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Commentary

Dopamine (D1) Receptors and Single Nucleotide Polymorphisms (SNPs) in Patients with Cognitive Impairment of Major Depressive Disorder (MDD)

Commentary

A gene is the basic component of each chromosome in any cell of human body. It controls the heredity in human being and all other species. Adenine, Guanine, Thymidine and Cytosine (A, G, T, and C) are the bases of nucleotides that are ordered in a well-designed and in a proper sequence on the surface of each chromosome in the form of genes together with sugar and phosphate.

Each gene is responsible for encoding of a certain "well-identified" protein to control human body homeostasis in a healthy manner to maintain healthy structure and functions of all body organs.

Unfortunately, mutation of these genes may occur due to various reasons as exposure to pollution, radiation, excessive heat, etc... Mutation is defined as a genetic abnormality in the base sequence of genes forming nuclear DNA in the form of either substitution, deletion, insertion... that results in a "frame shift" in the affected gene, may be shift to the right in the majority of cases if it occurs in the form of abnormal insertion of a base. This type of genetic shift manifests itself as phenotypic changes with abnormal body structure and/or functions that lead, in the majority of cases, to serious disastrous diseases in either CVS, CNS, blood, respiratory or GIT systems etc...

Genetic researches focus on "gene polymorphism" that must be represented, from the physiological point of view, in a balanced manner so as if a disorder occurs in a homozygotic pattern, it would be in balance with the normal gene structure and function in a heterozygotic pattern.

A single nucleotide polymorphism (SNP), by definition, is a sequence variation in DNA in the form of a change in a single nucleotide - A, T, C, or G - in the genome that results in a difference between paired chromosomes in an individual or a

difference between members of a species. According to genetic studies, SNP is a common disorder in DNA sequence that caused by pathological insertion or deletion or substitution of a nucleotide in an abnormal manner in either coding (gene) or non-coding regions of the genome.

Major Depressive Disorder with cognitive impairment is reported, as described by DSM-V, to be a genetically determined biochemical disorder. Dopamine receptors, in both limbic system and striatum, are highly affected in this type of depression. Genetic disorder needs to be investigated in such mood disorder to allow improvement in either prevention/management of both depressed mood with cognitive impairment in such cases.

Dopamine (D), as a central neurotransmitter, plays an important role in cognitive functions. Its receptors are classified to be: D1 receptors that are abundantly expressed in many brain areas including the striatum and limbic system, areas of mood control, D2 receptors are auto-regulatory receptors that inhibit both synthesis and release of dopamine in these brain areas. Also, D₃ & D₄ are reported to be located in striatum. Anatomically, each dopamine neuron is made up of: a cell body, dendrites and nerve terminals.

According to a proposed hypothesis of a positive role of SNP of D1 receptor in psychiatric diseases, genetic researchers [1], reported a type of SNP in the rs 5326-A allele at the promotor region of D1 receptor (DRD1) locus in a cohort study on patients with schizophrenic and Alzheimer's disease compared to healthy persons. This SNP was found to be associated with cognitive impairment in these patients [2].

Revealed a pathological role of gene expression of D1 receptors in cases of neurodegenerative disorders [3]. There is a strong recommendation to study this genetic abnormality using the most advanced genetic tests to identify and hence to provide an evidence for a relationship between SNP of gene of D1 receptors in both striatum and limbic system and the

incidence of cognitive impairment in patients with MDD. The recommendation of these genetic studies (if well-designed as well-controlled randomized clinical trials) would be of high importance in persons with strong family history of MDD.

These kinds of genetic studies will reinforce the clinical importance of personalized medicine in a very precise manner.

A Hope of Positive Therapeutic Benefit of Phosphodiesterase enzyme-4 inhibitors as “rolipram” in Prevention/Therapy of cognitive impairment in MDD [4].

D-1 receptor is a G-protein coupled trans-membrane receptor in both striatum and limbic system. It is linked to Gs protein that activates adenylate cyclase enzyme which increases intracellular cAMP that stimulates intracellular protein kinases with phosphorylation of intracellular proteins that mediate the synthesis and release of dopamine via a probable mechanism of regulation of cAMP/PKA signaling in the striatum [5].

Rolipram, as PDE-4 inhibitor, increases the dopaminergic bioavailability via stimulating the cAMP/PKA signaling pathway [6], that, in turn, stimulate, both synthesis and release of dopamine with a minor reduction in auto-regulatory effect of D2 receptors in striatum.

Recommendation

These central biochemical signaling studies could be considered as scientific signals to plan for further genetic studies on possible role of SNP of gene (s) controlling D1 receptors expression in both striatum and limbic system to

have a full blown picture about the dopamine gene (s) in the selected brain areas biochemical cAMP/PKA signaling pathway cognitive function in MDD.

Meanwhile, the focus on these types of genetic studies will provide both more understanding of pathogenesis of genetic diseases as MDD and will help to apply “personalized therapy” in a more precise way.

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