

Therapeutic Potential of DNA Methyltransferase (DNMT) Inhibitors in Schizophrenia

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DESCRIPTION

Schizophrenia is a chronic mental disorder in which reality is perceived by patients abnormally. Schizophrenia may include hallucinations, delusions, and extremely irrational thinking and behavior, which can make it difficult to perform daily activities and be disabling. People with schizophrenia are unable to perform in normal social situations as a result of these phenomena, and they usually exhibit fear, withdraw, and disorganized thought and speech. Early adulthood or late adolescence is when schizophrenia initially occurs, and a stressful life event is frequently activated. Although some symptoms are reduced by contemporary treatments, most people with schizophrenia continue to have symptoms throughout their lives.

DNA is maybe the main sub-atomic part of neurons that is not frequently broken down and resynthesized, and represents a special and potent substrate for cellular information storage. DNA exists in the nucleus as a densely compacted protein-DNA complex known as chromatin. Additionally, compressing DNA into the nucleus, chromatin act as a molecular substrate for signal integration and long-term information storage. For example, each cell in a metazoan must remember its phenotype. This information is stored in the cell as stable marks that are directly applied to the chromatin and modify the chromatin's structure, gene expression, and cellular physiology permanently.

The method involved with marking DNA and its related proteins is generally referred to as epigenetics. Epigenetics has different implications depending upon the context that is utilized. The broadest meaning of epigenetics is to processes of transmission and propagation of information through mitosis or meiosis that do not depend on DNA sequencing. In this unique situation, epigenetics envelops DNA, RNA, and protein-based mechanisms.

DNA methyltransferase (DNMT) inhibitors are drugs that are utilized to study the role of DNA methylation in various tissues and model systems, and these compounds represent a

potential therapeutic option for disorders that include altered DNA methylation. Based on their structure and mechanism of action, they are classified either nucleoside analogue inhibitors or non-nucleoside inhibitors. Nucleoside analog inhibitors closely resemble the structure of cytidine. 5-Azacytidine and its deoxy analog, 5-aza-2'-deoxycytidine (decitabine), are analogs of cytidine that have a nitrogen atom instead of carbon in the fifth position of the ring. These drugs have been utilized for a significant long time and are the DNA methyltransferase (DNMT) inhibitors that are food drug administration (FDA)-approved for the treatment of myelodysplastic syndromes.

Zebularine is a newer and more stable cytidine analog that lacks the mark on amino group at carbon 4 (C-4). The three cytidine analogs functions as mechanism-dependent self-destruction inhibitors of DNMTs. To be significant, they should initially be metabolized and phosphorylated to deoxynucleotide triphosphates and then integrated into replicating DNA instead of cytidine. DNMTs recognize the modified bases as natural substrate and are initiate the methylation reaction. DNA demethylation effect of cytidine analogs is a direct consequence of DNA methyltransferase (DNMT) depletion, if cells partition and replicate DNA within the presence of diminished DNA methyltransferase (DNMT) levels, this results in moderate DNA demethylation.

RG108 is a non-nucleoside compound that represents the main rationally designed small-molecule inhibitor of DNA methyltransferase (DNMTs). This drug acts through a direct inhibitory system and was distinguished in an silico screen with a functioning site model of the human DNA methyltransferase (DNMT1) enzyme. RG108 was the first compound that showed DNA methyltransferase (DNMT) inhibitor activity in both a cell-free *in vitro* assay with purified recombinant DNA methyltransferase (DNMT) and human disease cell lines, which confirms it is capable of direct enzyme inhibition. It has almost no harmfulness both *in vitro* and *in vivo*. RG108 has additionally been utilized in neuroscience research and has been displayed to induce DNA demethylation in the brain with subsequent changes in gene expression.

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Received: 01-Nov-2022, Manuscript No. AUO-22-20791; **Editor assigned:** 03-Nov-2022, Pre QC No. AUO-22-20791 (PQ); **Reviewed:** 17-Nov-2022, QC No. AUO-22-20791; **Revised:** 24-Nov-2022, Manuscript No. AUO-22-20791(R); **Published:** 02-Dec-2022, DOI: 10.35248/2165-7890.22.12.351.

Citation: Olive E (2022) Therapeutic Potential of DNA Methyltransferase (DNMT) Inhibitors in Schizophrenia. Autism Open Access. 12:351.

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CONCLUSION

DNA methyltransferase (DNMT1) overexpression with abnormal neurogenesis are starting to emerge. The accessibility of genome wide methylation and transcriptome analysis techniques, it is now possible to examine the effects of DNA methyltransferase(DNMT1) overexpression in brain tests of Schizophrenia patients. This effort requires an understanding

on the rate of DNA methyltransferase(DNMT) overexpression in these samples. Specifically is to analyses the impacts of overexpression of DNA methyltransferase (DNMT1 or DNMT3A) or both during the process of neuronal separation and the nature of the altered transcript levels. Whether the genes impacted are simply connected with Schizophrenia or other neuropsychiatric disorders or neurodevelopmental disorders are a significant inquiry that should be tended.