Drug and Alcohol Dependence 120 (2012) 220–224

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

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

Short communication

The aldehyde dehydrogenase 2 gene is associated with heroin dependence

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ARTICLE INFO

Article history:
Received 17 February 2011
Received in revised form 3 June 2011
Accepted 7 June 2011
Available online 1 July 2011

Keywords:
ALDH2
DRD2
Heroin dependence
Addition
Han Chinese in Taiwan

ABSTRACT

Background: Determining the influences of genes involved in metabolizing dopamine and encoding dopamine receptors, such as the *aldehyde dehydrogenase 2* (*ALDH2*) and *dopamine D2 receptor/ankyrin repeat and kinase domain containing 1* (*DRD2/ANKK1*) genes, is critical for understanding addictive behavior. Therefore, we investigated the association between the *ALDH2* and *DRD2/ANKK1 Taq IA* polymorphisms and heroin dependence.
Methods: Heroin-dependent Han Chinese patients (250) and healthy controls (312) were recruited. *ALDH2* and *DRD2/ANKK1 Taq IA* polymorphisms were genotyped.
Results: The frequency of *ALDH2*1/*2* and **2/*2* genotypes was significantly higher in heroin-dependent patients than in controls, but the frequency of *DRD2 Taq IA* genotypes was not significantly different. Logistic regression analysis showed no significant interaction between *ALDH2* and *DRD2 Taq IA* genotypes in patients.
Conclusions: The *ALDH2* polymorphism, but not the *DRD2*, was associated with heroin dependence.

1. Introduction

The pathogenesis of addiction is multifactorial and associated with genetic and environmental risk factors (Tsuang et al., 1996). Although genetic factors contribute to heroin dependence (Tsuang et al., 1998), the susceptibility genes remain unknown. The dopamine pathway in the mesocorticolimbic region is the major candidate for analysis of addiction (Wise, 2004; Robbins and Everitt, 1999). Therefore, genes involved in the metabolism of dopamine and encoding dopamine receptors may be important targets for investigating heroin dependence.

Human and animal studies have hypothesized that the dopamine D2 receptor (DRD2) contributes to addiction. In studies of mice lacking the D2 receptor (Maldonado et al., 1997; Elmer et al., 2002), the reward effects of opiate were absent. Some genetic studies (Blum et al., 1990; Comings et al., 1996; Lawford et al., 2000; Noble, 2003; Xu et al., 2004; Perez de los Cobos et al., 2007; Hou and Li, 2009) reported that the *DRD2/ANKK1 Taq IA A1 allele* was associated with several substance abuse/dependence outcomes, including heroin dependence. Subsequent studies (Li et al., 2002; Barratt et al., 2006; Crettol et al., 2008), however, were unable to confirm the association. One possible explanation for this discrepancy may be the heterogeneity of heroin dependence groups with complex comorbidities.

Several enzymes are involved in dopamine metabolism. Dopamine is metabolized by monoamine oxidase to form 3,4-dihydroxyphenyl-acetaldehyde (DOPAL) (Westerink and de Vries, 1985; Cesura and Pletscher, 1992). DOPAL is subsequently oxidized to 3,4-dihydroxyphenylacetic acid (DOPAC) by aldehyde dehydrogenase (ALDH) (Cesura and Pletscher, 1992; Lamensdorf et al., 2000). ALDH2 is one of the major ALDH isozymes that catalyzes the oxidation of dopamine (Keung and Vallee, 1993). The *ALDH2*1/*1*-genotype-encoded enzyme is an active form in the metabolism of acetaldehyde, while the ALDH2*1/*2 and the ALDH*2/*2-polymorphisms-encoded enzyme are partially and completely inactive, respectively (Crabb et al., 1989; Yoshida et al.,

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doi:10.1016/j.drugalcdep.2011.06.008

Table 1
Genotype and allele distributions of *ALDH2* and *DRD2 Taq-IA* polymorphisms in heroin dependent patients and healthy controls.

	Heroin dependence	Controls	χ^2	*P*-value
Genotype frequency				
Size (n)	250	312		
ALDH2 genotype (%)			11.000	0.004*
*1/*1	98 (39.2%)	154 (49.4%)		
*1/*2	112 (44.8%)	133 (42.6%)		
*2/*2	40 (16.0%)	25 (8.0%)		
DRD2 genotype (%)			4.618	0.099
A1/A1	34 (13.6%)	54 (17.3%)		
A1/A2	124 (49.6%)	127 (40.7%)		
A2/A2	92 (36.8%)	131 (42.0%)		
Allele frequency				
Size ($2n$)	500	624		
ALDH2 allele (%)			10.278	0.001*
*1	308 (61.6%)	441 (70.7%)		
*2	192 (38.4%)	183 (29.3%)		
DRD2 allele (%)			0.064	0.800
A1	192 (38.4%)	235 (37.7%)		
A2	308 (61.6%)	389 (62.3%)		

* $P < 0.05$.

1991; Wurst et al., 2005). Although the *ALDH2*2* allele is rarely seen in Caucasians, about 50% of the Asian population carries this allele (Agarwal and Goedde, 1992), including Han Chinese in Taiwan (Thomasson et al., 1991; Chen et al., 1999). As a metabolizing enzyme for dopamine, we hypothesize that the *ALDH2* gene is involved in the pathogenesis of heroin dependence and interacts with the *DRD2* gene in dopamine system.

Researchers have suggested that how the phenotype of the clinical group was defined and how the controls were selected might affect the results (Lee, 2003; Young et al., 2004). The aim of the present study was to investigate the association between the *ALDH2* and *DRD2/ANKK1 Taq IA* polymorphisms in heroin-dependent Han Chinese patients, using a relatively homogeneous study group.

2. Methods

2.1. Participants

The research protocol was approved by the Institutional Review Board for the Protection of Human Subjects at National Cheng Kung University Hospital. The procedures were fully explained to each participant before they were asked to give written informed consent.

We recruited heroin-dependent Han Chinese patients from the methadone maintenance treatment program at National Cheng Kung University Hospital. Each participant was initially interviewed by an attending psychiatrist and then by a research team member well trained in using the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV) (American Psychiatry Association, 1994) criteria and the Chinese Version of the *Mini International Neuropsychiatric Interview* (MINI) (Sheehan et al., 1998). The MINI was used to evaluate patients because it is difficult for them to complete 4–6 h of structured interviews, such as the Chinese Version of the Modified Schedule of Affective Disorder and Schizophrenia-Lifetime (SADS-L) (Endicott and Spitzer, 1978). We initially recruited 300 heroin dependent patients free of major and minor psychiatric illness except substance abuse/dependence, and then we excluded 48 patients comorbid with alcohol abuse/dependence and 6 patients comorbid with antisocial personality disorder, 4 of whom were also comorbid with alcohol abuse/dependence. Our final study sample consisted of 214 men and 36 women; 85 of these patients had a history of amphetamine use.

The healthy control group included 312 volunteers (male/female: 244/68) recruited from the community. The Chinese Version of the SADS-L (Endicott and Spitzer, 1978; Huang et al., 2004) was used to screen their psychiatric conditions. All controls were free of present and past mental illness and none had a family history of psychiatric disorder among their first-degree relatives.

2.2. Blood samples and genotyping

Twenty milliliters of venous blood was drawn and DNA was extracted. The *DRD2/ANKK1 Taq IA* polymorphism was genotyped using a polymerase chain reaction–restriction fragment length polymorphism (PCR–RFLP) assay (Grandy et al., 1993). The *ALDH2* gene was genotyped using protocols described elsewhere (Dandre et al., 1995).

2.3. Statistics

The differences in the frequency of *ALDH2* and *DRD2/ANKK1 Taq IA* genotypes between patient and control groups were calculated using Pearson's χ^2 analysis (two-tailed). Fisher's exact test was substituted for the χ^2-test when values were smaller than expected (<5). Student's t-test was used to estimate differences in mean age between two groups. Significance was set at $P < 0.05$. Logistic regression was used to control for (1) the covariates of age and sex when examining the possible interaction between the *ALDH2* and *DRD2/ANKK1* genes and (2) their main effects for the risk of heroin dependence. SPSS 17.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. The power estimation was calculated using G-power 3.1 software (Faul et al., 2009). Our total sample size ($n = 562$) had a power of 0.55 to detect a small effect (effect size = 0.1) and of 1.00 to detect a medium effect (effect size = 0.3) and a large effect (effect size = 0.5) of genotype distributions. For allele frequencies ($n = 1124$), this study had a power of 0.92 to detect a small effect and 1.00 to detect medium and large effects.

3. Results

The mean age of the patients and controls was not significantly different: 37.2 years (SD = 7.3) and 36.5 years (SD = 10.6), respectively, ($t = -0.89$, $P = 0.37$). However, there were more women in the control group ($\chi^2 = 5.03$, $P = 0.03$).