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Original Article

Dopamine D2 Receptor and Dopamine Transporter mRNA Expression in Addicted Peripheral Blood Lymphocytes

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Abstract

Introduction: This study aimed to detect the effects of opioid addiction on the mRNA expression levels of the dopamine D2 receptor (DRD2) and dopamine transporter (DAT) in peripheral blood leukocytes.

Methods: Four groups, each comprising 30 individuals, were included in the study: opioid-addicted, methadone-maintained (MM), long-term abstinent, and normal subjects. We measured the mRNA levels of DRD2 and DAT in peripheral blood leukocytes via real-time quantitative reverse transcription–polymerase chain reaction (real-time RT–PCR).

Findings: The results of the study showed that DAT mRNA expression was not statistically significant in the affected subjects compared to the control group. Regarding DRD2, mRNA expression was increased significantly in the MM subjects compared to the control group ($P=0.002$).

Conclusion: Our study could guide further research to refine the clinical applicability of biomarkers related to dopamine signaling proteins in opioid addiction.

Keywords: Dopamine receptor, Dopamine transporter, mRNA, Leukocyte, Addiction

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Introduction

Drug addiction is a chronic relapsing disorder that is characterized by compulsive drug seeking.[1] The genetic, environmental, and effects of drugs on gene expression are involved in the development of addiction.[2] Numerous genes associated with addiction have been discovered, affecting the pathological mechanisms of drug addiction.[3] The dopamine (DA) system has an important role in reinforcing the effects of drug abuse.[4] The dopamine transporter (DAT) is commonly considered a homeostatic regulator that regulates extracellular DA[5] in response to acute and long-term physiological demands. The increased DAT activity has been observed in individuals with substance use disorders.[6] DAT expression has been detected in lymphocytes and shows similar patterns to those observed in the brain.[7]

Dopamine receptors are the key elements of the DA system. The role of dopamine D2 receptor (DRD2) polymorphisms in heroin addiction has been reported.[8,9] The presence of dopamine receptors has been reported in normal human leukocytes[10-12] and reflects the status of homologous brain receptors.[12-14] The dopamine D2 receptor is altered in the different phases of substance abuse.[15] Therefore, analysis of dopamine receptors in peripheral blood leukocytes (PBLs) is a useful tool for evaluating the functional properties of DA function that underlie the variation in complex psychological and psychopathological traits,[10,16] and helps to further research in drug development.

The present study aimed to investigate DAT and DRD2 mRNA expression in the PBLs of opioid addicts, patients receiving methadone maintenance treatment (MMT), and long-term abstinent former opioid addicts in comparison with the healthy control group.

Methods

Participants

One hundred and twenty male subjects were included in the study: 30 opioid addicts and 30 MM subjects were recruited from an MMT clinic, 30 long-term abstinent subjects from the Narcotics Anonymous Organization, and 30 matched normal control subjects. The diagnosis of

opioid dependence was made according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)[17] criteria evaluated by the structured clinical interview. The duration of abstinence from opioids was at least 6 months. Participants were excluded from the study if (1) they were dependent on other substances; (2) they were taking other prescribed medications that could affect the central nervous system; or (3) they had any past or current major neurological, psychiatric, cardiovascular, or endocrinological disorders and any current infectious or inflammatory disease. The control group consisted of age-matched healthy individuals with no history of drug abuse. If any abused drugs (cocaine, amphetamine, methamphetamine, marijuana, opioid, phencyclidine, barbiturates, benzodiazepines, methadone, or tricyclic antidepressants) were detected in the urine samples of abstinent or control subjects, the samples were excluded. The study protocol was explained to all participants. They were enrolled voluntarily and provided written informed consent.

Sample Collection and Separation of Lymphocytes

Peripheral blood samples (5 ml) were collected via antecubital venipuncture. The samples were transferred into ethylene diamine tetraacetic acid (EDTA)-containing tubes. They were then placed on a cell separation medium (Histoprep/BAG, Lich, Germany) and centrifuged according to the manufacturer's protocol for 35 minutes at 1200 g using a horizontal rotor at room temperature. The lymphocyte layer was collected and washed three times in calcium– magnesium-free phosphate-buffered saline (pH = 7.4). Lymphocyte separation was completed within 4 hours after blood sampling.

Total RNA Isolation and Reverse Transcription

Total RNA from lymphocytes was extracted via RNA gents® (TRAIZOL RIBOEX). To determine the quantity and purity of the RNA, spectrophotometry and gel electrophoresis (1.2% agarose; Gibco/BRL) were used. By following the manufacturer's protocol, 1 µg of extracted RNA was reverse transcribed into first-strand cDNA via a reverse transcription kit (SMOBIO, Taiwan) in a final volume of 20 µl.

Primers Used for Real-Time PCR Amplification

To normalize target gene expression, the glyceraldehyde-3-phosphate dehydrogenase (GAPDH) gene was used as a housekeeping gene, due to its stable expression in peripheral blood lymphocytes, as confirmed in previous studies.[16] The primers for GAPDH were obtained from Qiagen's PrimerBank. The DRD2 and DAT primer sequences were designed using Primer Blast software on the United States National Center for Biotechnology Information (NCBI) website. The locations of all primer sequences were selected in common sequences in different isoforms to avoid the effect of alternative splicing. Moreover, exon-exon junction oligonucleotide primers were used for real-time PCR amplification of DRD2 and DAT genes (Table 1).

Real-Time PCR

All real-time PCRs were performed with 2 µl of synthesized cDNA, 10 µl of SYBR Green I Master Mix (Ampliqon), and 5 picomoles of forward and reverse primers in a total volume of 20 µl on an ABI Step One Plus. The thermal cycling conditions were as follows: Initial denaturation

at 95°C for 15 min, followed by 40 cycles of 95°C for 15-30 s and 60-63°C for 1 min. The specificity of the PCR product for each gene was assessed through verification of a single peak by melting curve analysis and visualization of the PCR product on a standard 6% acrylamide gel stained with ethidium bromide.

Statistical Analysis

For data analysis, the expression levels of target genes were measured via comparative 2. The expression levels of target genes were measured via the comparative $2^{-\Delta\Delta CT}$ (fold change) method. REST-XL version 2 software (http://www.wzw.tum.de/gene-quantification) was used for statistical analysis to identify significant differences from the control group and to calculate and compare the relative expression levels of the sample and control groups. In one equation, the software simultaneously performs the functions of normalizing and quantifying the genes. The program calculates and compares the relative levels of gene expression, and there are notable differences between the two groups based on the mean Ct deviations and the PCR effectiveness of the runs. A randomization test for fixed pair-wise reallocation determines the significance of the results in REST-XL. Besides being just as efficient as standardized tests, randomization tests serve as a valuable alternative to parametric tests since they do not require assumptions regarding the data's distribution. The results are presented as fold change variations of mean normalized expression amounts ± standard error of the mean. Three separate analyses (addicted, MM, and abstinent groups in comparison with the control group) were performed for each target gene (DAT and DRD2). $P < 05$ was considered

Table 1. The primer sequences for the GAPDH, DRD2, and DAT genes

Size	Location accession number	Primer Sequences	Gene
120 bp	NM_001256799.2	F: 5'-CATCAAGAAGGTGGTGAAGCAG-3' R:3'-GCGTCAAAGGTGGAGGAGTG-5'	GAPDH
167 bp	NM_016574.4	F: 5'-CCATTGTTCTCGGCGTGTTC-3' R:3'- AATGTTGAAGGTGGTGTAGATGATG-5'	DRD2
53 bp	NM_001044.5	F:5'-CGGCCAGACCAAGAGGGAAGAAGCA-3' R:3'-TGGGCACACTGGGAGTTGAGGAA-5'	DAT

statistically significant, and the data are presented as the fold differences in the mean normalized expression values ± standard error of the mean (S.E.M.).

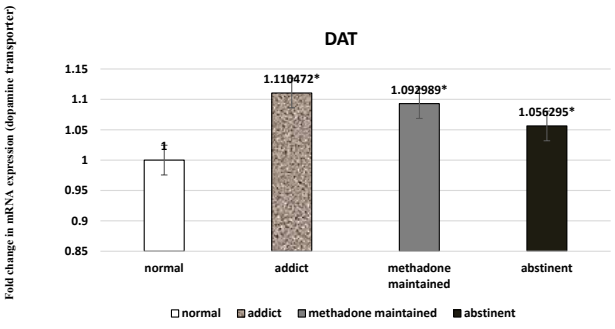
Results

The demographic information of the participants is shown in Table 2. The duration of drug abuse in the addicted group and the duration of methadone maintenance in the MM group were 14.23 ± 11.74 and 4.03 ± 3.29 years, respectively. For abstinent subjects, the duration of abstinence was 185.63 ± 29.52 days. The data were evaluated for normality via the Kolmogorov–Smirnov test, which indicated a normal distribution. A comparison of the dopamine transporter (DAT) gene expression ratios in PBLs among the study groups is shown in Figure 1. DAT mRNA expression was increased (not significant) in the addicted, abstinent, and MM groups by factors of 1.11, 1.06, and 1.09, respectively, compared with that in the control group (addicted: $P = 0.26$; abstinent: $P = 0.56$; MM subjects: $P = 0.28$).

Regarding the DRD2 gene (Figure 2), this gene's mRNA expression was decreased in the abstinent group and increased in the addicted group by factors of 0.59 and 1.37, respectively, compared to the control group; these changes were not statistically significant (abstinent: $P = 0.06$; addicted: $P = 0.000$). On the other hand, DRD2 mRNA expression was increased significantly in the MM group by a factor of 2.59 compared to controls ($P = 0.002$).

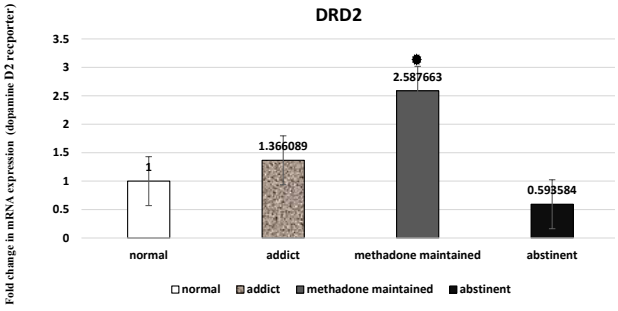
Discussion

Dopamine is one of the most important neurotransmitters involved in reward pathways in the brain and is believed to be essential for strengthening the properties of substance abuse.[11] An important key component in drug addiction is the mesolimbic pathway. Axons of dopaminergic cell bodies in the ventral tegmental area that project primarily to the nucleus accumbens in the ventral striatum constitute this pathway. The lateral septal area, amygdala, lateral hypothalamus, and bed nucleus of the stria terminalis also receive the axons of this pathway.[18] Dysfunction of dopamine neurotransmission in the central nervous system (CNS) plays an important role in the development and progression of behavioral dysregulation and drug addiction.[19-21] Investigating the DR in the human CNS has evident restrictions. Dopamine receptors (DRs) are among the key elements of the dopaminergic system. Five types of DR, D1 through D5, are co-expressed at different levels and in various combinations in the CNS and peripheral tissues.[10,20] Dopamine D2 receptor expressions in human peripheral blood lymphocytes using molecular biology techniques and binding assays are controversial.[22] Several studies utilizing receptor binding assays or RT-PCR methods have reported the existence of this receptor gene in normal human leukocytes.[10] On the other hand, a review has also supported the feasibility of PBLs as a cellular tool to explore DA derangement in neuropsychiatric disorders.[13] DAT expression was found in lymphocytes as well, exhibiting patterns similar to those observed in the brain.[23] Therefore, establishing peripheral sources of DR, reachable in a minimally invasive way, would be useful for research and clinical purposes. Human peripheral blood lymphocytes have attracted attention as accessible samples for the assessment of the functional features of DR, and may reflect the status of homologous brain receptors.[12,13] We thus aimed to detect the effects of opioid addiction on



*$P > 0.05$ in addicted, methadone maintained, and abstinent groups compared to the control group.

Figure 1. A comparison of the DAT gene expression ratios in PBLs among the study groups. DAT mRNA expression showed an increase (not statistically significant) in the addicted, abstinent, and MM groups by factors of 1.11, 1.06, and 1.09, respectively, compared with that in the control group (addicted: $P = 0.26$; abstinent: $P = 0.56$; MM subjects: $P = 0.28$)



*$P < 0.05$ from the control group.

Figure 2. A comparison of the DRD2 gene expression ratios in PBLs among the study groups. The mRNA expression of this gene was decreased in the abstinent group and increased in the addicted group by factors of 0.59 and 1.37, respectively, when compared to the control group; these changes were not statistically significant (abstinent: $P = 0.06$; addicted: $P = 0.000$). Conversely, DRD2 mRNA expression was increased significantly in the MM group by a factor of 2.59 compared to controls ($P = 0.002$)

Table 2. Demographic characteristics of the participants.

	Control (n = 30)	Addict (n = 30)	Methadone maintained (n = 30)	Abstinent (n = 30)
Age (years, mean ± SD)	40.21 ± 9.88	40.52 ± 6.64	39.74 ± 7.32	39.42 ± 5.30
Duration of drug use (years, mean ± SD)	____	14.23 ± 11.74	____	____
Duration of methadone maintenance (years, mean ± SD)	____	____	4.03 ± 3.29	____
Duration of abstinence (days, mean ± SD)	____	____	____	185.63 ± 29.52

The individuals in all groups had no significant difference in age ($P > 0.05$).

the mRNA expression levels of DRD2 and DAT in PBLs via qRT-PCR methods.

Maintenance of higher levels of dopamine in certain brain regions may be part of the mechanism of addiction to a variety of drugs, including nicotine, cocaine, cannabis, and opiates.[24] The release of dopamine from a neuron in the nucleus accumbens, and its interaction with a dopamine receptor in the mesolimbic brain region, induces a reward.[24] Therefore, a dopaminergic mechanism may be responsible for interindividual differences in susceptibility to developing drug dependence.[24] Chronic morphine exposure has been suggested to increase gamma-aminobutyric acid (GABA) signaling in the ventral tegmental area,[25,26] and reduce excitatory postsynaptic currents,[27] which might reduce dopamine transmission.[28] Although dysregulation of dopamine transmission is similar across different addictions in humans, the correlation between neurochemistry and drug-seeking behavior might differ with the particular drug of abuse.[27] The biological mechanisms of genes that affect the risk of initiating substance use, dependence, responding to treatment, and relapse have not been extensively studied.[3] On the other hand, genetic variations that influence dopamine and its receptors can change vulnerability to substance abuse disorders.[29] In the present study, we examined the mRNA expression levels of DRD2 and DAT in PBLs from three groups of patients with opioid dependence, namely, opioid-addicted, MM, and long-term abstinent patients, compared with those in normal subjects. Compared with those in the control group, DRD2 mRNA expression was increased in the addicted and MM groups, but this increased mRNA expression level was statistically significant only between the MM and control groups. Compared with that in the control group, the mRNA expression of the DRD2 gene in the abstinent DRD2 group was decreased, but the difference was not statistically significant. Additionally, the abstinent and MM groups presented increased DAT mRNA expression compared with the control group, but the difference was not significant. Increases in DAT function have been observed in individuals with substance use disorders.[30] A decrease in D2 receptor binding in the striatum was associated with opiate exposure in rodents.[31,32] In addition, withdrawal is associated with the downregulation of postsynaptic D2 receptors.[31]

Considerable attention has been focused on the possible relationship between DRD2 gene polymorphisms and drug dependence. Numerous studies have reported an allelic association between the A1 allele at the TaqI 'A' restriction fragment length polymorphism at DRD2 and drug dependence.[33-36] Compared with control individuals, polysubstance abusers presented an increased frequency of DRD2 alleles.[33] A strong association has been reported between DRD2 gene polymorphisms and cocaine-abusing study participants.[34] In addition, an association has been found between the DRD2 TaqI A1 allele and drug and alcohol dependence, which is significantly associated with measures of the severity of substance dependence.[37] The same allele has also been found to be a risk factor for cigarette smoking and psychostimulant-preferring polysubstance abusers (cocaine or amphetamine).[35,37]

Treatment of heroin addiction involves the use of methadone hydrochloride as a synthetic opioid that occupies opioid receptors and leads addicts to change their behavior and discontinue heroin use. This drug provides much slower withdrawal than heroin does; thus, it is possible to maintain an addiction to methadone without harsh side effects.[38] The dopamine D1 and D2 receptors are involved in the rewarding and addictive effects induced by mu-opioid receptor agonists.[39] The compulsion to seek and take drugs of abuse is characteristic of drug addiction as a chronically relapsing disorder.[40] Elevated expression of dopamine receptors in peripheral blood lymphocytes in patients with schizophrenia,[41] which is believed to be related to increased central dopaminergic neurotransmission,[42] suggests that the neuroreceptors of PBLs are parallel to homologous brain receptors. The mechanisms and therapeutic possibilities of this still need to be explored. In this study, we focused on the mRNA rather than the protein expression of peripheral blood lymphocyte dopamine receptors. However, a correlation between dopamine D3 receptor mRNA expression and the binding of the dopamine D3 receptor-specific ligand [3H]7-OH-DPAT to peripheral blood lymphocytes has previously been reported.[43]

This study has some limitations: 1) our subjects were only male. To avoid gender bias, in the future, this research is suggested to be conducted on female subjects. 2) The study focused solely on gene expression analysis without assessing corresponding protein levels. Future studies incorporating protein-level measurements are recommended to provide a more comprehensive understanding and to address this limitation. 3) We did not include participants' smoking status in the study, although it does not have a confounding effect as reported in the study conducted by Goodarzi et al. [12]; however, we mention it as a limitation. 4) Although the sample size in the present study is similar to that in previous studies, a study design with a larger sample size would strengthen the results.

Conclusion

Dopamine transporter and dopamine D2 receptor deficiency may be risk factors that increase the vulnerability of individuals to drug addiction.

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Authors' Contribution

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Data curation: Nasrin Hamedanian, Morteza Karimipoor, Sadegh Yoosefee.

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Investigation: Nasrin Hamedanian, Sadegh Yoosefee.

Methodology: Nasrin Hamedanian, Morteza Karimipoor, Sadegh Yoosefee.

Project administration: Nasrin Hamedanian, Morteza Karimipoor, Sadegh Yoosefee.
Resources: Nasrin Hamedanian, Sadegh Yoosefee.
Software: Nasrin Hamedanian, Morteza Karimipoor, Sadegh Yoosefee.
Supervision: Morteza Karimipoor, Sadegh Yoosefee.
Validation: Nasrin Hamedanian, Morteza Karimipoor, Sadegh Yoosefee.
Visualization: Nasrin Hamedanian, Sadegh Yoosefee.
Writing–original draft: Nasrin Hamedanian, Morteza Karimipoor, Meysam Amidfar, Sadegh Yoosefee.
Writing–review & editing: Nasrin Hamedanian, Morteza Karimipoor, Meysam Amidfar, Sadegh Yoosefee.

Competing Interests
The authors declared no conflict of interest.

Ethical Approval
The study protocol was explained to all participants. They were enrolled voluntarily and provided written informed consent. The research followed the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of Qom University of Medical Sciences (Ethical code: IR.MUQ.REC.1396.20).

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