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New Discernment of Pathophysiological Aspects of Multiple Sclerosis Based On Mono Amino Oxidase (MAO) and Ion Channel Receptor 5HT3RA as Activator of T-Cells

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Abstract

Background: Multiple sclerosis (MS) is a chronic, inflammatory and autoimmune disease of central nervous system. MS affects nearly 2.5 million people in the world and is twice more common in women than men. Autoimmune T-cells target the myelin sheath in central nervous system, causing inflammation, demyelination and eventual destruction of neurons. We examined changing expression of serotonin receptor (5-HT_3R_A) as well as monoamine oxidase (MAO-A) genes in peripheral blood mononuclear cells in MS patients.

Materials and methods: In this study, peripheral blood mononuclear cells (PBMC) were first isolated from 30 healthy controls and 30 volunteers with MS using Ficoll-hypaque. Total RNA was extracted and cDNA was synthesized. In this process, mRNA concentration of 5-HT_3R_A and MAO-A as target genes as well as β-actin as reference gene was compared in PBMC of healthy subjects and patients using Real-time PCR.

Results: After statistical analysis of resulting data, a significant increase was observed in the expression of 5-HT_3R_A receptor gene as well as MAO-A gene in PBMC of patients with multiple sclerosis (P=0.001).

Conclusion: According to previous studies on the association between serotonin level with MS importance of 5-HT_3R_A serotonin receptor in the function of this neurotransmitter as well as T-cell activation along with significant increase in the expression of 5-HT_3R_A receptor in MS patients, it can be concluded that overexpression of this receptor has a significant correlation with MS progress. On the other hand, considering the fact that monoamine oxidase is a key enzyme responsible for oxidation of serotonin in the nervous system, perhaps the body is not capable of maintaining normal level of this enzyme in MS patients. Therefore, considerable increase in MAO level may be responsible for reduced level of serotonin in MS patients, which is a likely reason for depression in these patients.

Keywords: Serotonin receptor (5-HT_3R_A); Monoamine oxidase (MAO-A); Gene expression; Multiple sclerosis

Introduction

Multiple Sclerosis is a common disease of central nervous system associated with multifocal destruction of myelin sheath in neurons, which leads to gradual neuronal damage due to autoimmune response against self-antigens in neurons of genetically predisposed individuals. The disease usually begins between 22 and 42 years of age and is more prevalent in women than men [1-4]. T-cells play an important role in organizing the mechanism of cascade complex in MS, which involves chronic inflammation, initial demyelination and axonal damage [5]. Neurobiology and immunology studies indicate that immune system regulation is affected by external factors in the nervous system known as neurotransmitters, including serotonin or 5-hydroxytryptamine (5-HT) [6]. Evidence has shown that fluctuation of serotonin level can be effective in progress of MS [7,8]. Seven families of serotonin receptors (5-HT_{1-7}) have been identified. All the receptor families (except for 5-HT3) are G-Protein Coupled Receptor (GPCR), while 5-HT_3 belongs to ligand gated ion channel family (Cys-loop type). Nine exons in its gene make up the protein-coding region. Among the subunits of serotonin (5-HT_{3E}, 5-HT_{3D}, 5-HT_{3C}, 5-HT_{3B}, 5-HT_{3A}), 5-HT_{3A} is the crucial subunit in the function of receptor [9,10].

Evidence has indicated the presence of 5-HT3 receptors on immune cells, including dendritic cells, monocytes, macrophages, T-cells and B-cells [11-14]. Serotonin binding to 5-HT_{3A} receptor causes the influx of calcium ions into cells along with other input and output ions [15]. Influx of calcium ions into T-cells is one way to activate T-cells [16]. Therefore, we have discussed 5-HT_{3A} receptor in this paper.

Monoamine oxidase is a dimer protein of flavoprotein family responsible for the oxidation of monoamines such as serotonin. There are two isozymes of this enzyme: MAO-A and MAO-B [17]. MAO-A has affinity for serotonin and is found outside the central nervous system in the liver, gastrointestinal tract and placenta, while MAO-B is mainly present in blood platelets and has affinity for phenyl ethylamine. The genes of both enzymes are juxtaposed on x chromosome. Given the basic role of MAO in neutralizing the neurotransmitters, malfunction of this enzyme causes a variety of problems and diseases such as depression, schizophrenia, impaired concentration, migraine and abnormal sexual development [18]. Thus, this regulatory enzyme of serotonin level in peripheral blood, which is also a key enzyme of central nervous system, has been discussed in this article [19].

In this study, we evaluate the expression of $5HT_{3A}$ receptor and MAO-A enzyme genes in mRNA level in PBMC of MS patients and healthy controls.

Materials and Methods

Study population

Subjects included 2 groups, the control group and MS patients, the

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control group included 30 volunteers, they were healthy (19 Females and an 11 males, aged 22 to 45 years old). The target group consists of 30 MS patient. (19 Females and 11 males aged 22 to 45 years old) Sampling of Imam Khomeini Hospital of Tehran. All subjects consented to take part in this study and approved by ethical committee.

PBMCs isolation and RNA extraction

For each individual 5 ml of peripheral blood from cubital vein was obtained, and then transferred to Falcon 15 ml, containing 0.5 ml of ethylene di-amine tetra-acetic acid (EDTA). Samples transferred to laboratory in flask. Peripheral blood mononuclear cells isolated from 4 ml of whole blood each sample based on the gradient density centrifugation technique via Ficoll-hypaque [20]. Then the cells in phosphate buffered saline (PBS) were washed and cell viability was determined by trypan blue staining and concentration of cells was normalized (Concentration 7×10^6 cells/ml).the percentage of viable cells was more than 99%. Then, according to Roche high pure RNA isolation kit instructions (Roche, Germany), Total RNA was extracted. Finally, total RNA concentration of all samples normalized (70 ng/µl).

cDNA synthesis, primer designing and PCR

The synthesis of cDNA by using Primer Oligo (dT) and 11 ml mRNA and cDNA synthesis kit instructions (Fermentas, Germany) was performed. Then, final cDNA concentration and purity were detected by measuring its absorbance by means of NanoDrop 2000 instrument (Wilmington,USA) at 260/280 nm. Primer designing was performed for target genes and β-actin as internal control, for this purpose we used primer express software. Then, the designed primers were blasted (http://www.ncbi.nlm.nih.gov/tools/primerblast); they just adhered to accurate loci in mentioned gene (Table 1). PCR was performed by Using gene-specific primers and cDNA and according to manufacturer's instructions PCR kit (Roche Germany). the product of PCR were loaded on 2% agarose gel and sharp appropriate bands acknowledged the accuracy of the exact segments amplification of 5-HT_3R_A and MAO-A.

5-HT_3R_A and MAO-A mRNA quantitation by real-time PCR

Real-Time-PCR for target genes and β-actin was set up on Termo cycler Rotor-GeneTM6000 (Corbet Research, Australia) by using of SYBR® Green fluorescent dye (Light Cycler Fast Start DNA Master Plus SYBR Green I, Roche, Germany). Rotor Gene instrument can detect the fluorescent emission radiation. We synchronized differences in total RNA volume of each reaction by using β-actin as internal control. Real-Time-PCRs were carried out on 1 µL cDNA templates by using 0.4 µL pairs of primers (200 nM β-actin, 5-HT_3R_A and MAO-A) and 2 µL of SYBR® Green I Master Mix in 10 µL of final reaction volume. appropriate RT-PCR programs were determined, so that conditions for β-actin were 10 s at 95°C, 10 s at 63°C and 10 s at 72°C, for 5-HT_3R_A were 10 s at 95°C, 10 s at 62°C and 24 s at 72°C and for MAO-A were 10 s at 95°C, 10 s at 60°C and 12 s at 72°C. Finally, Real-Time PCR products were loaded on 2% agarose gel followed by staining the gel with Ethidium bromide.

Statistical analysis

First, we used LinReg PCR software for obtaining the Cycle of threshold (C_t) and efficiency of each reaction, and then data were imported to REST 2009 software, this software calculating is based on pfaffle equation which is as follow:

In our study R shows Relative expression ratio of a target gene in comparison to control. (E) refers to real-time PCR efficiencies calculated by LinReg software, and (ΔC_t) imply the Ct difference between MS patients or exposed individuals against normal individuals (C_t normal-C_t MS patients/exposed individuals).

Results

Real-time PCR in MS patients and control group

cDNA samples was gained from reverse transcription of mRNAs, then Real-Time PCR was performed on cDNA samples by using specific primers designed for 5-HT_3R_A and MAO-A genes. SYBR® Green fluorescent dye just can attach to double strand DNA and these florescent emission signals detected by Rotor gene at each cycle, this process followed by drawing a plot by instrument. If the first copy number of one sample is high, it is detected by Rotor gene earlier and vice versa. By using LinReg and REST2009 software and data analysis, we found that, relative expression of 5-HT_3R_A receptor and MAO-A has shown significant increase (p=0.001) in PBMC of MS patients (Table 2 and Figures 1 and 2).

Sequencing of coding region of target genes (mutations in 5-HT3RA and MAO-A cDNA). The results of sequencing acknowledged accuracy sequence of 5-HT_3R_A and MAO-A in PBMCs of attendants and MS patient no changes in their sequences.

Discussion

Multiple sclerosis (MS) is associated with lesions in brain and spinal cord that often lead to debilitating disease and sometimes death. MS is caused by autoimmune inflammatory invasion to myelin sheaths covering the neurons. T-cells in the thymus are sensitized against self-

Accession Number	Primer Sequence 5 '-3'	Length PCR (bp)	mRNA Target
NM_001101	F-AGACGCAGGATGGCATGGG R-GAGACCTTCAACACCCCAGCC	161	B-actin
NM_001161772	F-GGTACCGGCAGTACTGGACT R-CGGCGGATGACCACATAG	496	5-HT_3R_A
NM_001270458	F-GCTGGACAAAGACTGCTAGGCGG R-GCTTCACTTGGTCTCCGAGGAGGT	180	MAO-A

Table 1: Primer used in quantitative real-time PCR.

Gene	Type	Reaction Efficiency	Expression	Std. Error	P(H1)	Results
B-actin	REF	0.8993	1			
MAO	TRG	0.9205	7.96	± 0.9	0	UP
5-HT_3R_A	TRG	0.5646	8	± 0.9	0	UP
(P value) P (H1): The possibility that the increase in the MAO-A and 5-HT3RA genes expression in comparison to normal people is only due to chance; REF: Reference Gene, TRG: Target Gene						

Table 2: Statistical analysis information for 5-HT_3R_A and MAO gene expression in PBMCs of MS patients in comparison with normal cases.

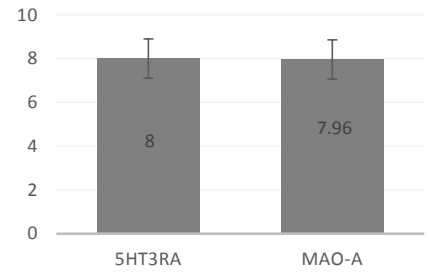

Figure 1: The 5-HT_{3A} receptor and MAO-A gene expression is up-regulated in individuals who MS patients (in comparison to control group) respectively by mean factors of 8 and 7.96.

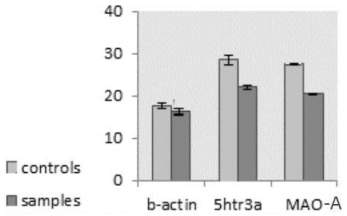

Figure 2: Diagram difference Delta CT in three genes B-actin and MAO-A and 5-HT_3R_A in patients compared to control samples. For each gene, the plot on the left related to control group and the plot on the right related to MS patients.

antigens of myelin sheath, resulting in secretion of tumor necrosis factor, cytokines and other inflammatory mediators that destroy the myelin sheath around axons and sometimes axon itself [21]. Recent studies have highlighted the important role of T-helper CD^{4+} cells in pathogenesis of MS, which result in the secretion of IL-17 that induces the production of T-cells in MS patients [22]. It means that genetic factors, viral or bacterial pathogens provoke the communication between CD^{4+} T-cells and class II MHC molecules on antigen-presenting cells, activating the lymphocyte and recruiting other immune cells [23-25]. Afterwards, with the help of adhesion molecules and via specific mechanisms, the immune cells pass through. The blood–brain barrier (BBB) by diapedesis. After the influx of blood cells into central nervous system, CD^{4+} T-cells are reactivated through contact between TCR and class II MHC on APCs presenting myelin self-antigens, leading to secretion of several pro-inflammatory cytokines and chemokines [23,26].

Serotonin is a key neurotransmitter that can direct the immune system by nervous system via different serotonin receptors on cells of several body tissues [27,28]. 5-HT3A receptor is a Ligand Gated Ion Channel (LGIC) responsible for transporting Na^+ and Ca^{2+} from extracellular fluid into the cell as well as transporting K^+ from intracellular to extracellular environment [29-31]. In a study conducted by Yang et al. on lymphocytes of humans and rhesus monkeys, the presence of these receptors on PBMC was demonstrated [32]. The results of recent studies also indicate the presence of 5-HT_{3A} receptor on monocytes, macrophages, B and T-cells as well as monocyte-derived dendritic cells. In this study, PCR results and sequencing of samples demonstrated the presence of 5HT_{3A} receptors on PBMC. The majority of studies on these receptors have been related to neurological diseases such as alcoholism, mania, depression, schizophrenia and behavioral diseases since these receptors are involved in the regulation of electric charge of cell membranes [27,33]. The results of this study showed that the expression of 5-HTR_{3A} in MS patients was significantly increased compared to control group. There is other study indicating overexpression of this receptor in certain diseases, including the study of Ahangari et al. [18] in which the expression of this receptor was increased in patients with asthma and breast cancer. In addition, in a study conducted by Saberi et al. [20] overexpression of this receptor was indicated in lupus patients. In contrast, in a study in patients with schizophrenia and Tardive dyskinesia, it was found that the expression of this receptor in these diseases is reduced compared to healthy controls. These studies suggest that the expression pattern of this gene is different in various diseases and these changes may play a significant role in the development of these diseases.

van Heerden et al. in 2009 showed that the changes in expression of serotonin receptor genes of PBMC cells are similar to the changes occurring in neurons [34]. This is another indication of the impact of nervous system on disorders of immune system. Studies show that serotonin receptors affect lymphocytes as well as central nervous system [35]. According to the results of mentioned studies as well as what we know about Ca^{2+}-calmodulin-calcineurin signaling pathway, influx of calcium into the cell exerts its effects through calcineurin, a calmodulin-Ca^{2+} dependent protein phosphatase. This protein is activated and via dephosphorylation activates NFAT, a critical transcription factor transferred to the nucleus, which is important for a number of key genes involved in immune response of T-cells. Considering the presence of active calcium channels on T-cells, which open when ligand-gated potassium channels are opened as a result of calcium influx into the cell causing depolarization of the membrane [16], it can be presumed that this receptor activates the mentioned factor through influx of calcium into the cell, which ultimately activates T-cells. Therefore, the activation of T-cells is likely to be dependent upon the activation of type 3 serotonin receptors. According to our study, which is based on increased expression of type 3 serotonin receptor on PBMC of patients, perhaps increase in 5HT_3A receptor is a reason for development of MS symptoms. These symptoms include increased secretion of cytokines provoking increased proliferation and immunologic function of T-cells [16].

MAO is an enzyme of flavoprotein family. The gene of this enzyme is located on X chromosome and includes 91,917 base pairs in 16 exons [36]. This protein has two isozymes of A and B, with a higher affinity of the former for serotonin [17]. This enzyme not only degrades and neutralizes serotonin but epinephrine, norepinephrine, dopamine and other types of neurotransmitters. Thus, it is a key enzyme in the regulation of the activity of nervous system and any disruption in the function of this enzyme can cause severe neurological problems. Disorders such as depression, schizophrenia, impaired concentration and anti-social behavior have been attributed to malfunction of this enzyme [36].

There was significant change in the expression of MAO gene in MS patients compared to healthy subjects, which was increased in MS patients.

In the study of Bortolato and Shih [17], it was found that increased MAO-A level is associated with acute depression. Since depression is the first symptom of MS, MAO is likely to be a sign of depression in MS patients. The role of serotonin in MS is known from previous studies. Lower plasma level of serotonin is directly correlated with multiple sclerosis [17] and since MAO is the most important regulator of serotonin in the body [37], increasing expression of this enzyme can be justified in MS patients in whom impaired homeostasis of nervous system increases the expression of the gene encoding this enzymes, resulting in increased degradation of serotonin in plasma, which can be one reason for reduced serotonin level in this disease.

In this study, the impact of increased expression of 5HT_3A receptor

on activation of T-cells as well as the role of MAO in progress of MS was examined for the first time. However, due to limitations of this study, we suggest further studies to ensure the exact mechanism of $5HT_3A$ in T-cell function.

Conclusion

MS is developed due to autoimmune inflammatory attack to myelin sheath covering the neurons. With regard to different studies conducted on MS patients showing the involvement of T-cells in attacking myelin sheath, no study has been so far conducted on the role of serotonin receptor in the activation of T-cells nor the role of monoamine oxidase enzyme in progress of MS. According to the study of Hossein-Nezhad et al. [18] on the role of serotonin receptor in the activation of T-cells in autoimmune diseases like asthma and given the correlation between MAO enzyme with behavioral disorders, depression and migraine that can be a cause of depression in MS patients, we decided to study the role of serotonin receptor and MAO in this autoimmune disease. Although further studies are needed to determine the mechanism of disrupted expression of the gene encoding this receptor and enzyme in MS, we hope this study to be a step to find a definite safe therapy for multiple sclerosis.

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