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ORIGINAL INVESTIGATION

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Dopamine D4 receptor polymorphism modulates cue-elicited heroin craving in Chinese

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Abstract *Rationale:* Subjective craving, which contributes to the continuation of drug use in active abuser and the occurrence of relapse in detoxified abusers, is considered to be a central phenomenon in addiction. Dopamine pathway has been implicated in the mechanism underlying the cue-elicited craving for a variety of addictive substances. *Objectives:* The objective of this study was to test the hypothesis that heroin addicts carrying D4 dopamine receptor gene (*DRD4*) variable number tandem repeat (VNTR) long type allele would have higher craving after exposure to a heroin-related cue. *Materials and methods:* Craving was induced by a series of exposure to neutral and heroin-related cue and were assessed in a cohort of Chinese heroin abusers (n=420) recruited from the Voluntary Drug Dependence Treatment Center at Shanghai. *Results:* Significantly stronger cue-elicited heroin craving was found in individuals carrying *DRD4* VNTR long type allele than the non-carriers (F=31.040, p<0.001). As for baseline craving and mean change in craving responding to neutral stimuli, no significance was found (1.06±0.34 vs 1.07±0.36, F=0.067, p =0.797 and 0.42±0.34 vs 0.45±0.37, F=0.277, p=0.599, respectively). *Conclusions:* The results of our study suggest that *DRD4* VNTR polymorphism contributes to cue-elicited craving in heroin dependence, indicating *DRD4* VNTR represents one of potential genetic risk factors for cue-induced craving.

Keywords Heroin · Craving · Polymorphism · *DRD4*

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Introduction

Although the etiology of heroin dependence remains controversial, drug dependence is believed to be a result from the interaction between multiple genetic and environmental factors (Imlah 1989; Duaux et al. 2000). The vulnerability to drug dependence in the population is attributable to genotypic differences of several candidate genes related to the function of the central nervous system (CNS) (Hutchison et al. 2002a,b; Grove et al. 1990). It is believed that the dopaminergic system is involved in the mechanisms of reward and reinforcing in the brain, especially the mesolimbocortical region, and the reinforc-

ing effects are related with dopamine release (Robin and Everitt et al. 1999; Koob and Nestler 1997). The function of dopamine is mediated by two classes of dopamine receptors—D1- and D2-like families. The D2-like receptors (including D2, D3, and D4 dopamine receptors) mediate the reward and reinforcement effects, in contrast to the family of D1-like receptors which may mediate a reduction in the drive to seek reinforcement (Self et al. 1996). *DRD4* was cloned by Van Tol et al. 1991 and has similar structural and pharmacological characteristics to D2 and D3 receptor (Van Tol et al. 1991, Gelernter et al. 1992). In addition, a highly polymorphic 48-bp variable number tandem repeat (VNTR) in exon III of *DRD4* occurs within a praline-rich coding region, with the most common variants being the 2, 4, and 7 repeats. The 7 allele exhibits more poor response to dopamine in comparison with that of the 2 and 4 allele, which may affect receptor function (Van Tol et al. 1992, Asghari et al. 1995). *DRD4* VNTR polymorphism has been thought to associate with addictive disorder (Gelernter et al. 1997). Two studies, for example, reported an excess of 7 repeat allele or long repeat allele (5–7 repeats) in opioid-dependent subjects from Israel and China, respectively (Kotler et al. 1997; Li et al. 1997). Later, however, Li et al. (2000) didn't replicate the previous result with a larger sample. Furthermore, a study with German samples failed to find an association between long allele and opioid dependence either (Franke et al. 2000).

One possible reason for the conflicting findings in the literature may be the lack of experimental control over the multiple factors that affect the addiction in the real-world settings (Lerman and Swan 2002). One of the approaches to solve the problem is to examine the genetic influence on a more narrowly defined and tightly characterized endophenotype which should be closely connected with a potential biological mechanism. Cue-elicited craving is a candidate endophenotype, which has been employed in previous reports that CNS dopamine pathway is critical in the biological mechanism underlying cue-induced smoking craving and alcohol craving (Erblich et al. 2005, Hutchison et al. 2002a,b). Although the definition and clinical relevance of craving are still a matter of controversy (Sayette et al. 2000), numerous studies showed that craving plays a crucial role in persistent drug-taking and relapse, and it has been the available target of pharmacological and behavioral therapy. Furthermore, both animal models and human studies demonstrated that the craving for heroin and other substance abuse could be induced in the laboratory by drug-related cue, stress, or priming dose of drug itself (Lu et al. 2002, Dackis and O'Brien 2001). It has been conceptualized that craving is an incentive sensitization model of addiction depending on the mesolimbic dopamine system (Robinson and Berridge 1993). The burst firing of mesolimbic dopamine affects the motivational and appetitive attribute of heroin and other addictive substances by confining incentive salience to drug-related cue (Robinson and Berridge 1993, 2000; Wise 1988). Increasing attention, therefore, has been focused on the relationship between craving and dopamine system genes (Erblich et al. 2005 Hutchison et al. 2002a,b). The individual differences, however, in nature and extent of the cue-elicited craving remain (Rees and Heather 1995). Therefore, craving might represent an underlying useable endophenotype for exploring genetic contribution to substance dependence.

Given that dopamine receptors get involved in the initiation of craving, *DRD4* should be one of the candidate genes because *DRD4* VNTR may express the function differences in dopamine receptors (Asghari et al. 1995). The objective of the present study was, therefore, regarding cue-elicited heroin craving as an endophenotype, to test the hypothesis that participants with long variants of *DRD4* VNTR should manifest greater craving after exposure to heroin-related cues compared with the short variants.

Materials and methods

Participants

Hospitalized heroin addicts, 420, in the Shanghai Voluntary Drug Dependence Treatment Center for detoxification were recruited. All subjects were of Han Chinese origin. The following inclusion criteria were used: age 18–60 years old, met DSM-IV (American Psychiatric Association 1994) criteria for heroin dependence evaluated by the structured clinical interview according to DSM-IV [structured clinical interview for DSM-IV (SCID-P)], abstinence from heroin for 1 month (to avoid obviously protracted physical withdrawal symptoms). Participants were excluded if they: met DSM-IV criteria for an additional Axis I disorder; depend on other substances such as alcohol, cigarette, amphetamine, barbiturate, benzodiazepine, cocaine, or marijuana according to the criteria of DSM-IV (some of the participants were smokers and alcohol consumer, but not dependent on those substances), were taking other prescribed medications that could affect the central nervous system, had a history of seizures, hematological diseases, liver, or kidney severe impairment; were pregnant for females. All subjects participated voluntarily and provided a written informed consent before enrollment. Protocols for this study were approved by the Ethics Committee of Fudan University (Shanghai).

Experimental session measures

Background questionnaire Demographic questionnaire was employed to collect information including age, sex, education, marital status, and vocation. Heroin taking history questionnaire was utilized to gather data on frequency and quantity of heroin use daily, years as a heroin addicts, and route of administration.

Craving measure The craving measure, we applied to evaluate craving, has been used to estimate craving in a great deal of cue-elicited craving studies, consisted of five items that were rated on a scale of 0–100 and that were

averaged to form a craving scale (Chronbach's alpha ranged from 0.91–0.93) (Shiffman et al. 2003, Erblich et al. 2004, 2005, Hutchison et al. 2002a,b). The five items consist of "I crave heroin right now," "I have an urge for heroin," "I have a desire for heroin right now," "If it were possible, I would use heroin now," and "All I want right now is heroin."

Procedure

Cue-induced heroin craving program, is involved in exposure to both neutral (light bulb and pencil) and heroin-cue (heroin analogue, instruments such as tinfoil, lighter, and syringe used during heroin taking) stimuli. To avoid a possible carryover effect, neutral stimuli were always presented first followed by the heroin cue and a 3-min video about scenes of nature before cue exposure. At the beginning of the experiment, participants were instructed to relax for 3 min, then completed baseline measures of craving. Subsequently, they were exposed to neutral stimuli for 60 s followed by a measurement of craving and a 3-min video interval before exposure to the heroin cue. When exposed to the cue, the participants were instructed to handle stimuli such as heroin analog, lighter, syringe, and tinfoil, as they usually did before for 60 s. Then the craving score was indicate on the questionnaire. Finally, subjects fulfilled background questionnaires and donated 3-ml venous blood for genotyping right after finishing the laboratory cue-induced craving procedure to ensure least disturbance.

Genotype assessment

Genomic DNA was extracted from leukocytes and the DNA sequence spanning the DRD4 VNTR polymorphisms was amplified by a 2-step nested polymerase chain reaction (PCR) amplification using two sets of primers. For the long PCR primers, the sense primer was: 5′-AGC TGC GCG CCC CAT CCC GAG GAA T-3′, and the anti-sense primer was: 5′-TCG AGT TAT AGG AAG CGT TTC AGA G-3′. For the nested PCR primers, the sense primer was: 5′-FAM CAC TCG AGG CCC GCT GCG ATG TTG C-3′, and the anti-sense primer was: 5′-TCA AGC TTT TAT GAG TTC TTC TGA GGC ACT TTG AC-3′. (Lichter et al. 1993) PCR products were run on an ABI PRISM 3100 automated sequencer (Applied Biosystem, Foster City, CA) and analyzed using GENOTYPER (PE Applied Biosystems) software.

Statistical method

The statistical analyses were performed using SPSS for Windows 10.0. The continuous variables were expressed as the mean±SD and were compared with the analysis of variance (ANOVA). The categorical variables were expressed as percentage and the χ^2 test was applied for the determination of significance of the associations. Pre- and postexposure to heroin-related cue change scores were calculated as an index of craving reactivity. The craving score before the stimulus scene exposure (baseline) was included to yield baseline-adjusted change scores, as reported previously (Erblich et al. 2005). One way ANOVA was employed to estimate the effect of these variants on cue-induced heroin craving. The criterion for significance was set at $p<0.05$. The effect of the covariants such as the amount of daily heroin use, baseline, and neutral activity score was examined to exclude the possibility that the difference may be due to the amount of daily heroin use, baseline or neutral.

Results

In total, 420 heroin addicts were recruited for our study. Seventy-six percent of the heroin abusers were male. Mean age of participants was 31.15±8.09 years (range, 17 to 48). Among them, 42.7% were married and 53% obtained junior school (JS) diploma. The mean time year of heroin using was 5.29±2.52 years, and the mean dose of heroin was 0.85±0.28 g/day. Route of administration: 68% subjects was i.v. or i.m. injection, 22% was nasal inhalation ("chasing the dragon"), and 10% was both injection and nasal inhalation.

Table 1 represents the distribution of genotype for the *DRD4* VNTR polymorphisms in the recruited heroin addicts. We identify six alleles (2–7 repeats allele), with the 4 repeat alleles (4 R) being the most frequent among all the subsample, followed by the 2 repeat allele (2 R). As some genotypes and alleles were rare, we grouped individual genotypes into long (5–7 repeats) and short (2–4 repeats) according to the categorization scheme reported previously (Li et al. 1997, 2000), but they didn't explain how to categorize 2/5, 2/6. In terms of recent work which suggested that the *DRD4* VNTR 2 allele lies midway between the 4 allele and the 7 allele in the coding for D4 receptor potency in reducing cAMP (Wang et al. 2004), we

Table 1 The genotype frequency for the *DRD4* VNTR polymorphism for the heroin addicts

DRD4 genotype	Number	Frequency (%)
2/2	51	12.1
2/3	1	0.2
2/4	94	22.4
2/5	1	0.2
2/6	6	1.4
3/3	2	0.5
3/4	1	0.2
4/4	229	54.5
4/5	17	4.0
4/6	14	3.3
4/7	1	0.2
5/5	2	0.5
5/7	1	0.2

therefore, defined "carriers" subjects as those who contain at least one 5–7 R allele. The distribution for the genotypes of the polymorphisms was in Hardy–Weinberg equilibrium. We found that 10% of the sample (n=42) carried the *DRD4* VNTR long type allele, while 90% (n=378) was "noncarrier".

To assess the possibility of genotype differences in background variables, we compared the demographic and heroin addiction characteristics by each genotype in the addicts group, as shown in Table 2. *DRD4* VNTR long type allele carriers consumed significantly more heroin daily than noncarriers (p=0.012). There were no other differences between groups on background variables.

The present results show that heroin-related environmental cue could induce significant craving reaction. In noncarriers, mean change in cue craving was much higher than that in neutral craving (0.42±0.34 vs 2.45±0.71, t=−52.249, p<0.001). In carriers, mean change in cue craving was much higher than that in neutral craving (3.03±0.81 vs 0.45±0.77, t=−17.794, p<0.001). Mean change in craving induced by cue for carriers was much higher than that for noncarriers (see Fig. 1). As for baseline craving and mean change in craving responding to neutral stimuli, no significance was found (1.06±0.34 vs 1.07±0.36, F=0.067, p=0.797 and 0.42±0.34 vs 0.45±0.37, F=0.277, p=0.599, respectively). As depicted in Fig. 1, carriers of *DRD4* VNTR long type allele exhibited significantly higher change in craving after exposure to a heroin related-cue, as compared to the noncarriers (F=31.040, p<0.001), which is consistent with the hypothesis and previous positive results among smokers (Hutchison et al. 2002b). The association between carrier status and cue-induced craving was significant with sex, age and education, marriage status, amount of daily heroin use, baseline, and neutral activity score included as covariates; thus, it is unlikely that the present results are confounded by these factors.

Table 2 Demographic and heroin abuse characteristic by *DRD4* VNTR genotype

	DRD4 VNTR long type allele carrier status	
	Carrier	Noncarrier
N	42	378
Age (years)	33.81±8.39	30.88±8.00
Sex (%female)	25.43	23.55
Marriage status (%married)	40.35	49.89
Education		
%did not complete JS[a]	4.76	9.26
%completed JS[a]	69.05	51.85
%completed HS[b]	23.81	35.98
% completed college or >	2.38	2.91
Onset (years)	27.30±8.59	27.20±7.74
Dependence (years)	5.57±2.57	5.27±2.51
Amount* (g/day)	0.94±0.25	0.83±0.28
Frequency (times/day)	4.79±2.98	4.73±2.34

*Values differ at p< 0.05
[a] *JS* denotes junior school
[b] *HS* High school

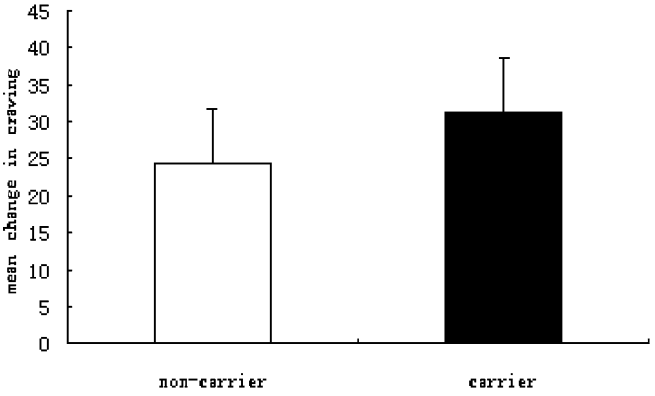

Fig. 1 Adjusted mean change in craving following exposure to heroin-related cues grouped by *DRD4* VNTR polymorphism long type allele carrier statuses

Discussion

The findings of the present study showed that *DRD4* VNTR polymorphism related to dopamine function in the CNS is involved in cue-elicited heroin craving so that individuals with *DRD4* VNTR long repeat allele demonstrate greater craving in response to heroin-related stimuli as compared with that carrying short repeat allele, which is agreement with the previous report that long repeat of *DRD4* exon III VNTR polymorphism was associated with cue-elicited smoking or alcohol craving (Hutchison et al. 2002a,b). The finding lends direct support to the hypothesis that the dopamine system is involved in cue-induced craving and *DRD4* VNTR polymorphism contributes to cue-elicited craving in heroin dependence, suggesting that *DRD4* VNTR represents one of the potential genetic risk factors for cue-induced craving.

Compared with the previous mixed results about the relation between *DRD4* VNTR polymorphism and heroin dependence, the results demonstrated here may be due to the utility of a narrowly defined phenotype under controlled conditions. Heroin addiction is a complex disorder which may be determined by the multiple genetic and environmental factors, and different pathways may play different roles in different circumstances, which may be the leading cause of the conflict findings in previous studies. That is to say, despite the evidence of genetic factors in drug abuse, one specific gene cannot interpret all forms of substance dependence (Schuckit 1998; Li et al. 2000). A certain pathway (such as *DRD4*) may be important for some abusers (with environmental cue), whereas, for other addicts (without environmental related cue), this pathway may be less important. *DRD4* VNTR, hence, may not increase susceptibility to dependence per se, but partially determine some aspect of addiction, such as cue-elicited craving.

Behavioral scientists have recently recommended examining specific genetic effects on a particular, tightly

defined phenotype or an endophenotype under controlled conditions, which is experientially relevant to the clinical presentation of the disorder and is involved in a potential biological mechanism underlying addiction behavior. Craving can be reliably induced in the laboratory with cue in humans and it has been implicated as the primary target of biological and behavioral interventions. Thus cue-elicited craving represents a potential powerful endophenotype. The mesolimbic dopamine system may be activated when exposed to a related cue, which makes incentive salience to be confined to the neural area related to drug-related stimuli. It has also been postulated that dopamine release in the nucleus accumbens attributes "incentive salience" to drug-associated stimuli (Robinson and Berridge 1993).

It has been reported that the rewarding and reinforcing effects of opiate are, at least partially, mediated by non-dopaminergic mechanisms, whereas, the incentive to seek opiates due to the release of dopamine are not (Di Chiara and North 1992). *DRD4* is suggested to be related to incentive sensitization by the fact that this receptor is localized in the limbic brain structures underlying incentive sensitization (Van Tol et al. 1991). Also, this has been confirmed by the observation that the sensitization of these pathways can be blocked by selective D4 dopamine receptor inhibitor (Feldpausch et al. 1998). The cAMP upregulation resulting from repeated exposure to drugs results in a significant enhancement of the signals produced by dopamine system stimulation after exposure to drug-related cues (Nestler and Aghajanian 1997; Self 1998). (Asghari et al. 1995) demonstrated that the potency of dopamine to inhibit cAMP formation was about twofold reduced for long type than that of short type variants, which makes it reasonable that individuals carrying *DRD4* VNTR long allele have elevated cyclic adenosine monophosphate (cAMP) and protein kinase A (PKA) compared with noncarriers. If the raised cAMP levels can increase dopamine signals in the central nervous system (CNS) (Self 1998), the *DRD4* VNTR long type allele may improve the function of neuronal structures responding to heroin-related cue. Accordingly, the carrier may be more susceptive to the dopamine stimulation kindled by exposure to the heroin-related cue.

A strong association between *DRD4* 7R allele and attention deficit/hyperactivity disorder (ADHD) which is typically characterized by marked inattention, hyperactivity, and impulsiveness has been reported (Faraone et al. 2001; Swanson et al. 2001; Grady et al. 2003; Bhaduri et al. 2006; Hawi et al. 2005). A meta-analysis showed greater prevalence of *DRD4* 7 repeat allele in ADHD probands (Faraone et al. 2001), indicating that the 7 repeat allele is associated with a significant fraction (25–50%) of the attributable genetic risk of ADHD (Grady et al. 2003). Although the sample was not characterized with regard to ADHD phenotype, it is possible that ADHD diagnosis is a mediator of the differences noted in heroin craving, which is a worthwhile topic for further study.

The results of the present study indicate that the dopamine system is involved in the mechanism underlying the cue-induced craving for heroin, and thus, may be one of the pathways responsible for opiate addiction. Further animal and human studies are necessary to elucidate the mechanism of the effect of *DRD4* VNTR long type allele on the cue-induced craving. As the cue-elicited craving plays an important role in the persistence of drug abuse and relapse, the D4 receptor antagonist may be useful in reducing cue-induced craving so as to facilitate abstinence or prevent relapse. The present study may provide insight into the mechanism underlying the heroin dependence and other addiction and may help in establishing novel pharmacogenetic approaches on addiction therapy and relapse prevention.

Although our findings apparently show that *DRD4* VNTR long type allele genotypes were associated with greater craving in response to heroin-related stimuli, the complex nature of drug addiction also suggests that this disorder is likely to display genetic architectures similar to those of other complex disorders heterogeneously influenced by variants at multiple gene loci. Further study was warranted to investigate the roles of polymorphisms in other candidate genes of dopamine system and non-dopamine candidate genes involved in the mechanism underlying the cue-induced craving for heroin.

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