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Research Article

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The Dopamine Level and Dopaminergic Receptor Gene: *DOR1* VNTR in Smokers

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Abstract

The smoking is a common habit in the world which contributed in several diseases, the dopamine and its receptors were found to be related with addictive, in Iraq high percentage of population was smokers and others suffer from passive smokers, thus current study aims to detect, the Dopamine Level and Dopaminergic receptor Gene In young Smokers. The dopamine level and Dopaminergic Genes VNTR were detected using VNTR-PCR and ELIZA technique, the results show that non-significant differences in age and BMI (p=0.553, and p=0.638) and non-significant differences in dopamine levels between groups (p=0.823), three VNTR were observed 11(520 bp), 10 (483 bp) and 7(361 bp). The VNTR11 is more frequent in the smoker group (83.33%) in non-significant variation (p=0.966), also VNTR 10 are more frequent in the smoker group (16.66%) in non-significant variation (p=0.894), and VNTR 7 didn't observe in the smoker group. Significant differences observed in non-smoker dopamine level according to VNTR frequency (p=0.025) while non-significant observed in the smoker group (p=0.324). The study concluded that the dopamine level didn't effect by smoking and VNTR of *DAT1* gene didn't associate with the smoking habit also.

Keywords: Dopamine • Dopaminergic • Genes • VNTR • Smokers

Introduction

The smoking habit still prevalent in the world, it's the risk factor of a large number of diseases, like cardiovascular disease and cancers that leads to largest morbidity and mortality [1-3]. The continuous smoking causes Nicotine dependence that known as a psychoactive substance disorder [4,5], this behavior is multifactorial represented by genetic and environmental interaction, complex associations have been found by several investigations [6,7]. The human behavior affected by different factors like neurotransmitter level, genes polymorphisms of its receptors and numerous hormones that lead to nicotine addiction [8]. The nicotine intake effects in different body organs like the central nervous system, studies found the metabolism of nicotine is regulated by some biological pathways, the Genetic researches introduced a method for developing insights into the genes involved in the metabolism pathways, however a strongest genetic contribution to smoking-related traits comes from diversity in the nicotinic receptor subunit genes and genes coding for enzymes involved in nicotine metabolism that proved by genome wide association and meta-analysis studies [9-11].

Dopamine is one of the neurotransmitter have a vital role in the human body, the level of dopamine is affected by different factors, there are several dopamine receptor genes, including *DRD1-5* [12-17]. These receptors have been found to be associated with smoking behavior in different populations. All these receptors are G-protein-coupled receptors, In the present work the *DRD1*is studied, its located at 5q35.2 4147 bases encoded to five subtypes D1-D5, that most abundant in the central nervous system the function trigger by adenylyl cyclase and cyclic AMP-dependent protein kinases activation [18]. Researchers found that *DRD1* subtypes is linked with several behavioral disorders, despite of large number of human studies have focused indistinctively on the role of DA activity at the D2 and D3 receptor, different lines of evidence, mostly from preclinical work have shown that the D3 dopamine receptor may be particularly involved in nicotine addiction, D3 antagonism reduces the influence of cues on behavior using Pavlovian conditioning procedure, nicotine-induced place preferences , nicotine-induced reinstatement of nicotine seeking , and cue-induced reinstatement of nicotine seeking [19,20]. The polymorphism in this gene also mediated several disorders like depressive symptoms, alcohol dependence, bipolar disorder, and nicotine dependence [21-23]. Bipolar disorder formerly called depression, it is a mental health condition that causes utmost mood swings that include higher emotions (mania or hypomania) and lows (depression).When you become depressed, you may feel very low or hopeless and lose interest or pleasure in most of the activities. When your mood shifts to mania or hypomania (less extreme than mania), you may feel euphoric, full of energy or unusually irritable. These mood swings can affect sleep, energy, activity, judgment, behavior and the ability to think clearly. There are many types of bipolar and related disorders. Depression and mania or hypomania may be among them. These symptoms can lead to erratic changes in mood and behaviour, which can cause great distress and make life difficult.

Materials and Methods

The aim of this study is to determine the dopamine level and dopaminergic receptor gene *DOR1* in smokers using VNTR-PCR and ELIZA techniques. The participants in the present study have age (22-34) years, data and blood

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samples were collected with participants approval and according to ethical approval of ministry of higher education and scientific research, its classified to smoker and non-smoker group, dopamine were detected by ELIZA and DNA isolated by favor gene extraction kit.

Amplification conditions and oligos

The VNT-PCR were detected using f-TGTGGTGTAGGGAACGGCCTGAG, r-CTTCCTGGAGGTCACGGCTCAAGG at the following PCR program 95ºC for 5 min, then 35 cycle included (95ºC for 30 sec. annealing tm 57ºC for 1 min and extension 72ºC for 30 sec) then final 72ºC for 7 min. the VNTR variations were detection by electrophoresis using 1% agaros, 70 V for 30 min with ethidum bromide staining and TBE 0.5X. The VNTR frequents detection as following VNTR 11 repeats (520 pb), VNTR 10 repeats (483 pb), VNTR 9 repeats (441 pb), VNTR 7 repeats (361 pb), VNTR 6 repeats (321 pb).

Exclusion criteria

Current study excluded alcohol abuse cases, neurotransmitter disorder cases, cancer cases, virus infection patients, diabetes mellitus type 1 and 2, hypertension cases and patients with kidney disease. All samples were male and apparently healthy.

Data analysis

Data were represented as mean ± stander error, statistical analysis implemented using independent t test, ANOVA one way at p value<0.05 and odd ratio at confidence intervals 95% using SPSS version 23.

Results

The study deal with smoker and non-smoker individuals that have non-significant differences in age and BMI (p=0.553, and p=0.638) respectively (Table 1). The dopamine level was estimated in both groups, output referred to non-significant differences between groups (p=0.823) (Figure 1).

Table 1. Age and BMI differences of smoker and non-smoker group.

Categories	Smoker	Non-smoker	Sig
Age	26.0000 ± 1.87972	27.2174 ± 0.91314	0.553
BMI	23.9500 ± 1.53683	24.7843 ± 0.80089	0.638

Note: Independent T test at p value<0.05.

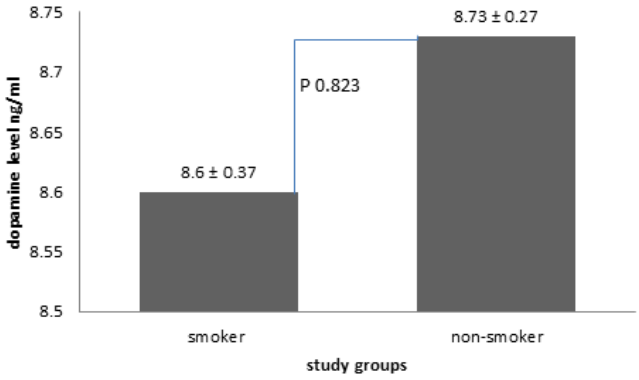

Figure 1. The dopamine level in smoker and non-smoker group.

The VNTR in Dopaminergic Genes *Dat1* was estimated using VNTR-PCR, three VNTR were observed 11(520 bp), 10 (483 bp) and 7(361 bp) (Figure 2). The VNTR11 is more frequent in the smoker group (83.33%) in non-significant variation (p=0.966), also VNTR10 more frequent in the smoker group (16.66%) in non-significant variation (p=0.894) and VNTR7 didn't observed in in smoker group (Table 2).

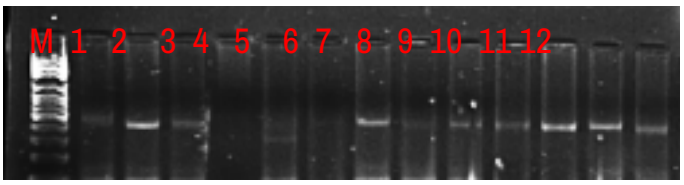

Figure 2. The VNTR frequency in Dopaminergic Genes in study group.

Note: M DNA ladder (100 bp to 1 kb), lanes 1,3,7 VNTR to 12 VNTR 11, Lane 2 VNTR 10, Lane 5 VNTR 7. Electrophoresis condition (1% agaros, 70 V, 30 min with ethidum bromide staining).

Table 2. The Dopaminergic Genes VNTR frequency in the smoker and non-smoker group.

VNTR frequency	Smoker	Non-smoker	Odd ratio	Sig
11(520 bp)	83.33	79.16	0.9500 0.0860 to 10.4993	0.966
10(483 bp)	16.66	12.5	0.7778 0.0187 to 32.3738	0.894
7 (361 bp)	0	4.16	Reference group	

Note: p value<0.05.

The effect of Dopaminergic Genes, *Dat1* VNTR in dopamine level was evaluated, results show there was significant differences observed in non-smoker dopamine level according to VNTR frequency (p=0.025) while non-significant observed in the smoker group (p=0.324) (Table 3).

Table 3. The Dopaminergic Genes VNTR impact on the dopamine level ng/ml in smoker and non-smoker group.

VNTR frequency	Smoker	Non-smoker
7 (361 bp)	0	11.00 ± 0[a]
10(483 bp)	8.00 ± 0	7.866 ± 0.56960[b]
11(520 bp)	8.72 ± 0.43635	8.747 ± 0.29184[ab]
Sig	0.324	0.025

Note: ANOVA one way, different letter refer to signiicant Differences among group at p value less than 0.05. a and b refer to significant differences between 7 and 10 and ab referred to non-significant differences between 11 and 10.

Discussion

Present study deal with effect of Smoking in the dopamine level and VNTR frequency in the *DOR1* gene, this study was suggested because increased the smoking habit among young's and teenagers in the last years; the harmful effects of smoking have been fully described. Non-significant in dopamine level was observed among smoker and non-smoker, present finding deal with other study found that moderate smoking isn't related with changes in the striatal dopamine synthesis capacity [24], while another found elevated in dopamine synthesis in smokers than non-smokers [25], on the other hand the dopamine synthesis is higher in female than male [26]. Belong to *DOR1* VNTR frequency present output indicated that non-significant differences with a smoker, Ruzilawati, et al. found that the genotype of *DOR1* (rs686) was significantly associated with smoking behavior [27]. Others pointed that the polymorphism in *DRD1* is significantly correlated with nicotine dependence in an African American population, which eventually affects the expression of *DOR1* [28]. The passive smoker Non- significant interaction between parental smoke exposure and DOR4 VNTR or *OPRM1* A118G [29].

Furthermore the Dopaminergic changes are hypothesized to underlie addictive behavior [30]. Deal with this, nicotine trigger Nicotinic Acetyl Cholinergic (nACh) receptors leading to release dopamine [31]. The preclinical investigations found that the acute nicotine rewarding impacts are associated with two primary ways. First, nicotine stimulate VTA dopaminergic neurons

directly, that expressed dopamine in the nucleus accumbens, Second, it stimulates nAChR receptors located on the dopaminergic terminals augmenting dopamine release, [32], the dopamine studies that included expression, transporter of dopamine and its receptor levels in smokers found robustness association results while others remains unclear, thus further investigations should be implemented.

The current study has several limitations, first of all the sample size was modest, because most of smokers in Iraq suffered from different disease and health disorder in addition to smoking complications. Till now there is a study that has examined the effect of tobacco smoking on DA release in D3-rich extra-striatal areas or has investigated whether activity at this receptor accounts for motivation to smoke, craving, or mood (anxiety).

Conclusion

The role of dopamine in addictive has been reported; despite of the high percent of smokers and passive smokers in the population, the present study concluded that the smoking didn't effect in the dopamine level and dopamine recptor1 gene polymorphism. The effects of genetic variation on dopamine neurotransmission and that such an approach may be useful for understanding the inter-individual differences in the motor learning, plasticity, and the response to a dopaminergic drug. It also need more investigation to study other SNPs in Dopaminergic Genes that may be related to smoking habit which also included the passive smoker.

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