effect on BACE1 activity in an AD cell model [23].

Autoimmunity and autoantibodies play a role in the pathogenesis of many diseases. Recently, a research team in Germany demonstrated the presence of functional autoantibodies against G-protein bound receptors in the serum of Alzheimer's and vascular dementia patients [24]. And the aptamer BC007, which is selective for the GPCR-AAB FAB fragment as a "broad-spectrum neutralizer," has been developed based on binding and epitope mapping studies [24]. The fact that BC007

aptamer was successful in neutralization in an in vitro study revealed the possibility of being a potential therapeutic tool for dementia patients.

Parkinson's disease (PD), the second most common neurodegenerative disease after AD, affects over 7 million people worldwide. The pathology is characterized by loss of dopaminergic neurons, leading to decreased production of dopamine, a neurotransmitter that regulates movement and cognition. In the previous immunotherapy, targeting the α-syn in PD models with monoclonal antibodies has established α-syn protein as an effective target for neuronal cell death. The pathogenesis of Parkinson's disease involves the accumulation of α-synuclein protein in neurons. Anti-α-synuclein antibody treatment has achieved some success. However, this antibody-based immunotherapy is limited by the inherent immunogenicity of antibodies and the inability of antibodies to reach intracellular targets.

To date, there is no recognized cure for Parkinson's disease. Aptamer-based immunotherapy is an attractive alternative. Researchers in China have reported preliminary results for a selective aptamer to α-synuclein. The purified human α-syn was used as the target for in vitro selection of aptamers using systematic evolution by exponential enrichment in Zheng et al.'s study [25]. This resulted in the identification of two 58-base DNA aptamers with a high binding affinity and good specificity to the α-syn. Both aptamers could effectively reduce α-syn aggregation in vitro and in cells and target the α-syn to intracellular degradation through the lysosomal pathway. In vitro, the aptamer inhibited the accumulation of α-synuclein and its association with the mitochondria [26]. It also induced intracellular α-synuclein degradation, and the neuron maintained viability despite overexpression of α-synuclein. In vivo, the a-synuclein aptamer can potentially inhibit the accumulation of a-synuclein in the cell while at the same time promoting the destruction of existing aggregates and reducing the toxic effects of α-synuclein aggregates on neurons. These effects consequently rescued the mitochondrial dysfunction and cellular defects caused by α-syn overexpression [26].

Numerous examples in the literature have shown the efficacy of aptamers against several important targets. Aptamers have been developed to bind to α-synuclein monomers or its oligomer. These aptamers recognized β-sheet structure, the moiety though which they can bind not only to α-synuclein oligomer but also Aβ oligomer. This indicates that these aptamers could also potentially be deployed as drugs treat Parkinson's and Alzheimer's diseases (**Figure 3**).

Multiple sclerosis (MS) is a chronic inflammatory and demyelinating disorder of the nervous system. Currently, there is no cure for MS, and the available medications only shorten the duration of attacks to slow the progression of the disease. Remyelination is a naturally occurring process in the body to restore damaged myelin sheaths after an MS attack. Rozenblum et al. identified a 40-nucleotide DNA aptamer which exhibits affinity towards murine myelin and binds to multiple myelin components in vitro [27]. In mice, it has been shown that aptamer is introduced into CNS tissue by intraperitoneal (IP) injection and dispersed in the tissue [28]. In addition, the aptamer allowed remyelination of CNS lesions in mice infected with Theiler virus [29]. Therefore, this aptamer can be used for recovery following an episode of MS and may alleviate the symptoms of MS.

The toll-like receptor 4 (TLR4) plays a crucial role in the adaptive immune response. It plays a role in many pathologies including stroke, myocardial infarction, atherosclerosis, sepsis, multiple sclerosis, and chronic pain. A research group from Spain investigated TLR4 blocking DNA aptamers, especially for the treatment of stroke. In an in vivo study involving mice and rats exposed to permanent middle cerebral artery occlusion (pMCAO), the TLR4-blocking aptamer reduced ischemic brain injury 4–6 h after injury [30]. The presence of aptamer in the blood and brain has been demonstrated by imaging studies [30]. Although tissue plasminogen
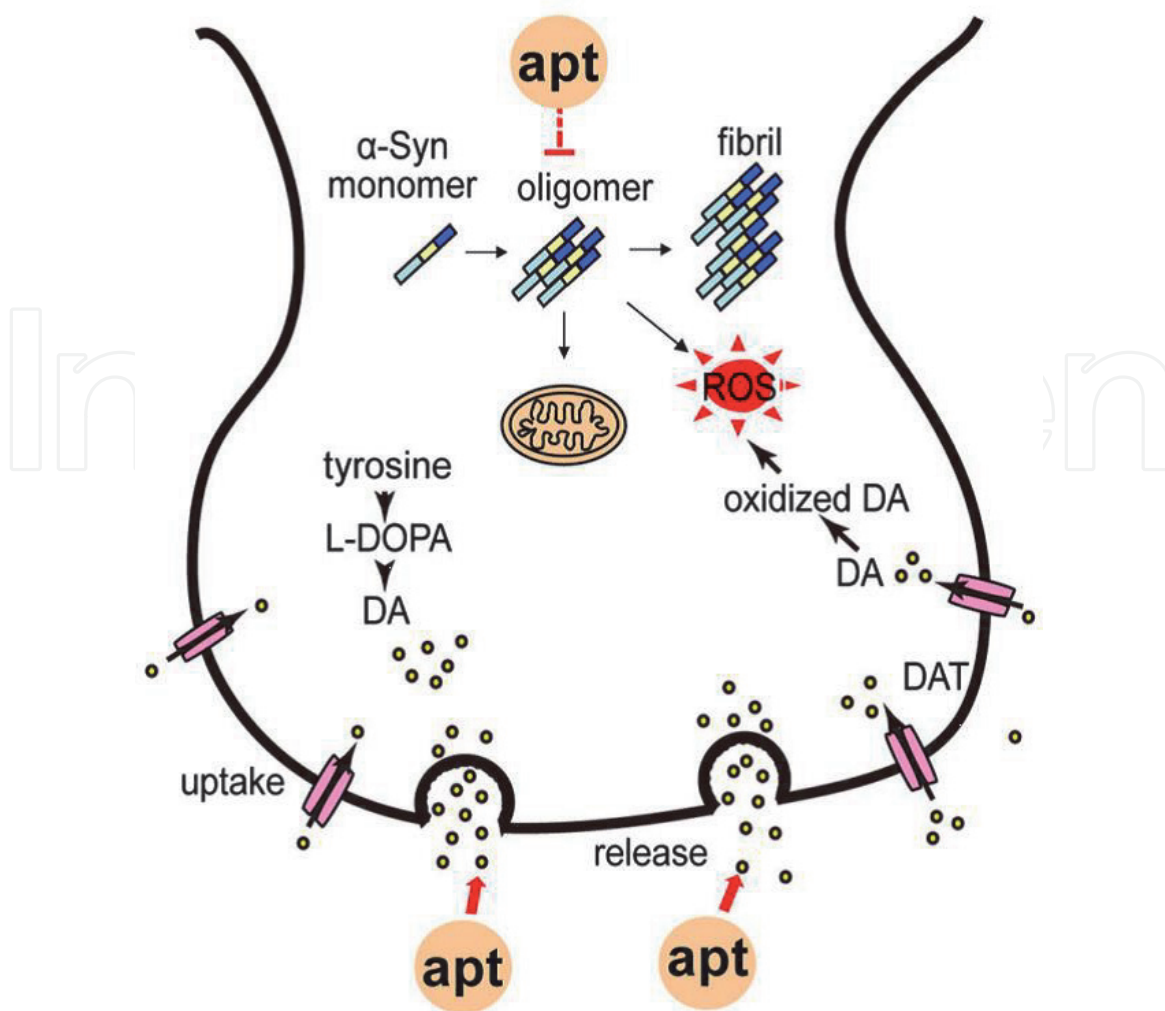
Figure 3.
Aptamers targeting α-Syn oligomers for diagnosing and preventing onset of PD and dopamine for diagnosing dopamine concentrations [26].

activator, tPA, is a viable option in only 5% of stroke treatment cases, TLR4 blocking aptamers have been shown to be a promising and nontoxic alternative.

Signal cascades play an important role in various aspects of cellular homeostasis and are also connected to several diseases [3, 31]. AMPA receptors are involved in excitatory synaptic transmission in the CNS and contribute to synaptic plasticity, as it is known in learning and memory processes [32]. They are hetero-oligomeric proteins, constituted of different combinations of four subunits GluR1-R4. The phosphorylation of GluR1 at the amino acid residues Ser831, Ser845, and Ser818 located at the receptor's intracellular domain has been found to have a strong impact on AMPA-mediated neurotransmission. Liu et al. identified an RNA aptamer, termed A2, which modulates the phosphorylation of the serine residue Ser845 of the GluR1, whereas the phosphorylation of the Ser831 and Ser818 has been found to be unaffected [33]. Another work identified an RNA aptamer, named C5, which specifically binds and inhibits the mitogen-activated protein kinase (MAPK) Erk1/2 [34].

Aptamers may be of therapeutic use in treating neurological diseases. One of its biggest advantages is that aptamers are better able to penetrate tissues, cells, and blood-brain barrier (BBB) because they are small. They are essentially non-immunogenic and chemically synthesized. Therefore, they eliminate concerns about biological contamination or long-term reagent formation that is often encountered in antibody treatments. Although new drug therapies are a risk to follow, there is a great potential in terms of increasing survival rates, decreasing healthcare costs, and high quality of life in aptamers.

3. Limitations and opportunities of aptamers

Around 50 million people worldwide have Alzheimer's disease, and more than 10 million people have Parkinson's disease. The most common type of cancer in children younger than 19 years is brain tumors and central nervous system tumors and is the leading cause of cancer-related deaths in children under 14 years of age in the United States. Although antibody drugs have taken major steps in cancer therapies, the passage of these drugs through the blood-brain barrier and proper cleansing of the brain limit the use of antibody drugs for the treatment of neurological diseases.

Aptamers have a number of advantages, such as their high specificity and affinity, their enzymatic or chemical production, and their high reliability and their renewability in simple ways. Furthermore, they have a higher inhibitory potential than monoclonal antibodies and have the possibility of wider chemical modification as they can be synthesized enzymatically or chemically. Aptamers can also remain stable in a wide variety of buffer environments without loss of activity and are more resistant to harsh processes such as physical or chemical denaturation. Since aptamers are developed completely in vitro without the need for cells or animal immune systems, aptamer production offers a wide variety of binding options. Aptamers can be produced against a large number of targets, such as molecules that are toxic to the cell, targets where an immune response does not occur, and compounds that are soluble only in solvents other than water [35]. Given the chemical and physical properties of aptamers, it is unlikely that they will enter the brain via paracellular aqueous pathways or transcellular lipophilic pathways. However, the aptamer may enter the brain by any of the pathways of adsorptive-mediated transcytosis and channels and/or receptors for absorption or liquid-phase pinocytosis. A recent study has shown that a quadruplex DNA aptamer binds to nucleotide by micropinocytosis [36]. Cheng et al. identified an aptamer that can enter brain endothelial cells under physiological conditions, and in vivo, into the brain parenchyma [36]. This development has shed light on the use of aptamers in the investigation of neurological diseases.

As all technologies and classes of substances, the use of aptamers has certain limitations as well as advantages. In vitro selection experiments are the major obstacle to success, which means whether a specific combination of the target protein and the nucleic acid library will produce an aptamer. Essentially, this limitation binds to a limited number of nucleotide groups and building blocks from which a nucleic acid library is made. The four canonical nucleotides, together with ribose (in the case of RNA) or deoxyribose (in the case of DNA) and phosphate backbone, are highly limited chemical diversity in comparison to 21 proteinogenic amino acids that are capable of forming a large number of molecular interactions and properties such as polar, charged, basic, acidic, aromatic, and aliphatic. Therefore, the success rate of in vitro selection experiments for protein targets was found to be 30% [37].

The inability of aptamers to cross cell membranes autonomously (e.g., passive diffusion represents a further limitation in their applicability and is mainly attributed to their macromolecules and polyanionic nature). Nevertheless, several options are available to overcome this restraint (e.g., transfection with liposomes, through plasmid or viral delivery or using nanoparticles). In experiments with isolated cells and cell culture, intracellular distribution of aptamers can be achieved, but this is more complicated in vivo, especially when the targeted tissue is CNS. The barrier (blood-brain barrier) cannot passively pass aptamers and other macromolecules. However, by performing in vivo experiments, aptamers that cross the blood-brain barrier in mice and penetrate into the brain parenchyma could be identified [36].

Aptamer technology has emerged into almost every field in the life sciences since its inauguration 25 years ago. To date, a wide variety of aptamers have been selected and characterized and also allowed to bind to a wide variety of target molecules. Aptamers are suitable for diagnostic and therapeutic applications because of their unique properties. In this chapter, we explained that because of the specific properties of aptamers, it can be a valuable tool for basic research in the field of neuroscience. In the future, neurobiology approaches will reveal a number of interesting target proteins in which specific and potent inhibitors are required. Analysis of target proteins in neurons and neuronal systems requires identification and availability of specific inhibitory compounds. Thus, the identification of new aptamers may be crucial for the timely acquisition of new inhibitors for the treatment of disorders in the neurological system. Together, we believe that aptamers will be a valuable research tool for neurological studies and that data from new studies in the field of aptamer and neuroscience will reveal the full potential of aptamers.

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References

[1] Delac M, Motaln H, Ulrich H, Lah TT. Aptamer for imaging and therapeutic targeting of brain tumor glioblastoma. Cytometry Part A. 2015; **87A**:806-816

[2] Zhang Y, Lai BS, Juhas M. Recent advances in aptamer discovery and applications. Molecules. 2019;**24**:941

[3] Wolter O, Mayer G. Aptamers as valuable molecular tools in neurosciences. The Journal of Neuroscience. 2017;**37**(10):2517-2523

[4] Lakhin AV, Tarantul VZ, Gening LV. Aptamers: Problems, solutions and prospects. Acta Naturae. 2013;**4**(19):5

[5] Veedu RN. Aptamers: Tools for Nanotherapy and Molecular Imaging. Boca Raton, FL, USA: CRC Press; 2017

[6] Ali MH, Elsherbiny ME, Emara M. Updates on aptamer research. International Journal of Molecular Sciences. 2019;**20**:2511

[7] Meyer C, Hahn U, Rentmeister A. Cell-specific aptamers as emerging therapeutics. Journal of Nucleic Acids 2011:904750

[8] Michaud M, Jourdan E, Villet A, Ravel A, et al. ADNA aptamer as a new target-specific chiral selector for HPLC. Journal of the American Chemical Society. 2003;**125**:8672-8679

[9] Sun H, Zu YA. Highlight of recent advances in aptamer technology and its application. Molecules. 2015;**59**:1980

[10] Zhu Q, Liu G, Kai M. DNA aptamers in the diagnosis and treatment of human diseases. Molecules;**20**:20979-20997. DOI: 10.3390/molecules201219739

[11] Germer K, Leonard M, Zhang X. RNA aptamers and their therapeutic and diagnostic applications. International

Journal of Biochemistry and Molecular Biology. 2013;**4**(1):27-40

[12] Adler A, Forster N, Homann M, Goringer HU. Post-SELEX chemical optimization of atrypanosome-specific RNA aptamer. Combinatorial Chemistry & High Throughput Screening. 2008;**11**: 16-23

[13] Reverdatto S, Burz DS, Shekhtman A. Peptide aptamers: Development and applications. Current Topics in Medicinal Chemistry. 2015; **15**(12):1082-1101

[14] Colas P, Cohen B, Jessen T, Grishina I, et al. Genetic selection of peptide aptamers that recognize and inhibit cyclin-dependent kinase 2. Nature. 1996;**380**:548-550

[15] Li J, Tan S, Chen X, Zhang CY, et al. Peptide aptamers with biological and therapeutic applications. Current Medicinal Chemistry. 2011;**18**(27): 4215-4222

[16] Tuerk C, Gold L. Systematic evolution of ligands by exponential enrichment: RNA ligands to bacteriophage T4 DNA polymerase. Science. 1990;**249**:505-510

[17] Parashar A. Aptamer and its role in diagnostics. International Journal of Bioassays. 2016;**5**(2):4799-4809

[18] Stoltenburg R, Reinemann C, Strehlitz B. SELEX: A (r)evolutionary method to generate high-affinity nucleic acid ligands. Biomolecular Engineering. 2007;**24**:381-403

[19] Schutze T, Wilhelm B, Greiner N, Braun H, et al. Probing the SELEX process with next-generation sequencing. PLoS One. 2011;**6**:e29604

[20] Tolle F, Mayer G. Preparation of SELEX samples for next-generation

sequencing. Methods in Molecular Biology. 2016;**1380**:77-84

[21] Robinson SW, Fernandes M, Husi H. Current advances in systems and integrative biology. Computational and Structural Biotechnology Journal. 2014;**11**(18):35-46

[22] Das U, Wang L, Ganguly A, Saikia JM, et al. Visualizing APP and BACE-1 approximation in neurons yields insight into the amyloidogenic pathway. Nature Neuroscience. 2016;**19**(1):55-64

[23] Liang H, Shi Y, Kou Z, Peng Y, et al. Inhibition of BACE1 activity by a DNA aptamer in an Alzheimer's disease cell model. PLoS One. 2015;**10**(10):e0140733

[24] Walukat G et al. Functional autoantibodies in patients with different forms of dementia. PLoS One. 2018;**13**(3):e0192778

[25] Zheng Y, Qu J, Xue F, Zheng Y, et al. Novel DNA aptamers for Parkinson's disease treatment inhibit α-synuclein aggregation and facilitate its degradation. Molecular Therapy. Nucleic Acids. 2018;**1**(11):228-242

[26] Qu J, Yu S, Zheng Y, Zheng Y, et al. Aptamer and its applications in neurodegenerative diseases. Cellular and Molecular Life Sciences. 2017;**74**(4):683-695

[27] Rozenblum GT, Kaufman T, Vitullo AD. Myelin basic protein and a multiple sclerosis-related MBP-peptide bind to oligonucleotides. Molecular Therapy. Nucleic Acids. 2014;**3**(9):e192

[28] Aaldering L, Krishnan S, Fletcher S, Wilton SD, et al. Aptamers as Therapeutic Tools in Neurological Diseases. Aptamers, Tools for Nanotherapy and Molecular Imaging. 1st ed, Chapter 6. 2016. ISBN: 9781315364780

[29] Nastasijevic B, Wright BR, Smestad J, Warrington AE, et al. Remyelination induced by a DNA aptamer in a mouse model of multiple sclerosis. PLoS One. 2012;**7**:e39595

[30] Fernandez G et al. TLR4-binding DNA aptamers show a protective effect against acute stroke in animal models. Molecular Therapy. 2018. DOI: 10.2016/j.ymthe.2018.05.019

[31] Cohen P. The origins of protein phosphorylation. Nature Cell Biology. 2002;**4**:E127-E130

[32] Boudreau AC, Wolf ME. Behavioral sensitization to cocaine is associated with increased AMPA receptor surface expression in the nucleus accumbens. The Journal of Neuroscience. 2005;**25**:9144-9151

[33] Liu Y, Sun QA, Chen Q, Lee TH, et al. Targeting inhibition of GluR1 Ser845 phosphorylation with an RNA aptamer that blocks AMPA receptor trafficking. Journal of Neurochemistry. 2009;**108**:147-157

[34] Lennarz S, Alich TC, Kelly T, Blind M, et al. Selective aptamer-based control of intraneuronal signaling. Angewandte Chemie (International Ed. in English). 2015;**54**:5369-5373

[35] Famulok M, Blind M, Mayer G. Intramers as promising new tools in functional proteomics. Chemistry & Biology. 2001;**8**(10):931-939

[36] Cheng C, Chen YH, Lennox KA, Behlke MA, et al. In vivo SELEX for identification of brain-penetrating aptamers. Molecular Therapy. Nucleic Acids. 2013;**8**(2):e67. DOI: 10.1038/mtna.2012.59

[37] Gold L, Ayers D, Bertino J, Bock C, et al. Aptamer-based multiplexed proteomic technology for biomarker discovery. PLoS One. 2010;**5**(12):e15004