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Gene Expression and In Vitro Pharmacogenetic Studies of Dopamine and Serotonin Gene Receptors in Tuberculosis

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Background: Dopamine and serotonin receptors are present in lymphocytes, macrophages, and neutrophils, and have a mediating role in the immune system to respond to infections, including bacterial tuberculosis.

Materials and Methods: In this study, at first, the changes in the expression pattern of 5 dopamine and 2 serotonin (5HTR2B & 5HTR2C) gene receptors were examined in the two groups of healthy and Tuberculosis patients using Real-Time PCR. Then pharmacogenetic studies aimed to induce autophagy on a lung monocyte cell line (THP1) infected with the standard strain of *Mycobacterium tuberculosis* (H37RV) were performed. Stimulation of the pro-inflammatory pathway by secreting cytokines before and after drug efficacy was investigated.

Results: According to the result, dopamine receptor 2 genes showed decreased expression in patients with tuberculosis compared to normal individuals, and serotonin receptor genes showed increased expression. Additionally, with the effects of Bromocriptine and Fluoxetine, pro-inflammatory pathways were activated in macrophages infected with H37RV, and ELISA results showed that the levels of IL6 and TNFα secreted in these cells were significantly increased.

Conclusion: According to the results, these receptors agonists or antagonists can activate the autophagy pathway to kill TB bacteria.

Key words: Dopamine receptors; Serotonin receptors, *Mycobacterium tuberculosis;* Cytokines; Autophagy

INTRODUCTION

Tuberculosis (TB) is an infectious disease that is caused by Mycobacteria, typically *Mycobacterium Tuberculosis* (MTB), which mainly affects the lungs. TB is the second leading cause of mortality in the world compared to other diseases that are caused by pathogens. Most of these infections are asymptomatic, which is then referred to as occult TB (1). Until the mid-1980s, TB was widespread in the world so that the World Health Organization (WHO) announced its first "global emergency" in 1993 for TB. One-third of the world's population is infected with tubercle bacillus (2). TB seems to be ready, as we progress into the 21st century, as the "great killer" to expand its frequency (3). According to a report of WHO, as many as 8.6 million TB new cases and related 1.3 million deaths were estimated to have occurred in 2012 (4). People infected with HIV/ AIDS or other immune compromising conditions are at increased risk of TB (5). The response of the mammalian acquired immune system to the MTB pathogen is divided into two antagonistic subsets named as TH1 and TH2, which each is divided based on its set of cytokine intermediates. By altering the cytokine profile, infectious

diseases can balance TH1 and TH2 responses, which may have positive or negative effects on health.

Interestingly, bacterial infections are likely to play a role in atopy, a particular type of increased allergic reaction, which causes mucosal inflammatory properties of asthma caused by an overactive TH2 response. Because Mycobacteria stimulates a strong TH1 response and disrupts the balance between TH1 and TH2 towards TH1, TB infection protects the body against asthma (6).

Historically, TB is an important infectious disease in the world, and various communities are constantly trying to control and combat this disease. More than a third of the world's population is infected with TB, and without being susceptible to the disease and act as a reservoir of infection. Also, with the emergence of immunodeficiency diseases such as HIV and various types of cancers and unusual use of a variety of immunosuppressive drugs, the difficulty of global control of TB has increased. Although TB alone can be a huge threat to human health, therefore, it is more worrying to know that the disease can be closely related to lung cancer (7). Lung cancer is one of the most important causes of death in the world (8). Several studies have shown that those infected with TB are at significant increased risk of lung cancer (9). Having TB before lung cancer increases the risk of dying and is significantly correlated with mortality due to lung cancer, especially adenocarcinoma. Besides, smokers are at increased risk compared to non-smokers. It is also reported that about 25% of all types of cancer can be attributed to infectious agents such as TB, Human Papillomavirus (HPV), HIV, and hepatitis C (10). Several studies on the types of cancers that were developed about one year after the onset of TB have reported a higher prevalence of liver, lung, bladder, and biliary cancers in men, while and in women, lymphatic leukemia, esophagus, and lung have the highest rates. However, lung cancer has the highest rate in any case (11). TB is a marker for a variety of cancers, especially lung cancer, and can be considered as a prognosis for the long-term risk of lung cancer. TB and lung cancer have similar symptoms, and TB has symptoms similar to malignancy, Sometimes it's diagnosis confused with lung cancer (12).

On the other hand, signaling pathways of dopamine and serotonin receptors are common in central and peripheral immune and nervous systems, and theses systems are linked to health and disease. They have mediating roles in responding to TB infection, in the immune system, and also in control of proliferation and migration of cancer cells and leukocytes. Besides, dopamine and serotonin receptors exist in lymphocytes, macrophages, and neutrophils. Lymphocytes can even play a role in the pathogenesis of the disease because B lymphocytes secrete autoantibodies, supply antigens, activate T lymphocytes, and affect cellular activities (13).

The nervous and immune systems are connected to each other and a variety of message signaling molecules, including cytokines and neurotransmitters, are involved between these two systems. Two important neurotransmitter systems in the human nervous system are dopaminergic and serotonergic systems. Dopamine and serotonin, are mediators of the nervous and immune systems and their receptors are present on lymphocytes. Therefore, gene expression profile study of these receptors on human peripheral blood leukocytes may lead to a better understanding of the pathogenesis of diseases (14).

Dopamine receptors include five subgroups D1, D2, D3, D4, and D5. D5 and D1 receptors belong to the D1-like family and bind to Gs receptors. D4, D2, D3 receptors belong to the D2-like family and bind to Gi / G0 receptors. There is some indication about D7 and D6 dopamine receptors may be present, but they have not yet been identified (15).

Serotonin receptors also contain seven groups that respond to a variety of serotonin agonists and antagonists. To date, 14 serotonin receptors have been identified and sequenced in mammals that eventually are classified into seven pharmacological groups, ranging from 5-HT1 to 5-HT7. The 5-HT1 receptor has subgroups A, B, D, E, and F. The 5-HT2 receptor has subgroups A, B, and C, and the 5-HT3 receptor has subgroups A and B (16).

Other reliable studies have shown that the use of agonists or antagonists of these receptors may stimulate the autophagy pathway to kill TB bacteria. Research has

shown that the use of a host of small molecules called 'Host-targeted inhibitors' can target TB-infected macrophages and halt the growth of Mycobacterium tuberculosis. G-protein coupled receptors are among these molecules. Using drugs such as Fluoxetine, a selective serotonin reuptake inhibitor, can increase the secretion of pro-inflammatory TNFα cytokines and autophagy in T-infected macrophages (17). Fluoxetine is a 5-HT2C receptor antagonist and a 5-HT2B receptor agonist and has similar effects. Since the interactions between macrophages and bacteria are crucial to overcoming infection, such compounds have been identified as novel anti-tuberculosis agents (18, 19). In other studies, drugs such as Butyrophenones, which are highly prone to type 2 dopamine receptors and are used to treat neurodegenerative diseases, have been used as antibiotic sensitizers and their similarities with Phenothiazines have enabled them to be introduced as effective adjuvants in TB treatment (20).

Therefore, the researchers focused on investigating the changes in the expression pattern of type 2 dopamine receptors (D2, D3, and D4) and serotonin (5HTR2B & 5HTR2C) in two groups of healthy and TB patients. Then, based on the results of the first phase, pharmacogenetic studies aimed at inducing autophagy on a TB-infected monocyte cell line (TB) were performed and stimulating pro-inflammatory pathways through the release of cytokines before and after drug efficacy was investigated.

MATERIALS AND METHODS

Sampling

The study population included 30 normal individuals and 30 active TB patients. Patients with active TB were aged 25 to 55 years before treatment and without any history of neuropsychiatric, glandular, or malignant disease. Healthy individuals were also aged 25 to 55 years with no history of autoimmune, rheumatic, neuropsychiatric, endocrine, and malignant diseases. Using 0.05 M EDTA tubes, fasting 5ml venous blood was collected from all participants. Then the isolation of peripheral blood mononuclear cells (PBMCs) was carried out by Ficoll Hypaque (Lymphoprep TM, Olso, Norway).

The RNA extraction and cDNA synthesis

After sampling from patients, their RNA was extracted from samples (PBMC and Whole blood), both normal individuals and PBMC isolation. The RNA was extracted using a Roche company RNA extraction kit from Germany (High Pure RNA Isolation Kit-Cat No. 1 828 665). After the extraction of RNA, cDNA synthesis was performed using the Fermentase Company kit and Reverse Transcriptase PCR.

The Real-Time PCR and gel electrophoresis

Expression changes of dopamine receptors type 2 and serotonin 5-HT2B and 5-HT2C receptor genes were examined by Real-Time PCR in TB patients and normal individuals with the related primers (table 1). The Light Cycler Fast Start DNA Master plus Kit SYBR Green and specifically designed primers were used for Real-Time PCR (Light cycler Roche, Germany).

Statistical analysis

Data were saved in SPSS software version 19. After correcting the data, Levene's test was used to compare the variance and independent samples t-test, and the following formula were used for the mean values. A p-value of < 0.05 Significance level was set at P-value < 0.05.

ΔΔCt formula $R = 2^{-\Delta\Delta Ct}$

A standard curve was used to determine gene expression levels. Also, relative concentration was used instead of crude values, which means that the concentration of each gene was first calculated using the relevant standard curve from the cross in real-time reaction and then divided into the beta-actin concentration measured as the internal control.

Cell Culture

In the present study, we prepared a type of lung monocyte cell line THP1 from Immunotherapy and Leishmania Vaccine Research Department, Pasteur Institute of Iran. The cell culture was carried out in RPMI medium supplemented with 10% FBS and 1% Pen/Strep in a humid incubator at 37˚C.

Differentiation and Infection studies

At this stage, cells were transferred to culture plates (500,000 cells were cultured in 6 well plates) and 50 ng / µL phorbol-12-myristate-13-acetate (PMA, Santa Cruz Biotechnology) was added to each well to induce macrophage and then incubated in a 37 ° C incubator for 48 hours(21). After 48 hours, the supernatant was emptied, and the new medium was added. The cells were then incubated for another 24 h. The standard strain of *Mycobacterium tuberculosis* (H37RV) was used to infect macrophages. The medium used was RPMI and FBS without antibiotics. The contamination was performed from Stoke half McFarland 10 (CFU/ml=1.5% with MOI=10). After 4 hours of incubation at 37 ° C for washing extracellular bacteria, washing was performed with PBS twice.

Induction of macrophages with drugs and ELISA test to measure the secretion of IL6 and TNF-α cytokines

At this stage in each well, cells infected with a bacterium containing 3 ml of medium were added and were incubated at 37 ° C for 24h. Then, the infected cells were treated by bromocriptine (dopamine receptor agonist) at a concentration of 30 µl and 2.5 mg/ml and fluoxetine (serotonin receptor antagonist) at a concentration of 120 µl at a concentration of 10 mg/ml. The supernatant obtained after each treatment was collected after 48 hours, and ELISA assay was performed to measure the secretion of IL6 and TNF-α cytokines using ELISA kits (IBL International, Germany).

RESULTS

Demographic data analysis

Demographic data analysis showed that 90% of patients had low income and were poor in the community, which unfortunately did not have the financial support for follow-up until complete treatment. 35% of them were immigrants with non-Iranian nationality, and 30% were aged less than 25 years. Also, 13-15% of patients had co-infection of TB and AIDS or TB and hepatitis, and 35% of patients have a history of consuming cigarettes or tobacco (Table 2).

Molecular analysis

As shown in figure 1, in TB patients compared to normal individuals, the mean expression of dopamine receptor type 2 genes decreased significantly both in peripheral blood and on the surface of mononuclear cells. Whereas serotonin receptor genes were expressed in peripheral blood mononuclear cells of patients higher than the healthy controls, and this was significant for 5 HT2C (Figures 1 and 2).

Cell culture studies

As shown in figure 3, after induction of THP1 cells by PMA, cell differentiation into macrophages was observed and confirmed by an invert microscope.

Table 1. Information on dopamine, serotonin, and beta-actin primers

Locus	Primer (Forward)	Primer (Reverse)	Product (bp)
β-actin	5'-AGACGCAGGATGGCATGGG -3'	5'-GAGACCTTCAACACCCCAGCC -3'	161
DRD1	5'-CTTCCTCAACGTTTCGGAGCC-3'	5'-AGCTCTCCAAACGCCTTGCCTT-3'	100
DRD2	5'-TGTACAATACGCGCTACAGCTCCA-3'	5'-ATGCACTCGTTCTGGTCTGCGTTA-3'	127
DRD3	5'-TCTGTGCCATCAGCATAGACAGGT-3'	5'-TAAAGCCAAACAGAAGAGGGCAGG-3'	156
DRD4	5'-TCTTCGTCTACTCCGAGGTCCA-3'	5'-TGATGGCGCACAGGTTGAAGAT-3'	125
DRD5	5'-TCATCTATGCCTTCAACGCCGACT-3'	5'-AGCTGCGATTTCCTTGTGGAAGAC-3'	120
HTR2C	5'-CGCTGACGATTATGGTGATTACG-3'	5'-TCTGGTCTTGGTTAGGGTTTGC-3'	177
HTR2B	5'-GCTGATTTGCTGGTTGGATTG-3'	5'-GGCAGGACATAGAACAAGTGG-3'	96

Table 2. The results of patient's biographical information

Risk factors and demographic characteristics	Under 25 years	Hepatitis	HIV	Family history of tuberculosis	The low-income community	Non-Iranian	Smoking
Percentage	35%	35%	90%	30%	15%	13%	30%

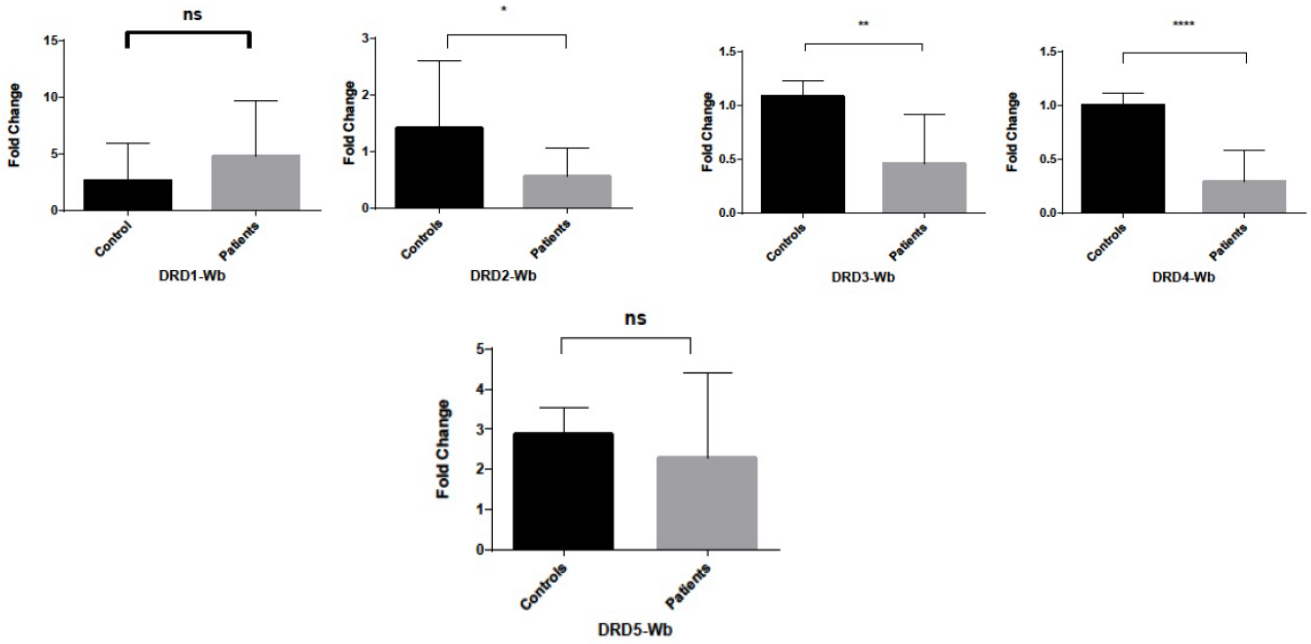

Figure 1. Comparison chart of the expression level of dopamine receptor genes (DRD1,DRD2,DRD3,DRD4,DRD5) on PBMC of patients compared to the control group

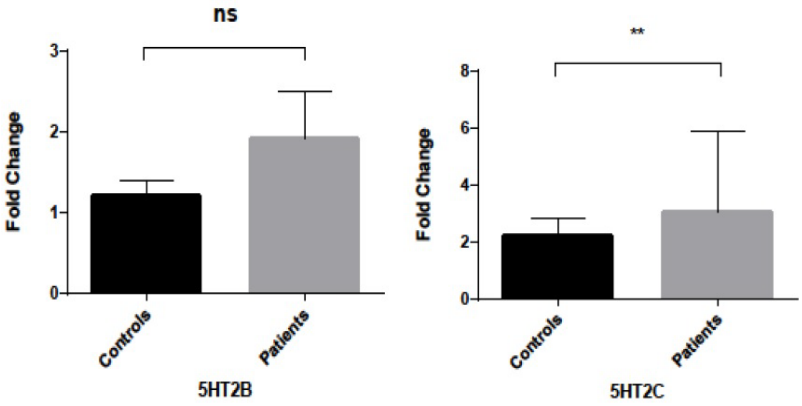

Figure 2. Comparison chart of expression of serotonin receptor genes(5HT2B, 5HT2C) in patients compared to control group

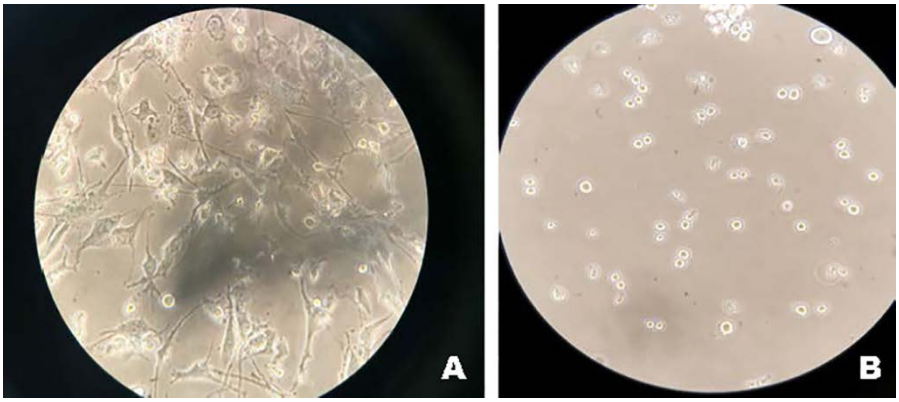

Figure 3. Morphological observations; A) THP1 cells B) Cells differentiated into macrophages

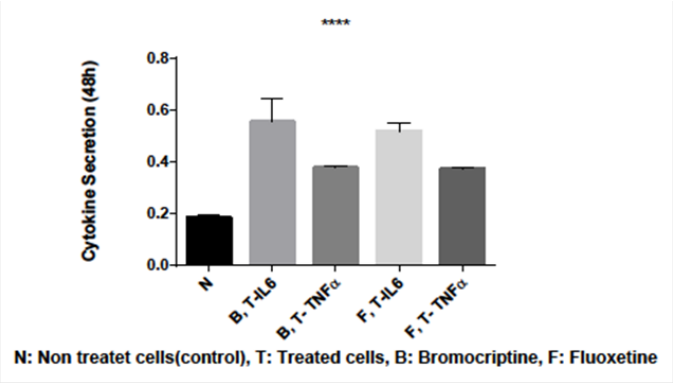

Figure 4. The secretion of IL6 and TNF-α cytokines from TB-infected macrophages were increased significantly after administration of Bromocriptine and also Fluoxetine

ELISA test results to measure the secretion of IL6 and TNF-α cytokines

As shown in figure 4, the levels of IL6 and TNFα secretion in the study groups were significantly increased after drug administration, indicating that the drugs were able to induce pro-inflammatory pathways in TB-infected macrophages.

DISCUSSION

Although relatively few studies are conducted on neuropsychiatric disorders in dopamine receptors, there has been no definitive study of the importance and role of these receptors in TB, and this study is a completely new investigation.

In all studies, only the expression levels of ligands related to these receptors have been measured in some pulmonary diseases and defects. Little research has been done on the receptor genes that increase or decrease their expression and can play a key role in initiating cellular signaling pathways. Besides, the effect of altering the levels of these molecules by genetic engineering has not so far been determined. It should be noted that most studies on these are conducted on their nervous systems and diseases, going back to 1998-2002. Whereas, in recent years, especially since 2007, more attention has been drawn to the potential impact of alterations of these receptor genes in the development of major and fatal cancer diseases. Besides, given the increasing global population and the crisis of contaminants and infectious agents as well as the serious threat that it poses to human health, deeper studies in these areas are needed.

The results of the current study indicated that dopamine and serotonin receptors are expressed on mononuclear cells of the blood, which make them a suitable and accessible model for evaluation of the diseases, as well as the efficacy of drugs and follow-up treatment.

Until now, there has also been no report on the use of the receptor agonists or antagonists studied, particularly bromocriptine, which is a specific agonist of type 2 dopamine receptors. The only reports available are related to the author's previous researches. Our previous researches on NSCLC-type lung cancer showed that the expression pattern of type 2 dopamine receptors in individuals with this type of cancer was different and lower than normal. Therefore, they were able to induce apoptosis up to 50% in lung cancer cells using in vitro bromocriptine, a specific agonist of these receptors (22, 23).

Hu and colleagues have used new anti-tuberculosis drugs such as Bedaquiline and Delamanid, along with insulin analogs in diabetic patients with drug-resistant Tb (MDR-TB) and showed that several drugs, including fluoxetine, increase the effect of insulin on blood sugar and facilitate the treatment of TB (24).

In 2017, scientists observed significant antibacterial effects, both in vitro and in vivo, by stabilizing the multilayer polymer loaded with isoniazid using the poly-dopamine linker. In this study, a poly (ethylene glycol) - based hydrogel film embedded with isoniazid-loaded alginate (INH) microparticles to bone implants via polydopamine linker was stabilized and subsequently used by (lactic-glycolic acid) membranes for Stable and local delivery of anti-TB drugs (25).

A study on a large number of central nervous system (CNS) drugs (2018) introduced a synthetic fluoxetine analog as a selective and specific anti-tuberculosis agent.

Also, the antibacterial effects of this drug were tested on the standard strain of TB (H37RV) and approved(26).

On the other hand, the present study, as well as related articles, reported a strong association between TB and the risk of lung cancer, and the history of patients with TB at the Pasteur Institute of Iran diagnostic laboratory confirms this fact. Some have been diagnosed with long-term delays in treatment and diagnosis, and sometimes misdiagnosis of lung cancer and even anti-cancer drugs were prescribed for them, and have been diagnosed with TB after a relatively long period. Or people with a history of TB that developed lung cancer.

In the present study, alterations in the expression of type 2 dopamine receptor genes were decreased and the expression of serotonin receptor genes was increased in the peripheral blood mononuclear cells of TB patients compared to the control group. There are significant differences in the state of health and TB. Since previous studies have also reported a significant decrease in the expression of type 2 dopamine receptors in lung cancer, and the fact that TB and lung cancer are two related diseases, so changes in the expression profile of these receptors can be a good prognosis. On the other hand, using such drugs that have a high affinity to these receptors and can specifically target them can be helpful for providing new strategies in the diagnosis, treatment, and clinical management of TB.

Also, the researchers in the present study were able to activate proinflammation pathways in macrophages infected with TB bacteria, using bromocriptine, which is a specific agonist of type 2 dopamine receptors (decreased expression in this disease) and fluoxetine, a specific 5HT2C antagonist (increased expression). According to the results, the secretion of IL6 and TNFα cytokines was significantly increased after administering the abovementioned drugs in macrophages infected with TB (27-29). This could be a turning point in the development of genetically based prevention, screening, diagnostic, and therapeutic approaches.

Conflict of Interest

The authors have no any conflict of interest.

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