

Effect of μ -Opioid Receptor Gene Polymorphisms on Heroin-Induced Subjective Responses in a Chinese Population

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Background: Genetic factors that influence subjective responses to drug use (such as euphoria) contribute to the risk of addiction. μ -opioid receptor is the molecular target of heroin mediating its effects in both pain relief and euphoria.

Methods: To evaluate the association of μ -opioid receptor gene (OPRM1) variants with heroin-induced positive responses on first use, we studied 336 Chinese Han heroin addicts recruited in Shanghai and divided heroin addicts into two groups (positive vs. negative) according to the self-reporting feeling on first use. Association analyses with the genotypes and alleles in nine tagging single nucleotide polymorphisms (tSNPs) in OPRM1 with subjective responses were performed. Similar analysis with haplotypes of these tSNPs was also performed.

Results: Allele frequencies of three tSNPs were significantly different between the positive and negative groups. They were rs696522 (odds ratio [OR] = 3.06, p = .0013), rs1381376 (OR = 3.16, p = .0008), and rs3778151 (OR = 3.12, p = .0004). Such association remains after adjustment for demographic covariates and for multiple testing. The subjects with heroin-induced positive responses on first use consumed more drugs than the negative group (Mann-Whitney U = 224.0, Wilcoxon W = 16334.0, p $\leq$.0001).

Conclusions: Self-reported positive responses on first use of heroin were found to be associated with OPRM1. The findings suggest that heroin-induced positive responses are likely associated with more heroin consumption.

Key Words: Haplotype, heroin-induced subjective responses, OPRM1, tSNP

The use of heroin is a major public health threat, because the risks associated with heroin use, such as human immunodeficiency virus (HIV), viral hepatitis, and crimes, exceed most other abused drugs (Brown 2004). Recent investigations showed a substantial increase in the number of heroin addicts in China (Padmohoedjo 2004). Heroin activates the opioid system to produce a pleasurable response that is key to the addiction process (Maher *et al.* 2005). The μ -opioid receptor belongs to a large superfamily of seven transmembrane-spanning G protein-coupled receptors that are of fundamental physiological importance by mediating the actions of the majority known neurotransmitters, such as β -endorphin relating to euphoria (Waldhoer *et al.* 2004). In fact, heroin is among the most widely abused drugs, in terms of their actions on the μ -opioid receptor to produce euphoria (Chen *et al.* 1996). Both pharmacological and genetic experiments demonstrated that the human μ -opioid receptors were implicated in the mechanism underlying heroin dependence (Gerrits *et al.* 2003; Matthes *et al.* 1996). It has been shown that μ -opioid receptor is the molecular target of heroin, mediating its effects in both pain relief and euphoria (Raynor *et al.* 1994). The mice with disruption of μ -opioid Receptor1 gene (*Oprm*) showed no induction of place prefer-

ence after morphine conditioning as well as a complete lack of physical withdrawal syndromes (Matthes *et al.* 1996). Furthermore, *Oprm*-knockout mice are characterized by reduced opioid-mediated analgesia, reward, and physical dependence (Conardino *et al.* 2002; Matthes *et al.* 1996; Sora *et al.* 2001).

Several studies that probed the relationship between OPRM1 and heroin dependence concluded with conflicting results (Shi *et al.* 2002; Szeto *et al.* 2001). The +118G allele was reported to be positively associated with heroin addiction in Hong Kong Chinese (Szeto *et al.* 2001), whereas another research study indicated lack of significant frequency difference of this allele between heroin addicts and control subjects in Nanjing Chinese (Shi *et al.* 2002). The contradicting results apparently can not be simply explained by ethnic difference, and such discrepancy might be attributable to the lack of proper experimental control over multifactors influencing heroin dependence in real-world settings. Regardless of inconsistent association of this gene with heroin addiction, given the growing evidence on responses to cannabis, nicotine, and alcohol or overlapping neural pathways in the development of dependence, it is likely that the nature of early subjective responses to substances are prognostic of later substance dependence (Fergusson *et al.* 2003; Newlin and Thomson 1990; Pollock 1992). Individuals showing positive subjective responses to early drug use are more prone to become dependent than those showing negative subjective responses (Eissenberg and Balster 2000; Newlin and Thomson 1990; Pollock 1992). Initial positive responses to early drug use have been linked to susceptibility to addiction (Fergusson *et al.* 2003; Haertzen *et al.* 1983; Lott *et al.* 2005). It is commonly assumed that people abuse drugs because the drugs make them feel good (Jasinski 1977). Hence, heroin-induced subjective responses on first use might constitute a sensible measurable endophenotype to test genetic factors of heroin abuse.

In this study, we hypothesized that the specific variants of OPRM1 are associated with heroin-induced positive responses on first use. In the human OPRM1 gene, more than 100 poly-

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morphisms have been identified (Bergen *et al.* 1997; Bond *et al.* 1998; Hoehe *et al.* 2000; Ide *et al.* 2004; Ikeda *et al.* 2005; Shi *et al.* 2002). A comprehensive survey of all known common polymorphisms is unnecessary, because many of them are in strong linkage disequilibrium (LD) with each other. Therefore, to test the aforementioned hypothesis, we adopted a three-step approach by first characterizing the haplotype structure in OPRM1, then selecting a group of single nucleotide polymorphism tags (tSNP) that sufficiently capture the genetic variation of the common haplotypes, and finally investigating the association of these tSNPs with the phenotype (Weale *et al.* 2003). To our knowledge, this is the first large-scale tSNP-based association analysis of heroin dependence with heroin-induced subjective responses on OPRM1. In addition, we also examine the hypothesis that individuals having positive responses on first use of heroin consume more drugs than those having negative responses.

Methods and Materials

Participants

Heroin addicts ($n = 372$) in Shanghai Voluntary Drug Dependence Treatment Center were recruited. All subjects are of Han Chinese origin. Only those who were 18 years or older and met DSM-IV (American Psychiatric Association 1994) criteria for heroin dependence were recruited. The following subjects were excluded: 1) met DSM-IV criteria for an additional Axis I disorder; 2) had a history of alcohol, cigarette, amphetamine, barbiturate, benzodiazepine, or marijuana dependence according to DSM-IV; 3) were taking other prescribed medications that could affect the central nervous system; 4) had a history of seizures, hematological diseases, or liver or kidney severe impairment; or 5) were pregnant. Each subject participated in this study voluntarily and provided written informed consent before enrollment. Protocols for this study were approved by the Ethics Committee of School of Life Sciences at Fudan University (Shanghai).

Background Questionnaire

Demographic questionnaire was employed to collect information, including age and gender. Heroin-taking history questionnaire was used to gather data on reason for first heroin use, age at onset, the number of drug uses preceding the first occurrence of positive response, the amount of heroin consumption/day, the frequency of heroin-taking/day, years of heroin-taking, the route of heroin-using, the monthly average increment of dosage, and heroin-induced subjective responses on first use.

Subjective Responses to the First Time Use of Heroin

We used retrospectively determined descriptions of subjective responses to early opiate use to define positive and negative response groups. Heroin addicts were interviewed individually by trained interviewers to gather detailed information of their heroin use. They were asked to report their subjective responses on first use (focusing on comfortable or uncomfortable responses) and answer questions based on a modified opiate adjective checklist reflecting opioid agonist effects (Fraser *et al.* 1961; Yuan *et al.* 1998, 2002; Zacny *et al.* 1994). This list consisted of 16 items relating to positive and negative experience: “flushing,” “stimulated,” “numb,” “drunken,” “difficulty in concentrating,” “drowsy (sleepy),” “coasting or spaced out,” “turning of stomach,” “skin itch,” “dry mouth,” “dizzy,” “nauseous,” “getting really high,” “feeling carefree or happy,” “feeling relaxed,” and “feeling euphoria.”

Heroin addicts were separated into two groups on the basis of

their self-reported feelings on first use. Those mainly reporting comfortable responses on first use of heroin, such as getting really high, feeling happy, feeling euphoria, and feeling relaxed, were classified as “positive”; others mainly reporting uncomfortable responses were classified as “negative.” Overall, 36 subjects (9.7% of the total samples) were excluded for not being able to provide subjective responses to the first use of heroin. Furthermore, we conducted the analysis by selecting the individuals who started heroin use for 1 year or less at the date of interview.

Selection of tSNPs

Several methods have been developed for selecting tSNPs on the basis of haplotype data or genotype data (Daly *et al.* 2001; Gabriel *et al.* 2002; Patil *et al.* 2001; Wang *et al.* 2002; Zhang *et al.* 2002). In this study, the tSNPs were selected by using genotype data with an algorithm based on the r^2 statistic (Carlson *et al.* 2004). The genotype data of all SNPs in OPRM1 of a population with a mixed ethnic background were obtained from <http://egp.gs.washington.edu/data/oprm1>, because no data on OPRM1 in HAPMAP (haplotype map of the human genome) project were available in January 2005. Eleven tSNPs with their minor-allele frequency (MAF) exceeding 10% were selected with $r^2 > .5$, and they encompass the entire genomic region of the OPRM1 gene. They are rs1799971, rs510769, rs696522, rs1381376, rs570308, rs3778151, rs2075572, rs533586, rs550014, rs512053, and rs658156 (Figure 1).

Genotyping With Restriction Fragment Length Polymorphism and Taqman

Genotypes at rs1799971, rs510769, and rs533586 were determined by restriction fragment length polymorphism (RFLP) procedure and those at the others (rs696522, rs1381376, rs570308, rs3778151, rs2075572, rs550014, rs512053, and rs658156) by TaqMan (Applied Biosystems, Foster City, California). The sequences of primers and probes are available upon request. For each SNP, the rate of genotyping error was determined by typing the blind duplicates selected from 10% of the samples.

Statistical Analysis

Association Analysis. Association analysis of individual SNP, genotype, and allele frequencies between positive and negative groups were compared by χ^2 test on 2×3 and 2×2 categorical tables, respectively. For pairwise LD analysis, D' and p value for each pair of SNPs in OPRM1 were calculated with Arlequin 2.0 (Schneider *et al.* 2000), whereas r^2 for each SNP pair was calculated with HaploBlockFinder V0.7 (<http://cgi.uc.edu/cgi-bin/kzhang/haploBlockFinder.cgi>) (Zhang and Jin 2003).

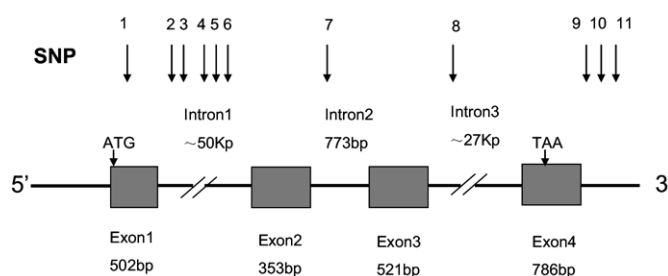


Figure 1. The human μ -opioid receptor gene (OPRM1) structure and 11 single nucleotide polymorphism (SNP) variants. SNP1 (rs1799971, 118A/G or Asn40Asp), SNP2 (rs510769, C/T), SNP3 (rs696522, C/T), SNP4 (rs1381376, C/T), SNP5 (rs570308, A/G), SNP6 (rs3778151, G/A), SNP7 (rs2075572, G/C), SNP8 (rs533586, C/T), SNP9 (rs550014, T/C), SNP10 (rs512053, A/C), SNP11 (rs658156, C/T).

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