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PSYCHIATRY AND PRECLINICAL PSYCHIATRIC STUDIES - ORIGINAL ARTICLE

Effects of *DRD2* splicing-regulatory polymorphism and *DRD4* 48 bp VNTR on crack cocaine addiction

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Abstract

There is evidence that dopamine receptors D2 (*DRD2*) and D4 (*DRD4*) polymorphisms may influence substance use disorders (SUD) susceptibility both individually and through their influence in the formation of DRD2–DRD4 heteromers. The dopaminergic role on the vulnerability to addiction appears to be influenced by sex. A cross-sectional study with 307 crack cocaine addicts and 770 controls was conducted. The influence of *DRD2* rs2283265 and *DRD4* 48 bp VNTR in exon 3 variants, as well as their interaction on crack cocaine addiction susceptibility and severity were evaluated in women and men separately. An association between the *DRD2* T allele and crack cocaine addiction was found in women. In this same group, interaction analysis demonstrated that the presence of *DRD2*-T allele and concomitant absence of *DRD4*-7R allele were associated with risk for crack cocaine addiction. No influence of *DRD2* and *DRD4* variants was observed in men regarding addiction severity. This study reinforces the role of dopaminergic genes in externalizing behaviors, especially the influence of DRD2–DRD4 interaction on SUD. This is the fourth sample that independently associated the DRD2–DRD4 interaction with SUD itself or related disorders. In addition, our findings point out to a potential difference of dopaminergic neurotransmission across sex influencing addiction susceptibility.

Keywords Cocaine · Crack · Dependence · Dopamine receptor D2 · Dopamine receptor D4 · Substance use disorder

Introduction

Substance use disorders (SUD) have an important prevalence worldwide, with significant rates of mortality and morbidity. Crack cocaine is one of the most severe drugs of addiction, with the reported lifetime prevalence of 1.5% in Brazil (Abdalla et al. 2014), generating relevant behavioral impairments and socioeconomic impacts. Clinical studies demonstrated that crack cocaine users have important clinical differences regarding sex. Women usually exhibit a greater withdrawal response and a faster escalation to addiction than men (Haas and Peters 2000; Becker 2016; Becker et al. 2017; Vernaglia et al. 2017). Moreover, women have earlier onset crack consumption and present more social problems and sexual abuse, while men frequently have problems with law (Pope et al. 2011; Vernaglia et al. 2017). These sexual differences could underlie different neural mechanisms related to crack cocaine addiction.

Crack cocaine, as well as other addictive drugs, modifies the functioning of the reward system in the nucleus

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accumbens and in the ventral tegmental area and impairs decision-making (Gardner 2011; Hulka et al. 2014). Addictive-related behaviors and many brain aspects, including the reward system, seem to be sex-specific (Hardee et al. 2017; Henricks et al. 2017; Logrip et al. 2017; Mosher Ruiz et al. 2017; Sawyer et al. 2017; Hogarth et al. 2018; Dong et al. 2019). Moreover, studies have reported that the maladaptive decision-making is sex-dependent, and the dopamine seems to be relevant to this difference (Georgiou et al. 2018). Considering this evidence, dopaminergic genes, such as the dopamine transporter (*DAT1*), and dopamine receptors D2 (*DRD2*) and D4 (*DRD4*), have been associated with susceptibility to addiction, reinforcing the role of this neurotransmitter system on SUD (Patriquin et al. 2015).

DRD2 is highly expressed in the mesolimbic pathway, which plays an important role in reward (Alcantara et al. 2003), and is associated with cognitive processes (Kellendonk et al. 2006; Blasi et al. 2009; Ward et al. 2010). It has two main splicing isoforms described: the long (D2L) and the short (D2S) isoforms—expressed presynaptic and postsynaptic, respectively (Giros et al. 1989). In this regard, one SNP in the *DRD2* gene—rs2283265—affects its alternative splicing, being related to different substances of abuse (Al-Eitan et al. 2012; Levran et al. 2015). The presence of the T allele was associated with increased expression of the D2L isoform (Zhang et al. 2007), risk to cocaine addiction (Moyer et al. 2011), and cocaine-induced death (Sullivan et al. 2013). In addition, DRD4 is highly expressed in brain areas involved with emotion, reinforcement, and motivation (Primus et al. 1997). The most frequently studied polymorphism in this gene consists of a 48 bp variable number of tandem repeat (VNTR) in exon 3, of which the most common alleles are 2R, 4R, and 7R (2-, 4-, and 7-repeats, respectively). This polymorphism has been largely associated with addiction and addiction-related phenotypes (reviewed by McGeary 2009; Chien et al. 2010; Chen et al. 2011; Das et al. 2011; Xu et al. 2014; Harrell et al. 2016; Mallard et al. 2016). Interestingly, studies indicated that *DRD2* and *DRD4* could interact, forming heteromers (Borroto-Escuela et al. 2011; González et al. 2012).

Regarding the interaction between these two dopamine receptors, it was demonstrated that the D2S isoform can heterodimerize with *DRD4* 2R and 4R variants, but not with the 7R variant (González et al. 2012). On the other hand, the D2L isoform can heterodimerize with all the common variants in *DRD4* 48 bp VNTR, but is less effective in the presence of the 7R variant (Borroto-Escuela et al. 2011). The previous studies demonstrated that *DRD2–DRD4* interaction is associated with externalizing behaviors, as alcohol dependence (Mota et al. 2013b) and conduct disorder (Mota et al. 2013a). However, no study has evaluated this interaction on crack cocaine addiction. In this sense, our aim was to evaluate the influence of *DRD2* rs2283265 and *DRD4* 48 bp VNTR variants, as well as their interaction, on crack cocaine addiction susceptibility and severity, in women and men separately.

Methods

Study design and sample

A cross-sectional study was conducted with crack cocaine addicted individuals in voluntary outpatient and inpatient addiction units of Brazil. The overall sample included 307 crack cocaine addicts and 770 healthy controls. Clinical characteristics of the sample are shown in Table 1. Inclusion criteria for crack cocaine addicts were: (1) diagnosis of crack cocaine addiction according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV-TR; American Psychiatric Association 1994), (2) self-reported as Caucasian, and (3) aged 18 or older. Individuals were excluded if they presented psychotic disorders and/or severe cognitive deficit that would impair the capacity of answering the instruments. The Addiction Severity Index-6

Table 1 Demographics and clinical characteristics of the sample

	Women		Men	
	Controls $n=334$	Cases $n=142$	Controls $n=436$	Cases $n=165$
Age	29.1 (8.9)	31.1 (7.2)	29.2 (8.5)	30.5 (8.7)
8 years or less of schooling (%)[a]	22 (6.6)	39 (46.4)	57 (13.1)	70 (42.4)
Smoking (%)[b]	23 (6.9)	114 (86.4)	47 (10.9)	131 (80.4)
Severity (ASI-6)		$n=270$		$n=270$
Age of first crack use	–	21.0 (8.0)	–	24.0 (9.0)
Years of crack use[c]	–	5.0 (5.0)	–	4.0 (5.0)
Drug score	–	48.4 (10.9)	–	52.7 (6.8)

[a]Sample size is smaller: cases = 249

[b]Sample size is smaller: controls = 764, cases = 295

[c]Median and (interquartile range)

(ASI-6) was used to assess the severity of dependence (Kessler et al. 2012).

A control sample of healthy non-addicted individuals was obtained in southern Brazil. The sample was obtained both from the community and from the blood donation center of a major public university hospital. Inclusion criteria consisted of: (1) negative screening for crack cocaine use and (2) self-reported as Caucasian and (3) aged 18 or older. In the community assessment, the Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST) was used to exclude crack cocaine individuals, followed by a negative urine test for cocaine metabolites. In the blood donation center, the Structured Clinical Interview for DSM-IV screening module—SCID-I/P for the Axis I psychiatric disorders (First et al. 2002)—was used to exclude drug use.

All diagnoses, including psychiatric comorbidities, followed DSM-IV criteria and were discussed on a clinical panel with a senior psychiatrist supervisor. This project was conducted in accordance with the Declaration of Helsinki. All subjects signed an informed consent form that was previously approved by the Institutional Review Boards of the participating institutions.

Laboratory methods and polymorphism selection

DNA was extracted from peripheral blood according to an adapted protocol from Lahiri and Nurnberger (1991), or from saliva samples using the Oragene© DNA Genotek kit (Canada). Polymorphisms evaluated in this study were selected due to the heterodimerization pattern mentioned above. *DRD4* 48 bp VNTR was genotyped through PCR followed by agarose gel electrophoresis. *DRD2* rs2283265 was genotyped through real-time PCR using the validated TaqMan® SNP genotyping assay (Applied Biosystems, Foster City, CA, USA). Allele frequencies and Hardy–Weinberg equilibrium are presented in Supplementary Table 1.

Statistical analyses

Logistic regression models were used to assess the influence of each polymorphism and the gene–gene interaction on crack cocaine susceptibility. Taking into account the described heterodimerization pattern, all analyses assessing the influence of both polymorphisms on different outcomes included only samples presenting the three main *DRD4* variants—2R, 4R, and 7R. Analyses were performed according to the presence of the *DRD4* 7R allele (2R7R, 4R7R, and 7R7R genotypes) compared to 2R2R, 2R4R, and 4R4R genotypes, while *DRD2* rs2283265 was assessed considering the presence of the T allele compared to G homozygous. To evaluate a possible interaction effect, four independent categories were considered (GG/7R+; GG/7R−; T+/7R+; T+/7R−). Effects of the genetic variables on the ASI-6 subscale for drugs were evaluated using *t* test or analysis of variance (ANOVA). Potential covariates (age, years of schooling, smoking, major depressive disorder, and bipolar disorder) were evaluated to perform possible adjustments in the statistical analyses; however, no variable was associated with both outcome and polymorphisms ($P \leq 0.2$). Considering evidence about sex differences in the clinical profile of crack cocaine addicted individuals, and also due to the putative influence of sex on dopaminergic neurotransmission, the effects of *DRD2* and *DRD4* genes were explored in women and men separately. All analyses were performed with SPSS version 18 software (SPSS, Chicago, IL, USA). Considering that analyses were based on defined biological evidence, we did not perform multiple test corrections. A significance level of 5% was set for all analyses.

Results

Case-control analyses are shown in Tables 2 and 3. In women, a main effect of *DRD2* rs2283265 was observed, in which the presence of the T allele was associated with risk to crack cocaine addiction (OR 1.524; $P = 0.0441$). No significant main effect of the *DRD4* 48 bp VNTR was detected. In addition, an association was observed when evaluating interaction effects. The presence of the *DRD2*-T allele in the absence of the *DRD4*-7R allele was associated with risk for crack cocaine addiction (OR 2.023, $P = 0.0351$) among women. In men, we observed no influence of *DRD2* and *DRD4* genes on crack cocaine addiction. Regarding addiction severity (ASI-6 drug score), no significant association was detected in both women and men (Supplementary Table 2).

Discussion

Our study showed an influence of the interaction between *DRD2* rs2283265 and *DRD4* 48 bp VNTR polymorphisms on crack cocaine addiction for the first time. This is the fourth independent sample to associate the *DRD2–DRD4* interaction with psychiatric disorders, extending findings to another addictive behavior. In addition, externalizing behaviors, such as conduct disorder—previously associated with the DRD2–DRD4 interaction—are correlated with the presence of impulse control disorders in adults, such as addiction (Fergusson et al. 2008). In this sense, our results demonstrate that this interaction is consistently implicated with substance use and related phenotypes, which could add crucial knowledge underlying neural mechanisms of drug dependence. Furthermore, we replicated the effect of *DRD2* rs2283265 T allele on crack cocaine addiction (Moyer et al. 2011).

Table 2 Effects of *DRD2* rs2283265 and *DRD4* exon 3 VNTR polymorphisms on crack cocaine addiction susceptibility (women only)

	B	SE	Wald	*df*	OR	CI 95%	*P* value
Main effects							
DRD2 rs2283265							
GG (reference)	0				1		
T+	0.421	0.209	4.053	1	1.524	1.011–2.296	**0.0441**
DRD4 exon 3 VNTR							
7R− (reference)	0				1		
7R+	−0.368	0.227	2.630	1	0.692	0.443–1.080	0.1049
Interaction effects							
GG/7R+ (reference)[a]	0			1			
GG/7R−	0.410	0.289	2.016	1	1.507	0.856–2.653	0.1557
T+/7R+	0.353	0.375	0.886	1	1.423	0.683–2.965	0.3464
T+/7R−	0.704	0.334	4.439	1	2.023	1.050–3.895	**0.0351**

Significant *P* values are in bold

SE standard error, *OR* odds ratio, *CI* confidence interval, − noncarrier, + carrier

[a]Coded according to Knol et al. (2011)

Table 3 Effects of *DRD2* rs2283265 and *DRD4* exon 3 VNTR polymorphisms on crack cocaine addiction susceptibility (men only)

	B	SE	Wald	*df*	OR	CI 95%	*P* value
Main effects							
DRD2 rs2283265							
GG (reference)	0				1		
T+	0.045	0.190	0.057	1	1.046	0.721–1.520	0.8117
DRD4 exon 3 VNTR							
7R− (reference)	0				1		
7R+	−0.224	0.199	1.269	1	0.799	0.541–1.180	0.2600
Interaction effects							
GG/7R+ (reference)[a]	0			1			
GG/7R−	0.254	0.247	1.059	1	1.289	0.795–2.092	0.3035
T+/7R+	0.035	0.320	0.012	1	1.036	0.553–1.940	0.9119
T+/7R−	0.204	0.287	0.509	1	1.227	0.699–2.152	0.4758

SE standard error, *OR* odds ratio, *CI* confidence interval, − noncarrier, + carrier

[a]Coded according to Knol et al. (2011)

The *DRD2* gene has been largely associated with several disorders and behaviors, and many studies investigated the importance of D2 alterative splicing, although findings with specific SNPs are usually inconsistent (reviewed by Moyer et al. 2011). The previous studies have associated the rs2283265 T allele in this gene with greater availability of the D2L receptor (compared to D2S isoform) and reduced mRNA stability (Duan et al. 2003). In line with our findings, this allele has been associated with increased risk of addiction to cocaine (Moyer et al. 2011), heroin (Levran et al. 2015), and substance abuse in general (Al-Eitan et al. 2012). The presence of the T allele has also been related to cocaine-induced death (Sullivan et al. 2013), reduction in cocaine-positive urine samples during disulfiram treatment for addiction (Spellicy et al. 2013) and lower dose of methadone for the treatment of opioid treatment (Levran et al. 2013).

This same SNP is involved in the other replicated finding presented here, the *DRD2–DRD4* interaction, being especially robust considering that all previous studies are either related to the pathway of SUD (Mota et al. 2013a) or SUD itself (Mota et al. 2013b). In addition, the gap between molecular heritability and the heritability estimated by twin studies suggests that non-addictive genetic components, such as gene–gene interactions, could be involved in different phenotypes (Mbarek et al. 2015; Stringer et al. 2016).

The DRD2–DRD4 heterodimerization mechanism was better understood through the studies of Borroto-Escuela et al. (2011) and González et al. (2012). In this sense, the absence of the 7R-allele may enhance affinity of D2L to

dopamine agonists, also presenting allosteric effects. Interestingly, the influence of the rs2283265 T allele seems to be more pronounced in the absence of the 7R-allele of *DRD4* gene on addicted women, whereas no risk effect was associated with the concomitant presence of *DRD2* T allele and *DRD4* 7R-allele. Such observations are in line with a previous study regarding conduct disorder, demonstrating that the risk conferred by the rs2283265-T allele is increased when in the absence of the 7R allele (Mota et al. 2013a).

Neurological differences between men and women have been highlighted in many studies, especially related to brain structural and functional features, and genetic and epigenetic factors (Zaidi 2010; McCarthy et al. 2012; Ratnu et al. 2017; Hyer et al. 2018). There is a discrepancy in the clinical profile and prognostic between sexes in many psychiatry disorders, which may reflect, at least partially, important neurobiological differences. Concerning addiction, a number of associated brain aspects and behaviors seem to be sex-specific (Hardee et al. 2017; Henricks et al. 2017; Logrip et al. 2017; Mosher Ruiz et al. 2017; Sawyer et al. 2017; Hogarth et al. 2018). Evidence demonstrated that addicted women had a more severe crack cocaine use disorder and are more vulnerable to the consequences of addiction than men (Haas and Peters 2000; Becker 2016; Becker et al. 2017; Vernaglia et al. 2017). In addition, preclinical and clinical studies suggest that the relationship between SUD and the dopaminergic system might also be influenced by sex differences (Becker 1999; Walker et al. 2006). For instance, women present more dopamine transporters than men in the striatum (Lavalaye et al. 2000; Mozley et al. 2001; Staley et al. 2001). Furthermore, dopamine agonists, such as cocaine, induce different behavioral and neuroendocrine effects in females and males (Bowman and Kuhn 1996; Walker et al. 2001a, b). Preclinical studies showed that female rats have greater acquisition, maintenance, and reinstatement of cocaine self-administration compared with males, suggesting sex differences on the vulnerability to addiction (Lynch and Carroll 1999; Lynch et al. 2000; Hu et al. 2004). Considering these findings, we suggest that the presence of the *DRD2* T allele and absence of *DRD4* 7R-allele might increase the susceptibility to crack cocaine dependence, especially in women, by increasing D2 receptor affinity and modulating dopaminergic and glutamatergic systems.

These findings should be interpreted in light of limitations. First of all, there may be lack of statistical power to detect the other individual or interaction effects due to our modest sample size, along with the small effect size of genes on psychiatric phenotypes. In addition, our study does not evaluate expression pattern or functionality of those dopaminergic receptors. However, in our study, the hypothesis tested was based on the previous findings. The use of other addictive drugs—such as alcohol or nicotine, among crack cocaine addicts should be carefully considered. Nonetheless, crack cocaine addicted individuals usually use multiple substances, making it difficult to overcome this issue.

Overall, a strong influence of the *DRD2* gene—especially rs2283265—in the pathophysiology of addiction is well established. Nonetheless, studies focusing in the interaction among dopamine receptors may improve our knowledge on complex traits. In summary, our results reinforce a role of *DRD2–DRD4* interaction on addiction and point to the relevance of considering a differential influence of dopaminergic neurotransmission across sexes. Our data must be understood in the context of a complex psychiatric trait with high heterogeneity, where further replication is required.

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Compliance with ethical standards

Conflict of interest The author(s) declare the following potential conflict of interest with respect to the research, authorship, and/or publication of this article: Dr. Grevet was on the speaker's bureau for Novartis and Shire for the last 3 years. He also received travel awards (air tickets and hotel accommodations) for participating in two psychiatric meetings from Shire and Novartis. All other authors reported no financial interests or potential conflicts of interest.

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