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ORIGINAL RESEARCH

Association of p.Val158Met *COMT* polymorphism with paranoid ideation in drug addicts

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Abstract

Introduction: Drug addiction is one of the most devastating brain disorders, involving the impairment of brain reward pathway. The enzyme catechol-O-methyltransferase (COMT) metabolizes dopamine and influences the reward pathway functioning. COMT activity is influenced by genetic variations, particularly the p.Val158Met (rs4680); the Met/Met genotype has been associated with a 40% reduction in enzyme activity. The aim of this study was to determine p.Val158Met *COMT* polymorphism in a Portuguese population of drugs addicts seeking treatment and its association with paranoid ideation.

Methods: A group of 106 drug addicts seeking treatment were evaluated, upon written informed consent, taking into account their clinical history. Sixty patients were submitted to an evaluation protocol for neuropsychological assessment. Genetic screening for the *COMT* polymorphism p.Val158Met was performed. Control subjects (n=77) without clinical history of addiction were included, matching for age and socioeconomic status. Statistical analysis was performed (SPSS 19.0®) and significance was considered if $p<0.05$.

Results: Significant differences were observed in genotype and allele frequencies between drug abusers and controls (p-value = 0.0068 and 0.0033, respectively). Moreover, paranoid ideation was associated with Met/Met genotype (p-value = 0.046).

Conclusions: Drug addicts have a higher frequency of Val allele. The Met/Met genotype is associated with higher risk of developing paranoid ideation, probably due to the lower enzyme activity that leads to higher synaptic dopamine levels. The results are preliminary but significant for the study of genetic variability influencing drug addiction and are a relevant contribution for therapeutic strategies.

Keywords: Drug Addiction, COMT, Dopamine, Paranoid Ideation, Reward Pathway.

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Introduction

Addiction is a neurodegenerative chronic disease involving brain reward, motivation, memory and related circuitry [1]. Dysfunction in these circuits leads to biological, psychological, and social characteristic manifestations. Typically, it is observed in subjects compulsively pursuing reward and/or relief by substance use and other similar behaviors. There is no cure available, but it can be brought into remission through a program of treatment, abstinence from all psychoactive substances and supported recovery [2].

Addiction has been conceptualized in a three-stage cycle: binge/intoxication, withdrawal/negative affect and preoccupation/anticipation [3]. The substance use and behaviors will be represented in the brain but, more importantly, drug use alters the brain chemistry in ways that maintain and potentially amplify consumption [4,5]. Addictive drugs produce neuronal changes in cortical and basal ganglia structures, as well as in the mesocorticolimbic dopamine system, leading to changes of synaptic reorganization and function [6-9].

Dopaminergic brain systems have been implicated in drug reward [10,11], so the genes involved in these circuits are plausible candidates for susceptibility to substance use disorders [12]. The catechol-O-methyltransferase (COMT) enzyme is responsible for the inactivation of catecholamines such as dopamine (DA), norepinephrine and epinephrine [13]. A functional polymorphism that involves a valine (Val) to methionine (Met) substitution at codon 158, p.Val158Met (rs4680) has been identified in the *COMT* gene. The alleles are codominant so that individuals with the Val/Val genotype have the highest activity of COMT, those with the Met/Met genotype have the lowest activity and heterozygous individuals have an intermediate level of activity. The Met/Met genotype has been associated with a 40% reduction in COMT activity compared to Val/Val genotype [14], due to differences in protein thermostability [15].

The COMT enzyme has a strong impact on the prefrontal cortex (PFC) functional activity, since it is widely expressed in this area and it is involved in the modulation of the dopamine system. The Met allele has been associated with lower enzyme activity and elevated dopamine levels. Conversely, the Val allele has been associated with higher enzyme activity and reduced dopamine levels [15,16]. Therefore, COMT can modulate aspects of cognition, emotion and behavior [15,17]. In fact, the most studied DA-related polymorphism in psychiatric and behavioral genetics is p.Val158Met. The PFC dysfunction might be important in drug abuse contributing to loss of control and denial [10,18]. Individual genetic differences modulating COMT activity might therefore influence the vulnerability to substance use disorders. The high-activity COMT variant, the Val allele, was found in higher rates in subjects with polysubstance abuse and addiction to nicotine and methamphetamine [19-21].

The present study aimed to investigate the p.Val158Met *COMT* polymorphism in a Portuguese sample of drugs addicts seeking treatment and estimate its association with paranoid ideation.

Material and Methods

Subjects

The study was approved by the Ethics' Committee of the Faculty of Medicine of the University of Coimbra (ID: CE-4/2012), following the Principles of the Helsinki Declaration, and informed consent was obtained from all participants.

A group of 106 drug addicts (93 males and 13 females) seeking detoxification at the Unidade de Desabituação de Coimbra (UDC), ARSC, IP were selected, upon written informed consent, taking into account their clinical history, including the patterns of consumption. Sixty patients were submitted to an evaluation protocol comprising the Montreal Cognitive Assessment (MoCA) [22], Behavioral Inhibition System (BIS11) [23], Brief Symptom Inventory (BSI) [24,25], Buss-Perry Aggression (QA) [26], Clinical, and nutritional habits, for psychological and clinical status. Subjects with significant cognitive deficits were excluded from the study.

Individuals with no clinical history of addiction, matching for age and socioeconomic status, were included as the control group (n = 77) and they did not receive monetary compensations for participating. Individuals carrying HIV or affected with AIDS were also excluded from the study.

Blood samples were collected at hospital admission.

DNA Extraction

The DNA used was extracted from lymphocytes of peripheral blood, collected in EDTA, using a standard phenol-chloroform method, followed by ethanol precipitation. Extracted DNA samples were stored at 4°C until use. The DNA concentration was determined by evaluating the optical density at 260nm and quality was checked by calculation of the ratio optical densities at 260/280nm (NanoDrop, Thermo Fisher Scientific, Inc., Wilmington, USA).

COMT p.Val158Met genotype

The exon and the flanking regions were amplified by polymerase chain reaction (PCR) reaction. For the amplification, 50 ng of DNA were pre-incubated at 95°C for 5 min. Subsequently was added a master mix with dNTPs, 0.16 mM of each (GE Healthcare Life Sciences, Uppsala, Sweden), 1 μM of each primer (forward primer: 5'- TCGTGGACGCCGTGATTCAGG-3', reverse primer: 5'- AGGTCTGACAACGGGTCAGGC-3') [27] (Invitrogen Life Technologies, Carlsbad, United States of America), 1X Taq Buffer and 0.5 U of Taq DNA polymerase (GE Healthcare Life Sciences, Uppsala, Sweden) were used. The PCR conditions were as follows: a initial denaturation at 95°C for 3 min followed by 30 cycles at 95°C for 30 s, 57°C for

30 s, 72°C for 1 min, and a final extension step at 72°C for 10 min. The samples were run in an agarose gel of 1% and visualized with ethidium bromide under UV radiation, the amplified fragment length is 217 base pairs (bp).

PCR products were digested with 2 U of Hps92II (Promega, Madison, WI), followed by an overnight incubation to attain complete digestion. The PCR-RFLP products were run in an agarose gel of 5% and visualized with ethidium bromide. Restriction by Hsp92II produces fragments of 114, 83 and 20 bp for homozygous Val/Val genotype; 114, 96, 83, 38 and 20 bp for heterozygous and 96, 83 e 38 bp for homozygous Met/Met genotype.

Statistical Analysis

For genotype and allele frequencies, Chi-Square or Fisher's exact tests with contingency tables were used. Categorical variables were characterized by determining the absolute and relative frequencies, and numerical variables by the means and standard deviations. Comparative analyses were carried out in relation to demographic variables, food preference, food choice, family drugs use, family alcohol use, MoCA, BSI, QA and BIS. Comparisons between two or more groups with regard to the categorical variables were conducted using the asymptotic Chi-Square Test, or Monte Carlo simulation Chi-Square Test. Regarding the continuous variables, T-Tests were used to compare the means whenever possible, otherwise, the Mann-Whitney U Test was used to compare the medians, for two groups. When comparing more than two groups, ANOVA was used to compare the means, and Kruskal-Wallis H Test to compare the medians. Pearson correlation coefficients were estimated to evaluate the linear relationship between two normally distributed continuous variables. Spearman correlation coefficients were considered when the normality assumption was violated by at least one of the variables. Statistical analyses were conducted using SPSS 19.0®, at a 5% significance level for hypothesis-testing.

For the calculation of adequate population size needed for this work, the software Raosoft® Sample size calculator [28] was used.

Results

The *COMT* allelic frequencies were in accordance with those predicted by Hardy–Weinberg equilibrium. The Val allele is significantly more frequent (frequency of 0.74) than the Met allele (frequency of 0.26) in drug addicts, compared to controls (p-value = 0.0033, Odds Ratio is 1.981, 95% CI 1.272-3.084). Additionally, the comparison of the genotypes' frequencies was also significantly different, p-value = 0.0068 (**Table 1**).

The association study between genotype-phenotype and clinical characteristics revealed significant statistical results for Paranoid Ideation; with the Met/Met individuals having the highest values, p-value = 0.046 (**Table 2**). The association analysis with the other characteristics did not show statistically significant results (results not shown).

Taking into account the Portuguese population that have used illicit drugs (n=655,926) [29] the sample in study represents the population with a confidence level of 90% (error of 8%).

Discussion

The main goal of this study was to investigate p.Val158Met *COMT* polymorphism in a Portuguese sample of drugs addicts seeking detoxification and estimate its association with paranoid ideation.

Although this polymorphism has been already studied in drug addicts [19,20,30], to our knowledge, this is the first screening to include a correlation with paranoid ideation.

In the present study, we found that drug addicts have a higher frequency of high-activity *COMT* variant (Val allele). These results are in accordance with the literature [20,21,31]. But other authors have not replicated these findings [18,32,33]. Therefore, there is no agreement in literature about which of the alleles increases the risk. However, it is logical to think that subjects with a genotype that favors a higher activity of COMT have lower dopamine levels and may be more prone to be addicted.

The explanation for the high frequency of the Val allele in drug addicts could be that this allele reduces DA availability at the synapse, which reduces postsynaptic activation, inducing hypodopaminergic functioning. This state of hypodopaminergic brain function predisposes individuals to seek substances (such as alcohol, psychoestimulants and opiates) and or behaviors (gambling, overeating) [34] that can be used to overcome this craving state by activating the mesolimbic dopaminergic centers [35,36]. Then the release of neuronal DA into the synapse at the nucleus

Table 1. Genotype and allele frequencies comparison between drug addicts and controls.

Genotype	Drug Addicts (n = 106)	Controls (n= 77)	Allele	Drug Addicts (n = 106)	Controls (n = 77)
Val/Val	56 (0.53)	24 (0.31)	Val	156 (0.74)	90 (0.58)
Val/Met	44 (0.41)	42 (0.55)	Met	56 (0.26)	64 (0.42)
Met/Met	6 (0.06)	11 (0.14)			
p	0.0068			0.0033	

Table 2. Results of the association analysis between *COMT* polymorphism and evaluation of paranoid ideation.

	Val/Val	Val/Met	Met/Met	Total
Valid N	23	33	4	60
Mean	1.54	1.70	2.50	1.69
Standard Deviation	0.64	0.69	1.09	0.72
Median	1.60	1.80	2.80	1.80
Minimum	0.40	0.40	1.00	0.40
Maximum	2.80	3.20	3.40	3.40
p		0.046		

accumbens is induced to overcome the hypodopaminergic state. Temporary relief from the discomfort and a pseudo sense of well-being is the product of this behavior [37].

The present paper has also revealed an association between the Met Allele and paranoid ideation, with higher scores for the individuals that carry the Met/Met genotype, which probably confers an increased risk for psychiatric symptoms.

In the brain, the reward effects of drugs of abuse are mediated through multiple sites and mechanisms. However, according to the literature, the activation of the mesocorticolimbic DA system is essential to mediate these reward effects [38,39]. Moreover, the prolonged use of drugs of abuse can lead to alterations in dopaminergic functioning, which has been postulated to underlie partially the development and persistence of addictions [40].

The COMT enzyme is responsible for the inactivation of DA. It has a strong impact on the PFC because it is widely expressed, unlike the dopamine transporter (DAT) [41,42]. In the synaptic cleft the resulting increase in the amount of DA available provides increased substrate to be catabolized by COMT. In contrast, abundant DAT can be observed in several subcortical areas, and thus dopamine levels are largely regulated through presynaptic reuptake by DAT in striatal regions [43].

The DA is one of the key molecular players influencing human behavior, with a major role in learning and motivation, having a particular importance in the context of personality. The link between the levels of dopamine (low or high) and positive emotionality is contradictory, but it has become clear that dopamine plays an essential role in this correlation [44-47]. This relationship may underlie associations between *COMT* p.Val158Met and symptoms in several psychopathologic conditions, including schizophrenia, bipolar disorder and depression [15,48,49].

Schizophrenia is by far the most studied phenotype associated with *COMT* variants, and it is estimated that there is an over-representation of the Val allele with an effect size of approximately 1.1 in schizophrenia patients [48]. Other phenotypes were investigated, such as obsessive-compulsive disorder [50], attention deficit hyperactivity disorder [20,51], panic disorder [52,53] and anorexia nervosa [54] but no significantly results were found, probably due to the polygenic effect occurring in these complex disorders.

According to Liu *et al.* 2017, the Met allele has a negative bias in affective processing, since the Met allele was associated with depressive symptoms and decreased well-being. They hypothesized that the Met allele predisposes individuals to be hyposensitive to positive life events and conversely hypersensitive to negative life events [55].

However, the mechanism of the cognitive consequences of *COMT* genetic variability is far from being simple. Tunbridge and colleagues suggested that the relation between COMT activity and PCF function is not just depending of a "good allele" or a "bad allele". The precise influence of COMT activity on PCF function is complex and depends of other environmental and genetic factors [56].

Although the results were significant, this was a preliminary evaluation and studies in larger samples are warranted to confirm these promising results. However, the data presented here are relevant, showing an association between the *COMT* Val variant and addiction status and a positive correlation between paranoid ideation and the *COMT* Met allele. Thus, our results contribute to shed some light to the understanding of *COMT* genetic variability influencing addiction and clinical manifestations associated to this condition. Additionally, these findings may contribute for developing more rational therapeutic approaches.

Abbreviations

ARSC: Administração Regional de Saúde do Centro; BIS: Behavioral Inhibition System; BP: Base Pairs; BSI: Brief Symptom Inventory; COMT: Catechol-O-methyltransferase; DA: Dopamine; DAT: Dopamine Transporter, HCR-20: Historical, Clinical, Risk Management-20; Met: Methionine; MoCA: Montreal Cognitive Assessment; PFC: Prefrontal cortex; PCR: Polymerase chain reaction; QA: Buss-Perry Aggression; Val: Valine.

Competing interests

The authors declare no conflict of interest.

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