Journal of Psychiatric Research 77 (2016) 8–14

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

Epistatic interactions involving DRD2, DRD4, and COMT polymorphisms and risk of substance abuse in women with binge-purge eating disturbances

Howard Steiger [a, b, c, *], Lea Thaler [a, b, c], Lise Gauvin [c, d], Ridha Joober [b, c], Aurelie Labbe [b, c], Mimi Israel [a, b, c], Audrey Kucer [a]

[a] Eating Disorders Program, Douglas University Institute, Canada
[b] Psychiatry Department, McGill University, Canada
[c] Research Centre, Douglas University Institute, Canada
[d] Research Centre, University of Montreal Hospital Centre, Canada

ARTICLE INFO

Article history:
Received 7 October 2015
Received in revised form
13 December 2015
Accepted 18 February 2016

Keywords:
bulimia nervosa
substance abuse
dopamine
genes
DRD2
DRD4

ABSTRACT

Substance abuse is common in individuals with bulimia-spectrum (binge-purge) eating disturbances, a co-occurrence that has been attributed to shared neurobiological substrates–notably alterations in dopaminergic activity. We examined the implications of variations of selected, dopamine-relevant polymorphisms (DRD2 Taq1A, DRD4 7R, and COMT) for risk of substance abuse in women with binge-purge eating syndromes. We genotyped 183 women (66.1% showing full-threshold BN and 33.9% showing sub-syndromic variants), and assessed lifetime presence of alcohol, cannabis, cocaine, and stimulant abuse or dependence using structured interviews. Tests for main and interaction effects of various allele combinations revealed that individuals who carried high function COMT and low-function DRD4 7R alleles (a combination expected to be associated with higher risk) did indeed show more lifetime substance abuse and, specifically, more cannabis abuse. Our findings suggest that a gene combination that, in theory, codes for low levels of dopaminergic neurotransmission coincides with sensitivity to substance abuse in a sample displaying binge-purge eating-disorder variants.

Eating disorders (EDs) and substance-use disorders (SUDs) co-aggregate within individuals and within families, especially in the context of ED variants characterized by binge-eating and/or purging. A 2007 US National Comorbidity Survey indicated lifetime rates of SUDs to be 55% in people with BN (Hudson et al., 2007), a trend that has been consistently replicated elsewhere (see Bulik et al., 2004; Holderness et al., 1994). Likewise, a recent community-based study associated "binge-eating/purging", "binge-eating alone", or "purging alone" variants of eating disturbance with higher risk of alcohol and drug abuse (Swanson et al., 2014). In binge-purge syndromes, concurrent substance abuse has been associated with more pronounced psychopathology (Lilenfeld et al., 1998), impulsivity and perfectionism (Bulik et al., 2004). The present study explored the extent to which genetic factors that correspond to substance-abuse potentials in other populations also predicted specific likelihood of substance abuse in people with binge-purge syndromes.

Among various mechanisms that could explain co-aggregation of substance-use disorders with binge-purge syndromes, there are reasons to consider a role of shared biology. First, binge-purge syndromes and substance misuse are likely to coincide with similar alterations in neurotransmitter, and notably dopamine, function. In active BN, frequency of binge-eating and purging has been associated with reduced CSF levels of the dopamine (DA) metabolite HVA (Jimerson et al., 1992). Likewise, research has shown people with BN to display decreased D2/D3 receptor binding in putamen and caudate (Broft et al., 2012), and reduced striatal activity during tasks involving reward (Wagner et al., 2010) or self-regulatory control (Marsh et al., 2009). Substance abuse is observed to coincide with parallel underactivity of dopaminergic systems associated with self-control, stress reactivity, reward sensitivity and incentive motivation (Volkow et al., 2013). For instance, in substance abusers, striatal PET [11C] raclopride (D2 receptor) binding

* Corresponding author. Eating Disorders Program, Douglas University Institute 6603-05 Lasalle Blvd, Verdun, Quebec H4H 1R3, Canada.
E-mail address: stehow@douglas.mcgill.ca (H. Steiger).

http://dx.doi.org/10.1016/j.jpsychires.2016.02.011
0022-3956/

potential is reduced (Volkow et al., 2009). Strengthening belief in a common, dopamine-linked diathesis, twin data indicate shared genetic liabilities for EDs and SUDS (Bulik and Tozzi, 2004), and molecular-genetic studies in BN and SUDs implicate genes that code for sensitivity of dopamine receptors.

Within the dopamine system, certain genes have been linked to substance abuse–including those coding for sensitivity of dopamine-2 (DRD2) and dopamine-4 (DRD4) receptors, and for DA breakdown via catechol-O-methyltransferase (COMT) activity. The Taq1A polymorphism is a commonly studied DRD2 gene variant. Across populations, carriers of the low-function T allele (T/T or T/C genotypes) show reduced brain dopamine function when compared to C/C homozygotes (Ritchie and Noble, 2003). The T allele has been associated with obesity (Stice et al., 2010), impulsivity (Eisenberg et al., 2007), substance use (Le Foll et al., 2009), and reward sensitivity in binge eaters (Davis et al., 2008). Also a candidate of interest, the Exon-3 seven-repeat (7R) allele of DRD4 codes for decreased dopamine receptor affinity (Asghari et al., 1995), and has been associated with impulsivity (Eisenberg et al., 2007) and frequent substance abuse (Vandenbergh et al., 2000). Suggesting a relevance to BN, studies have associated the 7-repeat allele with high-frequency binge eating (Levitan et al., 2004). Finally, COMT (rs4680) influences availability of DA in the synapse, especially in frontal regions, with Met and Val alleles respectively governing slower or more rapid DA degradation (Benjamin et al., 1996). Multiple substance abusers are reported to more frequently carry the high-activity Val/Val genotype than do people reporting negligible use of substances (Vandenbergh et al., 1997). Likewise, heroin addicts have been reported to more frequently carry the Val allele than do controls (Horowitz et al., 2000). Studies investigating associations between COMT rs4680 and BN have generally pointed to involvement of the higher activity (Val) allele as risk factor for BN (Mikołajczyk et al., 2010; Amorim-Barbosa et al., 2015; Thaler et al., 2012), although contradictory findings exist (Donofry et al., 2014).

1. The present study

To date, no study has explored the association between dopaminergic gene variations and substance use in individuals with binge-purge eating syndromes. To fill this knowledge gap, we examined the bearing of variations within the DRD2 Taq1A, DRD4 7R, and COMT polymorphisms upon risk of misuse of alcohol, cannabis, cocaine and stimulants in women with bine-purge eating disorder variants. Although phenomenological differences exist, evidence has shown women with binge-purge or purge-only eating disturbances to share many features–including personality traits like impulsivity (Brown et al., 2011), triggering effects of negative affect (Haedt-Matt and Keel, 2015), and experiences of loss of control over eating (Forney et al., 2014). Likewise, previous research has shown that women with full-blown BN do not differ substantially from those with sub-threshold forms (Fairburn and Harrison, 2003). We therefore opted, in this investigation, to include women with full-blown and sub-threshold binge-purge disorders, including “bingers-purgers”, “bingers only” and “purgers only”. We note, however, that we made efforts (described in sections to follow) to verify that inclusion of non-bingeing participants did not distort findings that might only apply to binge-eating individuals.

In general, we hypothesized that carriers of alleles coding for relatively low post-synaptic dopamine receptor sensitivity (i.e., low-function alleles of DRD2 or DRD4), or for relatively high DA breakdown (i.e., COMT Val/Val), might be more prone to substance use than would individuals carrying other alleles. In a related vein, we explored the possibility of epistatic (gene x gene) interactions in which individuals carrying gene combinations corresponding to particularly reduced dopamine activity—namely, either low-function DRD2 or low function DRD4 (implying low receptor sensitivity) with high-function COMT (implying rapid DA breakdown)—might evince particularly marked risk of substance misuse. In non-eating-disordered populations, epistatic interactions like those described have been demonstrated for various mental-health entities, including interactions between: DA transporter and DRD2 receptor variants and risk of lethal cocaine abuse (Sullivan et al., 2013), glutamatergic and dopaminergic genes and opiate abuse (Jacobs et al., 2013), DRD2, DRD3 and DRD4 receptor genes and nervousness (Vandenbergh et al., 2007), and DRD4 and COMT and prefrontal functions underlying response control (Heinzel et al., 2013). A basic assumption underlying our investigation was that dopaminergic propensities that increase risk of substance abuse in other populations (in which bulimic symptoms are absent) would heighten risk of substance abuse in our eating-disordered sample–and that dopaminergic tendencies associated with risk of substance abuse would act independently of those associated with severity of binge-purge symptoms.

2. Methods

2.1. Participants

All participants in this institutional ethics board approved study provided written informed consent and all received modest monetary compensation for time invested. Participants were recruited through a specialized eating disorders program using the criteria: Body Mass Index (BMI) above 17.5 and below 40, and meeting criteria for Bulimia Nervosa (BN) or Eating Disorder Not Otherwise Specified (EDNOS) with binge eating and/or purging according to the *Diagnostic and Statistical Manual of Mental Disorders*, DSM-IV-TR (American Psychiatric Association, 2000). Our sample consisted of 183 women, 121 (66.1%) meeting criteria for BN, and 62 (33.9%) meeting criteria for EDNOS. Mean number of binge episodes per month was 22.69 ($SD = 26.23$, range = 0–102.6), and mean number of episodes of vomiting or other forms of purging per month was 36.42 ($SD = 43.02$, range 0–177.0). Mean BMI (kg/m^2) in our sample was 22.34 ($SD = 3.98$; range = 17.5–38.23) and mean age was 26.16 ($SD = 6.85$; range = 17–49). Limiting recruitment to unmedicated individuals was impractical (and undesirable on grounds of representativeness), and we therefore included 73 participants (58.4% of the sample) who were taking a psychoactive medication when tested (data available from 125 out of 183 participants). We note that frequency of medication use did not differ significantly by allele frequency for any of the four genes tested. The Quebec population from which this sample was drawn is skewed towards individuals of Caucasian, Western-European descent. Consequently, our sample included mainly Caucasian individuals (n = 160, or 95.2% of the sample). However, isolated individuals with other ethnic and racial origins were also included–2 (1.2%) being Aboriginal, 2 (1.2%) Asian, 2 (1.2%) Black, 1 (0.6%) native Hawaiian or Pacific Islander and 1 (0.6%) Latin American (data available for 160 out of 183 participants). Using data on socioeconomic status (also available for 160 participants) we classified participants into 3 groups: Low income = total annual household income under $20,000; medium income = total household income between $20,000 and $50,000; high income = household income above $50,000 per year. A chi-squared test revealed no significant differences between the groups on rates of any form of substance use [$\chi^2_{(2)} = 1.22$, $p = .544$], which were as follows: Low income group = 41.1%; medium income = 36%, high income = 31.1%.