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Oligonucleotide based therapeutic strategies for tackling schizophrenia - A systematic review

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ABSTRACT

Schizophrenia is a serious mental disorder that affects the quality of life of patients, and the cure for the disease is yet a mirage. Drugs are having side effects and not giving satisfying results. Recently, genes have been isolated. The role of oligonucleotide in many diseases, such as multiple sclerosis and cancer, is promising. Since oligonucleotides can modulate gene expression, these molecules can be used as drugs in several conditions which are beyond the usage of conventional drugs. They are also important in the future as therapeutic drugs like rare diseases, which are genetic and in which specific sequences of genes are to be addressed. Since they can bind to Cas9 protein, they can be used for gene editing. Even though the delivery of oligonucleotides faces some limitations, they can be delivered to targets using chemical modification, bioconjugation, and nanotechnology. Overall, they can be used in research, diagnosis, and therapy. Since they are small in size, they have target affinity. They are also cheap to synthesize and more stable than antibodies. This review summarizes the pathophysiology of schizophrenia and its current treatment, recent updates, and insights into the role of oligonucleotide and its regulation of genes. In this article, we also reviewed the genetics of schizophrenia and the possible application of oligonucleotides in the therapeutics of schizophrenia. The introduction of oligonucleotides in the therapy of schizophrenia can be a possible strategy that can be put forward in the future for the management of schizophrenia.

Key words: Oligonucleotide; Aptamer; miRNA; Schizophrenia

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INTRODUCTION

Around 1% of world's population is affected with Schizophrenia which is a debilitating psychiatric disorder. The incidence is about 1.5/10,000 people. The global age-standardized point prevalence of schizophrenia is estimated to be 0.28%.[1] Suicidal tendencies present in this disorder up to 10–15% and one-third of mental hospital beds are occupied with schizophrenia. Risk of patients harming themselves and others, failure to maintain personal relationships, low education, and employment status are few among the problems met by schizophrenic patients. As per the World Health Organization ranking in 1990, schizophrenia is placed as the 10th-leading cause of disability with annual cost of 19 billion US dollars. Public assistance from government social security systems is required for two-thirds of people.[2]

Adverse effects of antipsychotics and poor patient compliance and relapse of disease makes the management more difficult. Poor compliance may be also due to stoppage of drugs by patients themselves when they get good response to treatment.[3] Some doctors considering side effects may stop treatment. Since there is no cure for schizophrenia and discontinuations of medicines by patients are frequent, relapse rates are high.[3] Above

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information shows the high need of treatment for schizophrenia.

PATHOPHYSIOLOGY OF SCHIZOPHRENIA

Although the pathogenesis of the disorder is unknown, it is almost certain that schizophrenia represents a syndrome comprised multiple diseases that present with similar signs and symptoms. Schizophrenia is thought to occur when a region of the brain called the prefrontal cortex becomes abnormally active because interneurons, which connect neuron circuits or neuron groups, become dysfunctional and stop regulating neuronal activity.[4] Pathophysiology of schizophrenia centered on the dopamine hypothesis and dopamine D2 receptor (DRD2) blockade is the key neurobiological mechanism on which antipsychotics were developed.[5] But tolerances towards drugs are hindrances for the treatment. Studies with lower doses of haloperidol in the first episode of the disease compared with multi-episode patients found that clinical responses are lower in multi-episode patients, pointing toward the tolerance of antipsychotic drugs.[6] Even though after a long five decades since the drug discovery, current drug treatments are found to be showing low prognosis, and all drugs have the same mechanism of action by DRD2 blockade.[7] Role of proteins like hippocampal parvalbumin (PV) and their genes are well evident now in pathogenesis of schizophrenia.[8]

The neurons that secrete dopamine have pacemaker properties. Hence, it is spontaneous and also depolarizing is slow in manner. This maintains basal activity. GABAergic neurons alter this pacemaker firing into a slow-irregular firing pattern. In case of response to rapid phasic stimuli tonic spontaneous discharge is important. Meanwhile, if the stimulus is a potential threat or a reward-related event, dopaminergic neurons transit to a phasic burst firing pattern (Figure 1).

In patients with schizophrenia, there is an overdrive in the area of hippocampus. This finally results in increased tonic dopaminergic neuronal firing and hyper responsive state in patients with schizophrenia.

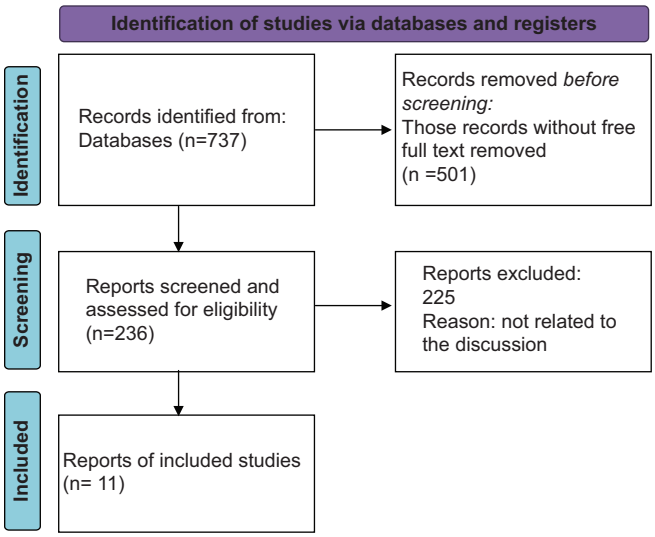
Usually, there are strong inhibitions to pyramidal neurons. This occurs by GABAergic interneurons. PV-labeled GABAergic interneurons in the ventral subiculum are having glutamate as their neruotranmitters acting on NMDA receptors. This PV-pyramidal neuron action is needed for rhythmic activity. If there is a loss of PV interneurons, there can be hyperactivity and dysregulation in rhythm of pyramidal neurons. This can be one of the causes of schizophrenia. In the case of schizophrenia, there is a loss of a large number of PV interneurons, causing the pyramidal neurons to be hyperactive and dysrhythmic (Figure 2).

MATERIALS AND METHODS

Searches of the articles from pubmed.com, Cochrane library, British medical journal.com, frontiersin.org, and online standardized journals have been done. Search keys were oligonucleotide, schizophrenia, aptamers, and miRNA. They were put in Boolean search.

RESULTS

A total of 737 articles were identified after the search. 501 were removed since those records were without free full text. The rest 236 were screened and assessed for eligibility and further 225 articles were removed since they were not relevant to the topic. 11 articles were included for the discussion.



CURRENT TREATMENTS IN SCHIZOPHRENIA

The methods of treatment of schizophrenia are classified as the first (mainly DRD2 antagonists), second (multi-target antagonists with greater antagonism at serotonin 5-HT2A receptor than at DRD2) and third-generation antipsychotics represented, for example, by aripiprazole, brexpiprazole and cariprazine.[9,10] Reelin, a large extracellular glycoprotein which controls neuronal migration and positioning neurons, found to be reduced to half of normal concentration in prefrontal cortex, temporal cortex, hippocampus, caudate nucleus and cerebellum in schizophrenic patients.[11] Current drug treatments target D2/3 receptors in the post synaptic membrane. However, it is well evident now there lays pathogenic abnormality in dopaminergic system in pre-

synaptic membrane affecting the capacity of dopamine synthesis, baseline synaptic dopamine levels and dopamine release. Even molecular imaging studies *in vivo* shows that increased dopamine synaptic availability and increased pre-synaptic dopamine synthesis in the striata of patients with psychosis.[12] Since present drug treatments act on these D2/3 receptors they fail to reverse these pathophysiology mentioned above. So there is an urgent need in development of drugs that modulate pre-synaptic dopamine synthesis and its release.[7]

Since the pathophysiology of schizophrenia can be explained by dysfunction in striatal pre-synaptic excessive dopaminergic discharge; targeted drug delivery like aptamers may be promising in the cure of the disease. Aptamers are synthetic single-stranded DNA or RNA molecules having of 60–100 nucleotides. These are selected by a process known as systematic evolution of ligands by exponential enrichment.[13]

Why aptamers?

Oligonucleotide aptamers are short, synthetic, single-stranded DNA or RNA able to recognize and bind to a multitude of targets ranging from small molecules to cells. Aptamers have emerged as valuable tools for fundamental research, clinical diagnosis, and therapy. Due to their small size, strong target affinity, lack of immunogenicity, and ease of chemical modification, aptamers are an attractive alternative to other molecular recognition elements, such as antibodies. Aptamers are easier to synthesize, offer little to no batch-to-batch variation, and are typically more chemically stable than antibodies. Furthermore, the binding functionality of oligonucleotide aptamers can be regulated through hybridization with their complementary sequences, providing an extra layer of therapeutic control.[14] In the diagnostic field they are used in the detection of antigens and toxins of bacteria and as biomarkers in cancer.[15] They may be used as an alternative to monoclonal antibodies. In 1997, the first RNA aptamer for DA (dopamine) was selected.[16] The authors proposed that DA interacts with a binding domain in the aptamer formed by the association of two stem-loop motifs. The first commercialized aptamer which was approved by FDA is macugen. This is effective in age-related macular degeneration by binding against vesicular endothelial growth factor 165. Aptamer are also developed against proteins such as cancer proteins, blood clotting proteins, antibody E, autoantibodies involved in autoimmune diseases. Promising results are coming in the field of treating viral infections where aptamers have been developed against viruses.[13]

Researchers are now interested in this molecule, and many modifications in them to improve their properties and potency, like affinity and potency, are undergoing.[17] A study was conducted in which DNA aptamer with binding affinity for dopamine is injected into the nucleus accumbens and its effect on the MK-801-induced deficit in extinction responding is determined.[18] Therapeutic role of aptmers in neurological disorders is well documented.[19] Studies shown aptamers may be used as diagnostic and therapeutic tools in Alzheimer's disease by targeting B1-CT, the short cytoplasmic tail of BACE1 protein, and beta A4, an amyloid peptide.[20] Certain aptamers *in vitro* competitively binds to Nogo-66 receptor has impicated in elongation of axons.[21] In cell culture aptamers shown to displace cocaine from the nicotinic type of acetylcholine receptor.[22] Even adenosine phosphates of brain extracts of rats can be detected by an aptamer-gold nanorod assay. Limitations of usage of aptamers include difference in aptamers produced in same laboratory for same target. To overcome this standardization of kits and protocols has to be done.[23]

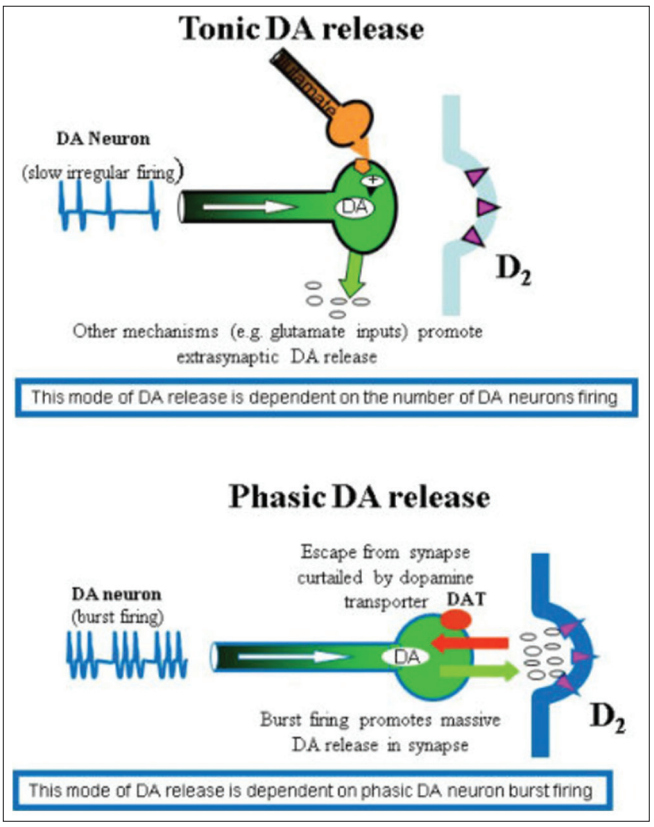


Figure 1: Tonic and phasic release of dopamine neurotransmitter. (Source: Anthony A. Grace. Dysregulation of the dopamine system in the pathophysiology of schizophrenia and depression. Published in final edited form as: Nat Rev Neurosci. 2016 August; 17(8): 524–532. doi:10.1038/nrn.2016.57)

GENETICS OF SCHIZOPHRENIA

No single gene is necessary or sufficient to determine the disease, rather, a combination of risk genes with small effects describe the highly heterogeneous genetic basis of schizophrenia.[24] Recent studies in epigenetics of schizophrenia

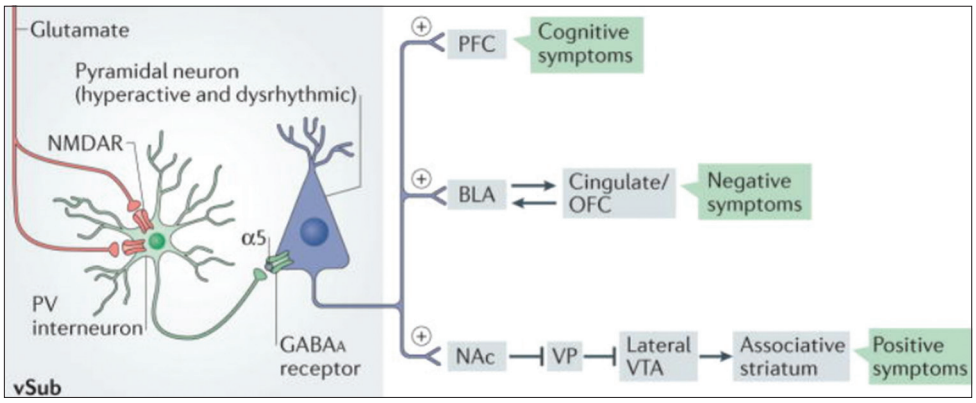


Figure 2: The pathophysiology of symptoms of schizophrenia. Interaction between PV interneuron and pyramidal neuron is shown. (Source: Anthony A. Grace. Dysregulation of the dopamine system in the pathophysiology of schizophrenia and depression. Published in final edited form as: Nat Rev Neurosci. 2016 August; 17(8): 524–532. doi:10.1038/nrn.2016.57)

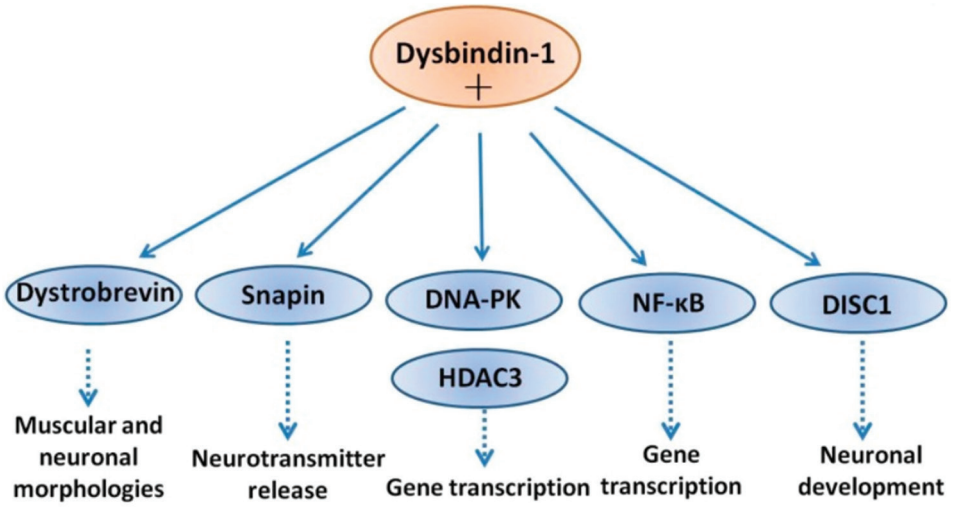


Figure 3: Role of Dysbindin in pos synaptic functions. (Source: Haitao Wang, Jiangping Xu, Philip Lazarovici, Wenhua Zheng. Dysbindin-1 Involvement in the Etiology of Schizophrenia. Int J Mol Sci. 2017 Oct; 18(10): 2044. Published online 2017 Sep 22. doi: 10.3390/ijms18102044)

show pathogenesis is related to methylation of DNA, modification of histones and microRNA.[25] Susceptible genes include neuregulin, dysbindin, catechol-O-methyl transferase (COMT), DISC1, the regulator of G protein signaling 4 (RGS4), GRM3, G and 72.[26] COMT has two types S COMT and MB COMT. MB COMT more important in schizophrenia. Many of these genes are involved in neuronal development dysregulation of which causes pathogenesis of schizophrenia and these genes are also involved in the ongoing process of schizophrenia in adulthood.[26] Dysbindin has role in post-synaptic functions, which include trafficking and tethering of receptors (including NMDA, nicotinic, and GABAA receptors) and signal transduction proteins.[26] Dysbindin reduction in post synapses causes schizophrenia (Figure 3).[27]

Transcription of miRNA gene by RNA-polymerase II produces primary miRNA (pri-miRNA). Complex of Drosha and DGCR8 (Di George syndrome Critical region 8) processes pri-miRNA into pre-miRNA. Pre-miRNA is transported into cytoplasm and again processed by endonuclease Dicer to miRNA ~ 22 nucleotide long. Then, one of these strands is loaded into RNA-induced silencing complex. miRNA can bind to target sequence on untranslated regions (3' – UTR) of mature mRNAs and results in degradation of mRNA or repression of its translation. By this mechanism, miRNA can achieve post-translational silencing (Figure 4).

Single-nucleotide polymorphisms (SNPs) in 3' UTRs of genes may affect miRNA binding to messenger RNA and contribute to the risk of disease.[28] mGluR1 mRNA is increased in prefrontal cortex.[29] Similarly, SNPs in MiR219-1 and MiR137 are associated with schizophrenia.[30] A study in postmortem specimens of schizophrenic patient brains showed protein expression of mGluR5, as well as Norbin and Tamalin in hippocampal CA1 region of schizophrenia subjects.[31] Norbin and Tamalin are modulator of mGluR5 signalling and trafficking. Production of oligonucleotides against these proteins

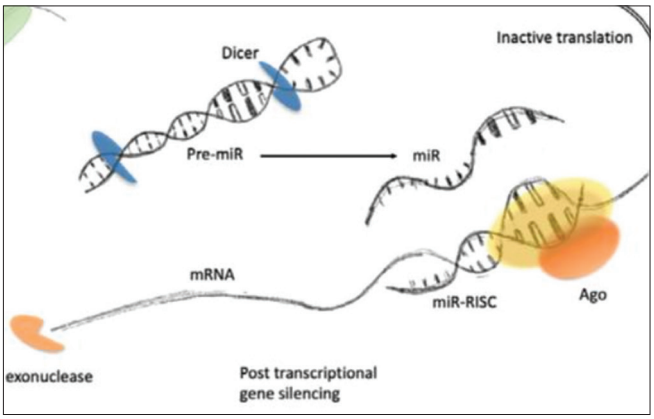


Figure 4: Showing role of miRNA in post transcriptional modification

Table 1: Showing genes involved in schizophrenia

Gene	Function	miRNA
DISC 1	Disrupted in schizophrenia 1: By its interaction with other proteins, it is involved in neural growth and brain development. It was found in many Scottish families. Gene translocation was noted at t(1:11)(q42.1;q14.3)	Let-7f, miR-18b, miR-510, miR-188, miR-502
NRG1	Neuregulin 1: Interacts with the NEU/ERB2 receptor tyrosine kinase to increase its phosphorylation on tyrosine residues and helps in neuronal, epithelial, and glial cells' growth and differentiation	miR-505
RGS4	Regulator of G protein signaling 4: It regulates signaling upstream or at the level of heteromeric G protein.	mir-18b, mir-502

RGS4: Regulator of G protein signaling 4

may be a promising for schizophrenia. Among these genes important ones include COMT, glutamic acid decarboxylase 67, and DRD2. Recent studies using microarray shown identified many other genes, including RGS4, 2',3'-cyclic nucleotide 3'-phosphodiesterase, and oligodendrocyte-lineage transcription factor 2.[32] Genes such as GRM3, G72, DAAO, CHRNA7, PRODH,PPP3CC associated with NMDAR.[21] In certain studies that related to pre-miRNAs' processing mutant alleles were detected which points that these microRNAs may results in development of schizophrenia.[33]

One of the risk factors for schizophrenia is 22q11.2 deletion. Here, 22q11.2-associated microRNA dysregulation during brain development in the postnatal period, up-regulation of a neural tissue maturation inhibitor, *Mirta22/Emc10* occurs and results in a defect in protein synthesis. This has been demonstrated in Mirta22 knockout mice.[34] Defects in miRNAs altering the interactions between miRNAs and their mRNA targets may contribute to schizophrenia.[33] Typically, miRNA 19 is implicated in schizophrenia.[35] However, the biological roles of miRNAs *in vivo* remain largely unknown. In particular, the physiological and pathological roles of individual microRNAs in the brain have not been investigated extensively, although expression profiles of microRNAs have been reported in many given conditions. In a recent study, authors identified miR-19, which is enriched in adult hippocampal neural progenitor cells (NPCs), as a key regulator for adult hippocampal neurogenesis. miR-19 is an intrinsic factor regulating the migration of newborn neurons by modulating the expression level of RAPGEF2. After observing the abnormal expression patterns of miR-19 and RAPGEF2 in NPCs derived from induced pluripotent stem cells of schizophrenic patients, which display aberrant cell migration, authors proposed miR-19 as a molecule associated with schizophrenia. The results illustrate that a single microRNA has the potential to impact the functions of the brain. Identifying miRNA-mediated posttranscriptional gene regulation in the brain will expand our understanding of brain development and functions and the etiologies of several brain disorders.[26]

Aptamers are already found be having a role as diagnostic biomarkers in fields of cancer, Alzheimer's disease.[36-38] Since there is no biomarker for diagnosing schizophrenia it can be hypothesized to introduce an aptamer as a biomarker for diagnosisng schizophrenia. New genes that are related to neuropsychiatric disorders include the retinoic acid-related orphan receptor alpha gene and the microRNA MIR137; former attributed to autism spectrum disease and the later to schizophrenia.[39] It has been shown that regulation of miR-137 is important for neural functioning while its disruption may be related to expression of schizophrenia. By genome-wide association studies show that risk for schizophrenia have an association with SNPs within the MIR137 gene locus.[40]

Due to the deficit of biomarkers for the diagnosis of schizophrenia, psychiatrists follow clinical evaluation for the management of the disease. However, recently, it has been hypothesized that exosomal miRNAs, which are resistant to degradation can be isolated easier and further can be used as a biomarker for the disease.[41] It was found in mice that expression of BACE 1 cleaved the neuregulin 1 gene related to schizophrenia.[42] inhibition of BACE 1 activity by DNA aptamers is already demonstrated.[43]

CONCLUSION

Even though aptamers are started in the therapeutics of some neurological diseases like macular degeneration, its application in neuropsychiatric diseases is yet to be explored. Genetics of schizophrenia is still challenging. Aptamers can be targeted against the proteins produced by the abnormal gene, which itself is the pathogenesis of schizophrenia.

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